Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;376:644-57. DOI: 10.1056/NEJMoa1611925

This supplement contains the following items:

1. Original and final study protocols for CANVAS (DIA3008) and CANVAS-R (DIA4003)
2. Original and final statistical analysis plans for CANVAS (DIA3008), CANVAS-R (DIA4003), and the integrated analysis

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Johnson & Johnson Pharmaceutical Research & Development*

Clinical Protocol

A Randomized, Double-Blind, Parallel, Placebo-Controlled, Multicenter Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus

CANVAS
(CANagliflozin cardioVascular Assessment Study)

Protocol 28431754DIA3008; Phase 3

JNJ-28431754 (canagliflozin)

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This study will be conducted under U.S. Food & Drug Administration IND regulations (21 CFR Part 312).

Issue/Report Date: 14 AUGUST 2009
Prepared by: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Document No.: EDMS-PSDB-9584804:2.0
Eudract No.: 2009-012140-16

Compliance: This study will be conducted in compliance with this protocol, Good Clinical Practice, and applicable regulatory requirements.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

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Signature: [redacted] Date: 18/Aug/09
(Day Month Year)

Note If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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SYNOPSIS

A Randomized, Double-Blind, Parallel, Placebo-Controlled, Multicenter Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus (CANVAS: CANagliflozin cardioVascular Assessment Study)

EUDRACT number: 2009-012140-16

Canagliflozin (JNJ-28431754) is an orally active inhibitor of the sodium-glucose transporter 2 (SGLT2) that is being developed as an oral antihyperglycemic agent (AHA) for the treatment of patients with type 2 diabetes mellitus (T2DM). Canagliflozin is selective for inhibition for SGLT2 relative to sodium-glucose transporter 1 (SGLT1) transporters.

The goals of this study (CANVAS) are to assess the overall safety and tolerability of canagliflozin and to demonstrate a reduction in major adverse cardiovascular events (MACE) with canagliflozin treatment. The study uses an adaptive design approach with 2 cohorts of recruited study subjects. Adequacy of sample size to demonstrate a reduction in cardiovascular (CV) events will be evaluated in an initial cohort of subjects (Cohort A); this evaluation will include the effect of canagliflozin on CV risk factors and on the observed hazard ratio (HR) for MACE in this initial cohort. Additional subjects may then be recruited into the study (Cohort B) to provide sufficient overall study power to demonstrate a reduction in CV risk with canagliflozin. This study will also examine the effect of long-term treatment with canagliflozin on albuminuria (based upon urinary albumin/creatinine ratio) and on beta-cell function (based upon homeostasis model assessment). An additional goal of CANVAS will be accomplished in 3 substudies that are intended to provide information on the efficacy and safety of canagliflozin in combination with specific AHAs. During the conduct of this study, CV events from this study will be pooled with CV events occurring in other large, well-controlled, double-blind, randomized studies of canagliflozin for meta-analyses (described in a separate statistical analysis plan [SAP]) to assess the CV safety of canagliflozin.

OBJECTIVES

Primary Objectives

In subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease:

- to assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care on CV risk as measured by the HR for a composite endpoint (MACE including CV death, nonfatal myocardial infarction [MI], and nonfatal stroke)
- to assess the safety and tolerability of canagliflozin

Secondary Objectives

In subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease, to assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care, at 52 weeks and at the end of the treatment period on:

- fasting measures of beta-cell function (ie, homeostatic model assessment [HOMA]-B and the proinsulin/insulin ratio) (note: this assessment will be conducted in a subset of subjects at designated sites, including only subjects who are not receiving insulin at randomization)
- the proportion of subjects with progression of albuminuria (progression defined as ≥1 step, ie, no albuminuria to micro- or macro-albuminuria or from micro-albuminuria to macro-albuminuria) and the proportion of subjects with regression of albuminuria (regression defined as ≥1 step, ie, macro- to micro- or normo-albuminuria, or micro-albuminuria to normo-albuminuria)

In subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease, to assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care at 18 weeks and at the end of the treatment period on:

- glycemic efficacy (ie, on hemoglobin A_{1c} [HbA_{1c}] and fasting plasma glucose [FPG])

- body weight
- blood pressure (ie, systolic and diastolic)
- fasting plasma lipids (triglycerides, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], total cholesterol, and the ratio of LDL-C to HDL-C)

Hypotheses
Primary hypotheses

In subjects with T2DM, with inadequate glycemic control, who have a history of or a high risk of CV disease:

- relative to placebo plus standard of care, canagliflozin plus standard of care reduces CV risk (as measured by the HR for a composite endpoint including CV death, nonfatal MI, and nonfatal stroke)
- canagliflozin is well tolerated

- Secondary hypotheses

In subjects with T2DM, with inadequate glycemic control, who have a history of or a high risk of CV disease, relative to placebo plus standard of care, canagliflozin plus standard of care at the end of the treatment period:

- improves beta-cell function (ie, change from baseline in HOMA-B)
- reduces progression of albuminuria (ie, proportion of individuals with ≥1-step progression of albuminuria as determined by the urine albumin/creatinine ratio)

Note: Separate objectives and hypothesis are provided for the meta-analysis (of results from this and other large, well-controlled studies in the canagliflozin program) in support of CV safety; these objectives and hypothesis are stated in a separate SAP.

Substudies: Objectives and Hypotheses (Cohort A)
The three 18-week substudies will be conducted with the data from Cohort A subjects of this study and are intended to assess the safety and tolerability and efficacy of canagliflozin in subjects with T2DM, with inadequate glycemic control in each of the 3 specific subgroups of subjects receiving (1) insulin ≥20 units/day monotherapy or in combination with other AHA(s), (2) sulfonylurea monotherapy at protocol-specified doses, or (3) PPARγ agonist (pioglitazone ≥30 mg/day or rosiglitazone ≥4 mg/day) plus metformin ≥2,000 mg/day (or at least 1,500 mg/day for subjects who have a history of not being able to tolerate higher metformin doses) and no other AHA. The following objectives and hypotheses will apply to each of these substudies. These are separate and distinct from the main study hypothesis testing.

Primary Substudy Objectives
In subjects with T2DM, with inadequate glycemic control, who have a history of or a high risk of CV disease:

- To assess the HbA_{1c}-lowering efficacy (ie, change from baseline in HbA_{1c}) of canagliflozin relative to placebo after 18 weeks of treatment
- To assess the safety and tolerability of canagliflozin

Primary Substudy Hypotheses
In subjects with T2DM, with inadequate glycemic control, who have a history of or a high risk of CV disease:

- After 18 weeks of treatment, canagliflozin provides a greater improvement in HbA_{1c} relative to placebo (ie, change from baseline in HbA_{1c})
- Canagliflozin is well tolerated

Secondary Substudy Objectives and Hypotheses
Objectives
After 18 weeks, in subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease, to assess the effect of canagliflozin relative to placebo, on:

- body weight
- FPG-lowering efficacy
- proportion of subjects reaching HbA_{1c} <7.0%
- systolic and diastolic blood pressure
- fasting plasma lipids (triglycerides, HDL-C, LDL-C, total cholesterol, and the ratio of LDL-C to HDL-C)

After 26 and 52 weeks, in subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease, to assess the effect of canagliflozin relative to placebo on:

- glycemic efficacy (ie, HbA_{1c} and FPG)
- body weight
- systolic and diastolic blood pressure
- fasting plasma lipids (triglycerides, HDL-C, LDL-C, total cholesterol, and the ratio of LDL-C to HDL-C)

Hypotheses
After 18 weeks, in subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease, relative to placebo, canagliflozin:

- provides a greater reduction in body weight
- provides a greater reduction in FPG
- leads to a greater proportion of subjects achieving HbA_{1c} <7%
- reduces systolic blood pressure
- increases HDL-C concentrations
- lowers triglyceride concentrations

Medical Resource Utilization Objective
To collect medical resource utilization (MRU) data that may be used in future economic modeling (the construction and reporting of the economic model will be conducted separately from this protocol).

OVERVIEW OF STUDY DESIGN
This is a randomized, double-blind, placebo-controlled, 3 parallel-group, multicenter, adaptively-designed study to evaluate the safety, tolerability, and CV safety, and subsequently, the benefit on CV risk with canagliflozin plus standard of care compared with placebo plus standard of care in subjects with T2DM who have either a history or high risk of CV disease. This study has an adaptive design, with an initial cohort of subjects randomized, a sample size re-estimation conducted, and then, if appropriate, a second cohort of subjects recruited to support the overall study power to demonstrate CV risk reduction, as described below.

In this study, an initial cohort of 4,500 subjects will be randomized (referred to as Cohort A) to treatment with 1 of 2 doses of canagliflozin (100 mg or 300 mg) or placebo, in a 1:1:1 randomization ratio. After a prespecified number of events at a planned time point have occurred, an interim analysis (conducted under the direction of the study's Independent Data Monitoring Committee [IDMC]) will be performed (1) to assess if CV benefit may be expected with canagliflozin treatment (at least 15% expected CV risk reduction for MACE based upon the effect of canagliflozin on CV risk factors and the observed HR), and, (2) if this extent of benefit is expected, to determine the size of the subsequent cohort (referred to as Cohort B) necessary to demonstrate CV risk reduction with canagliflozin treatment in the overall study population (ie, combined Cohorts A and B).

The determination as to the required sample size for Cohort B, or the decision not to recruit Cohort B if insufficient CV benefit is predicted, will be based upon protocol-specified criteria and implemented by the Executive Committee (composed of one member each from the Steering Committee, ARO, and sponsor) after hearing the recommendation from the IDMC.

STUDY POPULATION

Men or women with T2DM who have inadequate glycemic control (HbA_{1c} ≥7.0 and ≤10.5%), not on an AHA or on an AHA in monotherapy or combination therapy, and are either at high risk of CV events (2 or more risk factors; approximately 30% of subjects) or with known CV disease (at least 70% of subjects) are eligible.

STRATIFICATION FOR SUBSTUDIES

To ensure sufficient experience in subjects with documented, pre-existing CV disease—the highest risk group—not less than 70% of subjects must be in this group.

Subjects in Cohort A within the following 6 predefined strata, based upon AHA medication(s) that the subject is receiving at the screening visit and will be continuing at entry into the double-blind treatment phase, will have within-subgroup balanced (1:1:1) randomization to each of the 3 treatment groups:

- Stratum 1: insulin monotherapy ≥20 units per day, on stable doses at least 10 weeks before the run-in visit
- Stratum 2: insulin ≥20 units per day plus metformin, on stable doses at least 10 weeks before the run-in visit, and no other background AHA therapy
- Stratum 3: insulin ≥20 units per day plus any other AHA(s) on stable dose(s) for at least 10 weeks before the run-in visit
- Stratum 4: sulfonylurea monotherapy (at doses specified in the main protocol), on stable doses at least 10 weeks before the run-in visit
- Stratum 5: PPARγ agonist (pioglitazone ≥30 mg/day or rosiglitazone ≥4 mg/day) plus metformin ≥2,000 mg/day (or at least 1,500 mg/day for subjects who have a history of not being able to tolerate higher metformin doses) and no other background AHA therapy, on stable doses at least 10 weeks before the run-in visit
- Stratum 6: subjects not in one of the above AHA subgroups

No stratification will be applied for Cohort B

DOSAGE AND ADMINISTRATION

Study Drugs

Upon successful completion of the initial screening, all potentially eligible individuals will enter a 2-week run in period, during which they will receive single-blind placebo tablets (to be administered once-daily).

Subjects in Cohort A will be randomly assigned in a 1:1:1 ratio to 1 of 3 treatment groups: canagliflozin 100 mg, canagliflozin 300 mg, or matching placebo. Subjects will receive their dose of canagliflozin or matching placebo once daily, before the first meal of the day, according to their randomized treatment assignment, for the duration of the study or until discontinuation from the study.

Based upon the results of the Phase 3 program evaluation, one or the other dose of canagliflozin may not continue to be planned for registration. The randomization of subjects in Cohort B will be based upon balanced allocation to placebo and the dose(s) of canagliflozin planned for registration at the time the decision is made to initiate recruitment of Cohort B (ie, 1:1 if placebo and 1 dose, or 1:1:1 if placebo and 2 doses).

Concomitant Antihyperglycemic and Other Therapies

Detailed instructions are provided in the main protocol for management of (1) glycemic control and CV risk factors, and (2) glycemic rescue therapy through Week 18.

SAFETY EVALUATIONS

Safety will be evaluated on the basis of adverse events, CV events (examined in the prespecified meta-analysis of CV events from this and other large, well-controlled, double-blind, randomized studies), clinical laboratory tests, electrocardiograms (ECGs), vital signs (pulse, blood pressure), physical examination, and body weight.

EFFICACY EVALUATIONS/CRITERIA

The hypothesis of CV risk reduction for canagliflozin will be evaluated based upon the events in the CV benefit composite endpoint of MACE (CV death, nonfatal MI, nonfatal stroke). An independent Endpoint Adjudication Committee will assess all events that could potentially be in the specified CV endpoint and only those events where the committee, using methodology and definitions defined in the committee's charter, determines a specified endpoint has occurred will be included in the analysis. The independent Endpoint Adjudication Committee will apply the endpoint definitions contained in its charter and classify the outcome events while blinded to treatment assignment.

Other efficacy evaluations include HbA_{1c}, FPG, systolic and diastolic blood pressure, body weight, and fasting plasma lipids (triglycerides, HDL-C, LDL-C, total cholesterol, and the ratio of LDL-C to HDL-C). The change from baseline in HbA_{1c}, FPG, systolic and diastolic blood pressure, and body weight and percent change in fasting plasma lipids will be evaluated.

Urinary albumin/creatinine ratio (from first morning void) will be evaluated, as will beta-cell function with HOMA-B and proinsulin/insulin ratio. Measurements to assess HOMA-B and the proinsulin/insulin ratio will be collected in a subset of subjects of approximately 1,200 subjects (at designated sites) who are not receiving insulin at baseline. Homeostatic model assessment (HOMA)-B will be assessed using C-peptide and fasting glucose; for subjects who initiate therapy with insulin during the study, data from the last proinsulin and insulin measurement before initiation of insulin will be utilized for analyses of proinsulin/insulin ratio.

PHARMACOGENOMIC EVALUATIONS

A pharmacogenomic blood sample should be collected on Day 1 (or at a subsequent visit if not collected on Day 1) from subjects who consent separately to the pharmacogenomic component of the study to allow for pharmacogenomic research, as necessary (where local regulations permit).

STATISTICAL METHODS

Analysis Sets

The intent-to-treat (ITT) analysis set includes all subjects who are randomly assigned to a treatment group. The modified intent-to-treat (mITT) analysis set is a subset of the ITT set, consisting of subjects who received at least 1 dose of study medication. The primary CV analysis will be based on the time to the first occurrence of any component of the CV composite endpoint observed during the treatment or within 28 days post the last dose of study medication in the mITT set.

Sample Size Determination

Cohort A: The sample size for Cohort A of approximately 4,500 subjects is based upon a sufficient number to support, in concert with the other controlled clinical trials in the canagliflozin development program, a detailed assessment of the safety and tolerability of canagliflozin as well as to support the planned meta-analysis to demonstrate that the upper bound of the 2-sided 95% CI of the HR of canagliflozin relative to control in composite endpoint events (MACE and hospitalized unstable angina) is <1.8.

To exclude an upper bound of 1.8, the first planned meta-analysis will be performed when at least 104 CV safety composite events have occurred in the canagliflozin clinical development program. The occurrence of 104 such events will provide 80% power (assuming a true HR of 1.0). It is expected that approximately 40 events will be observed in the other large, well-controlled, double-blind, randomized studies that will be included in the meta-analysis. Assuming a per annum event rate of 2.25% and a per annum dropout rate of 5% with 4,500 subjects randomized to the 3 treatment groups will have 64 events from this study in about 2 years.

Cohort B: An interim analysis of CANVAS will be conducted around the time of the approval of canagliflozin in the US. Results from the interim analysis will (1) provide a *predicted* effect of canagliflozin on risk for CV events (ie, the HR) based upon the effect of canagliflozin on established CV risk factors (eg, blood pressure, fasting lipids, HbA_{1c}); and (2) determine the *observed* HR for MACE in the initial study cohort. These 2 components will be used by the IDMC to determine an *expected* effect of canagliflozin on CV risk based upon specific guidance provided in the IDMC charter. Cohort B will be initiated if the expected CV risk reduction (canagliflozin relative to placebo) is at least 15% (ie, expected HR $\leq$0.85, and the observed HR is not >0.95), *and* the CV risk reduction can be demonstrated (with 90% conditional power) with recruitment of no more than 14,000 additional subjects (Cohort B) and within a planned duration of double-blind treatment phase of approximately 4 years.

Safety Analyses

The safety analysis will be based on the mITT analysis set. There will be no imputation for missing values for clinical laboratory test results, ECG evaluations, vital sign measurements, and physical examination results in the analyses.

The co-primary study hypothesis, that canagliflozin is well tolerated, will be assessed based upon a review of the incidence of overall and specific adverse events, discontinuations due to adverse events, laboratory results, and other safety and tolerability measurements.

CV Outcomes and Efficacy Analyses

The CV outcomes from this study and other large, well-controlled, double-blind, randomized studies of canagliflozin will be integrated to assess the overall safety of canagliflozin as well as to support the assessment of CV safety to demonstrate no unacceptable increase in CV risk of canagliflozin relative to control (to meet regulatory agency requirements). *The analyses will be detailed in a separate meta-analysis plan.*

The primary endpoint for CV benefit (evaluated for both recruited cohorts will be for both canagliflozin dose groups combined versus placebo) will be time to MACE, which is calculated as the time from randomization to the first occurrence of MACE. The statistical hypothesis will be:

$H_{0(1.0)}$: The HR =1.0, versus $H_{1(1.0)}$: The HR $\neq$1.0.

The primary analysis will be based on the mITT analysis set and events that occur within 28 days following discontinuation if subjects discontinue treatment during the course of the study. The comparison of canagliflozin to placebo will be assessed via the HR estimate derived from Cox proportional hazards model with term for treatment, the factors for randomization stratification, history of a previous CV event, and cohort (A and B).

The assumption of the proportional HR will be examined. In case the assumption is deemed not reasonable, sensitivity analyses that do not rely on the constant HR assumption will be conducted to verify the results of the primary analysis.

Additionally, the HR and its 2-sided 95% CIs versus placebo will be assessed for each dose of canagliflozin. For individual components of the composite CV endpoint, the HR and its 2-sided 95% CIs between combined canagliflozin dosage groups and placebo will also be assessed.

The effects of different baseline demographic variables (eg, age, race, sex) as well as other important baseline disease characteristics (eg, history of prior CV disease, key concomitant therapy use, region) on the primary endpoint will be explored; a detailed discussion of subgroup analyses will be provided in the SAP for this study which will be filed before the first interim analysis.

Secondary Efficacy Analyses

Changes from baseline in the continuous variables of HOMA-B and the proinsulin/insulin ratio, HbA_{1c}, FPG, body weight, and blood pressure, and percent change in fasting lipids will be analyzed using an analysis of covariance (ANCOVA) model with treatments and stratification factors as fixed effects and the corresponding baseline value as a covariate. The treatment difference (each dose of canagliflozin minus placebo) in the least-squares means and the 2-sided 95% CI will be estimated based on this model. The analyses for beta-cell function will be conducted on subjects not receiving insulin at randomization and, for subjects who are started on insulin during the study, the last data point before the initiation of insulin will be included for these analyses.

The categorical secondary efficacy endpoint is *proportion of subjects with progression of albuminuria* (defined as ≥1 step, ie, no albuminuria to micro- or macro-albuminuria or from micro-albuminuria to macro-albuminuria) or *regression from albuminuria* (defined as ≥1 step, ie, macro- to micro- or normo-albuminuria, or micro-albuminuria to normo-albuminuria) at the end of the treatment period. The proportion of subjects with progression to albuminuria will be analyzed using the Cochran-Mantel-Haenszel (CMH) test with treatment group as factors, adjusting for randomization strata. A similar analysis will be conducted for subjects with regression from albuminuria.

Medical Resource Utilization Analyses

Medical Resource Utilization data analyses will be descriptively summarized by primary outcome variable (ie, those with a CV event versus those without) regardless of treatment group. These data may be used in future economic modeling to be done outside of the protocol.

Interim Analyses

A sequence of 3 analyses may be conducted during the conduct of the CANVAS study. *The first analysis* is a meta-analysis (described in a separate SAP) of data from CANVAS and other large, well-controlled, double-blind, randomized studies of canagliflozin, and is intended to support CV safety of canagliflozin (to show no unacceptable increase in CV risk) showing that the upper bound of the 95% confidence interval around the HR is <1.8, in support of initial regulatory submission. *The second analyses* will focus on CANVAS only, and is intended to determine if CV benefit is expected (considered to be at least 15% CV risk reduction), and if it is feasible to demonstrate CV risk reduction based upon maximum of 14,000 additional subjects with approximately 4 years of follow-up, and then to determine the sample size for Cohort B. *The third analysis* (described in a separate SAP) is to evaluate the hypothesis (for the meta-analysis, stated in the SAP) that there is no unacceptable increase in CV risk with canagliflozin relative to control treatments (with an upper bound of the confidence interval around the HR of <1.3). If Cohort B is recruited, this meta-analysis would be conducted at the *completion* of the CANVAS study. If Cohort B is not recruited, this meta-analysis would be conducted including subjects from Cohort A only.

Glycemic Efficacy Substudies

Analysis Sets: The mITT analysis set includes all subjects who are randomly assigned to a treatment group and received at least 1 dose of study medication. The per-protocol (PP) analysis set will consist of all mITT subjects who completed all 18 weeks of treatment, and have no major protocol violations (to be defined in the SAP before database lock and unblinding of the treatment groups) and have not received glycemic rescue therapy. The primary efficacy analysis will be based on the mITT set. The efficacy data measured after the initiation of rescue therapy will be treated as missing. Analysis based on the PP set will also be conducted as a sensitivity analysis.

Sample Size Determination: The primary objective of this study is to compare the HbA_{1c}-lowering efficacy of canagliflozin with placebo after 18 weeks of treatment.

Assuming a group difference of 0.55% and a common standard deviation of 1.0% with respect to change in HbA_{1c}, and using a 2-sample, 2-sided t-test with Type I error rate of 0.05, it is estimated that 165 randomized subjects (55 subjects in each of the 3 treatment groups) would provide 80% power.

Efficacy Analyses: For each substudy, the primary efficacy analysis will only be performed when sufficient subjects (≥55) in the subpopulation are randomized in each of the 3 treatment groups. The analysis will be conducted when the sponsor prepares for the regulatory submissions.

The primary efficacy endpoint will be the change in HbA_{1c} from baseline through Week 18. The last-observation-carried-forward (LOCF) method will be applied when the Week 18 values are missing. In subjects receiving rescue therapy, their measurements made before rescue will be used as the last observation. An ANCOVA model with treatment as a fixed effect and its corresponding baseline value as covariate will be used. The treatment difference (each dose of canagliflozin minus placebo) in the least-squares means and the 2-sided 95% confidence interval (CI) will be estimated based on this model.

The secondary efficacy evaluations of change in body weight, FPG, systolic and diastolic blood pressure, and percent change in fasting plasma lipids will be analyzed using an ANCOVA model similar to that used in the primary efficacy analysis. The percentage of subjects with HbA_{1c} <7% at Week 18 will be assessed by means of a logistic model with treatments, stratification factor, and baseline HbA_{1c} as covariate.

Multiplicity Adjustment: To ensure the family-wise Type I error rate (alpha level) in each substudy is at most 5%, a gatekeeping procedure will be applied in testing the hypotheses in the substudy. The superiority over placebo in HbA_{1c} reduction will be tested sequentially for the descending doses of canagliflozin. After the superiority of the 2 doses on HbA_{1c} is concluded, the hypothesis of the secondary endpoints will be tested via 2 testing sequences. The alpha level will be split evenly for the 2 sequences.

Safety*:* The safety analysis for the substudies will follow the methodology for the main protocol.

TIME AND EVENTS SCHEDULE

Phase	Pretreatment		Double-Blind Treatment											Posttreatment
Procedures and Evaluations	**Screening**	**Run-in[a]**	**Baseline**							**13-week intervals**	**26-week intervals**	**52-week intervals**	**EOT or EW[b]**	**Follow-up Contact[c]**
Week[d]	-3	-2	Day 1	6	12	18	26	39	52	65 to end	78 to end	104 to end		28 days after last dose of study drug[c]
Pretreatment/Administrative														
Informed consent[e]	X													
Pharmacogenomic consent[f]			X											
Inclusion/exclusion criteria	X	X	X											
Medical history and demographics	X	X												
Prestudy therapy[g]	X	X	X											
Run-in compliance assessment			X											
Randomize			X											
Pretreatment Procedures														
Follicle stimulating hormone (if necessary per inclusion criteria)		X												
Thyroid stimulating hormone		X												
Urine pregnancy test[h]		X	X											
Diet & exercise counseling / review hypoglycemia recognition and treatment[i, j]		X												
Dispense subject diary card[j]		X												
Study Drug														
Dispense single-blind placebo		X												
Administer/dispense double-blind study drug			X		X	X	X	X	X	X	X	X		
Procedures														
Physical examination[k]		X							X			X	X	
Vital signs, weight[l]		X	X	X	X	X	X	X	X	X	X	X	X	
Height		X												
12-lead electrocardiogram[m]		X							X			X	X	
Dispense blood glucose monitor[n]		X												
Self-monitored blood glucose review		X	X	X	X	X	X	X	X	X	X	X		

NOTE: Footnotes are provided after the table.
CV=cardiovascular; EOT=end-of-treatment; EW=early withdrawal; HbA_{1c}= hemoglobin A_{1c} (Continued)

TIME AND EVENTS SCHEDULE (CONTINUED)

Phase	Pretreatment		Double-Blind Treatment											Posttreatment
Procedures and Evaluations	**Screening**	**Run-in[a]**	**Baseline**							**13-week intervals**	**26-week intervals**	**52-week intervals**	**EOT or EW[b]**	**Follow-up Contact[c]**
Week[d]	-3	-2	Day 1	6	12	18	26	39	52	65 to end	78 to end	104 to end		28 days after last dose of study drug[c]
Procedures (continued)														
Provide container for urine collection for first morning void		X						X		X[o]				
Medical resource utilization[p]				X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Assessments														
Hematology[q]		X	X			X			X			X		
Urinalysis[q]		X	X			X			X			X	X	
Serum chemistry[q]	X		X	X		X		X	X		X	X	X	
HbA_{1c}	X		X		X	X	X	X	X		X	X	X	
Fasting plasma glucose[q]		X	X	X	X	X	X		X			X	X	
Fasting serum C-peptide, insulin, proinsulin[q, r] (subset of subjects not on insulin)			X						X			X	X	
Fasting lipids[q]		X	X			X			X			X	X	
First morning void urine for albumin/creatinine ratio[q, s]			X			X			X			X	X	
Plasma, serum, and urine archive samples[q]			X						X			X	X	
Plasma, serum, and urine samples for biomarker analysis[q]			X						X			X	X	
Pharmacogenomic specimen[f]			X											
Ongoing Review														
Review diary card[t]			X	X	X	X	X	X	X	X	X	X	X	
Concomitant therapy[t, u]				X	X	X	X	X	X	X	X	X	X	X
CV events / adverse events[t, v]		X	X	X	X	X	X	X	X	X	X	X	X	X

NOTE: Footnotes are provided after the table.
CV=cardiovascular; EOT=end-of-treatment; EW=early withdrawal; HbA_{1c}= hemoglobin A_{1c}

(Continued)

TIME AND EVENTS SCHEDULE (CONTINUED)

[a] Following the run-in visit, there will be a single-blind, placebo run-in period, during which therapy for diabetes should remain stable and therapy for CV disease will be optimized as needed, at the investigator's discretion. Subjects who fail protocol-specified screening criteria for study entry may be rescreened, at the discretion of the investigator and after approval by the sponsor's medical monitor, as clinically appropriate. Refer to Section 4.5, Rescreening, for additional details.

[b] End-of-treatment/early withdrawal evaluations will be performed when the double-blind treatment phase of the study is ended or at the time the subject discontinues the study drug or is withdrawn from the study. Evaluations will be performed as soon as possible after stopping the study drug. Subjects who discontinue treatment for any reason will be contacted by the investigator approximately every 6 months (or more frequently if necessary) for the duration of the study, until completion of the study, in order to document any events in the CV composite endpoint (including CV death, nonfatal MI, nonfatal stroke, and hospitalized unstable angina) and any adverse events of fracture.

[c] A telephone follow-up contact (or optional study visit, at the discretion of the investigator) will be conducted for all subjects approximately 28 days (and no more than 42 days) after the last dose of study drug to evaluate adverse events and concomitant therapy use; to collect self-reported MRU data since the last visit; and to document any events in the primary composite CV endpoint.

[d] The recommended visit window for the screening/run-in period is ±4 days. For each visit up to Week 26, the recommended visit window is ±7 days; after Week 26, the recommended visit window is ±14 days. For study visits that are unable to be held within the protocol-recommended visit windows, the visit should be conducted as closely as possible to the protocol-specified study visit timing. All subsequent visits should be scheduled based on the date of randomization, not the date of the rescheduled visit. After Week 65, on those occasions when the 13-, 26-, and/or 52-week-interval visits overlap, the more comprehensive requirements will be followed.

[e] The informed consent form must be signed before any study procedure is performed.

[f] To participate in the optional pharmacogenomics component of the study, subjects must sign the pharmacogenomics informed consent form indicating willingness to participate. Subject participation in the pharmacogenomics component of the study is optional. A blood sample will be collected only from subjects who give informed consent for the pharmacogenomics component of the study. A sample may be collected at any point in time during the study if inadvertently missed at baseline, if not taken at Day 1.

[g] Record as prestudy therapy any medications taken from 30 days before Day 1(within 1 year of screening for AHAs).

[h] Urine pregnancy tests will be performed for all women according to local procedures unless they are surgically sterile or unless there is a documented history of their postmenopausal status. Additional serum or urine pregnancy tests may be performed, as determined by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the study. If positive, the subject is not eligible to enter or continue in the study. A urine pregnancy test will be performed at all specified visits, unless a serum pregnancy test is preferred at the discretion of the investigator or if required by local regulations.

[i] Subjects will receive counseling on diet consistent with good dietary practices and exercise regimens for subjects with type 2 diabetes mellitus (T2DM).

[j] Subjects will receive information regarding the symptoms of and treatment for hypoglycemia. Symptoms of hypoglycemia, and concurrent blood glucose results, if available, will be captured in the subject diary, which the subject will be instructed to bring to the study center for review by research study staff at each visit.

[k] Physical examination will consist of a full review of all body systems as considered appropriate by the investigator. Prostate or gynecologic examination is not mandatory and will be done at the discretion of the investigator. Whenever possible, assessments will be made at the same time of day by the same investigator for each subject.

(Continued)

TIME AND EVENTS SCHEDULE (CONTINUED)

[l] Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (sitting position, after sitting for 5 minutes; record 3 consecutive blood pressure readings, at intervals of at least 1 minute apart).

[m] ECGs will be interpreted by a central vendor.

[n] Subjects will be provided with and instructed on the use of a self-monitored blood glucose (SMBG) system at the run-in visit only if the investigator considers it to be likely that enrollment criteria will be met at Day 1; glucose strips will be supplied as needed at each subsequent visit. All subjects are encouraged to measure blood glucose in case of hypoglycemia.

[o] Only required before a 52-week interval visit.

[p] Medical resource utilization (MRU) data will be collected in the subject diary. A sample list of MRU questions contained in the diary is provided in Attachment 9.

[q] Specific details about specimen collection, storage, packaging, and shipping will be provided in operations manuals. For fasting plasma glucose, insulin, proinsulin, C-peptide, and lipids, subjects must be fasting for at least 8 hours before blood sample collection, except for the screening visit when nonfasting blood samples may be collected. The urine collections for archive and biomarker specimens, as well as the routine urinalyses, should be obtained from a spot urine specimen in the clinic. The first morning void specimens will be used to measure albumin and creatinine.

[r] C-peptide, insulin, and proinsulin measurements will be performed on a subset of subjects (at designated sites) who are not receiving insulin at baseline; if a subject starts insulin therapy after baseline, no further assessments of these analytes will be made for that subject.

[s] The subject will provide a urine specimen from the first morning void on the morning of the clinic visit. If the subject inadvertently misses the first morning void collection on the day of the visit, the subject may return the next morning or anytime during the following week with a first morning specimen.

[t] Telephone contact (or an optional, unscheduled site visit, at the discretion of the investigator) will be made at Weeks 2, 4, and 9 to check the subject's status, including reviewing the subject's diary entries and any CV events or adverse events.

[u] Concomitant therapy includes all medications since the recording of prestudy therapy.

[v] Adverse events will be monitored throughout the study beginning from the time of the signing of the informed consent form before the first study-related procedure until the end of the study. Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until a clinically stable endpoint is reached or until further follow up is no longer considered by the investigator to be clinically meaningful.

ABBREVIATIONS

ADA	American Diabetic Association
AHA	antihyperglycemic agent
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARO	Academic Research Organization
AST	aspartate aminotransferase
BMI	body mass index
CPK	creatine phosphokinase
CRF	electronic case report form (electronic or paper, as applicable)
CV	Cardiovascular
CYP	cytochrome P450
ECG	Electrocardiogram
eDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMEA	European Medicines Agency
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HbA_{1c}	hemoglobin A_{1c}
HDL-C	high-density lipoprotein cholesterol
HOMA	homeostatic model assessment
HR	hazard ratio
IB	Investigator Brochure
ICH	International Conference on Harmonisation
ID	Identification
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IVRS / IWRS	interactive voice response system / interactive web response system
LDL-C	low-density lipoprotein cholesterol
LOCF	last-observation-carried-forward
MACE	major adverse cardiovascular events
MDRD	Modification of Diet in Renal Disease
MI	myocardial infarction
mITT	modified intent-to-treat
MRU	Medical Resource Utilization
MSRC	Medical Safety Review Committee
NAG	N-acetyl glucosaminidase
NOAEL	no-observed-adverse-effect level
NYHA	New York Heart Association
PG	plasma glucose
PP	per-protocol
PQC	Product Quality Complaint
SAP	statistical analysis plan
SGLT1 / SGLT2	sodium-glucose transporter 1 / sodium-glucose transporter 2
SMBG	self-monitored blood glucose
T2DM	type 2 diabetes mellitus
TSH	thyroid stimulating hormone
UGE	urinary glucose excretion
ULN	upper limit of normal
US	United States

UVA	ultraviolet A
UVB	ultraviolet B
VTE	venous thromboembolic event
WBC	white blood cell

1. INTRODUCTION

Over the past decades, the incidence of type 2 diabetes mellitus (T2DM) has been rapidly increasing worldwide, driven primarily by an increasing incidence of obesity and sedentary lifestyles. Patients with T2DM can develop severe microvascular complications, related to persistently elevated glucose concentrations, including blindness, renal failure, or nerve damage. However, the higher mortality rate in patients with diabetes, substantial morbidity, and increased costs of care are particularly related to a higher incidence of atherosclerotic vascular disease and related complications such as myocardial infarction (MI), stroke, and amputations due to vascular insufficiency (DCCTRG 1995a-c; Gaede 2003; Klein 1995). Improved glucose control has been demonstrated to reduce the incidence of microvascular complications in patients with both type 1 diabetes mellitus and T2DM. The impact of improved glycemic control on macrovascular complications is, however, less clear; epidemiological data suggests an increased risk of atherosclerotic vascular disease with poor glucose control, but recent clinical studies have failed to demonstrate convincingly the benefits of aggressive glucose-management on the incidence of macrovascular events or mortality. A report of a meta-analysis of recent outcome studies has indicated that improved glycemic control is associated with an important reduction in coronary heart disease events (nonfatal MI and cardiovascular [CV] death) (Ray 2009). There are now a number of classes of oral antihyperglycemic agents (AHAs) available for the treatment of patients with T2DM. Despite this range of therapeutic options, many patients do not achieve and/or maintain appropriate glycemic control. Moreover, many of these therapies have important limitations such as intolerance, weight gain, or hypoglycemia. Thus, there remains a need for new agents that offer improved durability and tolerance, and which might beneficially impact the macrovascular complications of diabetes. Canagliflozin (JNJ-28431754) is a member of a new class of AHAs with potential value in the treatment of T2DM: sodium glucose transporter 2 (SGLT2) inhibitors. The present study is intended to determine if canagliflozin can reduce the risk for CV events and to evaluate the safety and tolerability of this agent.

Pharmacologic inhibition of SGLT2 is a potential novel mechanism to decrease renal glucose reabsorption and increase urinary glucose excretion (UGE), thereby lowering plasma glucose. In healthy individuals, glucose is freely filtered through the renal glomerulus and then reabsorbed in the proximal tubules. SGLT2 is a high-capacity and low-affinity glucose transporter exclusively expressed at the luminal membrane of the S1 and S2 segments of the proximal renal tubules. SGLT2 is responsible for the majority of filtered glucose reabsorption from the lumen. SGLT1 expressed in the S3 segment, a low

capacity, high-affinity transporter, is also involved in resorption of filtered glucose from the lumen (Wright 2001). SGLT1 is also highly expressed in the intestine and is responsible for intestinal glucose and galactose absorption. Canagliflozin is an orally active inhibitor of SGLT2. This agent has much higher potency for SGLT2 relative to SGLT1; at the plasma drug concentrations achieved with the doses in this study, canagliflozin would be expected to provide systemic inhibition of SGLT2 and not of SGLT1.

Phase 2b clinical studies of canagliflozin have demonstrated glycemic efficacy with associated weight loss. In a 12-week, placebo-controlled study in subjects with T2DM on metformin background therapy, canagliflozin administration reduced hemoglobin A_{1c} (HbA_{1c}), fasting plasma glucose (FPG), and body weight, and improved beta-cell function. In a 12-week, placebo-controlled study in non-diabetic overweight and obese subjects, administration of canagliflozin provided clinically important weight loss. In addition, in both studies, trends towards improvements in several CV risk factors including blood pressure, high-density lipoprotein cholesterol (HDL-C), and triglycerides were observed.

The present study has an adaptive design, with an initial cohort of subjects randomized, an assessment of potential for CV risk reduction and a sample size re-estimation conducted, and then, if appropriate, a second cohort of subjects recruited to support the overall study power to demonstrate CV benefit.

The term “sponsor” used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

For more detailed and current information regarding the preclinical characterization of (including absorption, distribution, metabolism and excretion [ADME], pharmacokinetics [PK], toxicology) and clinical study results with canagliflozin, including references for all information provided below, refer to the latest version of the Investigator's Brochure for canagliflozin (IB-JNJ-28431754 2009).

1.1.1. Brief Overview of Nonclinical Studies

In Vitro Metabolism

There was no relevant inhibition or induction of cytochrome P450 (CYP) enzymes in the in vitro studies. Canagliflozin is primarily metabolized by UDP-glucuronosyl transferase (UGT) enzymes with a minimal role for CYP isoenzymes such as 3A4 and 2D6.

Preclinical Toxicology Studies

An increase in trabecular bone (hyperostosis) was seen in the 2-week, 3-month with 8-week recovery, and 6-month rat studies. In the 3-month study, hyperostosis was reversible. A 1-month mechanistic study showed that hyperostosis occurred in young, rapidly growing rats but not in 6-month old rats where bone growth had slowed. Hyperostosis did not progress with longer periods of dosing as it was more pronounced in the 1-month rat study compared with the 6-month rat study. The hyperostosis finding was observed in rats and was not observed in mice (3-month study) or in dogs (3- or 12-month studies). In rats, hyperostosis was associated with decreases in markers of bone turnover (serum osteocalcin and collagen type 1 carboxy telopeptide; urinary deoxypyridinoline) as well as decreases in serum 1,25-dihydroxy vitamin D, 25 vitamin D, calcitonin, and parathyroid hormone. Changes in these analytes were not observed in dogs. The relationship between these changes and hyperostosis in rats is unclear. Given that hyperostosis was observed only in young rats and was not observed in mice, dogs, or older rats, the clinical relevance of this increase in trabecular bone of normal quality is uncertain.

Renal toxicity was not seen in the 2-week or 3-month rat studies although dose-related increases were seen in kidney weights. In the 6-month rat study, tubular dilatation was seen at all dose levels and transitional hyperplasia was seen at the high dose only, 100 mg/kg. Increased urinary excretion of gamma-glutamyl transferase (GGT), N-acetyl glucosaminidase (NAG), and protein were also seen in drug-treated rats. There were no kidney-related observations of toxicity in the mouse. In the 3-month study in dogs, compound-related increases in kidney weight, tubular regeneration/degeneration, tubular dilatation (2 females dogs only), and elevated urinary GGT excretion were observed only at 200/100 mg/kg. In a 12-month study in dogs at doses up to 100 mg/kg of canagliflozin, increases in urinary GGT and NAG excretion were noted in the absence of any histologic findings.

Canagliflozin was phototoxic in vitro in mouse fibroblasts after exposure to ultraviolet A (UVA) light and phototoxic to the skin (≥50mg/kg) but not the eye (500 mg/kg) of pigmented rats after a single oral dose. Skin reactions in the rat (mild erythema, mild to moderate edema) occurred one day after study drug administration and UVA and ultraviolet B (UVB) radiation exposure.

Canagliflozin was not mutagenic in the photoAmes test. Based on all the genotoxicity studies completed thus far (Ames test, in vitro mouse lymphoma assay, single dose in vivo rat micronucleus test, in vivo single dose COMET test in rats), the overall genotoxic potential of this compound is considered minimal to humans.

Preclinical CV and pulmonary safety pharmacology studies suggest that canagliflozin has a low potential for inducing adverse CV or pulmonary events. No drug-related CV effects were detected in anesthetized guinea pigs at cumulative intravenous doses up to 9.86 mg/kg (a plasma concentration of approximately 13 μg/mL). Oral doses up to 400 mg/kg (mean plasma exposure at 24 hours post-dose of approximately 55 μg/mL) were not associated with notable CV and pulmonary effects in conscious dogs. These exposures in preclinical studies are far above those attained with clinical doses.

1.1.2. Clinical Studies

Overview

As of February 2009, 601 subjects had participated in multiple, completed Phase 1/1b studies. A 12-week Phase 2b clinical study in 376 overweight and obese subjects and a 12-week Phase 2b clinical study in 451 subjects with T2DM have been completed.

Pharmacokinetics

After oral administration at each dosage level, plasma concentrations of canagliflozin increased rapidly, with median time to maximum concentration (t_{max}) values of 1.25 to 2 hours. Mean half-life ($t_{1/2}$) values ranged from 13 to 23 hours. After repeated doses of canagliflozin, trough concentrations reached steady state by 4 days. There was no evident effect of food on exposure (area under the plasma concentration-time curve [AUC]) of canagliflozin.

Canagliflozin had no clinically significant effect on plasma concentrations of metformin, ethinyl estradiol or levonorgestrel, simvastatin, glyburide, and hydrochlorothiazide.

Pharmacodynamics

Urinary glucose excretion (UGE) increases rapidly, significantly, and in a dose-dependent manner after single oral doses of canagliflozin compared with baseline and placebo.

In a 14-day repeated dosing study in subjects with T2DM, as the dose increased from 30 to 400 mg once daily, the mean 24-hour UGE change from Day -1 increased in an apparently less than dose proportional manner ranging from 60 to 150 g. The daily UGE at each dose was maintained over the 14-day dosing period. The maximal UGE rate was

reached at about 4 to 6 hours. The increase in UGE rate is maintained over 24 hours at doses ≥100 mg. The mean value of the calculated renal threshold for glucose excretion in the overnight period decreased in a dose-dependent fashion from approximately 240 mg/dL in untreated subjects to 162 mg/dL in subjects given 30 mg of canagliflozin to 93 mg/dL in subjects given 400 mg of canagliflozin. The observed maximal reduction in the renal threshold for glucose excretion—to a level above the usual threshold glucose concentration at which hypoglycemia is observed—would suggest a low risk for hypoglycemia with canagliflozin.

Efficacy

A Phase 2b 12-week dose-ranging study was performed to assess the safety, tolerability, efficacy, and dose-response of canagliflozin on glycemic control in 451 subjects with T2DM receiving metformin therapy. In this study, the average age was 53 years, 48% of subjects were female, 73% of subjects were Caucasian, the average HbA_{1c} was 7.7% with an FPG of 162 mg/dL (9.0 mmol/L), and the average BMI was 31.5 kg/m^2. The least-squares mean differences compared with placebo in the change in HbA_{1c} at Week 12 LOCF were -0.45%, -0.51%, -0.54%, -0.71%, and -0.73% for the 50 mg, 100 mg, 200 mg, and 300 mg once daily and 300 mg twice daily doses of canagliflozin, respectively (all comparisons to placebo $p<0.01$). Dose-related improvements in FPG were also observed, with a maximal decrease of 32.4 mg/dL (1.8 mmol/L) relative to placebo. A reduction in body weight was also seen, with decreases of 1.5% and 2.3% at the 100 mg and 300 mg once daily doses, respectively, observed relative to placebo. Beta-cell function assessed by homeostasis model assessment (HOMA)-B improved relative to placebo in all groups treated with canagliflozin over 100 mg. In addition to improvements in HbA_{1c}, FPG, and body weight, trends towards improvements in several important CV risk factors such as blood pressure, HDL-C and triglyceride were observed, especially at the 300 mg once-daily dose. For example, changes from baseline at Week 12 in systolic/diastolic blood pressure of -4.3/-2.1 mmHg for canagliflozin 300 mg and -1.4/-1.1 mmHg for placebo were observed. The studies were not designed to precisely evaluate the extent of these changes, which will be evaluated in further, larger clinical studies of this medication, including in the present study.

Safety

The following is a summary of the pertinent clinical safety findings.

In Phase 1 studies, canagliflozin has been generally well tolerated in healthy lean and obese subjects and in subjects with T2DM after single and multiple doses.

In the Phase 2b obesity study, the average age was 45 years, 86% of subjects were female, 83% of subjects were Caucasian, and the average BMI was 37 kg/m^2. In this study, adverse events were reported in 61% of placebo-treated subjects and ranged from 58% to 74% for canagliflozin-treated subjects. Discontinuation due to an adverse event occurred in 0%, 5%, 3%, and 4% of subjects receiving placebo or canagliflozin 50 mg, 100 mg, and 300 mg, respectively. There was no apparent pattern of adverse events leading to discontinuation or of serious adverse events.

In the Phase 2b diabetes study adverse events were reported in 40% of placebo-treated subjects and ranged from 40% to 56% for subjects treated with canagliflozin. Discontinuation due to an adverse event occurred in 3% of placebo-treated and 2% to 5% canagliflozin-treated subjects. There was no pattern of adverse events leading to discontinuation or of serious adverse events.

In the Phase 2b diabetes and obesity studies, a treatment-dependent increase was seen in vulvovaginal adverse events in all canagliflozin treatment groups, ranging from 12% to 25% of female subjects, compared with 3% in the placebo groups and 7% in the sitagliptin group from the diabetes study. Vulvovaginal adverse events, such as candidal vulvovaginitis, were generally mild in intensity, responded to treatment, did not appear to be related the dose or to the magnitude of UGE, and resolved while continuing canagliflozin. Urinary tract infections were not increased relative to placebo in canagliflozin-treated subjects in either study.

In the Phase 2b diabetes study, hypoglycemia was infrequently reported in subjects treated with canagliflozin. Hypoglycemic events were reported in 0% to 6% of canagliflozin treatment groups without evidence for dose dependency, compared with 2% of subjects in the placebo group. A similar and low incidence of hypoglycemia was observed in the placebo and canagliflozin treatment groups in the Phase 2b obesity study.

In the Phase 2b obesity and diabetes studies, small increases in blood urea nitrogen were observed from baseline for the canagliflozin treatment groups. Serum creatinine increased (<9%) from baseline at Week 3 in all canagliflozin treatment groups but returned toward baseline by Week 12. No clinically important increase was noted in adverse events suggestive of osmotic diuresis, such as polyuria, nocturia, onset or worsening of urinary incontinence symptoms, dehydration, or hypovolemia-related symptoms.

In the Phase 2b diabetes study, but not in the obesity study, modest increases (approximately 5%) in serum magnesium were seen in subjects treated with canagliflozin. In both studies, serum uric acid concentrations decreased by 15% to 20% in the groups treated with canagliflozin relative to placebo. There was an increase (<6%) from baseline at Week 12 for hemoglobin across all canagliflozin treatment groups. No other apparent trends in serum chemistry or hematology parameters were observed.

Renal glomerular and tubular biomarkers were assessed in the Phase 2b diabetes and obesity studies. Urinary NAG levels increased in all canagliflozin treatment groups with maximal placebo-subtracted increases seen at Week 3 and declining towards baseline by Week 12. The maximal increase was approximately 35% and 100% above baseline in the diabetes and obesity studies, respectively. No changes relative to placebo were detected in other renal markers including in urinary albumin/creatinine ratio or beta-2-microglobulin. Since the rise in NAG was not accompanied by a change in other renal biomarkers, was transient with improvement by Week 12, the rise in urinary NAG may represent an effect of canagliflozin on increased flow in the proximal tubule or related to the induction of glucosuria (Brouhard 1984; Watanabe 1987; Watts 1988); this rise in NAG has been observed with other SGLT2 inhibitors (List 2008).

There were no consistent changes noted in serum or urinary calcium or phosphorus or in serum 25-hydroxy vitamin D, 1,25-dihydroxy vitamin D or parathyroid hormone levels in either Phase 2b study.

Bone turnover biomarkers were assessed in both Phase 2b studies. In the Phase 2b diabetes and obesity studies, a placebo-subtracted increase of up to 20% to 25% from baseline to Week 12 in serum collagen type 1 carboxy telopeptide (a marker of bone resorption) levels was observed in subjects receiving canagliflozin with a possible dose trend. The increase was detectable by Week 3 and was not influenced by age, sex, or renal function status. Urinary N-telopeptide excretion, another marker of bone resorption, was not increased by treatment with canagliflozin. No consistent changes were seen in markers of bone formation (serum bone specific alkaline phosphatase, osteocalcin, or propeptide amino-terminal type 1 procollagen). Due to the modest magnitude of the observed increase and the biologic variability associated with this marker (Herrmann 2008) as well as the lack of change in other markers of bone turnover, the increase in serum collagen type 1 carboxy telopeptide levels is of uncertain significance. It should be noted that increased trabecular bone formation associated with a reduction in markers of bone resorption, including serum collagen type 1 carboxy telopeptide, was seen in rats treated with canagliflozin.

To assess photosensitizing potential of canagliflozin in humans, single dose (200 and 400 mg) and multiple dose (300 mg once a day and 300 mg twice a day) studies were conducted in Caucasian subjects using an established clinical photosensitivity test method at wavebands representing the terrestrial solar spectrum spanning UVB and UVA into the visible region (290-430 nm) (Dawe 2003). Results from these studies indicate a mild, UVA dependent (335 nm), delayed phototoxic effect of canagliflozin at 300 mg twice a day, but not at 300 mg once a day. An immediate photosensitivity response, ie, asymptomatic, transient edematous responses at the irradiated skin site, within 30 minutes of exposure to only the 335 nm waveband, was observed with canagliflozin at 300 mg once a day and twice a day. Additional clinical photosensitivity studies will be conducted to assess whether the immediate photoresponse will be seen with phototesting that more closely approximates the intensity of natural sunlight.

In the two Phase 2b studies, subjects were advised to avoid excessive exposure to sunlight and to use photoprotection if exposed to light. No meaningful difference in the incidence of skin adverse events, including light-related skin adverse events, was apparent in subjects receiving canagliflozin relative to subjects receiving placebo.

1.2. Overall Rationale and Goals for the Study

Patients with T2DM have an increased risk of both microvascular and macrovascular complications which lead to morbidity and mortality. New therapies are needed that can provide improved glycemic control—which has been shown to reduce microvascular complications—and lower the risk of macrovascular complications.

Prior clinical studies of canagliflozin in patients with T2DM have demonstrated improvements in glycemic control (with reductions in FPG and HbA_{1c}), reduction in body weight, and trends towards improvements in other CV disease risk factors (including increases in HDL-C, decreases in triglyceride levels, and decreases in blood pressure, especially at the 300-mg dose), with generally good tolerance and appropriate safety to support continued clinical development of this medication. With improved glycemic control, which itself may provide a benefit in CV risk (Ray 2009), and the trends towards benefit on other CV risk factors including body weight, the potential for a benefit of long-term treatment with canagliflozin on CV disease is raised. The present study is intended to demonstrate that treatment of subjects with T2DM with canagliflozin reduces CV risk for major adverse cardiovascular events (MACE, including CV death, nonfatal MI, and nonfatal stroke) and also is intended to achieve a number of other important goals. These goals include the evaluation of overall safety and tolerability, glycemic efficacy (in the overall study population and in subjects on specific

antihyperglycemic agents), long-term effects on beta-cell function, and long-term effects on renal function with canagliflozin treatment. The key goals are described in the following paragraphs.

Effects on CV Risk and Overall Safety and Tolerability

As discussed above, CV events contribute importantly to the overall increased morbidity and mortality in patients with T2DM. Hence, assessing the impact of new AHAs on CV risk is of key importance. Recent requirements by the United States (US) Food and Drug Administration (FDA) for the development of medications to improve glycemic control in patients with T2DM include the need to show *no unacceptable increase in CV risk*. The benefits observed with canagliflozin on glycemic control and body weight, and possibly on other CV risk factors, suggests the potential for this medication to have a meaningful benefit in reducing the risk of CV events in patients with T2DM. Because CV events are the major cause of the increased mortality seen in patients with T2DM, an AHA that both improves glycemic control and reduces CV-related events could be a highly valuable addition to the diabetes treatment armamentarium. This study is intended to demonstrate that the addition of treatment with canagliflozin reduces CV risk compared to placebo when used in combination with current standard of care glucose-lowering and CV risk factor management. To address the regulatory requirements regarding demonstration of CV safety described above, during the conduct of this study, interim results will be integrated, in a prespecified meta-analysis, with results from other large, well-controlled, randomized double-blind studies of canagliflozin, to show no unacceptable increase in CV risk.

Assessment of glycemic efficacy of canagliflozin – overall and in key subgroups

The present study is also intended to provide important information on the glycemic efficacy of this medication. To achieve this goal, in the initial cohort (Cohort A), subjects will enter an 18-week AHA regimen stable period to provide an opportunity to characterize the glycemic efficacy of canagliflozin relative to placebo in this high CV risk population, and support important analyses aimed at understanding the response to this medication in patient subgroups defined by key demographic and anthropometric components, disease characteristics, and concomitant AHA treatments. After this 18-week AHA regimen stable period, and for the remainder of the double-blind treatment phase, investigators will adjust the subject's AHA regimen with the goal of achieving target glycemic control.

Embedded within Cohort A of this study are 3 substudies which will compare the glycemic efficacy and assess the safety of canagliflozin relative to placebo in subjects receiving regimens with (1) insulin as monotherapy or in combination therapy, (2) sulfonylurea monotherapy, or (3) PPARγ agonist and metformin combination therapy. These substudies are being conducted to better characterize the safety, tolerability, and efficacy profile of canagliflozin when used in conjunction with these specific glucose-lowering therapies.

Assessment of long-term effects of canagliflozin on beta-cell function and renal function

Patients with T2DM usually have a progressive deterioration in glycemic control, with the need for stepwise added therapies. Underlying this progressively worse glucose control is a progressive deterioration in beta-cell function. Canagliflozin, by increasing UGE and possibly improving insulin sensitivity through weight loss, may "unload" the beta-cells, lowering secretory demand and potentially improving function over time. In addition, improved glycemic control itself, through reversal of so-called "glucotoxicity," may also improve beta-cell function. Analysis of results from a Phase 1 study in subjects with T2DM did show an improvement in a model-based assessment of beta-cell function, and HOMA-B, a measure of fasting beta-cell insulin secretion, was improved in the Phase 2b study of subjects with T2DM. To assess the effect on beta-cell function over time in the present study, standard fasting measures of beta-cell function (HOMA-B, proinsulin/insulin ratio) will be evaluated.

Another key issue in patients with T2DM is the potential for hyperglycemia to lead to progressive damage to the kidney. Early on, this damage is reflected by micro-albuminuria that may progress to macro-albuminuria and eventually loss of renal function. By virtue of its improvement in glycemic control, which has been shown to reduce micro-albuminuria progression in prior studies (ADVANCE 2008), and possible effects to reduce blood pressure (if confirmed in larger studies), canagliflozin may slow the progression of diabetic nephropathy. Additionally, proximal tubule inhibition of SGLT2 by canagliflozin is predicted to increase the distal delivery of sodium which could, via the macula densa, lead to a reduction in intraglomerular pressure and a decrease in glomerular damage (Vallon 1999). For these reasons, the study will also examine the potential benefit of canagliflozin on albuminuria.

2. OBJECTIVES

2.1. Primary Objectives

In subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease:

- to assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care on CV risk as measured by the hazard ratio (HR) for a composite endpoint (MACE including CV death, nonfatal MI, and nonfatal stroke)
- to assess the safety and tolerability of canagliflozin

2.2. Secondary Objectives

In subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease, to assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care, at 52 weeks and at the end of the treatment period on:

- fasting measures of beta-cell function (ie, HOMA-B and the proinsulin/insulin ratio) (note: this assessment will be conducted in a subset of subjects at designated sites, including only subjects who are not receiving insulin at randomization)
- the proportion of subjects with progression of albuminuria (progression defined as ≥1 step, ie, no albuminuria to micro- or macro-albuminuria or from micro-albuminuria to macro-albuminuria) and the proportion of subjects with regression of albuminuria (regression defined as ≥1 step, ie, macro- to micro- or normo-albuminuria, or micro-albuminuria to normo-albuminuria)

In subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease, to assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care at 18 weeks and at the end of the treatment period on:

- glycemic efficacy (ie, on HbA_{1c} and FPG)
- body weight
- blood pressure (ie, systolic and diastolic)
- fasting plasma lipids (triglycerides, HDL-C, low-density lipoprotein cholesterol [LDL-C], total cholesterol, and the ratio of LDL-C to HDL-C)

2.3. Hypotheses

2.3.1. Primary Hypotheses

In subjects with T2DM, with inadequate glycemic control, who have a history of or a high risk of CV disease:

- relative to placebo plus standard of care, canagliflozin plus standard of care reduces CV risk (as measured by the HR for a composite endpoint including CV death, nonfatal MI, and nonfatal stroke)
- canagliflozin is well tolerated

2.3.2. Secondary Hypotheses

In subjects with T2DM, with inadequate glycemic control, who have a history of or a high risk of CV disease, relative to placebo plus standard of care, canagliflozin plus standard of care at the end of the treatment period:

- improves beta-cell function (ie, change from baseline in HOMA-B)
- reduces progression of albuminuria (ie, proportion of individuals with ≥1-step progression of albuminuria as determined by the urine albumin/creatinine ratio)

Note: Separate objectives and hypothesis are provided for the meta-analysis (of results from this and other large, well-controlled studies in the canagliflozin program) in support of CV safety; these objectives and hypothesis are stated in a separate statistical analysis plan (SAP), and are also described in Section 11.7.3.1, Objectives and Hypothesis for Meta-analysis.

2.4. Substudies: Objectives and Hypotheses (Cohort A)

The three 18-week substudies will be conducted with the data from Cohort A subjects of this study and are intended to assess the safety and tolerability and efficacy of canagliflozin in subjects with T2DM, with inadequate glycemic control in each of the 3 specific subgroups of subjects receiving (1) insulin ≥20 units/day monotherapy or in combination with other AHA(s), (2) sulfonylurea monotherapy at protocol-specified doses (Attachment 1), or (3) PPARγ agonist (pioglitazone ≥30 mg/day or rosiglitazone ≥4 mg/day) plus metformin ≥2,000 mg/day (or at least 1,500 mg/day for subjects who have a history of not being able to tolerate higher metformin doses) and no other AHA. The following objectives and hypotheses will apply to each of these substudies. These are separate and distinct from the main study hypothesis testing.

Primary Substudy Objectives

In subjects with T2DM, with inadequate glycemic control, who have a history of or a high risk of CV disease:

- To assess the HbA_{1c}-lowering efficacy (ie, change from baseline in HbA_{1c}) of canagliflozin relative to placebo after 18 weeks of treatment
- To assess the safety and tolerability of canagliflozin

Primary Substudy Hypotheses

In subjects with T2DM, with inadequate glycemic control, who have a history of or a high risk of CV disease:

- After 18 weeks of treatment, canagliflozin provides a greater improvement in HbA_{1c} relative to placebo (ie, change from baseline in HbA_{1c})
- Canagliflozin is well tolerated

Secondary Substudy Objectives and Hypotheses

Objectives

After 18 weeks, in subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease, to assess the effect of canagliflozin relative to placebo, on:

- body weight
- FPG-lowering efficacy
- proportion of subjects reaching HbA_{1c} <7.0%
- systolic and diastolic blood pressure
- fasting plasma lipids (triglycerides, HDL-C, LDL-C, total cholesterol, and the ratio of LDL-C to HDL-C)

After 26 and 52 weeks, in subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease, to assess the effect of canagliflozin relative to placebo on:

- glycemic efficacy (ie, HbA_{1c} and FPG)
- body weight
- systolic and diastolic blood pressure
- fasting plasma lipids (triglycerides, HDL-C, LDL-C, total cholesterol, and the ratio of LDL-C to HDL-C)

Hypotheses

After 18 weeks, in subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease, relative to placebo, canagliflozin:

- provides a greater reduction in body weight
- provides a greater reduction in FPG
- leads to a greater proportion of subjects achieving HbA_{1c} <7%
- reduces systolic blood pressure

- increases HDL-C concentrations
- lowers triglyceride concentrations

2.5. Medical Resource Utilization Objective

To collect medical resource utilization (MRU) data that may be used in future economic modeling (the construction and reporting of the economic model will be conducted separately from this protocol).

3. OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, 3 parallel-group, multicenter, study to evaluate the safety, tolerability, and CV risk with canagliflozin plus standard of care compared with placebo plus standard of care in subjects with T2DM who have either a history or high risk of CV disease. This study has an adaptive design, with an initial cohort of subjects randomized, a sample size re-estimation conducted, and then, if appropriate, a second cohort of subjects recruited to support the overall study power to demonstrate CV risk reduction, as described below.

In this study, an initial cohort of 4,500 subjects will be randomized (referred to as Cohort A) to treatment with 1 of 2 doses of canagliflozin (100 mg or 300 mg) or placebo, in a 1:1:1 randomization ratio. After a prespecified number of events at a planned time point have occurred, an interim analysis (conducted under the direction of the study's Independent Data Monitoring Committee [IDMC]) will be performed (1) to assess if CV benefit may be expected with canagliflozin treatment (at least 15% expected CV risk reduction for MACE based upon the effect of canagliflozin on CV risk factors and the observed HR), and, (2) if this extent of benefit is expected, to determine the size of the subsequent cohort (referred to as Cohort B) necessary to demonstrate CV risk reduction with canagliflozin treatment in the overall study population (ie, combined Cohorts A and B). Refer to Section 11.7, Interim Analysis, for criteria for initiation of the subsequent cohort (Cohort B) and sample size re-estimation to determine the sample size of Cohort B.

Because this study has additional key objectives including the assessment of overall safety and tolerability of canagliflozin and the demonstration of CV safety of this medication (as part of a prespecified meta-analysis, refer to Section 3.1, Overview of Study Design), the study would be continued (with Cohort A only) until the evaluation of these objectives was completed, even if Cohort B was not initiated.

To provide an appropriate assessment of the effects of canagliflozin on CV risk, the population for this study will include subjects with T2DM who have inadequate glycemic control, either on no current AHA therapy or on a range of other agents either in monotherapy or in combination therapy, and who have an increased risk of or prior documented CV disease.

In this study, investigators will be counseled to assure appropriate management of CV risk factors (eg, blood pressure and lipids) according to standard guidelines (eg, the American Diabetes Association [ADA] or other local diabetes guidelines) for the care of patients with T2DM. In addition, after a relatively brief period during which the subject's AHA regimen is to be kept stable (described in the section below), investigators will also be counseled to attempt to achieve good glycemic control, consistent with standard diabetes guidelines, individualized as considered clinically appropriate, with up-titration or stepwise addition of AHA therapies. Thus, this study will examine the safety, tolerability and impact on CV risk of treatment with canagliflozin along with standard of care CV risk factor and glycemic management ("standard of care") relative to placebo with standard of care management.

3.1. Study Design

The following section provides an overview of subject management including screening, run-in, and double-blind treatment – differences in the management of subjects entering the initial cohort (Cohort A) and the subsequent cohort (Cohort B) are specifically noted.

Screening / Run-in Period Management

Subjects will undergo a screening visit for a preliminary determination of eligibility. Men or women with T2DM who have inadequate glycemic control (HbA_{1c} ≥7.0 and ≤10.5%), not on an AHA or on an AHA in monotherapy or combination therapy, and are either at high risk of CV events (2 or more risk factors; approximately 30% of subjects) or with known CV disease (at least 70% of subjects) (refer to Section 4.2, Inclusion Criteria) are eligible.

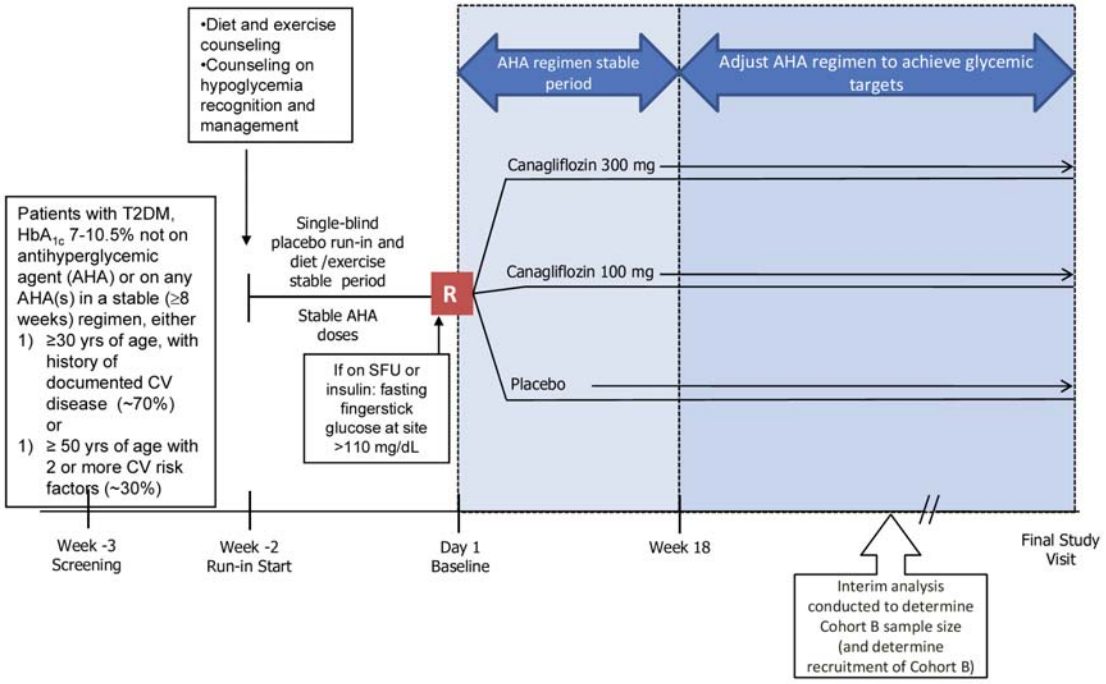
A subject meeting initial enrollment criteria will return to the investigational site at Week -2 (single-blind run-in start visit) to complete the evaluation of enrollment criteria. At this visit, subjects continuing to be eligible will enter a 2-week single-blind placebo, diet/exercise, and CV risk factor (eg, blood pressure and lipids) management optimization period. All subjects will receive diet/exercise counseling *at entry* into the 2-week run-in period, be counseled on hypoglycemia recognition and management, be dispensed single-blind placebo tablets, and be given a monitor and materials for fingerstick glucose measurement.

For the initial cohort (Cohort A): subjects meeting all inclusion and none of the exclusion criteria, and successfully completing the 2-week run-in period, will be randomized to treatment with canagliflozin 100 mg, 300 mg, or matching placebo administered once daily (in a 1:1:1 ratio). Approximately 4,500 subjects will be randomized into this initial cohort. Subjects will remain on a stable regimen (medications and doses) of their current AHA regimen (if on AHA) from run-in entry (Week -2) until the Week 18 visit of the double-blind treatment phase (see below for details).

For the subsequent cohort (Cohort B): subjects in Cohort B will meet the same enrollment criteria and have the same run-in period management as described above for Cohort A. In Cohort B, one or both (ie, 100 mg and 300 mg) doses of canagliflozin may be studied, based upon results from Cohort A and from other Phase 3 studies (refer to Section 6.1, Study Drugs). Subjects in Cohort B will undergo a balanced randomization to placebo and dose(s) of canagliflozin (ie, 1:1:1 if 2 doses of canagliflozin and placebo are studied, or 1:1 if a single dose level of canagliflozin and placebo are studied). If a dose of canagliflozin is not continued in this study, subjects in Cohort A on the canagliflozin dose not continued will be *switched* in a completely blinded fashion to the continuing dose (refer to Section 6.1, Study Drugs). The sample size for Cohort B will be determined as described in Section 11.3.2, Cohort B.

An overview of the study design for *initial cohort (Cohort A)* is illustrated in Figure 1.

Figure 1: Study Design Outline (Cohort A)



R = randomization; SFU=sulfonylurea

Double-blind Treatment Phase Management

For the initial cohort (Cohort A): Subjects will remain on a stable regimen (medications and doses) of their current AHA regimen until Week 18 of the double-blind treatment phase, unless down-titration is required to manage or avoid hypoglycemia, or unless rescue glycemic criteria are met (refer to Section 6.2.2, Glycemic Rescue Therapy Through Week 18 for Cohort A: Criteria and Implementation). Once the AHA regimen stable period is completed at Week 18, the investigator should adjust the subject's AHA regimen so as to achieve target glycemic control, per standard diabetes care guidances, individualized as considered appropriate by the investigator. *Adjustments in the AHA regimen should be carefully implemented throughout the study to avoid events of hypoglycemia.*

For the subsequent cohort (Cohort B): Throughout the double-blind treatment phase, subjects may have adjustment of their AHA regimen to achieve target glycemic control, per standard diabetes care guidances, individualized as considered appropriate by the investigator. *Adjustment to the AHA regimen should be avoided in the weeks after initiation of double-blind treatment and should be carefully implemented throughout the study so to avoid events of hypoglycemia.*

Planned Meta-analysis (CANVAS and other Canagliflozin Studies)

As described in Section 11.7, Interim Analysis, during the conduct of this study, data from the initial cohort (Cohort A) will be included in a prespecified meta-analysis of large, well-controlled, double-blind, randomized studies of canagliflozin to assess the rate of important CV events in a prespecified composite endpoint. This meta-analysis is intended to demonstrate that, relative to control therapies (either placebo or active comparator therapy), canagliflozin does not have an unacceptable increase in CV risk (occurrence of important CV events, ie, MACE, including CV death, nonfatal MI, and nonfatal stroke, plus hospitalized unstable angina) so as to meet US regulatory agency requirements for approval of new AHAs (support filing of a new drug application for canagliflozin). Analyses in support of this assessment will be conducted based upon a specified number of CV events (refer to Section 11.7, Interim Analysis) having occurred in the pooled study population.

This meta-analysis will be the subject of a separate SAP in which the objectives, hypotheses, and analytic strategy are described. Note that the primary composite endpoint to show CV risk reduction includes MACE, while the meta-analysis utilizes a composite endpoint that includes MACE plus hospitalized unstable angina. For discussion of these 2 CV composite endpoints, refer to Section 3.2, Study Design Rationale.

Study Duration

This is an event-driven study; hence, the study duration will be based upon the occurrence of sufficient events to evaluate study hypotheses and objectives. If Cohort B is recruited, this event-driven study will continue until sufficient events have occurred in the CV benefit composite endpoint (ie, MACE) to support assessment of the study primary hypothesis of CV risk reduction with canagliflozin (refer to Section 11.7.4, Adaptation Plan, for determination of number of events). If Cohort B is *not initiated*, this study will continue (with Cohort A only) until the meta-analyses to demonstrate CV safety (ie, no unacceptable increase in CV risk) are finished, after which the study will be considered completed and subjects will be discontinued. Thus, the duration of this study will be event driven: if Cohort B is recruited, the total duration of the study is expected to be approximately 8 to 10 years; if Cohort B is *not* recruited, the study is expected to be 4 to 8 years in duration.

Collection of Study Endpoints and Safety Measures

Events in the CV composite endpoint: Investigators will be counseled to report any event that they assess as potentially to be a component of the study CV composite endpoint: CV death, nonfatal MI, nonfatal stroke, or hospitalized unstable angina (note: MACE is the primary study composite endpoint; MACE plus hospitalized unstable angina is collected to support the planned meta-analysis for CV safety). In addition, all deaths and events of hospitalized congestive heart failure will be submitted for adjudication. To report events that they have assessed as potentially being in the CV composite endpoint, investigators will complete a separate case report form (CRF) and must provide a specific package of information to be submitted for adjudication evaluation, details of which will be provided in a procedural manual.

Collection of Information After Early Withdrawal: Early withdrawal (for subjects prematurely discontinued) or end-of-treatment (for subjects completing the study) evaluations will be performed at the end of the double-blind treatment phase or at the time the subject discontinues study drug or is withdrawn from the study or when the study ends. These evaluations will be performed as soon as possible after stopping the study drug. Subjects will have a telephone follow-up contact (or optional study visit, at the discretion of the investigator) approximately 28 days (and no more than 42 days) after the last dose of study drug. In addition, subjects who discontinue treatment early for any reason (except withdrawal of consent for any further contact) will be contacted by telephone approximately every 6 months (or more frequently if necessary based on the investigator's knowledge of the subject) until completion of the overall study with the goal of collecting any CV outcome events or adverse events of fracture.

Safety Evaluations and AEs Requiring Collection of Additional Information: Safety evaluations will include the monitoring of adverse events and concomitant therapy, clinical laboratory tests, 12-lead electrocardiograms (ECGs), vital sign measurements, physical examinations, and measurement of body weight. In addition, detailed collection of information on possible hypoglycemic events will be performed, as described in Section 9.1.1, Overview. For selected specific adverse events, investigators will be asked to provide additional information so as to support more detailed analyses. These include vulvovaginal adverse events, adverse events of urinary tract infection, adverse events of fractures, skin adverse events, events of increased alanine aminotransferase (ALT) (≥3-fold the upper limit of normal [ULN]), and hypoglycemia (see section below). Additional information will also be requested from investigators to support a detailed assessment of events of venous thromboembolism/pulmonary embolism, hospitalized congestive heart failure, and all deaths (including information and documents to support

adjudication of these events). Investigators may also be asked to provide additional information on other adverse events, based upon review by the Medical Safety Review Committee (MSRC) or the study IDMC (refer to Sections 9.3.3, Medical Safety Review Committee, and 9.3.5, Independent Data Monitoring Committee). Refer to Section 3.2, Study Design Rationale, for review of rationale for collection of additional information on these selected adverse events.

Pharmacogenomic Blood Sample: A pharmacogenomic blood sample should be collected on Day 1 (or at a subsequent visit if not collected on Day 1) from subjects who consent separately to the pharmacogenomic component of the study to allow for pharmacogenomic research, as necessary (where local regulations permit). Subject participation in pharmacogenomic research is optional. Refusal to consent for this component does not exclude a subject from participation in the clinical study.

Urine Pregnancy Testing: Urine pregnancy testing will be performed according to local procedures and will be conducted on all women unless they are surgically sterile or unless there is a documented history of their postmenopausal status. A urine pregnancy test will be performed at clinic visits as specified in the Time and Events Schedule that follows the Synopsis unless a serum pregnancy test is preferred at the discretion of the investigator or if required by local regulations. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the study (refer to Section 12.2.3, Pregnancy, for instructions in cases of a positive pregnancy test).

Substudies – Add-on Use with Specific AHAs

Randomized subjects on specific concomitant AHAs, listed below, will be included in 3 substudies. These substudies will assess the glycemic efficacy and safety of canagliflozin in subjects on one of the following concomitant AHAs: insulin ≥20 units per day as monotherapy or in combination with other AHA(s); sulfonylurea monotherapy (at doses specified in Attachment 1); or PPARγ agonist (pioglitazone ≥30 mg or rosiglitazone ≥4 mg) plus metformin ≥2,000 mg/day (or at least 1,500 mg/day for subjects who have a history of not being able to tolerate higher metformin doses) and no other AHAs. These subjects will follow the same procedures and assessments as described for the overall study (refer to the Time and Events schedule that follows the Synopsis); no additional procedures or assessments are required for subjects in these substudies. Results from subjects in these substudies will be analyzed based upon prespecified objectives and hypotheses (refer to Section 2.4, Substudies: Objectives and Hypotheses [Cohort A]).

Section 9.3, Study Management: Committees, provides details regarding the committees commissioned to provide oversight for the management of this study.

3.2. Study Design Rationale

Overall Design, Blinding, Control, Study Phases/Periods, Treatment Groups

This study was designed in general accordance with the FDA and European Medicines Agency (EMEA) guidances on the development of medications and clinical investigations for the treatment and prevention of diabetes mellitus (FDA 2008; EMEA 2002, 2008), and will contribute CV events (for a prespecified meta-analysis) to meet the requirements of the FDA guidance for industry on evaluating CV risk in new AHAs to treat type 2 diabetes issued in December 2008 (Guidance for Industry: Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes).

The study has an adaptive design–with the decision to recruit Cohort B and sample size re-estimation performed based upon a protocol-specified interim analysis of results from Cohort A planned around the time of US regulatory agency approval. Results from the interim analysis will (1) provide a *predicted* effect of canagliflozin on risk for CV events (ie, the predicted HR) based upon the effect of canagliflozin on established CV risk factors (eg, blood pressure, fasting lipids, HbA_{1c}); and (2) determine the *observed* HR for MACE in the initial study cohort. These 2 components will be used by the IDMC to determine an *expected* effect of canagliflozin on CV risk based upon specific guidance provided in the IDMC charter. Cohort B will be recruited if the expected CV risk reduction is at least 15% and the observed HR is not >0.95, *and* CV risk reduction can be demonstrated (with 90% conditional power) with recruitment of no more than 14,000 additional subjects (Cohort B) and with a double-blind treatment phase of approximately 4 years. As noted, the determination to initiate Cohort B, so as to provide an overall study population with sufficient power to demonstrate risk reduction, will be based upon an expected risk reduction of at least 15%. While a lesser extent of benefit would still be clinically relevant, this extent of benefit or greater would be of substantial importance in the management of patients with T2DM.

Randomization and blinding will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints. A placebo control will be used to establish the frequency

and magnitude of changes in clinical endpoints that may occur in the absence of the active treatment.

The 2-week single-blind placebo period before randomization allows sufficient time for investigators to assess whether subjects demonstrate compliance with study procedures, and to study medication, and provides an opportunity to adjust treatment for other CV risk factors, by titration or addition of background medications at the investigator's discretion, before randomization.

The stable AHA regimen period of 18 weeks was chosen because it is sufficiently long to evaluate the effect of canagliflozin on HbA_{1c}. Maintaining stable background AHAs, permits an assessment of the effect of canagliflozin not confounded by changes in other agents, and hence supports the determination of glycemic efficacy of this potentially valuable medication across the entire study population as well as in the substudies.

Study Population

The study population includes subjects on a variety of different AHAs, with a range of baseline glycemic control - from mildly elevated to more moderately elevated HbA_{1c} values - and at higher risk of or having documented CV disease. This population was selected to provide a broad experience with canagliflozin so as to enhance the characterization of this new medications efficacy, safety, and tolerability profile, and to support assessment of CV risk with this agent. The substudy populations were selected to provide information on concurrent use of canagliflozin with important AHAs that are not being assessed in separate Phase 3 studies.

Dosage Selection, Route of Administration, Dose Interval, Treatment Period

The once daily oral therapy is an acceptable dosage regimen given the half-life of canagliflozin.

Based on findings from the Phase 2b diabetes study, 100 mg once daily is deemed to be the lowest dose providing clearly sufficient efficacy in terms of HbA_{1c}-lowering for approval as an AHA and 300 mg once daily is deemed to provide an incremental improvement in glycemic efficacy and possibly weight loss and blood pressure lowering greater than that achieved with the 100 mg once daily regimen. The safety and tolerability profile of these 2 doses appeared to be generally similar. In Phase 1 studies of canagliflozin, at doses above 200 mg, a decrease in incremental glucose and an increase in the time to peak glucose were observed after a meal challenge when study drug was administered before the meal. The mechanism of this reduction in post-meal glucose is not known, but could relate to inhibition of SGLT1 gut glucose transport based upon

transiently high gut concentrations of canagliflozin after dose administration. If this effect on post-meal glucose is established, it may provide an additional mechanism of glucose-lowering benefit. In the present study, double-blind study drug is to be taken before the first meal of the day so as to obtain this potential benefit of canagliflozin. Additional studies in the canagliflozin program will evaluate this effect on post-meal glucose.

As indicated, Cohort A will be used to evaluate both the 100 mg and 300 mg doses of canagliflozin. For Cohort B, one or both doses may be studied, based upon the safety, tolerability, and efficacy results from the Phase 3 studies of this medication and the determination as to what dose(s) of canagliflozin will be registered for clinical use, and the results observed at the interim analysis of Cohort A. If only one dose of canagliflozin is continued in this study, subjects in Cohort A who are on the dose not continued will be switched in a completely blinded fashion to the continued dose.

Collection of Additional Information for Selected Adverse Events

For selected specific adverse events, investigators will be asked to provide additional information so as to support more detailed analyses of these events, including vulvovaginal adverse events, adverse events of urinary tract infection, adverse events of fractures, skin adverse events, events of increased ALT (≥3-fold the ULN), and hypoglycemia. Additional information will also be requested from investigators to support a detailed assessment of events of venous thromboembolism/pulmonary embolism, hospitalized congestive heart failure, and all deaths (including information and documents to support adjudication of these events). The rationale for collection of additional information on these specific adverse events is provided in the next paragraphs.

As previously discussed (refer to Section 1.1.2, Clinical Studies), canagliflozin increases urinary glucose excretion; before availability of clinical study results, the potential for this increase in UGE to lead to an increase in genitourinary infections was considered. Clinical studies to date, as reviewed in Section 1.1.2, Clinical Studies, have shown an increase in vulvovaginal adverse events, but no evident increase in urinary tract infections. Investigators will be asked to collect additional information on vulvovaginal adverse events and on urinary tract infection adverse events during this study.

Preclinical toxicity studies in rats, described in Section 1.1.1, Brief Overview of Nonclinical Studies, showed a finding of hyperostosis that was associated with decreased bone turnover markers, and marked changes in renal calcium and phosphate handling-changes not observed in clinical studies. In clinical studies, only a modest and

isolated rise in a bone turnover marker (serum collagen type 1 carboxy telopeptide) was observed. Although these preclinical and clinical observations are likely of limited clinical significance, to provide a robust assessment of bone safety, detailed information will be collected on any fracture adverse events in this study.

As described in Section 1.1.2, Clinical Studies, a signal for photosensitivity of uncertain clinical relevance was observed with high light exposure at the 300 mg dose of canagliflozin; no patterns of photosensitivity adverse experiences were observed in the clinical studies of this medication. However, additional information will be collected on skin adverse events to support a detailed assessment of any photosensitivity-related skin adverse events with canagliflozin.

As is the practice with clinical studies for registration of new treatments for T2DM, additional data collection and follow-up will be performed in subjects who experience liver function test abnormalities (ie, ALT ≥3-fold ULN) or hypoglycemia during the study.

No signal for an increase in venous thromboembolic events (VTEs) has been observed in clinical studies with canagliflozin, and no preclinical toxicity signal for increased thrombotic events was observed. However, VTEs were observed with another SGLT2 inhibitor in development, with unclear relation to drug; so to assure appropriate assessment of VTE adverse events, additional information on such adverse events will be collected, and these events will undergo adjudication. Finally, events of hospitalized congestive heart failure will also undergo adjudication by the Endpoint Adjudication Committee, as well as all deaths, to determine whether CV disease was a proximate or underlying cause.

Choice of Cardiovascular Outcome Composite Endpoint

In this study, 2 CV outcome composite endpoints will be included: a CV benefit composite and a safety composite endpoint (to support the planned meta-analysis). To evaluate the study's primary hypothesis of CV benefit (ie, a reduction in CV risk), the endpoint of MACE only (CV death, nonfatal MI, nonfatal stroke) will be used. This has become the standard composite endpoint utilized for this purpose, and hence was selected for use in the current study. The effect of canagliflozin relative to placebo on the HR of the individual components of these endpoints will also be characterized. The safety composite endpoint (to support the planned meta-analysis of integrated results from this and other large, well-controlled, double-blind, randomized studies of canagliflozin) will include MACE *and* hospitalized unstable angina. This endpoint will be utilized to support the CV safety of canagliflozin, evaluating the hypothesis (in the separate meta-analysis

SAP) of no unacceptable increase in CV risk. The event of hospitalized unstable angina was included in this composite to cast a wider net, given the importance of such events, and their close relationship to, and prediction of, progression of coronary artery disease.

Choice of Renal Efficacy Measures

The onset and progression of nephropathy is a major morbidity outcome in diabetic patients. Hyperglycemia, possibly through production of advanced glycation end products (Diabetes Control and Complications Trial [DCCT], Brownlee 2001), systemic hypertension (DCCT), and increases in intraglomerular pressure (Anderson 1986; ADA 2004) are known to be risk factors for the onset and progression of diabetic nephropathy.

In the Phase 2b diabetes study, canagliflozin improved glycemic control, with a trend towards reduced blood pressure in the 300 mg once daily group. By virtue of its mechanism, canagliflozin will reduce the increased glucose flux across the proximal tubule and through the interstitium to be resorbed into the bloodstream. The reduced glucose flux within the kidney could lead to a reduction in renal advanced glycation endproduct (AGE) accumulation resulting in a delay in the onset and/or progression of diabetic nephropathy. Because SGLT2 in the proximal tubule cotransports both sodium and glucose, SGLT2 inhibition by canagliflozin will increase the distal delivery of sodium, which could lead to a reduction in intraglomerular pressure via the macula densa and a decrease in glomerular damage (Vallon 1999).

The development and progression of renal disease in people with diabetes follows a clearly defined pathway starting with micro-albuminuria, progressing to macro-albuminuria, then to reduced renal function (lower glomerular filtration rate), and finally to renal failure with the need for dialysis or transplantation. To assess the effects of canagliflozin on the progression of diabetic nephropathy, the proportion of subjects maintaining stable or with reduced albuminuria based upon the albumin/creatinine ratio in the first morning void was selected as the key secondary endpoint and will be assessed according to the categorizations defined in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Guideline #1 (KDOQI 2007): the definition of micro-albuminuria is albumin/creatinine ratio of 30 to 300 mg/g, and the definition of macro-albuminuria is albumin/creatinine ratio greater than 300 mg/g.

In diabetes, the onset of urinary albumin excretion is a strong signal for progression of diabetic nephropathy (ADA 2004), and is associated with an increase in CV events (de Zeeuw 2004). In the present study, first morning void urine collections are being used. These collections have been shown to be more accurate than spot urine collections

(Witte 2009) because they are less influenced by urinary albumin changes associated with physical activity.

Choice of Beta-cell Function Measures

Type 2 diabetes mellitus (T2DM) is a progressive disease characterized by the progressive loss of beta-cell function and insulin secretory capacity (UKPDS 1998). In large clinical trials, HOMA-B is a well-accepted means of assessing fasting beta-cell function (Wallace 2004). Homeostatic model assessment (HOMA)-B is calculated using fasting insulin or C-peptide and glucose levels (Wallace 2004). Because C-peptide is not, but insulin is, extracted by the liver, the use of C-peptide to calculate HOMA-B is not confounded by increased hepatic extraction such as that which can occur in conditions of improved hepatic insulin sensitivity. Given that canagliflozin is predicted to cause weight loss, which could lead to improved hepatic insulin sensitivity, C-peptide was chosen to be used for HOMA-B calculations, which will be assessed in a subset of subjects who are not receiving insulin at baseline. Approximately 1,200 subjects (400 per treatment group) will be studied in this subset, at designated sites.

In this subset of subjects, fasting proinsulin and insulin will also be measured to assess beta-cell function. Elevated proinsulin/insulin ratios reflect increasing degrees of impairment in beta-cell function in T2DM (Roder 1998).

DNA Collection

It is recognized that genetic variation can be an important contributory factor to interindividual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to a drug. The goal of the pharmacogenomic component is to collect DNA to allow the identification of genetic factors that may influence glucose and lipid metabolism, and supporting interpretation of dynamic effects measured in the study or to characterize genes potentially affecting drug absorption, distribution, metabolism, or excretion of canagliflozin. DNA samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies in the future. Details are provided in Section 9.6, Pharmacogenomic Evaluations.

Medical Resource Utilization

Should canagliflozin reduce the risk of CV events, the risk of onset and progression of nephropathy and improve beta-cell function, the utilization of medical resources such as physician visits (outside of protocol-specified), hospitalizations, and medication requirements may be lower in the canagliflozin group than in the standard care group. To assess this, information will be collected in order to characterize differences in the need for additional medical interactions (eg, physician visits, hospitalizations).

4. STUDY POPULATION

4.1. General Considerations

The Cohort A study population will comprise a total of 4,500 subjects with a diagnosis of T2DM and a history or high risk of CV disease. Subjects randomized to the subsequent cohort (Cohort B) will meet the same study inclusion and exclusion criteria as applied for Cohort A. The decision to recruit Cohort B and the number of subjects that will be randomized into Cohort B are to be determined by the Executive Committee based upon recommendations from the IDMC, refer to Section 11.7, Interim Analysis.

Subjects must have inadequate glycemic control (as defined by HbA_{1c} ≥7.0 to ≤10.5% at screening) and be either (1) not currently on AHA therapy or (2) on AHA monotherapy or combination therapy with any approved class of agents: eg, sulfonylurea, metformin, PPARγ agonist, alpha-glucosidase inhibitor, GLP-1 analogue, or DPP-4 inhibitor, or insulin. Subjects receiving AHA therapy must be on a stable dose of that therapy for at least 8 weeks before the screening visit.

As noted, subjects must also either have a prior history of documented CV disease or be at high risk of CV disease (on the basis of 2 or more specific CV risk factors). For details, refer to Section 4.2, Inclusion Criteria, below.

Subjects will be recruited from centers in Asia-Pacific, North America, Latin America, Europe, and possibly other regions for this study (it is estimated that at least 20% of the total number of subjects will be from the US).

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling the subject in the study.

For a discussion of the statistical considerations, refer to Section 11.3, Sample Size Determination.

4.2. Inclusion Criteria

The inclusion criteria for this study are designed to maximize the clinical applicability of the study findings to the management of patients with diabetes while ensuring event rates are met for the outcomes defined for the safety and efficacy evaluations.

Potential subjects must satisfy all of the following criteria to be enrolled in the study:

Inclusion Criteria at Screening Visit

- Man or woman with a diagnosis of T2DM with HbA_{1c} level ≥7.0% to ≤10.5% at screening and be either (1) not currently on AHA therapy or (2) on AHA monotherapy or combination therapy with any approved class of agents: eg, sulfonylurea, metformin, PPARγ agonist, alpha-glucosidase inhibitor, GLP-1 analogue, DPP-4 inhibitor, or insulin.
- History or high risk of CV disease defined on the basis of either:
  - Age ≥30 years with documented symptomatic atherosclerotic CV disease, eg, stroke, MI, hospital admission for unstable angina, coronary artery bypass graft, percutaneous coronary intervention (with or without stenting), peripheral revascularization (angioplasty or surgery), symptomatic with documented hemodynamically significant carotid or peripheral vascular disease, or amputation secondary to vascular disease
  - Age ≥50 years with 2 or more of the following risk factors determined at the screening visit: duration of T2DM of 10 years or more, systolic blood pressure >140 mmHg on at least 1 blood pressure-lowering treatment, current daily cigarette smoker, or documented micro- or macro-albuminuria or HDL-C of <1 mmol/L (<39 mg/dL).

    ***Note**: a maximum of approximately 30% of subjects across each region may be entered in this second category; the proportion of subjects in these categories will be monitored centrally. When this category of subjects has been filled, sites will be notified that no further subjects in this category may be randomized.*
- Women must be:
  - Postmenopausal, defined at screening as either: a) >45 years of age and absence of menses for at least 12 months, or b) >45 years of age and absence of menses for at least 6 months and with a serum follicle stimulating hormone (FSH) level >40 IU/mL, *or*
  - Surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy), *or*
  - Not heterosexually active (subjects who are not heterosexually active may be enrolled at the discretion of the investigator/per local regulations), *or*

    if heterosexually active, be practicing a highly effective method of birth control such as hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (eg, condoms,

diaphragm, or cervical cap with spermicidal foam, cream, or gel), male partner sterilization, before subject randomization and must agree to continue to use a highly effective method of birth control throughout the study, as local regulations permit.

Note: women of childbearing potential must have a negative urine β-human chorionic gonadotropin (β-hCG) pregnancy test at the screening visit and Day 1 visit (predose)

- Willing/able to adhere to the prohibitions and restrictions specified in this protocol
- Subjects must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study and abide by the restrictions specified in the protocol
- To participate in the optional pharmacogenomic component of this study, subjects must have signed the informed consent form for pharmacogenomic research indicating willingness to participate in the pharmacogenomic component of the study (where local regulations permit). Refusal to give consent for this component does not exclude a subject from participation in the clinical study

Inclusion Criterion for Randomization

Subjects must meet the following criterion at Day 1 to be eligible for randomization:

- taken ≥80% of their single-blind placebo tablets during the 2-week run-in period

4.3. Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

Diabetes-Related/Metabolic

- History of diabetic ketoacidosis, type 1 diabetes mellitus, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy
- On an AHA and not on a stable regimen (ie, agents and doses) for at least 8 weeks before the screening visit

  Note: a stable dose of insulin is defined as no change in the insulin regimen (ie, type[s] of insulin) and ≤10% change in the average total daily dose of insulin
- Fasting fingerstick glucose >270 mg/dL (>15 mmol/L) at Baseline/Day 1
- *For patients on a sulphonylurea agent or on insulin*: fasting fingerstick glucose <110 mg/dL (<6 mmol/L) at Baseline/Day 1

  Note: at the investigator's discretion, based upon an assessment of recent SMBG values, subjects meeting either this fingerstick glucose exclusion criteria may return to the investigational site within 7 days and be randomized if the repeat fasting fingerstick value no longer meets the criterion. Subjects with fingerstick glucose

>270 mg/dL (>15 mmol/L) may have their AHA regimen adjusted, and be rescreened once on a stable regimen for at least 8 weeks

- History of hereditary glucose-galactose malabsorption or primary renal glucosuria
- History of ≥1 severe hypoglycemic episode within 6 months before screening

  Note: a severe hypoglycemic episode is defined as an event that requires the help of another person. Refer to Attachment 2, Hypoglycemia: Definitions, Symptoms, and Treatment, for a definition of severe hypoglycemia
- Run-in visit thyroid stimulating hormone [TSH] value that is <0.1 or >10 mIU/L. Subjects taking a thyroxine supplementation for thyroid disorder should be on a stable dose for at least 6 weeks before baseline

Renal/Cardiovascular

- Renal disease that required treatment with immunosuppressive therapy or a history of dialysis or renal transplant. **Note**: subjects with a history of treated childhood renal disease, without sequelae, may participate
- Myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident within 3 months before screening, or a planned revascularization procedure, or history of New York Heart Association (NYHA) Class IV cardiac disease; refer to Attachment 3, New York Heart Association Classification of Cardiac Disease, for a description of the classes
- Findings on 12-lead ECG that would require early diagnostic evaluation or intervention (eg, new conduction disturbance or clinically important arrhythmia)

Gastrointestinal

- History of hepatitis B surface antigen or hepatitis C antibody positive (unless associated with documented persistently stable / normal range aspartate aminotransferase [AST] and ALT levels), or other clinically active liver disease

Laboratory

- Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 at screening (provided by the central laboratory)
- *For subjects taking metformin*: serum creatinine ≥1.5 mg/dL (133 μmol/L) for men and ≥1.4 mg/dL (124 μmol/L) for women, at screening; eGFR <60 mL/min/1.73m^2, at screening
- ALT levels >2.0 times the ULN or total bilirubin >1.5 times the ULN, at screening, unless in the opinion of the investigator and as agreed upon by the sponsor's medical officer, the findings are consistent with Gilbert's disease

Other conditions

- Major surgery (ie, requiring general anesthesia) within 3 months of the screening visit or any surgery planned during the study (except minor surgery, ie, outpatient surgery under local anesthesia)

- History of malignancy within 5 years before screening (exceptions: squamous and basal cell carcinomas of the skin and cervical carcinomas in situ, or a malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence)
- History of human immunodeficiency virus (HIV) antibody positive
- Investigator's assessment that the subject's life expectancy is less than 1 year, or any condition that in the opinion of the investigator would make participation not in the best interest of the subject, or could prevent, limit, or confound the protocol-specified safety or efficacy assessments

Medications/Therapies

Current use of a disallowed therapy:

- Any other SGLT2 inhibitor
- Digoxin

  Note: Subjects who are taking a disallowed therapy at screening may be eligible to participate if the investigator feels, based on clinical judgment, that it is appropriate to switch the subject from a disallowed therapy to a comparable allowed therapy. Subjects may be rescreened on one additional occasion after a period of 30 days from the time that treatment with the allowed therapy was initiated.

- Known allergies, hypersensitivity, or intolerance to canagliflozin or its excipients (refer to Section 14.1, Physical Description of Study Drug(s))
- Current use of, or likely to require treatment with, a corticosteroid medication (for longer than 2 weeks in duration), or an immunosuppressive agent. **Note**: subjects using inhaled, intranasal, intra-articular, or topical corticosteroids, or corticosteroids in therapeutic replacement doses may participate
- Received an active investigational drug (including vaccines) or used an investigational medical device within 3 months before the planned start of treatment or received at least one dose of canagliflozin in a prior study

General

- History of drug or alcohol abuse within 3 years before screening
- Pregnant or breast-feeding or planning to become pregnant or breast-feed during the study
- Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator

4.4. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

- Women of childbearing potential must remain on a highly effective method of birth control (refer to Section 4.2, Inclusion Criteria)(refer to Section 12.2.3, Pregnancy, for instructions in cases of a positive pregnancy test)
- Subjects should use photoprotective measures (eg, topical sunscreen) as appropriate and should avoid excessive sunlight or tanning with artificial ultraviolet light
- Prohibited medications include other SGLT2 inhibitors and digoxin; subjects must not take any other investigational agents during the study
- Factors such as strenuous exercise may affect urine protein excretion. Therefore strenuous exercise should be avoided within 72 hours before planned urine collections

4.5. Rescreening

Subjects who do not meet all inclusion criteria or who meet an exclusion criterion may, at the discretion of the investigator, be rescreened one time if the reason for non-eligibility relates to duration (eg, time from an MI, or duration on a stable dose of thyroid hormone, or duration on a stable AHA regimen), or appropriate clinical management leads to study eligibility (eg, HbA_{1c} >10.5% that prompts adjustment of the subject's AHA regimen, or treatment of an abnormal TSH value leads to no longer meeting TSH exclusion criteria).

Subjects rescreened within 4 weeks may use the initial screening laboratory results to determine eligibility. Rescreening for an abnormal laboratory value is only allowed as indicated for the specific laboratory exclusion criterion.

5. TREATMENT ALLOCATION

To ensure sufficient experience in subjects with documented, pre-existing CV disease - the highest risk group - not less than 70% of subjects must be in this group.

Stratification for Substudies (Cohort A only)

Subjects in Cohort A within the following 6 pre-defined strata, based upon AHA medication(s) that the subject is receiving at the screening visit and will be continuing at entry into the double-blind treatment phase, will have within-subgroup balanced (1:1:1) randomization to each of the 3 treatment groups:

- Stratum 1: insulin monotherapy ≥20 units per day, on stable doses at least 10 weeks before the run-in visit
- Stratum 2: insulin ≥20 units per day plus metformin, on stable doses at least 10 weeks before the run-in visit, and no other background AHA therapy
- Stratum 3: insulin ≥20 units per day plus any other AHA(s) on stable dose(s) for at least 10 weeks before the run-in visit

- Stratum 4: sulfonylurea monotherapy (at doses specified in Attachment 1), on stable doses at least 10 weeks before the run-in visit
- Stratum 5: PPARγ agonist (pioglitazone ≥30 mg/day or rosiglitazone ≥4 mg/day) plus metformin ≥2,000 mg/day (or at least 1,500 mg/day for subjects who have a history of not being able to tolerate higher metformin doses) and no other background AHA therapy, on stable doses at least 10 weeks before the run-in visit
- Stratum 6: subjects not in one of the above AHA subgroups

Note: a stable dose of insulin is defined as no change in the insulin regimen (ie, type[s] of insulin) and ≤10% change in the average total daily dose of insulin

The stratification process will be handled via queries in the Interactive Voice Response System (IVRS) or after logging on to the Interactive Web Response System (IWRS) being used for the study, described below.

No stratification will be applied for Cohort B.

Randomization and Blinding Procedures

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 3 treatment groups (or, for Cohort B if only 1 dose of canagliflozin is studied, 1 of 2 treatment groups) based on a computer-generated randomization schedule prepared by or under the supervision of the sponsor before the study. The randomization will be balanced by using randomly permuted blocks and will be stratified for Cohort A based on the use of specific concomitant antihyperglycemic medications at baseline (as noted above). Based on this randomization schedule, the study drug will be packaged and labeled. Medication numbers will be preprinted on the study drug labels and assigned as subjects qualify for the study and are assigned to double-blind treatment.

At baseline (Day 1), the randomization number and medication numbers, the treatment code, which is linked to the randomization schedule, will be assigned after telephoning into the IVRS or after logging on to the IWRS designated by the sponsor. The requestor must use his/her own user identification (ID) and personal identification number (PIN) when contacting the IVRS/IWRS, and will then give the relevant subject details to uniquely identify the subject. Based on this information, the IVRS/IWRS will assign a unique treatment code, which will dictate the treatment assignment and study drug kit for the subject. As subjects are randomly assigned to treatment, the IVRS/IWRS will assign a study drug kit to be dispensed at that visit. New medication numbers will be assigned each time the IVRS/IWRS is contacted for dispensing additional study drug. The randomization (or initial subject allocation) number at baseline will be the identifying number linking all subsequent kits to the individual subject.

The study drug kit numbers will be entered in the electronic CRF when the drug is dispensed. The study drugs will be identical in appearance and will be packaged in identical containers.

The randomization code that links the randomization number assigned to the subject with a treatment group assignment will be maintained within the IVRS/IWRS. This randomization code will not be provided to the investigator unless required, as described below, for unblinding in emergency situations.

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment through the IVRS or IWRS. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. The reason for unblinding is not captured through IVRS. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the appropriate section of the CRF and in the source documents. The documentation received from the IVRS indicating the code break must be retained with the subject's source documents in a secure manner (eg, sealed envelope) so as not to unblind the treatment assignment to the study site or sponsor personnel. The investigator is also advised not to reveal the study treatment assignment to the study site or sponsor personnel.

Subjects who have had their treatment assignment unblinded will be discontinued (refer to Section 10.2, Withdrawal from the Study).

Randomization codes will be released based upon protocol-specified interim analyses, and after completion of the study. At the time of the interim analyses, the translation of randomization codes into treatment and control groups will be disclosed only to those authorized and only for those subjects included in the interim analysis (refer to Section 11.7, Interim Analysis).

Urine glucose measurements will not be performed on first morning void urine specimens, or on urinalyses during the study as an additional step to ensure the maintenance of the treatment blind. Unless required by urgent subject management, investigators should obtain all urinalyses through the central laboratory and not by a local

laboratory so as to avoid potential for unblinding related to urine glucose results (which will not be reported by the central laboratory).

6. DOSAGE AND ADMINISTRATION

6.1. Study Drugs

Run-in Period Single-Blind Placebo

Upon successful completion of the initial screening, all potentially eligible individuals will enter a 2-week run in period, during which they will receive single-blind placebo tablets (to be administered once-daily).

Double-Blind Study Medication

Initial cohort (Cohort A): Subjects in Cohort A will be randomly assigned in a 1:1:1 ratio to 1 of 3 treatment groups: canagliflozin 100 mg, canagliflozin 300 mg, or matching placebo.

Subsequent Cohort (Cohort B): Subjects in Cohort B (if recruited) will be randomized in an equal distribution to placebo and to canagliflozin (1 or 2 doses, determined by the Executive Committee at the time of initiation of Cohort B recruitment). Based upon initial results of this study (ie, based upon the results of the planned interim analysis of Cohort A) or of the Phase 3 program evaluation (based upon by dose efficacy and tolerability assessment) one or the other dose may not be continued in development and/or continued in this study. The randomization of Cohort B will be based upon balanced allocation to placebo and the dose(s) of canagliflozin continuing in the study at the time of Cohort B recruitment (ie, 1:1 if placebo and 1 dose, or 1:1:1 if placebo and 2 doses). If a dose of canagliflozin is not continuing in this study, subjects in Cohort A on the canagliflozin dose not continuing will be *switched* in a completely blinded fashion to the continuing dose.

Subjects will be counseled to take their dose of canagliflozin or matching placebo once daily, before the first meal of the day for the duration of the study or until discontinuation from the study. Subjects will take the first dose of study drug at the study center.

On the days of study visits when fasting blood samples are collected (refer to the Time and Events Schedule that follows the Synopsis), subjects will be instructed to refrain from taking the study drug before the clinic visit. The subject will be instructed to take the dose of study drug before the subject's next meal.

The study drug must be swallowed whole with liquid and not chewed, divided, dissolved, or crushed. If the subject does not take the study drug within 12 hours after the first meal of the day, the dose of study drug should be skipped for that day and the subject should be instructed to take the study drug on the following day before the first meal of the day.

6.2. Concomitant Antihyperglycemic and Other Therapies

6.2.1. Management of Glycemic Control and CV Risk Factors

Run-in Period Management

Subjects will receive diet/exercise counseling at entry into the 2-week run-in period and will remain on a stable regimen (medications and doses) of their current AHA regimen (if on an AHA[s]), except as described below.

Double-blind Treatment Phase Glycemic Management

For subjects in Cohort A**:** subjects should remain on a stable AHA regimen (doses and medications) from screening *through* Week 18, unless a down-titration is considered necessary to manage or avoid hypoglycemia, or if glycemic rescue criteria are met (refer to Section 6.2.2, Glycemic Rescue Therapy Through Week 18 for Cohort A: Criteria and Implementation). At and after Week 18, the AHA regimen should be adjusted to achieve glycemic goals, as suggested by standard guidances, and as considered appropriate by the investigator for the individual subject. *Adjustment to the AHA regimen (after Week 18) should be carefully implemented so as to avoid events of hypoglycemia.*

For subjects in Cohort B: Subjects randomized into Cohort B may have their AHA regimen adjusted to achieve glycemic goals, as suggested by standard diabetes guidances, and as considered appropriate by the investigator for the individual subject, throughout the double-blind treatment phase (*including* during the first 18 weeks). *Adjustment to the AHA regimen should be avoided in the weeks after initiation of double-blind treatment and should be carefully implemented throughout the study so as to avoid events of hypoglycemia.*

For subjects in both cohorts, adjustment of AHA therapy will be performed by the investigator, consistent with standard diabetes guidances: no specific AHA treatment algorithm is utilized in this study. Treatment may include reinforcement of lifestyle counseling, up-titration to maximum labeled doses of current AHAs, the addition of oral AHAs, addition of GLP-1 analogue, or the initiation and up-titration of insulin (intermediate or long-acting insulin and subsequent short-acting, pre-meal insulin, if needed). Investigators should make all reasonable efforts to achieve and maintain the subject's individualized target glycemic control, and may add unscheduled visits, if

clinically appropriate, to monitor glycemic control, and adjust the subject's regimen. All adjustments to the AHA regimen should be documented in the appropriate CRF. Use of AHAs and adjustments to the AHA regimen (dose or agents) should be consistent with the labeled use of the AHA within the country of the investigational site.

Therapeutic Management of CV Risk Factors

Before randomization, and throughout the study, investigators will be expected to manage the subject's diet/exercise and medication regimens so as to achieve goals for CV risk factors (eg, lipid levels, blood pressure) based upon standard guidances for the care of patients with T2DM.

During the 2-week single-blind placebo run-in period, investigators should adjust the subject's regimen as needed to optimize the subject's CV risk factors and thereby to reduce the need for adjustments of medications after randomization.

6.2.2. Glycemic Rescue Therapy Through Week 18 for Cohort A: Criteria and Implementation

For subjects in Cohort A, so as to avoid poorer glycemic control during the 18-week AHA dose-stable period, glycemic rescue criteria will be applied. After Week 18, as noted above, investigators will determine subject's glycemic goals and the need for adjustments in the AHA regimen.

For subjects in Cohort A, from Day 1 to Week 18, the criteria for starting glycemic rescue therapy are based on an FPG value exceeding the glucose cutpoints shown in the table below. Subjects should be counseled to contact the site if their SMBG consistently exceeds these values and an FPG measurement (ie, venous blood collection) to determine eligibility for initiation of glycemic rescue therapy should be obtained.

Rescue Criteria Recommendations Through Week 18

Time point	Glucose
After Day 1 through Week 4	>270 mg/dL (15 mmol/L)
After Week 4 through Week 12	>240 mg/dL (13.3 mmol/L)
After Week 12 through Week 18	>200 mg/dL (11.1 mmol/L)

FPG=fasting plasma glucose

Glycemic rescue therapy should be as determined to be clinically appropriate by the investigator: either up-titration of current AHA medications or the stepwise addition of oral and then insulin therapies. After initiation of rescue therapy, the glycemic goals will be based upon standard diabetes guidances, individualized for the subject, as considered appropriate by the investigator.

7. COMPLIANCE

The investigator or designated study research staff will maintain a log of all drug dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study. Subjects who are poorly compliant with taking the study drug (based on capsule counts) should receive counseling on the importance of dosing compliance and may continue in the study, at the investigator's discretion.

Subjects will receive clear instructions on compliance with study procedures at the screening visit. During the course of the study, the investigator or designated study research staff will be responsible for providing additional instructions to reeducate any subject who is not compliant with taking the study drug or with completing the diary, as required.

8. PRESTUDY AND CONCOMITANT THERAPY

All prestudy therapies administered up to 30 days before baseline (Day 1) must be recorded at screening and baseline. Any AHA used within 1 year of screening should be documented.

All concomitant therapies taken, beginning at baseline (Day 1), must be recorded throughout the study.

All therapies (prescriptions or over-the-counter medications, including vitamins and herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study drug must be recorded in the concomitant therapy section (from Day 1 on) or prior therapy section (before Day 1) of the CRF.

Concomitant therapies will not be provided or reimbursed by the sponsor.

Disallowed Therapies

Digoxin or other SGLT2 inhibitors may not be used concurrently, and subjects should not take any other investigational agents during the study.

The sponsor must be notified as soon as possible of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule that follows the Synopsis summarizes the frequency and timing of efficacy, safety, and other measurements applicable to this study.

Visit Schedules and Visit Windows

A screening visit should occur 1 to 2 weeks before the run-in visit. The single-blind placebo run-in period should be 2 weeks in length (with a visit window of ±4 days). Subsequent scheduled study visits during the first year of the study should occur at Day 1 (baseline, the day of randomization), Weeks 6, 12, 18, 26, 39, and 52. After the first year, scheduled study visits should occur at 13 week intervals. For each visit up through Week 26, the recommended visit window is ±7 days. After Week 26, the recommended visit window is ±14 days. Telephone contacts, or optional (unscheduled) site visits, should be conducted at Weeks 2, 4, and 9. Refer to the Time and Events Schedule that follows the Synopsis for further details.

For study visits that are unable to be held within the protocol-recommended visit windows, the visit should be conducted as closely as possible to the protocol-specified study visit timing. All subsequent visits should be scheduled based on the date of randomization, not the date of the rescheduled visit. The study visits at Week 52, and annual visits, should occur as closely as possible to this scheduled time.

Pregnancy Testing

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the study.

Subject Diary: Collection of Self-Monitoring of Blood Glucose (SMBG), Possible Hypoglycemic Event Information, Medical Resource Utilization Information

A standard, protocol-specified diary will be provided to each subject. Routine SMBG measurements may be recorded in the diary at the investigator's discretion, and all events of possible hypoglycemia will be documented as well as associated fingerstick glucose measurements, if available.

The diary may also be used to keep track of medications and/or medication changes at the investigator's discretion. In addition, the diary will be used for the subject to record doctor visits (other than protocol-specified study visits), emergency care, and hospital visits (refer to Section 9.8, Medical Resource Utilization).

The diary will be reviewed by study research staff at each scheduled visit.

Collection of Other Endpoints: Archive Samples for Exploratory Research and Optional Specimens for Biomarker Analysis

Fasting plasma, serum, and urine samples will be collected at baseline and all 52-week intervals to allow for exploratory research related to canagliflozin or T2DM and obesity. Refer to Section 9.7, Exploratory Evaluations, for further details. Refer to Attachment 4, Archive Samples for Exploratory Research - Sample Collection and Handling, for further information regarding the collection and handling of exploratory blood and urine samples.

A second set of fasting plasma, serum, and urine samples will be collected at baseline and at all 52-week intervals for optional biomarker analyses that may provide further understanding regarding the diagnosis and treatment of T2DM. Sample collection and processing procedures will be outlined in a separate laboratory manual. Subject participation in these collections is optional and additional consent is required. Refusal to consent for this component does not exclude a subject from participation in the clinical study.

Pharmacogenomic Testing

A blood sample will be collected on Day 1 (or any time after Day 1 if the specimen is inadvertently missed on Day 1) from subjects who have consented to participate in the pharmacogenomic component of the study. Refer to Attachment 5, Pharmacogenomic Sample Collection and Shipment Procedures, for details on collecting and handling blood samples for pharmacogenomic research. In the event of DNA extraction failure, a replacement pharmacogenomic blood sample may be requested from the subject. Signed informed consent will be required to obtain a replacement sample.

9.1.2. Pretreatment

The screening and run-in visits apply to subjects in both Cohort A and Cohort B.

Screening Visit (Week -3)

Potential subjects will be seen at a screening visit, approximately 3 weeks before scheduled randomization, at which informed consent will be obtained and an initial assessment of eligibility will be performed.

At the screening visit, a focused medical history and initial screening assessment of inclusion/exclusion criteria will be performed and key laboratory studies (including serum chemistry and HbA_{1c}) will be obtained.

Run-in Visit (Week -2)

At the Week –2 run-in visit, a complete medical history will be obtained and a physical examination and additional laboratory evaluations (including hematology, urinalysis, FPG, and fasting lipids), and an ECG will be performed, as per the Time and Events Schedule that follows the Synopsis.

Subjects who continue to meet enrollment criteria may then be dispensed single-blind placebo tablets (through IVRS or IWRS, refer to Section 5, Treatment Allocation) and enter the 2-week single-blind placebo run-in period. An assessment of the subjects' adherence to protocol procedures during the run-in will be made at the end of the period, before randomization, and will provide investigators with an opportunity to assess subjects' compliance with taking the single-blind study drug (by counting capsules), and have a stable diet and exercise regimen.

Subjects who do not meet all inclusion criteria or meet a study exclusion criterion based upon the results of the screening or run-in visit laboratory studies should be excluded from the study, and discontinue single-blind placebo.

At the run-in visit and during the 2-week run-in period (ie, at additional visits as considered appropriate), investigators should evaluate CV risk factors (eg, blood pressure, and fasting lipid levels) and adjust therapies, if necessary. At the run-in visit (Week -2), subjects who continue to be eligible will be provided with a glucose meter and testing supplies and instructed on the performance of SMBG. In addition, a standard, protocol-specified diary will be provided to each subject. Subjects will also receive counseling regarding diet and exercise consistent with standard diabetes guidance recommendations (eg, ADA), and will be counseled regarding recognition and management of hypoglycemia, including recording of possible hypoglycemic events on

the subject diary along with concurrent fingerstick glucose measurements. Subjects should be counseled by the study research personnel regarding the importance of good compliance with all study procedures throughout the study.

9.1.3. Double-Blind Treatment

Day 1/Day of Randomization

Potential subjects who return for the Day 1 (baseline), who have taken ≥80% of the scheduled single-blind placebo tablets during the run-in period, and who meet the enrollment criteria will be randomly assigned in a 1:1:1 ratio (for subjects in Cohort A) to once-daily treatment with canagliflozin 100 mg, canagliflozin 300 mg, or matching placebo. For Cohort B treatment groups, refer to Section 6.1, Study Drugs. Subjects will continue treatment until the study completes or the subject is withdrawn from the study (refer to Section 10.2, Withdrawal From the Study, for reasons for withdrawal).

In addition, pharmacogenomic informed consent will be obtained (only from those subjects who agree to participate in this component).

Visits Following Randomization

Subjects will be seen in the clinic at visits or contacted by telephone as described above and in the Time and Events schedule. Procedures and clinical laboratory assessments for each visit or contact are outlined in the Time and Events schedule.

Subjects who experience nonfatal events in the CV composite endpoint (ie, nonfatal MI, nonfatal stroke, or hospitalized unstable angina) during the double-blind treatment phase will continue in the study, continuing to receive double-blind study drug and complete all assessments at all scheduled visits, if possible.

9.1.4. End-of-Treatment/Early Withdrawal

End-of-treatment/early withdrawal evaluations will be performed when the double-blind treatment phase of the study is ended or at the time the subject discontinues the study drug or is withdrawn from the study. Evaluations will be performed as soon as possible after stopping the study drug. Subjects who discontinue treatment will continue to have follow-up contact as described below.

9.1.5. Posttreatment Phase (Follow-Up)

A telephone follow-up contact (or optional study visit, at the discretion of the investigator) will be conducted for all subjects approximately 28 days (no later than 42 days) after the last dose of study drug to complete the evaluations specified in the Time and Events Schedule that follows the Synopsis.

Subjects who discontinue treatment early for any reason will be contacted by telephone approximately every 6 months (or more frequently if necessary based on the investigator's knowledge of the subject) until completion of the overall study, with the goal of collecting any CV outcome events (ie, events in the CV composite endpoint) and adverse events of fractures. Subjects who discontinue treatment less than 6 months before the completion of the study will be contacted by telephone at the end of the study to collect any CV outcome events and adverse events of fracture.

9.2. Reporting / Adjudication of Events in the CV Composite Endpoint and Other Events for Adjudication

Investigators will be counseled to report any event that they assess as potentially to be a component of the study CV composite endpoints: CV death, nonfatal MI, nonfatal stroke, or hospitalized unstable angina. In addition, all deaths and events of hospitalized congestive heart failure will be submitted for adjudication.

Investigators will complete a separate CRF and must provide a specific package of information to be submitted for adjudication evaluation that will be provided in a procedural manual. An independent Endpoint Adjudication Committee will assess all events that could potentially contribute to the specified CV endpoints and only those events that the committee, using methodology defined in the committee's charter, determines are prespecified endpoint events will be included in the analysis. The Endpoint Adjudication Committee will classify the outcome events while blinded to treatment assignment. The same Endpoint Adjudication Committee will adjudicate events from all of the studies that will contribute to the meta-analysis of the pooled large, well-controlled, randomized studies of canagliflozin (including CANVAS).

Note that events assessed by the investigator as an event in the CV composite endpoints, with the exception of CV death, should not be reported as adverse experiences/serious adverse experiences (refer to Section 12, Adverse Event Reporting). If the event is adjudicated by the Endpoint Adjudication Committee as **not** meeting the event definition, *then the event should be reported as an adverse event/serious adverse event* (with reporting timelines starting at the time of notification of this by the Endpoint Adjudication Committee).

9.3. Study Management: Committees

9.3.1. Academic Research Organization

An ARO will provide scientific and academic oversight of the study. The ARO will also have a role in site monitoring for a portion of the sites.

9.3.2. Steering Committee

A Steering Committee, made up of external scientific experts will provide scientific advice regarding the study conduct and data collection. The Steering Committee is responsible for providing academic leadership to study sites, reviewing study progress, and reviewing study results before publication. Details of the composition, roles, and responsibilities will be documented in its charter.

9.3.3. Medical Safety Review Committee

An MSRC will be established to ensure that the safety of subjects participating in the study is not compromised. The MSRC will include, but will not be limited to, at least one medical expert and at least one statistician. The MSRC will include members from the sponsor organization and may include ARO representatives. The MSRC will monitor the progress of the study by reviewing blinded data on a regular basis and will refer safety concerns to the IDMC.

9.3.4. Executive Committee

The Executive Committee consists of one member each from the Steering Committee, ARO, and the sponsor. The Executive Committee will be responsible for receiving recommendations from other committees including the IDMC and the Steering Committee. The Executive Committee will ultimately decide whether to accept the recommendations and will oversee the implementation of any modifications. The Executive Committee also will make the decision to initiate recruitment of Cohort B of the study, at the time of the Cohort A interim analysis, done approximately at the time of approval of canagliflozin in the US, based on available data from the IDMC (ie, the predicted HR based upon effect of canagliflozin on CV risk factors and the observed HR from Cohort A) and the study sponsor (refer to Section 11.3.2, Cohort B). The Executive Committee will make recommendations regarding study conduct and execution to the study sponsor. Details of the composition, roles, and responsibilities will be documented in its charter.

9.3.5. Independent Data Monitoring Committee

An IDMC will be commissioned for this study to review accumulated, unblinded safety information during the study. Deaths, serious adverse events and discontinuations due to adverse events will be reviewed on a regular basis during the course of the study. In addition, adverse events or laboratory results identified during blinded review of the data by the MSRC, and indicating a possible safety concern will be sent to the IDMC for review.

The IDMC will also have responsibility for review of the primary CV endpoints for this study as well as across the canagliflozin clinical development program. The planned meta-analysis of events from the pooled population of subjects from large, well-controlled, double-blind, randomized studies (including CANVAS) and the interim analysis for the CANVAS study will occur at prespecified points (refer to Section 11.7, Interim Analysis), with a chairman's report to the Executive Committee of the findings. The first planned meta-analysis will occur when approximately 104 composite events of MACE and hospitalized unstable angina are observed across the program. If an upper bound of the confidence interval around the HR excludes a risk of 1.8, the recommendation to the Executive Committee and the sponsor, to proceed with regulatory filing, will be made. The sponsor will be unblinded to the data during the preparation of the regulatory submissions; however, blinding to the subject's treatment allocation will be maintained for the subjects, investigators, Endpoint Adjudication Committee, and sponsor site monitoring personnel throughout the study. A subsequent interim analysis, at the time of FDA approval, of the MACE endpoint for CANVAS, will be conducted by the IDMC. The observed HR from this analysis, and the modeled CV benefit based on CV risk factors will be the basis for the information provided to the Executive Committee (refer to Section 11.3.2, Cohort B) for a decision regarding recruitment of Cohort B. If a decision to initiate recruitment of Cohort B is made, regulatory agencies will be informed of this determination. If Cohort B is not recruited, then the IDMC will continue to conduct sequential meta-analyses of the pooled population from large, well-controlled, randomized studies in the canagliflozin development program, including the continuing Cohort A, in order to support regulatory agency requirements regarding demonstration of CV safety for new medications to treat patients with T2DM (refer to Section 11.7, Interim Analysis).

9.3.6. Endpoint Adjudication Committee

An independent Endpoint Adjudication Committee composed of external specialists, blinded to treatment assignment, will be commissioned to review case information on CV events as well as other selected adverse events. The operations, processes, and endpoint definitions to be employed by the committee will be defined in its charter.

9.4. Safety Evaluations

Details regarding the IDMC are provided in Section 11.7, Interim Analysis.

Refer to Section 9.2 for reporting and adjudication of events in the CV composite endpoint.

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally-acceptable representative) for the duration of the study, beginning when the informed consent is signed. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

For purposes of reporting serious adverse events for this study, the components of the CV composite endpoints (with the exception of CV death) will not be considered adverse events or serious adverse events. Events in the CV composite endpoints will not be considered as unexpected but as disease-related, and as such will not be unblinded. Refer to Section 12, Adverse Event Reporting, for details regarding the handling of components of the CV composite endpoints.

After the decision to initiate recruitment of Cohort B, for subjects continuing from Cohort A and subjects entered in Cohort B, only serious adverse events, adverse events resulting in study drug discontinuation, and selected adverse events will be collected on CRFs. Information for all adverse events will be collected in source documents (eg, progress notes) retained at the investigative sites.

Collection of Additional Information for Selected Adverse Events

For selected, specific adverse events, investigators will be asked to provide additional information so as to support more detailed analyses. These include vulvovaginal adverse events, adverse events of urinary tract infection, adverse events of fractures, skin adverse events, events of increased ALT (≥3-fold the ULN), and hypoglycemia (refer to section below). Additional information will also be requested from investigators to support a detailed assessment of events of venous thromboembolism/pulmonary embolism, hospitalized congestive heart failure, and all deaths (including information and documents to support adjudication of these events). Investigators may also be asked to provide additional information on other adverse events, based upon review by the MSRC or the IDMC (refer to Sections 9.3.3, Medical Safety Review Committee, and 9.3.5, Independent Data Monitoring Committee).

Collection of Information on Possible Hypoglycemic Events

Subjects will be asked to collect fingerstick glucose determinations at the time of possible hypoglycemic events, and to document information on these events, including the glucose results, in a standard protocol-specific diary. This diary will be reviewed by study research staff at each scheduled visit.

If a hypoglycemic episode meets the criteria used to define a serious adverse event, the event must be captured on the Serious Adverse Event CRF pages.

Refer to Section 12.2.4, Hypoglycemia, for details regarding classification of hypoglycemic events.

Follow-Up Collection of Safety Information and Endpoint Events

Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until a clinically stable endpoint is reached, or until further follow up is no longer considered by the investigator to be clinically meaningful. A telephone follow-up contact (or optional study visit, at the discretion of the investigator) will be conducted for all subjects approximately 28 days (and no later than 42 days) after the last dose of study drug to complete the evaluations specified in the Time and Events Schedule that follows the Synopsis.

End-of-treatment/early withdrawal evaluations will be performed at the end of the double-blind treatment phase or at the time the subject discontinues study drug or is withdrawn from the study. Evaluations must be performed as soon as possible after stopping the study drug and subjects must have a telephone follow-up contact (or optional study visit, at the discretion of the investigator) approximately 28 days (and no later than 42 days) after the last dose of study drug according to the Time and Events Schedule that follows the Synopsis.

In addition, subjects who discontinue treatment early for any reason (except withdrawal of consent for any further contact) should be contacted by telephone approximately every 6 months (or more frequently if necessary based on the investigator's knowledge of the subject) until completion of the overall study with the goal of collecting any potential events in the CV safety composite endpoint ([MACE] including CV death, nonfatal MI, or nonfatal stroke, or hospitalized unstable angina) and adverse events of fracture.

Clinical Safety Laboratory Tests

Subjects will be monitored for safety laboratory analytes (hematology, chemistry, and urinalysis [with urine glucose remaining masked to avoid unblinding]) as described in Attachment 6.

In subjects with elevations in ALT meeting protocol-specified levels (ie, increases ≥3-fold ULN), further monitoring of liver function must be performed using the algorithm in protocol Attachment 7.

Alerts will be provided to investigators by the central laboratory identifying important laboratory changes or key out-of-range values, so the investigator can follow up as necessary with the subject. For creatine phosphokinase (CPK) elevations, the investigator should determine if follow-up evaluation is clinically appropriate to exclude a potential cardiac event.

The investigator must review the laboratory report, document this review, and record any changes that the investigator considers to be clinically relevant in the adverse event section of the CRF.

Urine samples from first morning void on day of designated visits will be collected for urine albumin and creatinine determinations. If the subject inadvertently misses the first morning void collection on the day of the visit, the subject may return the next morning or anytime during the following week with a first morning specimen. The urine collections for archive and biomarker specimens, as well as the routine urinalyses, should be obtained from a spot urine specimen in the clinic.

Urine glucose will not be measured in the first morning void urine specimens.

Urine pregnancy testing will be performed, unless a serum pregnancy test is preferred at the discretion of the investigator or if required by local regulations, for all women according to local procedures unless they are surgically sterile or unless there is a documented history of their postmenopausal status.

Electrocardiogram (ECG)

Twelve-lead ECGs will be interpreted by a central ECG reading center. After the ECG is recorded by site personnel, the machine will print the unverified measurements and interpretation. These findings will be subsequently verified by a qualified specialist, and the final report will be transmitted to the investigator within approximately 3 days.

Vital Signs (pulse, blood pressure)

Vital signs will consist of pulse and blood pressure measurements and will be obtained after the subject has been in the sitting position for 5 minutes and before blood sample collection for laboratory tests. Pulse rate will be measured once at each clinic visit. Blood pressure will be assessed manually with a mercury sphygmomanometer, or a properly calibrated automated blood pressure monitor; if neither of these is available, a high-quality aneroid sphygmomanometer calibrated according to manufacturer specifications will be acceptable. Three consecutive blood pressure readings will be taken and recorded, at intervals of at least 1 minute apart as specified in the Time and Events Schedule that follows the Synopsis.

In addition, blood pressure will be measured in both arms at the screening visit. If there is a difference between arms of >10 mmHg in either systolic or diastolic pressure, the arm with the higher pressure should be used to measure blood pressure and *should be used for all subsequent blood pressure measurements during the study*. If possible, if blood pressure is measured manually, it should be measured by the same individual, using the same equipment, at each clinic visit to reduce variability.

Physical Examination

Physical examinations will be performed. Refer to the Time and Events Schedule that follows the Synopsis for further details.

Body Weight

Body weight will be measured using the same calibrated scale at each visit. The study center will be responsible for calibrating the scale before the first subject enrolled in the study at the site is weighed and then at approximately 12-week intervals during the study. Calibration must be documented in a calibration log. Subjects should be weighed at approximately the same time of day on the same scale, wearing underwear and a gown and without shoes; subjects will be asked to urinate before being weighed. Refer to the Time and Events Schedule that follows the Synopsis for further details.

9.5. Efficacy Evaluations

The hypothesis of CV benefit for canagliflozin will be evaluated based upon the events in the CV benefit composite endpoint of MACE (CV death, nonfatal MI, nonfatal stroke). As previously described, an independent Endpoint Adjudication Committee will assess all events that could potentially be in the specified CV endpoint and only those events where the committee, using methodology and definitions defined in the committee's charter, determines a specified endpoint has occurred will be included in the analysis. The independent Endpoint Adjudication Committee (refer to Section 9.3.5, Independent Data Monitoring Committee) will apply the endpoint definitions contained in its charter and classify the outcome events while blinded to treatment assignment.

Other efficacy evaluations include HbA_{1c}, FPG, systolic and diastolic blood pressure, body weight, and fasting plasma lipids (triglycerides, HDL-C, LDL-C, total cholesterol, and the ratio of LDL-C to HDL-C). The change from baseline in these variables will be evaluated (refer to Section 11.5.2, Secondary Efficacy Endpoints).

Urinary albumin/creatinine ratio (from first morning void) will be evaluated, as will beta-cell function with HOMA-B and proinsulin/insulin ratio. Measurements to assess HOMA-B and the proinsulin/insulin ratio will be collected in a subset of subjects of

approximately 1,200 subjects (at designated sites) who are not receiving insulin at baseline. Homeostatic model assessment (HOMA)-B will be assessed based upon C-peptide and fasting glucose; for subjects who initiate therapy with insulin during the study, data from the last proinsulin and insulin measurement before initiation of insulin will be utilized for analyses of proinsulin/insulin ratio.

Refer to Section 11.5, CV Outcomes and Efficacy Analyses, for the evaluation of efficacy criteria.

9.6. Pharmacogenomic Evaluations

There are 2 parts to the pharmacogenomic component of this study.

Analysis Related to the Study (Part 1)

Part 1 of pharmacogenomic research allows for the analysis of genes that may be relevant to help to better understand canagliflozin, or T2DM or obesity. Candidate genes will only be genotyped, if it is hypothesized that this may help resolve issues with the clinical data. Analyses may involve the analysis of known candidate genes or the analysis of genetic variants throughout the genome (genome-wide association analysis), both in relation to canagliflozin, or T2DM or obesity (provided in Attachment 8). Genotyping of any of these candidate genes would be performed on identifiable samples.

Additional genes may be analyzed on identifiable samples if these genes are hypothesized to be relevant to canagliflozin, or T2DM or obesity between the time that the clinical protocol has been issued and the samples have been made nonidentifiable.

DNA Storage for Future Research (Part 2)

Part 2 of the pharmacogenomic research allows for the storage of DNA samples for future genetic research related to canagliflozin or the indication(s) for which it is developed. Stored DNA samples and relevant clinical data will be made nonidentifiable after the Clinical Study Report has been issued. This involves removing personal identifiers and replacing the study subject identifier with a new number to limit the possibility of linking genetic data to a subject's identity.

Subjects will be given the option to participate in Part 1 only, Part 2 only, both parts, or neither part of the pharmacogenomic component of this study (where local regulations permit).

9.7. Exploratory Evaluations

Two separate sets of fasting plasma, serum, and urine samples will be collected (where local regulations permit) at baseline and at all 52-week intervals for the following:

- exploratory analysis that may be done to provide insight into the actions of canagliflozin or assist in understanding any adverse events possibly associated with the compound. Samples may also be used for future exploratory research to improve understanding of the pathophysiology of T2DM or obesity or to assess other pharmacodynamic effects of canagliflozin, and
- to develop biomarkers that may provide further understanding regarding the risk of development of diabetes-related complications.

This exploratory evaluation is optional and will only be performed in subjects who give informed consent for this specific component of the study.

9.8. Medical Resource Utilization

Subjects will be requested to collect information in a protocol-specified diary on information related to their utilization of medical resources (see below and Attachment 9). This MRU data from the subject diaries will then be documented in the CRF by the investigator and study research staff for all subjects at each visit throughout the study as well as during the posttreatment telephone follow-up contact at 28 days (and no later than 42 days) after the last dose of study drug (or optional study visits, at the discretion of the investigator). Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- number of medical outpatient encounters (including physician and emergency department visits) and main reason for each of the encounters
- number of hospitalizations and main reason for each of the hospitalizations

No cost data will be collected in this study.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

A subject will be considered to have completed the study if he or she has experienced a clinical endpoint that precludes further study (eg, early mortality due to CV event) or when the study ends. Subjects who prematurely discontinue study treatment for any reason before completion of the double-blind treatment phase will not be considered to have completed the study.

10.2. Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up

- Withdrawal of consent (subjects who withdraw from the study should be appropriately treated for T2DM by their primary care physician)
- Subject is persistently in poor compliance with study treatment or procedures

Discontinuation of study treatment

A subject's study treatment will be discontinued if:

- The investigator believes that for safety reasons (eg, adverse event) it is in the best interest of the subject to stop treatment
- The subject becomes pregnant (study therapy should be immediately discontinued based upon a positive urinary hCG, and permanently discontinued if confirmed by a serum β-hCG test)
- The subject's eGFR is <15 mL/min/1.73m^2 (as reported by the central laboratory).

  Note: the central laboratory will alert the investigator for eGFR values <15 mL/min/1.73m^2. A repeat determination should be performed within 2 weeks, and study treatment discontinued if the repeat eGFR is <15 mL/min/1.73m^2 (unless a reversible cause is identified [eg, short-term illness or transient volume depletion] in which case an additional repeat determination can be performed after resolution of the short-term illness).
- Subject requires dialysis or renal transplantation
- Subject has liver function test abnormalities meeting criteria for permanent discontinuation of study drug as outlined in Attachment 7
- Subject's double-blind study medication is unblinded
- Subject initiates disallowed therapy (refer to Section 8, Prestudy and Concomitant Therapy)

If a subject discontinues treatment before the end of the double-blind treatment phase, end-of-treatment and follow-up assessments should be obtained. The end-of-treatment evaluations should be performed as soon as possible after stopping the study drug, and subjects should have a follow-up telephone contact (or optional study visit, at the discretion of the investigator) approximately 28 days (but no more than 42 days) after the last dose of study drug to: (1) evaluate adverse events; (2) events in the primary composite CV endpoint (CV death, nonfatal MI, nonfatal stroke, or hospitalized unstable angina); (3) concomitant therapy use; and (4) self-reported MRU data since the last visit.

All subjects who are discontinued by the investigator, or who elect to discontinue treatment before the completion of the study, will continue to be followed (ie, contacted approximately every 6 months) until the study completes in order to document any events in the CV composite endpoints (including CV death, nonfatal MI, nonfatal stroke, and hospitalized unstable angina) and adverse events of fracture.

If a subject is lost to follow-up, **all possible efforts must be made by the study site personnel to contact the subject and to determine endpoint status and the reason for discontinuation/withdrawal.** The measures taken to follow-up must be documented. The informed consent form will stipulate that even if a subject decides to discontinue participation in the study, he/she will agree to be contacted periodically, eg, every 6 months, by the investigator to assess his/her endpoint status. Furthermore, the subject will be asked to agree to grant permission for the investigator to consult family members or public records, including the use of locator agencies as permitted by local law, to determine the subject's endpoint status, in the event the subject is not reachable by conventional means (eg, office visit, telephone, e-mail, or certified mail).

Subjects who decide to withdraw from the study must be interviewed by the investigator so as to determine if a specific reason for withdrawal can be identified. If the subject elects to withdraw due to an adverse event, the event should be recorded as the reason for withdrawal, even if the investigator's assessment is that the adverse event would not require study drug withdrawal and discontinuation from the study.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source documentation. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

A subject who elects to withdraw consent for the biomarker specimen collections will not have further collections made after withdrawing consent, and has the following options:

- to allow the previously collected specimens to remain for biomarker analysis, or
- to request that the previously collected specimens be destroyed.

A subject who withdraws from the main part of the study will have the following options regarding pharmacogenomic research:

- The DNA extracted from the subject's blood will be retained and used in accordance with the subject's original pharmacogenomic informed consent.
- The subject may withdraw consent for pharmacogenomic research, in which case the DNA sample will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor site contact to request sample destruction. The sponsor site contact will, in turn, contact the pharmacogenomics representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the sample has been destroyed.

Withdrawal from Pharmacogenomic Research Only

The subject may withdraw consent for pharmacogenomic research while remaining in the clinical study. In such a case, any DNA extracted from the subject's blood will be destroyed. The sample destruction process will proceed as described above. However, all samples will be made nonidentifiable after the Clinical Study Report is issued and thereafter cannot be identified for destruction. If the sample has already undergone conversion to the nonidentifiable format, the sponsor will notify the investigator in writing.

11. STATISTICAL METHODS

11.1. Analysis Sets

The intent-to-treat (ITT) analysis set includes all subjects who are randomly assigned to a treatment group. The modified intent-to-treat (mITT) analysis set is a subset of the ITT set, consisting of subjects who received at least 1 dose of study medication. The primary CV analysis will be based on the time to the first occurrence of any component of the CV composite endpoint observed during the treatment or within 28 days post the last dose of study medication in the mITT set.

CV endpoint events that occur more than 28 days after the last dose of blinded study medication will not be included in the primary CV analysis, but will be used for sensitivity analyses (as described below). Efficacy data and CV outcome data will be analyzed according to the randomization assignment, regardless of actual treatment received.

The secondary efficacy analyses will be performed in the mITT analysis set.

11.2. Handling of Dose in Analysis

The primary comparison, to assess CV risk reduction, will be between canagliflozin (100 mg and 300 mg dose groups combined) versus placebo. Additionally, the HR and its 2-sided 95% CIs versus placebo will be assessed for each dose of canagliflozin. For demonstration of CV benefit, to address the study's primary hypothesis, if a dose is deselected (refer to Section 6.1, Study Drugs), the primary comparison will assess events in subjects randomized to the canagliflozin dose group continuing in the study versus subjects randomized to placebo. For analysis for CV safety (ie, to show no unacceptable increase in CV risk), events in subjects from both dose groups will be included (including events in subjects that occur after a subject undergoes a dose switch from a deselected dose).

11.3. Sample Size Determination

11.3.1. Cohort A

The sample size for Cohort A of approximately 4,500 subjects is based upon a sufficient number to support, in concert with the other controlled clinical trials in the canagliflozin development program, a detailed assessment of the safety and tolerability of canagliflozin as well as to support the planned meta-analysis to demonstrate that the upper bound of the 2-sided 95% CI of the HR of canagliflozin relative to control in composite endpoint events (MACE and hospitalized unstable angina) is <1.8.

To exclude an upper bound of 1.8, the first planned meta-analysis will be performed when at least 104 CV safety composite events have occurred in the canagliflozin clinical development program. The occurrence of 104 such events will provide 80% power (assuming a true HR of 1.0). It is expected that approximately 40 events will be observed in the other large, well-controlled, double-blind, randomized studies that will be included in the meta-analysis. Assuming a per annum event rate of 2.25% and a per annum dropout rate of 5% with 4,500 subjects randomized to the 3 treatment groups will have 64 events from this study in about 2 years.

In addition, this sample size should provide a reasonable amount of information at the planned interim analysis for sample size re-estimation. This analysis will include effect of canagliflozin on CV risk factors (ie, fasting lipids, blood pressure, HbA_{1c}) and the observed HR for CV risk (for MACE). See Section 11.3.2, Cohort B, below for details

11.3.2. Cohort B

An interim analysis of CANVAS will be conducted around the time of the approval of canagliflozin in the US.

Results from the interim analysis will (1) provide a *predicted* effect of canagliflozin on risk for CV events (ie, the HR) based upon the effect of canagliflozin on established CV risk factors (eg, blood pressure, fasting lipids, HbA_{1c}); and (2) determine the *observed* HR for MACE in the initial study cohort. These 2 components will be used by the IDMC to determine an *expected* effect of canagliflozin on CV risk based upon specific guidance provided in the IDMC charter. Cohort B will be initiated if the expected CV risk reduction (canagliflozin relative to placebo) is at least 15% (ie, expected HR ≤0.85, and the observed HR is not >0.95), *and* the CV risk reduction can be demonstrated (with 90% conditional power) with recruitment of no more than 14,000 additional subjects (Cohort B) and within a planned duration of double-blind treatment phase of approximately 4 years.

If Cohort B is recruited, a minimum of 1,500 additional subjects per treatment group (ie, 3,000 subjects if one canagliflozin dose and 4,500 subjects if 2 canagliflozin doses are studied) and no more than 14,000 additional subjects will be randomized. The guidance to determine the conditional power, the target number of CV events, and the sample size for Cohort B will be determined as a function of the observed and predicted HR and will be detailed in the IDMC charter, with the final determination as to the initiation of Cohort B recruitment made by the Study Executive Committee.

11.4. Safety Analyses

The safety analysis will be based on the mITT analysis set. There will be no imputation for missing values for clinical laboratory test results, ECG evaluations, vital sign measurements, and physical examination results in the analyses.

The co-primary study hypothesis, that canagliflozin is well tolerated, will be assessed based upon a review of the incidence of overall and specific adverse events, discontinuations due to adverse events, laboratory results, and other safety and tolerability measurements.

Adverse Events

The original terms used in the CRFs by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the treatment phase (ie, treatment-emergent adverse events) will be included in the analysis. For each adverse event, the percentage of subjects who experienced at least 1 occurrence of the given event will be summarized by treatment group. An adverse event will be considered to be a treatment-emergent event if it occurs within 28 days of the last date of blinded study medication. The percentage of subjects with specific treatment-emergent adverse events will be summarized by severity and relationship to study drug, as classified by the investigators, for each treatment group.

Special attention will be given to those subjects who died, or who discontinued treatment due to an adverse event, or who experienced a severe or a serious adverse event (eg, summaries, listings, and narrative preparation may be provided, as appropriate).

Hypoglycemic events will be classified as severe (requires assistance of a third party), documented symptomatic (symptoms of hypoglycemia with a SMBG of ≤70 mg/dL), probable symptomatic (symptoms of hypoglycemia without a SMBG measurement) and asymptomatic (SMBG of ≤70 mg/dL without symptoms)(ADA 2007; Attachment 2). For each type of hypoglycemia, the percentage of subjects with at least 1 of the events will be summarized by treatment group. The differences in percentage (each dose group of

canagliflozin versus placebo) and their 2-sided 95% CIs will be estimated. The hypoglycemia rate, based on the number of episodes adjusted by exposure duration, will be reported by treatment group and for each classification of hypoglycemia.

Further analyses, to be described in the SAP for this study, will be conducted on the prespecified adverse events for which additional information is collected from the investigators (refer to Section 9.4, Safety Evaluations).

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges (specified in the SAP) and markedly abnormal results (based on criteria defined in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point, and for change from baseline.

The change from baseline in eGFR (using the Modification of Diet in Renal Disease [MDRD] equation, Levey 1999) and proportion of subjects with decline in eGFR of >25% and >50%, and eGFR <15 mL/min/1.73m^2 will be summarized.

Electrocardiogram (ECG)

The change from baseline values in each of the ECG parameters will be summarized with descriptive statistics at each postbaseline visit.

Vital Signs

Changes from baseline in vital sign measurements will be summarized as appropriate for each treatment group.

Physical Examination

Selected physical examination results will be summarized as appropriate for each treatment group.

11.5. CV Outcomes and Efficacy Analyses

11.5.1. CV Outcomes (Primary Efficacy Endpoint)

The primary endpoint for CV benefit (evaluated in the overall study population for canagliflozin dose groups combined versus placebo) will be time to MACE, which is calculated as the time from randomization to the first occurrence of MACE. The statistical hypothesis will be:

$H_{0(1.0)}$: The HR =1.0, versus $H_{1(1.0)}$: The HR ≠1.0.

The primary analysis will be based on the mITT analysis set and events that occur within 28 days following discontinuation if subjects discontinue treatment during the course of the study. The comparison of canagliflozin to placebo will be assessed via the HR estimate derived from Cox proportional hazards model with term for treatment, the factors for randomization stratification, history of a previous CV event, and cohort (enrollment in Cohort A or B).

The assumption of the proportional HR will be examined. In case the assumption is deemed not reasonable, sensitivity analyses that do not rely on the constant HR assumption will be conducted to verify the results of the primary analysis.

Additionally, the HR and its 2-sided 95% CIs versus placebo will be assessed for each dose of canagliflozin. For individual components of the composite CV endpoint, the HR and its 2-sided 95% CIs between combined canagliflozin dosage groups and placebo will also be assessed.

The effects of different baseline demographic variables (eg, age, race, sex) as well as other important baseline disease characteristics (eg, history of prior CV disease, key concomitant therapy use, region) on the primary endpoint will be explored; a detailed discussion of subgroup analyses will be provided in the SAP for this study which will be filed before the first interim analysis.

11.5.2. Secondary Efficacy Endpoints

The continuous secondary efficacy endpoints, changes from baseline in HOMA-B and the proinsulin/insulin ratio, HbA_{1c}, FPG, body weight, and blood pressure, and percent change in fasting lipids, will be analyzed using an analysis of covariance (ANCOVA) model with treatments and stratification factors as fixed effects and the corresponding baseline value as a covariate. These will be summarized by individual cohort (ie, Cohort A and Cohort B) and for the combined cohorts. The treatment difference (each dose of canagliflozin minus placebo) in the least-squares means and the 2-sided 95% CI will be estimated based on this model. The analyses for beta-cell function will be conducted on subjects not receiving insulin at randomization and, for subjects who are started on insulin during the study, the last data point before the initiation of insulin will be included for these analyses.

The categorical secondary efficacy endpoint is *proportion of subjects with progression of albuminuria* (defined as ≥1 step, ie, no albuminuria to micro- or macro-albuminuria or from micro-albuminuria to macro-albuminuria) or *regression from albuminuria* (defined as ≥1 step, ie, macro- to micro- or normo-albuminuria, or micro-albuminuria to

normo-albuminuria) at the end of the treatment period. Albuminuria will be assessed according to the categorizations defined in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Guideline #1 (KDOQI 2007): the definition of micro-albuminuria is albumin/creatinine ratio of 30 to 300 mg/g, and the definition of macro-albuminuria is albumin/creatinine ratio greater than 300 mg/g. The proportion of subjects with progression to albuminuria will be analyzed using the Cochran-Mantel-Haenszel (CMH) test with treatment group as factors, adjusting for randomization strata. A similar analysis will be conducted for subjects with regression from albuminuria.

For the secondary endpoints of proportion of subjects with progression of albuminuria and for HOMA-B, the analyses will compare the dose groups, *combined* and *individually*, relative to placebo.

For the assessment of change from baseline in HbA_{1c} at Week 18, subgroup analyses (described in detail in the SAP for this study) will be conducted to enhance understanding of factors that might impact glycemic response to canagliflozin.

11.6. Medical Resource Utilization Analyses

Medical Resource Utilization data analyses will be descriptively summarized by primary outcome variable (ie, those with a CV event versus those without) regardless of treatment group. These data may be used in future economic modeling to be done outside of the protocol.

11.7. Interim Analysis

A sequence of 3 analyses may be conducted during the conduct of the CANVAS study.

- *The first analysis* is a meta-analysis (described in a separate SAP) of data from CANVAS and other large, well-controlled, double-blind, randomized studies of canagliflozin, and is intended to support CV safety of canagliflozin (to show no unacceptable increase in CV risk) showing that the upper bound of the 95% confidence interval around the HR is <1.8, in support of initial regulatory submission.
- *The second analyses* will focus on CANVAS only, and is intended to determine if CV benefit is expected (considered to be at least 15% CV risk reduction), and if it is feasible to demonstrate CV risk reduction based upon maximum of 14,000 additional subjects with approximately 4 years of follow-up, and then to determine the sample size for Cohort B (refer to Section 11.3.2, Cohort B).
- *The third analysis* (described in a separate SAP) is to evaluate the hypothesis (for the meta-analysis, stated in the SAP) that there is no unacceptable increase in CV risk with canagliflozin relative to control treatments (with an upper bound of the confidence interval around the HR of <1.3).

- If Cohort B is recruited, this meta-analysis would be conducted at the *completion* of the CANVAS study.
- If Cohort B is not recruited, this meta-analysis would be conducted including subjects from Cohort A only, as described in Section 11.7.3, Meta-analysis Post-regulatory Approval.

These 3 sequential steps are outlined in the sections below.

11.7.1. Meta-Analysis Pre-Regulatory Approval

To support submissions for marketing approval, the CV event data and other safety and efficacy results in this study will be extracted and integrated with the data from other large, well-controlled, double-blind, randomized studies in the canagliflozin clinical development program. A meta-analysis of the integrated CV data will be conducted to compare canagliflozin with active or placebo control and to exclude the upper bound of the 95% CI around the HR of 1.8.

It is projected that the first data extraction and the substudy analyses for regulatory submissions would be conducted when about 104 composite events of MACE (CV death, nonfatal MI, nonfatal stroke) and hospitalized unstable angina are observed across the canagliflozin clinical development program (including CANVAS).

The sponsor will be unblinded to the data during the submission of data from these analyses; however, blinding to the subject's treatment allocation will be maintained for the subjects, investigators, Endpoint Adjudication Committee, and sponsor site monitoring personnel throughout the study.

11.7.2. Interim Analysis to Determine Whether Cohort B Will be Recruited in CANVAS

An interim analysis of CANVAS will be performed around the time of FDA approval of canagliflozin. *This interim analysis will be conducted before the meta-analysis discussed in Section 11.7.3, Meta-Analysis Post-Regulatory Approval.* The objective of the interim analysis, as discussed in Section 11.3.2, Cohort B, is to determine the appropriate sample size for Cohort B to evaluate the study's primary hypothesis of reduction in CV risk with canagliflozin treatment.

Results from the interim analysis will (1) provide a *predicted* effect of canagliflozin on risk for CV events (ie, the HR) based upon the effect of canagliflozin on established CV risk factors (eg, blood pressure, fasting lipids, HbA_{1c}); and (2) determine the *observed* HR for MACE in the initial study cohort. These 2 components will be used by the IDMC to determine an *expected* effect of canagliflozin on CV risk (ie, HR), based upon specific

guidance provided in the IDMC charter. Cohort B will be initiated if the expected CV risk reduction is at least 15% (ie, expected HR ≤0.85) and the observed HR is not >0.95, and the CV risk reduction can be demonstrated (with 90% study power) with recruitment of no more than 14,000 additional subjects (Cohort B) and with a minimum follow-up period of approximately 4 years for all subjects.

If these criteria are met, the IDMC will recommend to the Executive Committee to recruit Cohort B (unless CV risk reduction can be established with results from study Cohort A alone). Provisions for adaptation of the study, including the target number of MACE events and the size of the additional enrollment in Cohort B, are in the next section, with more details in the IDMC charter and the SAP. If Cohort B is recruited, the minimum number of 1,500 subjects per studied dose group and no more than 14,000 additional subjects will be randomized into Cohort B.

If the interim analysis to assess adaptation demonstrates CV benefit (ie, alpha level 0.001 as specified in Section 11.7.4, Adaptation Plan), *the primary hypothesis will be considered as proven and the study will be concluded*.

11.7.3. Meta-Analysis Post-Regulatory Approval

11.7.3.1. Objectives and Hypothesis for Meta-Analysis

Results from the present study will be combined in a *prespecified pooled analysis* of large, well-controlled, double-blind, randomized studies of canagliflozin (including CANVAS) to assess the following:

In subjects with T2DM, with inadequate glycemic control:

Objective

To assess CV risk with canagliflozin relative to control (placebo or active comparator), as measured by the HR for a composite endpoint (including CV death, nonfatal MI, nonfatal stroke, and hospitalized unstable angina)

Hypothesis

The following hypothesis on the HR (canagliflozin versus control) corresponding to the analysis objective on CV safety will be tested.

$H_{0(1.3)}$: The hazard ratio ≥1.3, versus $H_{1(1.3)}$: The hazard ratio <1.3.

The null hypothesis $H_{0(1.3)}$ is 1-sided and will be tested at significant level 0.025. Operationally, it will be tested using the 2-sided confidence interval approach. $H_{0(1.3)}$ will be rejected if the upper bound of the 2-sided CI is <1.3 at the appropriate alpha level to controlled the 2-sided error rate at 0.05.

11.7.3.2. Timing of Meta-Analysis Post-Regulatory Approval

If a decision by the Executive Committee is made to recruit Cohort B based upon information provided from the IDMC, the CV meta-analysis will be conducted at the *completion* of CANVAS. No other interim analysis of CANVAS, except in support of ongoing IDMC monitoring of safety for the study or as necessary to support regulatory requests for safety information (which would be implemented with careful attention to avoiding unblinding outside the IDMC) will be conducted.

If Cohort B of this study is not recruited, up to an additional **3** planned meta-analyses integrating data from across the canagliflozin clinical development program will be performed to evaluate CV safety and to demonstrate that the upper bound of the confidence interval around the HR is <1.3 (to meet regulatory requirements). This analysis will address the hypothesis of noninferiority (canagliflozin relative to control) for CV event rates (in the composite endpoint of MACE and unstable angina). These analyses are intended to meet FDA regulatory requirements and will be conducted based upon timing related to number of CV events in the pooled population, as described below:

- The first meta-analysis will be performed around the time of FDA approval of canagliflozin (with an estimated approximate of 260 events in the safety composite endpoint in the meta-analysis). If this analysis establishes the hypothesis that canagliflozin is noninferior to placebo and active controls for CV safety (ie, the upper bound of the 2-sided 99.9% confidence interval around the between-group difference is <1.3), then no further testing of the hypothesis will be required.
- If the hypothesis is not established at the initial interim analysis, the next meta-analysis will occur when approximately 490 composite events in the predefined CV safety endpoint (MACE and hospitalized unstable angina) are observed across the entire canagliflozin clinical development program.
- If the hypothesis is not established in this analysis, a final analysis will be conducted when approximately 700 events in the composite endpoint have occurred.

For multiple evaluations of the hypothesis of noninferiority, strict control of alpha will be implemented using O'Brien-Fleming boundary: the alpha levels at these 3 analyses are 0.001, 0.014, and 0.045, corresponding to 2-sided 99.9%, 98.6% and 96.5% CIs, respectively. Note that if Cohort B is not recruited because the Executive Committee,

based upon the recommendation from the IDMC, determines that CV benefit can be demonstrated based upon events in Cohort A only, then the meta-analysis will be conducted at the completion of the study.

11.7.4. Adaptation Plan

The adaptation plan for event number re-estimation proposed here is based on conditional power consideration and the final-stage critical value will be adjusted to preserve the overall Type I error rate. This statistical approach was first published by Li, et al (2002) and its application to survival data was presented in Li, Shih, and Wang (2005). Let *HR* be the HR of canagliflozin versus placebo. The one-sided hypothesis is: $H_{0(1.0)}$: HR=1 versus $H_{1(1.0)}$: $HR \neq 1$.

Assume equal allocation of subjects to the control and active groups. At first interim analysis (stage 1), let d_1 be the number of events observed and Z_1 be the corresponding log-rank test statistic. Then the observed *HR* is $\widetilde{HR}_1 = \exp(-2Z_1/\sqrt{d_1})$. A *predicted* HR is calculated from a model on established CV risk factors (eg, blood pressure, fasting lipids, HbA_{1c}). These *observed* and *predicted HR*s will be used by the IDMC to determine an *expected* HR. There will be 3 possible decisions based on the interim data:

1) Claim significance if the test of $H_{0(1.0)}$ is rejected using Z_1 at level 0.001 (2-sided)

2) Conclude futility if the expected HR >0.85

3) Extend the study, if not cases 1 and 2. Calculate the additional number of events, d_2, required for stage 2 to ensure enough conditional power for the study.

If Case 3 occurs, the second stage event number d_2 is targeted at conditional power of 90% for the study assuming the expected HR is true. The additional MACE event number d_2 is to be determined.

The final test will use a critical value c that is calculated at α=0.049. The critical value calculation does not account for the futility. Therefore, the final test is conservative and over-controls the Type I error rate.

11.8. Glycemic Efficacy Substudies

11.8.1. Analysis Sets

The mITT analysis set includes all subjects who are randomly assigned to a treatment group and received at least 1 dose of study medication. The per-protocol (PP) analysis set will consist of all mITT subjects who completed all 18 weeks of treatment, and have no major protocol violations (to be defined in the SAP before database lock and unblinding

of the treatment groups) and have not received glycemic rescue therapy. The primary efficacy analysis will be based on the mITT set. The efficacy data measured after the initiation of rescue therapy will be treated as missing. Analysis based on the PP set will also be conducted as a sensitivity analysis.

Efficacy data will be analyzed according to the randomization assignment, regardless of actual treatment received. Safety data will be analyzed according to actual treatment received. The approaches to handle study treatment deviations will be detailed in the SAP.

11.8.2. Sample Size Determination

The primary objective of this study is to compare the HbA_{1c}-lowering efficacy of canagliflozin with placebo after 18 weeks of treatment.

Assuming a group difference of 0.55% and a common standard deviation of 1.0% with respect to change in HbA_{1c}, and using a 2-sample, 2-sided t-test with Type I error rate of 0.05, it is estimated that 165 randomized subjects (55 subjects in each of the 3 treatment groups) would provide 80% power.

11.8.3. Efficacy Analyses

For each substudy, the primary efficacy analysis will only be performed when sufficient subjects (≥55) in the subpopulation are randomized in each of the 3 treatment groups. The analysis will be conducted when the sponsor prepares for the regulatory submissions.

The primary efficacy endpoint will be the change in HbA_{1c} from baseline through Week 18. The last-observation-carried-forward (LOCF) method will be applied when the Week 18 values are missing. In subjects receiving rescue therapy, their measurements made before rescue will be used as the last observation. An ANCOVA model with treatment as a fixed effect and its corresponding baseline value as covariate will be used. The treatment difference (each dose of canagliflozin minus placebo) in the least-squares means and the 2-sided 95% confidence interval (CI) will be estimated based on this model.

As a supportive analysis, change from baseline in HbA_{1c} will be analyzed using a restricted maximum likelihood (REML) based on repeated measures approach. The analysis will be based on observed data and will include the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. An unstructured covariance will be used to model the within-subject errors. The treatment comparisons will be made

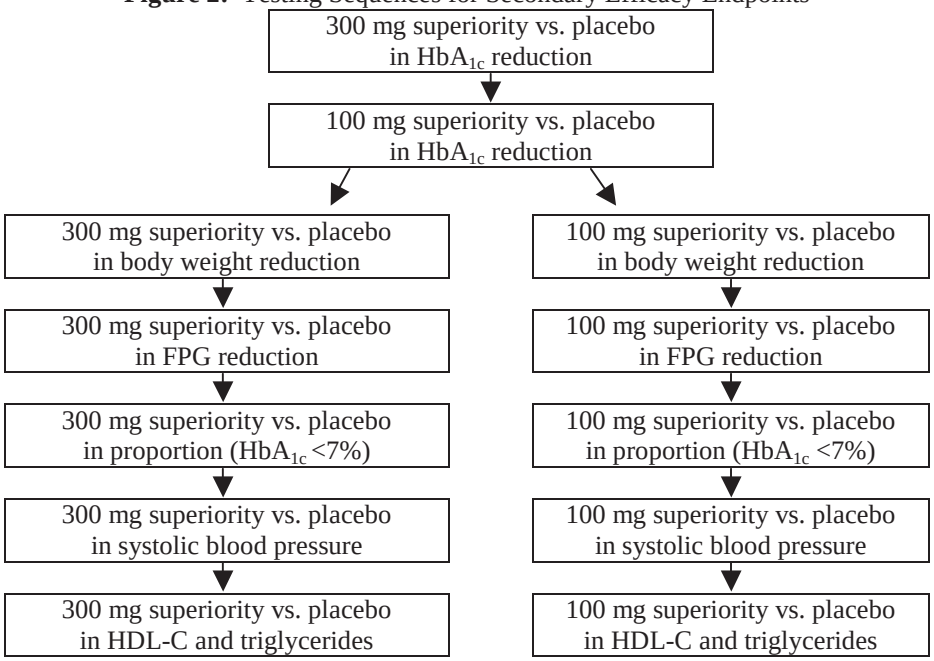
between each dose of canagliflozin and placebo at Week 18 and significance tests will be based on the difference of the least-squares means.

The secondary efficacy evaluations of change in body weight, FPG, systolic and diastolic blood pressure, and fasting plasma lipids will be analyzed using an ANCOVA model similar to that used in the primary efficacy analysis. The percentage of subjects with HbA_{1c} <7% at Week 18 will be assessed by means of a logistic model with treatments, stratification factor, and baseline HbA_{1c} as covariate.

11.8.4. Multiplicity Adjustment

To ensure the family-wise Type I error rate (alpha level) in each substudy is at most 5%, a gatekeeping procedure will be applied in testing the hypotheses in the substudy. The superiority over placebo in HbA_{1c} reduction will be tested sequentially for the descending doses of canagliflozin. After the superiority of the 2 doses on HbA_{1c} is concluded, the hypothesis of the secondary endpoints will be tested via 2 testing sequences as illustrated in Figure 2. The alpha level will be split evenly for the 2 sequences.

Figure 2: Testing Sequences for Secondary Efficacy Endpoints



Testing in each sequence stops as soon as any hypothesis in the sequence is failed to be rejected. The Hochberg procedure will be applied for the 2 lipid parameters at the end of the testing sequence. Note that the alpha level in the main study and the alpha level in each substudy are separately controlled.

11.8.5. Safety Analyses

The safety analysis for the substudies will follow the methodology as outlined in Section 11.4, Safety Analyses.

11.9. Pharmacogenomic Analyses

Allele and genotype frequencies for analyzed genes will be tabulated. Selected baseline measurements and efficacy endpoints will be assessed after stratifying for analyzed genes. Statistical evaluation of genotyping data will be reported separately from the Clinical Study Report.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures (SOPs) in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

All deaths and events that are assessed by the investigator as being one of the components of the CV composite endpoints* (ie, CV deaths, nonfatal MI, nonfatal stroke, or hospitalized unstable angina) should be handled as follows:

- Events in the CV composite endpoints will be captured on a CRF page specifically designed to record endpoint events.
- Because these events in the CV composite endpoint are not unexpected in this high CV risk population (and are considered part of the natural history of the disease), these events, *with the exception of CV deaths,* will *not* be reported (or recorded) as adverse events (ie, not recorded in the adverse event or serious adverse event CRF page).
- All deaths, including CV deaths, will be reported as serious adverse events, and submitted for adjudication to the Endpoint Adjudication Committee. These events will be subject to expedited reporting, *but will not be subject to unblinding* (unless it is determined by the Adjudication Committee that the death was non-CV related).
- Events that are *initially* reported by the investigator as a study endpoint event, but which are determined by the Endpoint Adjudication Committee as *not* meeting the definition of a study endpoint, will be reported as an adverse event or a serious adverse event upon the sponsor's receipt of this determination by the Endpoint Adjudication Committee (with the reporting timeline starting from the time of notification by the Adjudication Committee). Such serious adverse events will be handled as per serious adverse event reporting guidelines, after the sponsor is notified. The sponsor will notify the investigator to immediately report the event as a serious adverse event.

- Nonfatal CV events in the composite endpoint that are initially classified as a serious adverse event, but which are subsequently determined by the Endpoint Adjudication Committee as meeting the definition of a study endpoint should be recorded as such on the specific endpoint CRF page, and should be removed from the database as an adverse event or serious adverse event and clear documentation of the change in event status should be provided in the source documents.

Deaths or events with an outcome of death will be reported as outcome events if within the composite (ie, if considered a CV death) and the cause of death will also be reported as a serious adverse event (and hence managed per serious adverse event reporting guidelines).

For selected, specific adverse events, investigators will be asked to provide additional information so as to support more detailed analyses. These include vulvovaginal adverse events, adverse events of urinary tract infection, adverse events of fracture, skin adverse events, events of increased ALT (≥3-fold the ULN), and hypoglycemia (refer to section below). Additional information will also be requested from investigators to support a detailed assessment of events of venous thromboembolism/pulmonary embolism, hospitalized congestive heart failure, and all deaths (including information and documents to support adjudication of these events). Investigators may also be asked to provide additional information on other adverse events, based upon review by the MSRC or the study IDMC (refer to Sections 9.3.3, Medical Safety Review Committee, and 9.3.5, Independent Data Monitoring Committee). Refer to Section 3.2, Study Design Rationale, for review of rationale for collection of additional information on these selected adverse events.

*Note that in the for the study primary hypothesis of CV benefit, the CV composite endpoint includes MACE (CV death, nonfatal MI, nonfatal stroke); the composite endpoint to assess CV safety (as part of a meta-analysis of events from pooled large, well-controlled, randomized studies including CANVAS to assess CV safety) includes MACE plus hospitalized unstable angina (refer to Section 3.2, Study Design Rationale).

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or

non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the informed consent form (refer to Section 12.2.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

See above for handling of components of the composite CV endpoint other than CV deaths.

A serious adverse event as defined by ICH is any untoward medical occurrence that at any dose meets any of the following conditions:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above (eg, suspected transmission of an infectious agent by a medicinal product is considered a serious adverse event). Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

As described in the section above, nonfatal events in the CV composite endpoint (nonfatal MI, nonfatal stroke, and hospitalized unstable angina) will not be considered or reported as adverse events, but collected as study endpoints, subjected to adjudication, and only reported as adverse events if the Endpoint Adjudication Committee determines that the event does not meet the prespecified criteria for an endpoint event.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An unlisted adverse event, the nature or severity of which is not consistent with the applicable product reference safety information. For an investigational product, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2, Attribution Definitions, below.

12.1.2. Attribution Definitions

Not related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the intensity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Procedures

12.2.1. All Adverse Events

All adverse events, whether serious or nonserious, will be reported from the time a signed and dated informed consent form is obtained until completion of the last study-related procedure (may include contact for follow-up of safety).

Data will be collected in source documents and on the CRF for all adverse events. *Following recruitment of Cohort B, data will be collected on the CRF for all serious adverse events, nonserious adverse events that result in study drug discontinuation, and other selected adverse events (refer to Section 9.4, Safety Evaluations).* Information for all adverse events will be collected in source documents (eg, progress notes) retained at the investigative sites. Information will also be collected on the CRF for any adverse event that occurs within 28 days before a subject's discontinuation from the study for any reason. Serious adverse events, including those spontaneously reported to the investigator within 28 days (with the exception of those components of the clinical primary composite endpoints) after the last follow-up contact, must be reported using a Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All adverse events, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator all serious adverse events that are unlisted (unexpected) and associated with the use of the drug. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

Subjects (or their designees, if appropriate) must be provided with a "study card" indicating the name of the investigational study drug, the study number, the investigator's name, a 24-hour emergency contact number, and, if applicable, excluded concomitant therapies.

12.2.2. Serious Adverse Events

All serious adverse events occurring during clinical studies must be reported to the appropriate sponsor contact person by investigational staff within 24 hours of their knowledge of the event. For purposes of reporting serious adverse events for this study, the components of the clinical primary composite endpoints (with the exception of CV death, which, as with all deaths, will be reported as a serious adverse event) will not be considered adverse events or serious adverse events and will not be considered as unexpected but as disease related, and as such will not be unblinded. These events will be captured on the CRF as endpoint events only and will not be unblinded or subject to expedited reporting.

Events that are adjudicated as non-endpoints by the Endpoint Adjudication Committee will be subject to standard reporting requirements, but the reporting time limit will start when the sponsor learns that the event is not an endpoint as per the Endpoint Adjudication Committee.

Information regarding serious adverse events will be transmitted to the sponsor using a Serious Adverse Event Form (printout of the CRF), which must be completed and signed by a member of the investigational staff, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax) and accompanied by a completed fax cover sheet.

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The cause of death of a subject in a clinical study, whether or not the event is expected or associated with the investigational agent, is considered a serious adverse event. Suspected transmission of an infectious agent by a medicinal product should be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical study must be reported as a serious adverse event, except hospitalizations for the following:

- Related to a component of the clinical primary composite endpoints
- Social reasons in absence of an adverse event
- Surgery or procedure planned before entry into the study (must be documented in the CRF)

12.2.3. Pregnancy

All initial reports of pregnancy must be reported to the sponsor by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.2.4. Hypoglycemia

Hypoglycemic events will be classified as severe (requires assistance of a third party), documented symptomatic (symptoms of hypoglycemia with a SMBG of ≤70 mg/dL), probable symptomatic (symptoms of hypoglycemia without a SMBG measurement) and asymptomatic (SMBG of ≤70 mg/dL without symptoms) (ADA 2007; Attachment 2).

Hypoglycemia, which does not meet the criteria to be classified as a serious adverse event is to be documented only on the Hypoglycemia CRF page, and should not be captured on the Adverse Event CRF page. Refer to Section 12.1.1, Adverse Event Definitions and Classifications, which defines the qualifications for an event to be defined as "serious". If a hypoglycemic episode meets the criteria used to define a serious adverse event, the event must be captured on the Serious Adverse Event CRF pages.

12.3. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability of a product, including its labeling or package integrity. PQCs may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the investigational staff as soon as possible after being made aware of the event.

If the defect is combined with a serious adverse event, the investigational staff must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.2.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

Canagliflozin will be supplied for this study as over encapsulated 100- or 300-mg tablets in a gray-colored, hard, gelatin capsule. The over encapsulated tablet will be backfilled with microcrystalline cellulose to prevent the tablet from rattling in the capsule shell.

Matching placebo capsules will consist of microcrystalline cellulose within a gray-colored, hard, gelatin capsule.

14.2. Packaging

The study drug will be packaged as in individual blister cards. The study drug will be packaged according to good manufacturing practices and local regulations. The study supplies will be packaged according to the randomization code and each blister card will be labeled with a medication ID number.

All study drug will be dispensed in child-resistant packaging.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

All study drug must be stored at controlled temperatures ranging from 20°C to 25°C (68°F to 77°F) and kept out of reach of children. Where applicable, excursions from 15°C to 30°C (59°F to 86°F) are allowed.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject, must be documented on the drug accountability form. Subjects, or their legally-acceptable representative where applicable, must be instructed to return all original containers, whether empty or containing study drug. Study drug returned by study subjects will be stored and disposed of according to the sponsor's instructions. Site staff must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label and will be stored in a limited access area or in a locked cabinet under appropriate environmental conditions. Unused study drug and partially used study drug returned by the subject (if applicable), must be available for verification by the sponsor's or sponsor-delegated site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or partially used study drug returned for destruction, will be documented on the Drug Return Form. When the site is an authorized destruction unit and study drug supplies are destroyed on site, this must also be documented on the Drug Return Form.

Study drug should be dispensed under the supervision of the investigator, a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Recruitment and retention tools
- IVRS manual and worksheets
- CRF completion guidelines
- Study binder with all other necessary documentation (eg, protocol, IB, clinical trial agreement)
- Manual of instructions regarding endpoints, endpoint documentation required, and adjudication-related procedures
- Home blood glucose monitoring system, glucose strips, lancets, and calibration solution
- Diary card
- Materials to support diet and exercise counseling
- Standardized ECG recording device and instruction manual
- Laboratory manual, requisition forms, sampling supplies, and equipment, if necessary
- Computer, if the study site is assessed to require a laptop computer to enter electronic CRF data for the study

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

The primary ethical concerns of this study are that the safety profile of canagliflozin has not been fully established so that subjects may be placing themselves at an increased risk of unexpected adverse events by participating in this study, and that subjects with T2DM who have not achieved optimal glycemic control at study entry could fail to achieve optimal glycemic control for a prolonged period. In this study, there is no requirement to discontinue prestudy medications. The investigator is asked not to change the antihyperglycemic regimen during the first 18 weeks of the study, but rescue criteria are specified. The potential risks that are apparent in the present study include exposure to study drug, with the potential for side effects and the inherent risks associated with venipuncture and multiple blood sample collections. The study has been designed to mitigate these inherent risk factors.

Based on data from clinical studies with canagliflozin and the theoretical possibilities associated with SGLT2 and intestinal SGLT1 inhibition, potential human adverse effects may occur, including osmotic diuresis due to increased UGE, alterations in serum or urine electrolytes, gastrointestinal intolerability, hypoglycemia, changes in bone formation and/or bone resorption and in the hormones controlling calcium homeostasis,

abnormalities in renal function, photosensitivity, or vulvovaginal adverse events. Data from the Phase 1 studies as well as from Phase 2b studies involving over 700 subjects indicates that canagliflozin is generally well tolerated and serious adverse events are uncommon.

As described in Section 1.1.2, Clinical Studies, women subjects may be at an increased risk for vulvovaginal adverse events. In addition, until the clinical relevance of the observed immediate photoresponse is understood, subjects in this study will be advised to use photoprotective measures (eg, topical sunscreen) to avoid excessive sunlight and artificial tanning light. Also, because of the modest magnitude of the observed increase of serum collagen type 1 carboxy telopeptide levels and the biologic variability associated with this marker as well as it not being associated with changes in other markers of bone turnover, the increase in serum collagen type 1 carboxy telopeptide levels is of uncertain significance; nonetheless, this will be monitored in Phase 3 studies by careful collection of information on any fractures and additional assessments in selected Phase 3 studies. Renal glomerular and tubular integrity were assessed using several biomarkers in Phase 2b studies. A urinary NAG increase noted could be secondary to increased flow in the proximal tubule or to glucosuria. Based on the preclinical, theoretical, and clinical experience to date, appropriate safety measures have been included to help in the selection of subjects as defined in the inclusion and exclusion criteria in Sections 4.2 and 4.3, respectively.

This study will provide scientific guidance on using canagliflozin in a T2DM subject population requiring improved glycemic control, and it should answer important questions about canagliflozin. Subjects will be randomly assigned to either canagliflozin 100 or 300 mg, both of which have shown glucose-lowering activity in Phase 1 and Phase 2b clinical studies, or placebo. The use of placebo as a comparator in this study does not represent an ethical compromise because subjects will be allowed to remain on a background of standard care for diabetes or to add other agents as the investigator considers necessary according to established treatment guidelines.

One of the objectives of this study is to demonstrate safety in subjects treated with the compound. Safety will be evaluated on a frequent and ongoing basis, and all adverse events will be treated according to standard medical practice. Hypoglycemia is considered to be a side effect of treatment in T2DM. It occurs most frequently with insulin therapy, but hypoglycemia can occur with the use of other agents as well. Because canagliflozin does not alter the regulation of glucose-dependent insulin secretion,

hypoglycemia is not intrinsic to the mechanism of action of canagliflozin and should not be a frequent occurrence in subjects treated with this agent.

Clinical and laboratory evaluations will be performed throughout the study (according to the Time and Events schedule that follows the Synopsis) to monitor the safety of subjects. HbA_{1c} will be measured approximately every 3 months. Subjects will be required to report episodes of hypoglycemia and encouraged to report any changes in their clinical condition to the investigator.

Subjects will be followed after discontinuing study drug and early withdrawal from the study by a follow-up contact to evaluate adverse events and concomitant therapy use, and to document CV events.

Subjects may receive direct benefit from treatment with canagliflozin by improving glycemic control, lowering body weight (in subjects who are often obese or overweight); other benefits such as improvements in beta-cell function and possibly a decrease in systolic blood pressure might be seen, but there is as yet limited data on these potential benefits.

The investigator will be provided with detailed information about the study to ensure that the study research staff is fully informed. The risks and requirements of the study will be fully explained to each potential subject.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

Subjects will sign an informed consent form before any study-related procedure is performed.

The maximum blood volume that would be collected if a subject were to continue in the study for 8 years would be approximately 875 mL. The maximum amount that would be collected at a single visit would be approximately 80 mL. These volumes are considered to be well within the normal range for this subject population over this time frame according to blood donation standards (Redcross.org).

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board (IEC/IRB)

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents:

- Final protocol and, if applicable, amendments
- sponsor-approved informed consent form (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments
- sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any), the informed consent form, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the pharmacogenomic research component of the clinical study and for the pharmacogenomic informed consent form must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of approval for pharmacogenomic research.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments
- Revision(s) to informed consent form and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's Brochure amendments or new edition(s)
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted, and associated with the investigational drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Annual Safety Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or trial conduct), the amendment and applicable informed consent form revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this clinical study. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data or trial conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the sponsor and by the reviewing IEC/IRB. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the investigational staff must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor staff without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the informed consent form the subject is authorizing such access, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, or to obtain information about his or her survival status.

The subject will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's personally dated signature. After having obtained the consent, a copy of the informed consent form must be given to the subject.

Subjects will be asked to consent to participate in a pharmacogenomic research component of the study where local regulations permit. After informed consent for the clinical study is appropriately obtained, the subject will be asked to sign and personally date a separate pharmacogenomic informed consent form indicating agreement to participate in optional pharmacogenomic research. A copy of the signed pharmacogenomic informed consent form will be given to the subject. Refusal to participate will not result in ineligibility for the clinical study.

If the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the informed consent form after the oral consent of the subject is obtained.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational study drug(s) used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator to allow direct access to his or her original medical records for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

For those subjects who gave consent to store DNA samples for future genetic research (Part 2), samples and corresponding relevant clinical data will be made nonidentifiable by the removal of personal identifiers. Samples will be stored until completely used. Only research related to the drug or the indications for which the drug is developed will be done on stored samples. For data generated on identifiable samples (Part 1), the sponsor will provide the individual raw data, through the investigator, to subjects who submit a written request. The sponsor cannot make decisions as to the significance of any findings resulting from this pharmacogenomic research, and cannot, therefore, provide genetic counseling. Genotypic data generated on nonidentifiable samples (Part 2) cannot be returned to individual subjects.

16.2.5. Country Selection

Unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations, this study will only be conducted in those countries where the intent is to help ensure access to the developed product.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor or its designee. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (refer to Contact Information pages provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the investigational site:

- Protocol and amendment(s), if any, signed and dated by the investigator

- A copy of the dated and signed written IEC/IRB approval of the protocol, amendments, informed consent form, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee.
- Name and address of the IEC/IRB including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the investigational staff is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Photocopy of the site signature log, describing delegation of roles and responsibilities at the start of the study
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by initials and assigned number only.

The investigator must also complete a subject-screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the CRF: subject identification, eligibility, and study identification; study discussion and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events; and follow-up of adverse events; concomitant therapy; drug receipt/dispensing/return records; study drug administration information; and date of study completion, and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

It is recommended that the author of an entry in the source documents be identifiable.

At a minimum, the type and level of detail of source data available for a study subject should be consistent with that commonly recorded at the site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study personnel from the source documents onto an electronic CRF, and transmitted in a secure manner to the sponsor within 3 days of the subject's visit. The electronic file will be considered to be the CRF. Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subjects' source documentation. All data relating to the study must be recorded in CRFs prepared by the sponsor. Data must be entered into CRFs in English. Designated site personnel must complete CRFs as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

The investigator must verify that all data entries in the CRFs are accurate and correct.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or an authorized member of the investigational staff must adjust the CRF (if applicable) and complete the query. A query is to be answered within 5 days of generation of the query.

If corrections to a CRF are needed after the initial entry into the CRF, this can be done in 3 different ways:

- Site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool)
- Site manager (SM) can generate a query (field data correction form [DCF]) for resolution by the investigational staff
- Clinical data manager (CDM) can generate a query for resolution by the investigational staff

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated personnel before the study, and periodic monitoring visits by the sponsor, and transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, preparation, and shipment of blood, plasma, and urine samples.

Guidelines for CRF completion will be provided and reviewed with study personnel before the start of the study.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory

requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator must permit access to such reports.

17.8. Monitoring

The sponsor and ARO designated by the sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study center visit log that will be kept at the site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and investigational staff and are accessible for verification by the sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents will be discussed with the investigational staff. The sponsor expects that, during monitoring visits, the relevant investigational staff will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed with the last visit/contact of the last subject participating in the study. The final data from the investigational site will be sent to the sponsor (or designee) after completion of the final subject visit/contact at that site, 3 days after the subject's visit/contact (query generation and resolution excluded).

17.9.2. Study Termination

The sponsor reserves the right to close the investigational site or terminate the study at any time for any reason at the sole discretion of the sponsor. Investigational sites will be closed upon study completion. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigational site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further drug development.

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Subject privacy must, however, be respected. The investigator and staff are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding canagliflozin or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the clinical study will be used by the sponsor in connection with the continued development of canagliflozin, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain CRF data from all investigational sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of pharmacogenomic analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of pharmacogenomic results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

The sponsor shall have the right to publish such data and information without approval from the investigator. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy

approaches, results may need to be published in a given sequence (eg, substudies) should not generally be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not publishing data derived from the individual site until the combined results from the completed study have been published in full, within 12 months after conclusion, abandonment, or termination of the study at all sites, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

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Attachment 1:
Sulfonylurea Monotherapy Doses for Stratification Purposes

Monotherapy consisting of one of the following:

- glipizide ≥20 mg/day
- glipizide extended release ≥10 mg/day
- glyburide/glibenclamide ≥10 mg/day
- glimepiride ≥4 mg/day
- gliclazide ≥160 mg/day
- gliclazide modified release ≥60 mg/day

Attachment 2:
Hypoglycemia: Definitions, Symptoms, and Treatment

Hypoglycemia is defined and classified as follows:

Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose (PG) concentration ≤70 mg/dL (3.9 mmol/L)

Asymptomatic hypoglycemia is defined as an event not accompanied by typical symptoms of hypoglycemia but with a measured PG concentration ≤70 mg/dL (3.9 mmol/L)

Probable symptomatic hypoglycemia is defined as an event during which symptoms of hypoglycemia are not accompanied by a PG determination.

Severe hypoglycemia is defined as an event requiring the assistance of another person to actively administer a carbohydrate, glucagon, or other resuscitative actions. A subject is considered to "require assistance" if he/she is unable to help himself/herself. An act of kindness to assist a subject when it is not necessary does not qualify as "requiring assistance". These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurologic recovery attributable to the restoration of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration.

The classification of a hypoglycemic event will determine how the event is captured in the CRF. Refer to Section 12.2.4, Hypoglycemia, for further details.

Symptoms

Subjects will receive information regarding the symptoms of and treatment for hypoglycemia. Signs and symptoms of hypoglycemia and other specific details will be captured in the subject diary, which will be returned to the study center for review by research study staff at each visit. The following list of symptoms is not meant to be exhaustive but represents the more common symptoms associated with hypoglycemia:

- Seizure
- Loss of consciousness
- Headache
- Tremor
- Hunger
- Sweating
- Nervousness
- Palpitations
- Light headedness
- Blurred vision
- Disorientation
- Dizziness
- Syncope

Treatment

The treatment of hypoglycemia requires the ingestion of glucose- or carbohydrate-containing foods. The acute glycemic response correlates better with the glucose content than with the carbohydrate content of the food. Therefore, glucose (15 to 20 g) is the preferred treatment for hypoglycemia. Although pure glucose may be the preferred treatment, any form of carbohydrate that contains glucose will raise blood glucose and may be used. Adding protein to a carbohydrate does not affect the glycemic response and does not prevent subsequent hypoglycemia. However, adding fat may retard and then prolong the acute hypoglycemic response. Treatment effects should be apparent within 15 minutes although the effects may only be temporary. Therefore, PG should be retested in approximately 15 minutes, as additional treatment may be necessary.

Attachment 3:
New York Heart Association Classification of Cardiac Disease

The following table represents the NYHA classification of cardiac disease:

Functional capacity	Objective assessment
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain	A. No objective evidence of cardiovascular disease
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain	B. Objective evidence of minimal cardiovascular disease
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	C. Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	D. Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

Attachment 4:
Archive Samples for Exploratory Research - Sample Collection and Handling

(Note: collection and processing directions for Biomarker Specimens will be provided in a separate laboratory manual)

Materials and Labeling

- The central laboratory will provide the study site with blood collection tubes, storage tubes, preprinted J&JPRD labels (or tubes labeled with preprinted labels), and related supplies for the collection and shipment of exploratory samples.
- The central laboratory will provide the study site with urine collection containers, storage tubes, and preprinted J&JPRD labels (or tubes labeled with preprinted labels), for the collection and shipment of urine exploratory samples.
- Use of alternative materials will not result in a protocol amendment if preapproved by the Bioanalysis Scientist.
- Detailed information regarding the collection and storage containers will be provided in the laboratory manual from the central laboratory.

Preparation of Exploratory Plasma Samples

- Collect 10 mL of blood into the appropriate K_2EDTA-containing collection tube (eg, Vacutainer®) at the appropriate time point.
- Immediately after draw, gently invert the plasma tubes 8 times (up-down-up=1 inversion) to completely mix tube contents. Place tubes at room temperature, 15°C to 25°C, until processed.
- Record the exact date and time of sampling in the CRF or laboratory requisition form, as appropriate.
- Centrifuge blood samples at room temperature within 1 hour of collection in a clinical centrifuge at 1,100 to 1,300 RCF (x g) for 10 minutes, to yield a final volume of approximately 4.5 mL of plasma from the whole blood sample. If samples are allowed to sit for more than 10 minutes before centrifugation, they must be remixed (as above) immediately before beginning centrifugation.
- Immediately after centrifugation, transfer all separated plasma with a clean disposable plastic pipette to a prelabeled storage tube. Gently mix the tube by inversion.
- Dispense the plasma (0.5 to 1.0 mL aliquots) into prelabeled microfuge tubes or cryovials (1.5- to 2-mL size) and securely cap.
- Store the plasma samples in an upright position in a freezer at –70°C or colder until transfer to the central laboratory. Record the exact time of storage in the CRF or laboratory requisition form, as appropriate. Shipment on dry ice on the day of collection is acceptable if the site does not have a freezer at –70°C or colder.
- The time between blood collection and freezing the plasma must not exceed 2 hours.
- Ship specimens on dry ice according to the instructions provided by the central laboratory.
- Questions regarding handling the exploratory plasma specimens should be addressed to the contact person for the sponsor.
- Alternative procedures will not result in a protocol amendment if approved by the Bioanalysis Scientist.

Attachment 4: (Continued)
Archive Samples for Exploratory Research - Sample Collection and Handling Preparation of Exploratory Urine Samples

- Collect voided urine in the appropriate urine collection container at the time designated in the protocol.
- Thoroughly mix the urine.
- Transfer 3 separate 3-mL aliquots of each sample (9 mL total) into labeled cryovials.
- Store the urine samples in an upright position in a freezer at –70°C or colder until transfer to the central laboratory. Shipment on dry ice on the day of collection is acceptable if the site does not have a freezer at –70°C or colder.
- The time between urine collection and freezing should not exceed 1 hour.
- Ship specimens on dry ice according to the instructions provided by the central laboratory.
- Questions regarding handling the exploratory urine samples should be addressed to the contact person for the sponsor.
- Alternative procedures will not result in a protocol amendment if approved by the Bioanalysis Scientist.

Attachment 5:
Pharmacogenomic Sample Collection and Shipment Procedure

Pharmacogenomic Sample Supplies and Labeling
The central laboratory will provide the investigational site with prelabeled 10 mL blood collection tubes containing potassium or sodium EDTA. Detailed information is provided in the laboratory manual from the central laboratory.

Preparation of Pharmacogenomic Samples
Pharmacogenomic samples should be prepared as follows:

- Invert the tube 10 to 15 times immediately after collection, to prevent coagulation.
- DO NOT centrifuge the sample.
- Freeze the samples at or below -20°C in an upright position immediately after collection

Pharmacogenomic Sample Shipment
Once collected, the blood samples must immediately be frozen at or below -20°C in an upright position. Samples must remain at this temperature until shipment to the central laboratory. All samples must then be shipped with sufficient dry ice to ensure samples remain frozen during shipment. Detailed information will be provided in the laboratory manual from the central laboratory.

The following guidelines should be adhered to:

- Shipment of the frozen pharmacogenomic blood samples should be arranged with other clinical study samples. If this is not possible, a separate shipment for these blood samples should be organized, using the courier recommended by the central laboratory.
- Notify the courier, at least 24 hours in advance of the planned shipment. Provide the courier with the appropriate account number to be used, if applicable.
- Package the samples in sufficient dry ice to ensure that the samples remain frozen during shipment.
- Label the package with the study number and all other information required by the central laboratory.
- Include a return address (that includes the investigator's name) on the outside of each shipping container.
- Comply with all courier regulations for shipment of biological specimens (include all paperwork).
- Retain all documents indicating date, time, and signature(s) of person(s) making the shipment, in the study files.
- The blood samples should be shipped to the name and address indicated in the central laboratory manual.

NOTE: If there are changes regarding the courier or location to which samples are shipped during the course of the clinical study, written notification will be provided to the investigator; a protocol amendment will not be required.

Attachment 6:
Clinical Laboratory Tests

Blood samples for serum chemistry and hematology and a urine sample for urinalysis will be collected for the tests listed below. The investigator must review the laboratory report, document this review, and record any clinically relevant changes (in the investigator's judgment) occurring during the study in the adverse event section of the CRF.

The following tests will be performed by the central laboratory (the use of local laboratory studies should be limited to situations in which immediate availability of laboratory study results are necessary for appropriate care of the subject):

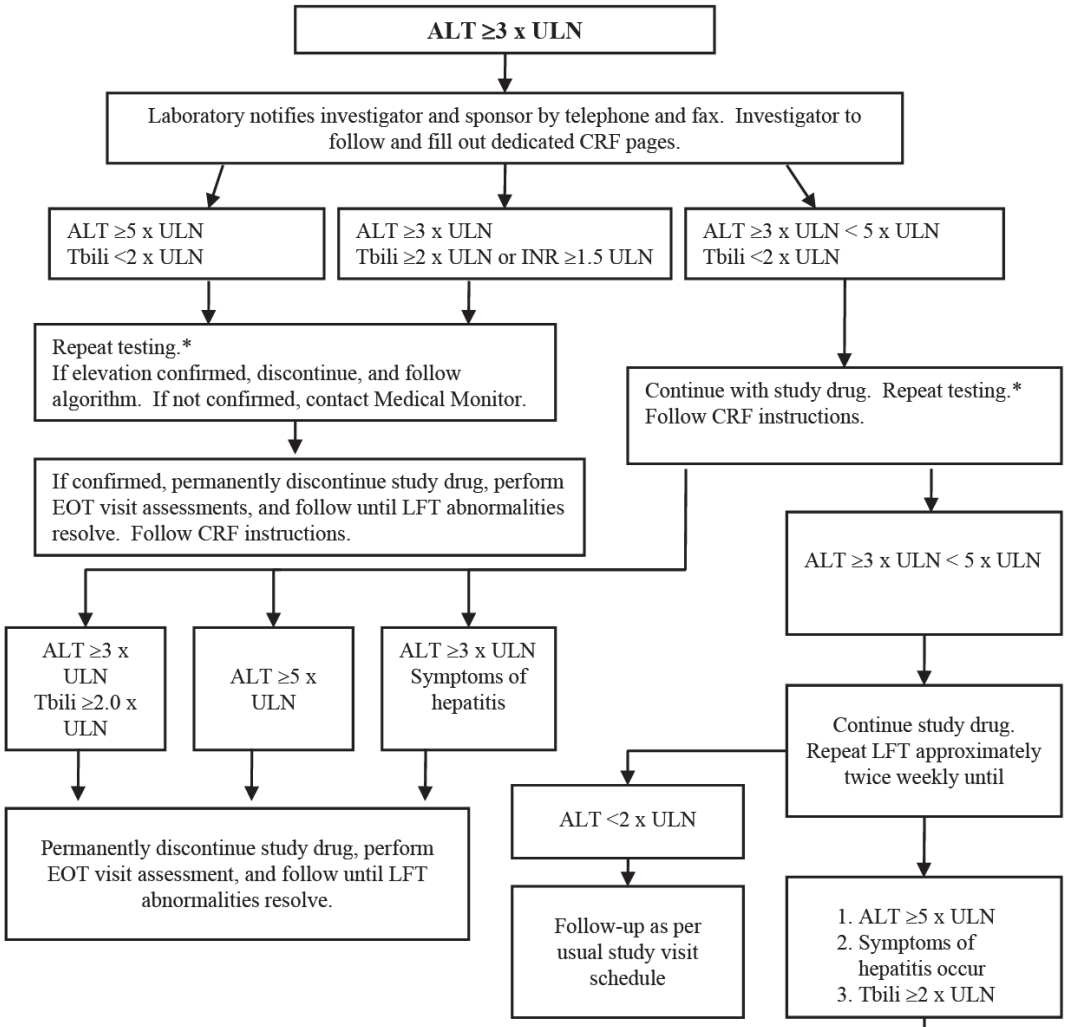
Hematology Panel	Chemistry Panel		Urinalysis*
Hemoglobin	Sodium, potassium, chloride, bicarbonate	Uric acid	Specific gravity
Hematocrit		Calcium	pH
RBC count	Blood urea nitrogen (BUN)	Phosphate	Protein
WBC with automated differential	Serum creatinine	Albumin	Blood
	Glucose	Total protein	Ketones
Platelet count	Aspartate aminotransferase (AST)	Magnesium	Bilirubin / urobilinogen
	Alanine aminotransferase (ALT)	Creatine phosphokinase (CPK)	Nitrate
	Gamma-glutamyl transferase (GGT)		Leukocyte esterase
	Total bilirubin		
	Alkaline phosphatase		
	Lactic acid dehydrogenase (LDH)		

Fasting lipid profile: triglycerides, HDL-C, LDL-C (using Friedewald [1972] equation), total cholesterol (Note, C-peptide, insulin, proinsulin are collected as efficacy assessments as described in Section 9.5)

*Urine glucose will not be measured by the central laboratory

At screening visit: Follicle stimulating hormone (FSH) only for women >45 years of age who have had amenorrhea for ≤6 months before screening; thyroid stimulating hormone (TSH)

Attachment 7:
Algorithm for Monitoring Abnormal Liver Function Tests



If the investigator feels that the subject cannot safely continue administration of the study drug regardless of algorithm, the subject should discontinue study drug and continue to the EOT visit.

* repeat the test within 2-3 days of investigator receipt of report – with earlier testing (ie, within 1 day of receipt of laboratory report) for more substantial elevations in ALT or bilirubin levels.

EOT = End of Treatment

Attachment 8:
Candidate Gene List for Part 1 of Pharmacogenomics

Absorption, Distribution, Metabolism, and Excretion Genes: *ABCB family, ABCC family, ABCG2, ADH family, AHR, ALDH family, AOX1, ARNT, ATP7A, ATP7B, BDH2, CDA, CHST family, COMT, CYP11A1, CYP11B1, CYP11B2, CYP17A1, CYP19A1, CYP1A1, CYP1A2, CYP1B1, CYP20A1, CYP21A2, CYP24A1, CYP26A1, CYP27A1, CYP2A13, CYP2A6, CYP2A7, CYP2B6, CYP2B7, CYP2C family, CYP2D6, CYP2E1, CYP2J2, CYP2S1, CYP39A1, CYP3A family, CYP46A1, CYP4B1, CYP4F family, CYP4Z1, CYP51A1, CYP5A1, CYP7A1, CYP7B1, CYP8A1, CYP8B1, DHRS family, DHRSX, DPYD, EPHX1, EPHX2, FMO family, FOM3, GPX family, GSR, GSS, GSTA family, GSTCD, GSTK1, GSTM family, GSTO1, GSTO2, GSTP1, GSTP2, GSTT1, GSTT2, GSTZ1, HAGH, HNMT, MAOA, MAOB, MGST1, MGST2, MGST3, MPO, NAT1, NAT2, NFE2L2, NNMT, NQO1, NR1I2, NR3C1, POR, PPARA, PPARD, PPARG, RALBP1, RLIP76, SLC10A1, SLC10A2, SLC13A1, SLC15A1, SLC15A2, SLC16A1, SLC19A1, SLC22A family, SLC28A family, SLC29A1, SLC29A2, SLC5A6, SLC7A5, SLC7A7, SLCO1A2, SLCO1B1, SLCO1B3, SLCO1C1, SLCO2A1, SLCO2B1, SLCO3A1, SLCO4A1, SLCO4C1, SLCO5A1, SLCO6A1, SPG7, STE, SULT1A1, SULT1A2, SULT1B1, SULT1C1, SULT2A1, SULT2B1, SULT4A1, TPMT, UGT1A family, UGT2A1, UGT2B family, UGT8, XDH.*

Target related genes: SGLT *gene family (SLC5 family), GLUT gene family (SLC2 family).*

Diabetes related genes: *ABCA1, ABCC8, ABCG5, ACE, ACP1, ACTN4, ADA, ADAMTS9, ADIPOQ, ADRB3, AKR1B1, ALB, ALMS1, ALX4, ANGPTL4, APOA1, APOA4, APOA5, APOB, APOC3, APOE, ARG1, ASIP, ASPN, BBS4, BCHE, CAMK1D, CAPN10, CART, CCK, CCKAR, CCL2, CD36, CD59, CDC123, CDKAL1, CDKN2A-2B, CELSR2, CETP, CIDEA, CILP2, COL2A1, CPE, CTLA4, CTNNBL1, CXCL12, CYP19A1, DF, DIANPH, DOCK7, DPP4, ENPP1, ESR1, EXT2, FABP10, FABP2, FABP4, FABP5, FADS1-3, FASN, FOLH1, FOXC2, FRZB, FTO, FXN, GAD1, GAD2, GAL, GALNT2, GCG, GCGR, GCK, GCKR, GDF8, GH1, GH2, GHRL, GIP, GIPR, GNB3, GPD2, GPKOW, GYS1, HBA1, HFE, HHEK1, HHEX-IDE, HK1, HK2, HK3, HLA-DQA1, HLA-DQB1, HMGA2, HMGCR, HNF4A, HSD11B1, HSD17B7, IAPP, IDE, IGF1, IGF1R, IGF2BP2, IKBKB, IL1R1, IL gene family, INS, INSIG2, INSR, IPF1, IRS1, IRS2, IRS4, ISL1, JAZF1, JPH3, KCNJ11, KCNJ9, KCNQ1, KIF11, LACT, LDLR, LEP, LEPR, LGR5, LIPC, LIPE, LIPG, LMNA, LPA, LPAL2, LPL, LRPAP1, MADD, MANT3, MAPK8, MAPK8IP1, MBL2, MC3R, MC4R, MIA3, MKKS, MLXIPL, MMAB, MMP13, MVK, NEGR1, NEUROD1, NEUROG3, NFKB1, NOS3, NOTCH2, NPY, NR0B2, NR3C1, NUCB2, PBX1, PCSK1, PCSK9, PDE3B, PFKP, PGC, PGR, PLG, PLIN, PNPLA3, POMC, PON1, PON2, PPARG, PPARGC1A, PPARGC1B, PPP1R1A, PPP1R3A, PRL, PSRC1, PTPN1, PTPRN, RBP4, REG1A, RETN, RPS6KB1, SCARB1, SERPINE1, SH2B1, SIM1, SLC2A1, SLC2A10, SLC2A2, SLC2A4, SLC30A8, SORBS1, SORT1, SPINK1, SREBF1, SST, TCF1, TCF2, TCF7L2, TGFB1, TH, THADA, TMEM18, TNF, TRAPPC2, TRIP1, TSPAN8, TUB, TULP2, UCN, UCP1, UCP2, UCP3, VDR, WFS1, WRN, XBP1, ZDHHC23 and ZFP36.*

Attachment 9:
Medical Resource Utilization Review

The questions below are representative but may not be exact wording of those that will be asked in the Diary.

How To Use Your Diary:

- There are two charts. Complete the chart for the type of medical care you receive.
- **Do not** include study visits.
  - Fill in the **Doctor Visit Chart** each time you receive medical care that is not part of the study. Do not list any care received for a medical emergency or during an overnight hospitalization.
  - Fill in the **Emergency Medical Care Chart** when you needed immediate attention for an illness or injury.
- Please be as accurate and complete as you can.

Sample Doctor Visit Chart

Visit Date	Doctor Type	Main Reason for Visit	Location of Visit
05 February 2010	Primary Care Doctor	Flu	Home
11 March 2010	Pulmonologist	Pneumonia	Hospital Outpatient Clinic
13 March 2010	Cardiologist	Chest Pain	Doctor's Office

Doctor Visit Chart

Visit Date	Doctor Type	Main Reason for Visit	Location of Visit

Attachment 9: (Continued)
Medical Resource Utilization Review

Sample Emergency Medical Care Chart

Date of Emergency	Main Reason for Emergency Medical Care	Location of Emergency Medical Care
13 March 2010	Chest Pain	Emergency Room
01 April 2010	High Fever	Home
10 April 2010	Toothache	Dentist

Emergency Medical Care Chart

Date of Emergency	Main Reason for Emergency Medical Care	Location of Emergency Medical Care

LAST PAGE

Janssen Research & Development*

Clinical Protocol

A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus

The CANVAS Trial
(CANagliflozin cardioVascular Assessment Study)

Protocol 28431754DIA3008; Phase 3
AMENDMENT INT-8

JNJ-28431754 (canagliflozin)

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

Issue/Report Date: 5 May 2016
Prepared by: Janssen Research & Development, LLC
Document No.: EDMS-ERI-13522077:12.0 (**Legacy No.:** EDMS-PSDB-9584804)
Eudract No.: 2009-012140-16

Compliance: This study will be conducted in compliance with this protocol, Good Clinical Practice, and applicable regulatory requirements.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Ngozi Erondu, MD, PhD

Institution: Janssen Research & Development, LLC

Signature: [redacted] Date: 29 April 2016

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	14 Aug 2009
Amendment INT-1	16 Sep 2009
Amendment INT-2	27 Apr 2010
Amendment INT-3	11 Mar 2011
Amendment INT-4	08 Sep 2011
Amendment INT-5	13 Dec 2012
Amendment INT-6	08 November 2013
Amendment INT-7	23 September 2015
Amendment INT-8	5 May 2016

Amendments are listed beginning with the most recent amendment.

Amendment INT-8 (5 May 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The primary reason to amend the study protocol is to include new safety information and guidance regarding subject management surrounding the event of lower-extremity amputations.

Applicable Section(s)	Description of Change(s)
Rationale: Decision to continue adjudication of hospitalized heart failure, VTE, and fracture events.	
Section 9.2 Reporting/Adjudication of Events in the CV Composite Endpoint and Other Events for Adjudication	The note that adjudication of hospitalized heart failure VTE, and fracture events would conclude with implementation of INT-6 was removed, since adjudication of these cases is continuing.
Rationale: Include guidance regarding subject management surrounding the event of lower-extremity amputations.	
Time and Events Schedule footnote “j”; footnote “v”; Time and Events Schedule (posttreatment) footnote “c”; Section 12.2.1 All Adverse Events	Added foot examination to be consistent with standard diabetes treatment guidelines. Added guidance regarding foot care and reducing risk of amputation.
Rationale: To address a request from a Health Authority.	
Time and Events Schedule (posttreatment)	Added collection of AHAs after study drug discontinuation.
Rationale: To address a request from a Health Authority.	
Section 9.4. Safety Evaluations	Events with characteristics of diabetic ketoacidosis will be adjudicated by an ad hoc adjudication committee, to verify whether or not the event meets a specified definition of DKA. In addition other categories of events (eg, renal) may undergo adjudication as necessary based on regulatory agency requests or to supplement data analyses.

Applicable Section(s)	Description of Change(s)
Rationale: Include new safety information and guidance regarding subject management surrounding the event of lower-extremity amputations	
Section 1.1.2. Clinical Studies; Section 6.1. Study Drug; Time and Events Schedule footnote "u"; Section 9.4. Safety Evaluations; Table 1;	Added amputation data from IDMC. Added statement that study drug should be interrupted for subjects who develop conditions that are associated with or leading to amputation. An additional AE of special interest was added, "amputation".
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment INT-7 (23 September 2015)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment
The primary reason for the amendment is to reflect a request by Health Authorities to amend the study protocol to include diabetic ketoacidosis (DKA) safety information and handling of subjects surrounding this event.

Applicable Section(s)	Description of Change(s)
Rationale: Balanitis was added as an AE of interest and DKA as an AE of special interest to obtain and collect safety information surrounding these events.	
Time and Events Schedule footnote "u"; Section, Section 9.4. Safety Evaluations; Table 1	An additional AE of interest was added, "male genital infections (balanitis, phimosis, events leading to circumcision)", and an AE of special interest, "diabetic ketoacidosis"; "other designated forms" was added; "In addition, non-serious adverse events" was added; and the statement "If adverse events of interest are identified in the future, guidance concerning the reporting of those events may be provided to investigators via appropriately-documented study communications" was added. A directive for reporting DKA to the sponsor within 24 hours was added.
Rationale: To provide the most up to date data results of safety findings.	
Section 1.1.2. Clinical Studies	Additional paragraph added stating additional AE results as of 11 May 2015.
Rationale: To ensure consistency with the Investigator's Brochure.	
Section 1.1.2. Clinical Studies	Wording updated regarding bone fracture events consistent with the Investigator's Brochure.
Rationale: To provide clarification on drug discontinuation.	
Section 6.1. Study Drugs	Additional wording added to last paragraph to clarify study drug discontinuation.

Applicable Section(s)	Description of Change(s)
Rationale: To include a serious adverse event of biochemically-confirmed diabetic ketoacidosis (DKA) to the list of reasons for withdrawal from study drug.	
Section 10.2. Withdrawal from Study Drug	The sentence "The subject experiences a serious adverse event of biochemically-confirmed (eg, pH, serum ketones, anion gap) diabetic ketoacidosis (DKA)." was added.
Rationale: Consistent with changes relative to DKA.	
Section 12.2.1. All Adverse Events	A description of diabetic ketoacidosis was added: "Study research staff should make study subjects aware of potential signs and symptoms of diabetic ketoacidosis such as difficulty breathing, nausea, vomiting, abdominal pain, feeling confused, fruity-smelling breath, and unusual fatigue or sleepiness. Study subjects should be instructed to contact the site if they experience such symptoms. If the investigator suspects these symptoms may be related to diabetic ketoacidosis (even if the subject's blood glucose levels are less than 250 mg/dL ([13.9 mmol/L]), testing for urine or blood ketones should be considered."
Rationale: Consistent with prior reduction in amount of plasma being stored; allows potential use of smaller collection tube.	
Attachment 4	Modified the archive specimen volume collection language.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical or formatting changes were made.

Amendment INT-6 (08 November 2013)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment:
The primary reason for the amendment is to reflect the changes required for compliance with the United States (US) Food and Drug Administration (FDA) post-marketing requirements for canagliflozin. According to these requirements, a post-approval cardiovascular (CV) meta-analysis will occur when at least 688 MACE events (ie, CV death, nonfatal myocardial infarction, nonfatal stroke) are accumulated from CANVAS plus a planned study evaluating renal events (CANVAS-R; A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects With Type 2 Diabetes Mellitus; 28431754DIA4003). Per the post-marketing requirement, the FDA believes it is most appropriate to characterize CV safety based on a composite of major adverse cardiovascular events (MACE) (not MACE plus hospitalized unstable angina) and using a population at high CV risk (ie, similar to the patients currently enrolled in CANVAS). In addition to the above-mentioned meta-analysis, the US FDA is requiring enhanced pharmacovigilance on select adverse events of interest, which are now described in INT-6. Since the safety profile of canagliflozin was well-established in the Phase 3 program, adverse event collection is being limited in INT-6 to serious adverse events, adverse events that result in study drug discontinuation, and adverse events of interest (as described in the protocol).

Applicable Section(s)	Description of Change(s)
Rationale: This change was made to comply with US FDA post-marketing requirements for canagliflozin.	
Synopsis; 1.2. Overall Rationale and Goals for the Study; 3. Overview Of Study Design; 11.3. Sample Size Determination; 11.8.2. Meta-Analysis Post-Regulatory Approval	The post-approval meta-analyses across all Phase 3 studies for assessment of CV safety when 500 and 700 events in the CV composite endpoint occur will no longer be done. Instead the post-approval CV meta-analysis will occur when at least 688 MACE events (ie, CV death, nonfatal myocardial infarction, nonfatal stroke) are accumulated from the CANVAS (28437154DIA3008) study plus a planned study evaluating renal outcomes (CANVAS-R; A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects With Type 2 Diabetes Mellitus; 28431754DIA4003). The projected date of occurrence (April 2017) of the total number of required events was added.
Synopsis; 2.1.1. Primary Objectives	A statement was added indicating that the data from CANVAS (28431754DIA3008) will be combined with CANVAS-R (28431754DIA4003) to meet US FDA post-marketing requirements for canagliflozin.
Rationale: This section was updated to reflect the current status of the study.	
Synopsis; 1.2. Overall Rationale and Goals for the Study	The description of the pre-approval CV meta-analysis was modified indicating that it has already been conducted.
Rationale: Hospitalized unstable angina is no longer part of the pre-specified CV composite endpoint, which now focuses only on MACE events (ie, CV death, nonfatal myocardial infarction, and nonfatal stroke). Hospitalized heart failure events observed in the ongoing CANVAS study occur infrequently due to the nature of the population enrolled which contains no subjects with NYHA Class IV heart failure and few subjects with NYHA Class III. With respect to venous thromboembolism and fracture events, there is a high concordance rate between investigator-reported events and adjudication committee confirmed events, such that the adjudication of these events does not impact the assessment of these events. Nevertheless, all reported venous thromboembolism and fracture events will be reported and captured by investigators. It is not anticipated that proposed changes to adjudication will impact procedures conducted by investigators. Data collection remains unchanged, with investigators still being required to provide the same level of data. Safety analyses will be conducted using investigator-reported safety results for hospitalized unstable angina, hospitalized heart failure, venous thromboembolism, and fracture events.	
9.2. Reporting/Adjudication of Events in the CV Composite Endpoint and Other Events for Adjudication; Synopsis; 9.4. Safety Evaluations; 12. Adverse Event Reporting	For events of hospitalized unstable angina and hospitalized heart failure, adjudication will conclude with implementation of amendment INT-6. However, investigators will continue to report such events that are serious or that lead to study drug discontinuation on the eCRF. For events of venous thromboembolism and fractures, adjudication will conclude. However, investigators will continue to report all events of venous thromboembolism and fractures on the eCRF. The implementation date to end adjudication of these events will be documented in an update to the adjudication charter(s).

Applicable Section(s)	Description of Change(s)
Rationale: This change is consistent with US FDA post-marketing requirements for canagliflozin, and the circumstances outlined in INT-5.	
Synopsis	The text describing the safety and tolerability assessments was modified to specify that CV safety will be assessed as part of the meta-analysis of CANVAS and CANVAS-R.
Rationale: Because the safety profile of canagliflozin was well-established in the Phase 3 program, adverse event collection is being limited in INT-6 to serious adverse events, adverse events that result in study drug discontinuation, and events of interest specified by the US FDA in their post-marketing requirements for canagliflozin. In addition, this process is consistent with the protocol (Section 9.4), which previously indicated (as of INT-2), "After the decision to re-open enrollment (and recruit Cohort B), for subjects continuing from the initial cohort (Cohort A) and subjects entered in the subsequent cohort (Cohort B), only serious adverse events, adverse events resulting in study drug discontinuation, and selected adverse events will be collected on CRFs."	
Time and Events Schedule (new footnote "u"); 3. Overview Of Study Design; 9.4. Safety Evaluations; 11.4. Safety Analyses; 12. Adverse Event Reporting	Only serious adverse events, adverse events resulting in study drug discontinuation, and adverse events of interest will be recorded on eCRFs. Adverse events of interest include: all malignancies, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (eg, angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, and pregnancy. Information on these events of interest will also be recorded on a supplemental electronic case report form (eCRF) for any event that is serious or that leads to study drug discontinuation. The only exceptions to the adverse event collection described above are for malignancies, photosensitivity reactions, fractures, and venous thromboembolic events for which information on non-serious adverse events will also be recorded on the supplemental eCRF pages (in addition to the information collected on serious adverse events and adverse events leading to study drug discontinuation). Also, as noted above, events of hospitalized unstable angina and hospitalized heart failure, will be reported the adverse event/serious adverse event eCRF if such events are serious or lead to study drug discontinuation (see Section 9.4. Safety Evaluations).
Rationale: This change is consistent with US FDA post-marketing requirements for canagliflozin in that only serious hypoglycemia events and those resulting in study drug discontinuation will be collected. This decision also reflects the fact that extensive safety data regarding hypoglycemia were collected in the canagliflozin Phase 3 program. The focus going forward will be on more clinically relevant hypoglycemia events and not all events. As noted above, because the safety profile of canagliflozin was well-established in the Phase 3 program, adverse event collection is being limited in INT-6 to serious adverse events, adverse events that result in study drug discontinuation, and events of interest specified by the US FDA in their post-marketing requirements for canagliflozin. In addition, this process is consistent with the protocol (Section 9.4), which previously indicated (as of INT-2), "After the decision to re-open enrollment (and recruit Cohort B), for subjects continuing from the initial cohort (Cohort A) and subjects entered in the subsequent cohort (Cohort B), only serious adverse events, adverse events resulting in study drug discontinuation, and selected adverse events will be collected on CRFs."	
12.2.4. Hypoglycemia; related text in Section 11.4. Safety Analyses	Section or text regarding hypoglycemia was deleted.

Applicable Section(s)	Description of Change(s)
Rationale: The decision to stop routine annual central ECGs was made due to there being no ECG signal from the extensive Phase 3 program.	
Synopsis; Time and Events Schedule; 3.1. Overview of Study Design; 9.4. Safety Evaluations; 11.4. Safety Analyses	Routine central ECGs will no longer be collected after Week 52.
Rationale: The urine pregnancy test requirement was removed, but the provision remains for investigators to continue testing if locally required or clinically warranted for individual subjects.	
Time and Events Schedule; 9.4. Safety Evaluations; 11.4. Safety Analyses	Urine pregnancy testing will no longer be required on a routine basis post-baseline, but the provision remains for investigators to continue testing women of childbearing potential if locally required or clinically warranted for individual subjects.
Rationale: The total blood collection was decreased because the collection volumes for exploratory samples have been decreased based on the projected need for minimal additional retention samples.	
16.1. Study-Specific Design Considerations	The total blood volume collected over the course of the study was lowered from 875 mL to 850 mL.
Rationale: More recent information regarding canagliflozin has become available since the CANVAS protocol was drafted. The description of pharmacokinetic, pharmacodynamic, efficacy, and safety information was outdated.	
Introduction	The introduction was updated to reflect the current benefit/risk profile of canagliflozin and its marketing approval in the United States and other countries. The background section was updated to describe the exposure in the Phase 1, 2, and 3 studies as of the end of 2012. The pharmacokinetic, pharmacodynamic, efficacy, and safety information was updated with current information.
Rationale: This change was made to correct a typographical error in INT-5 and clarify that the primary objective will be assessed using the ITT analysis set. Selected secondary objectives may be assessed using the mITT analysis (if appropriate) to comply with US FDA post-marketing requirements for canagliflozin.	
Synopsis; 3. Overview of Study Design; 11.1. Analysis Sets; 11.4. Safety Analyses	The modified intent-to-treat (mITT) analysis set definition is now randomized subjects who receive at least one dose of study drug (original definition) *plus* their data occurring between first dose and last dose plus 30 days. A statement was added that alignment of the analysis of the secondary endpoints with the ITT and mITT analysis sets will be detailed in the study statistical analysis plan (SAP).
Rationale: This section was updated to allow investigators more flexibility in scheduling subject contacts.	
Time and Events Schedule	Visits at 13-week in-clinic visits after Week 52 are no longer required and will now be performed as a telephone contact. An in-clinic visit at 13-week intervals may be performed at the investigator's discretion to resupply study drug.

Applicable Section(s)	Description of Change(s)
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, spelling or template changes were made.

Amendment INT-5 (13 December 2012)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment:
The CANVAS (DIA3008) study is being modified because the sponsor has been unblinded to the results of the analysis of the study's primary cardiovascular (CV) endpoint (MACE events), which was part of a cross-program CV meta-analysis. Originally, the cross-program CV meta-analysis results (and results from CANVAS) were only to be unblinded to the canagliflozin program Independent Data Monitoring Committee (IDMC) and a limited number of sponsor personnel not involved with the canagliflozin program, and then submitted to Health Agencies (who were to be requested to avoid public disclosure). The release of these CV meta-analysis results to the sponsor was based upon the observed small dose-related increase in LDL-cholesterol (4.4% and 8.0% for canagliflozin 100 mg and 300 mg, respectively, relative to placebo) observed in Phase 3 studies. This allowed an assessment by the sponsor of the LDL-C changes in the context of the CV meta-analysis results, including the hazard ratio (HR) for the composite MACE plus hospitalized unstable angina endpoint. Due to the release of the unblinded CV endpoint results from CANVAS, the study Steering Committee has determined that the second cohort (Cohort B), originally planned for future enrollment in CANVAS, would not be conducted; this decision was based upon the assessment that the unblinding interim primary endpoint (MACE CV HR) data from the ongoing CANVAS study did not allow a definitive assessment of the study objective. The Steering Committee indicated that a separate CV outcome study should be conducted to provide a definitive assessment of CV risk. After review of the CV HR results, the Steering Committee in concert with the sponsor (and after IDMC review) has recommended continuing CANVAS with the original cohort (Cohort A, which completed enrollment in March 2011) so as to provide an initial assessment of the study's primary objective of CV benefit. This initial assessment will provide important information supporting a subsequent separate CV outcome study, and will also support assessment of other study objectives.

Applicable Section(s)	Description of Change(s)
Rationale: Comprehensive follow-up of subjects who discontinue is important for analysis of the study results; these changes provide mechanisms for enhancing follow-up.	
Synopsis; Time and Events Schedule	Added mention of provision for alternative posttreatment follow-up options; added specific mention of expectation that the investigator will make every effort to ascertain the vital status of all subjects at the end of the study, including using all reasonable means to contact the subject, family members, the subject's physicians and medical records, and the use of locator agencies and checking public records, as allowed by local law.
Rationale: Refer to overall reason for amendment.	
1.2. Overall Rationale and Goals for the Study; 2.3. Substudies:	In light of overall reason for amendment, removed mention of Cohorts A and B.

Applicable Section(s)	Description of Change(s)
Objectives and Hypotheses 3. Overview of Study Design; 3.1. Study Design; 3.2. Study Design Rationale; 4. Study Population; 4.1. General Considerations; 5. Treatment Allocation; 6.1. Study Drugs; 6.2.1.Management of Glycemic Control and CV Risk Factors; 6.2.2. Glycemic Rescue Therapy; 9.1.2. Pretreatment Phase; 9.1.3. Double-Blind Treatment Phase; 9.1.4. End of-Treatment/Early Withdrawal; 9.4. Safety Evaluations; 9.8. Medical Resource Utilization; 10.2. Withdrawal from the Study; 11. Statistical Methods; 12.2.2 Serious adverse experiences	
Rationale: Refer to overall reason for amendment.	
Synopsis; 3. Overview of Study Design; 3.1 Study Design; 11.3 Sample Size Determination; 11.8.2. Meta-Analysis Post-Regulatory Approval	In light of overall reason for amendment, removed mention of Cohorts A and B and associated statements in the analysis; revised wording regarding meta-analyses to meet the CI <1.3 requirement for the upper bound of the 95% CI for the CV HR.
Rationale: Comprehensive follow-up of subjects who discontinue is important for analysis of the study results; these changes provide mechanisms for enhancing follow-up	
Synopsis; Time and Events Schedule; 9.1.4 End-of-Treatment/Early Withdrawal; 10.2 Withdrawal From the Study	Provided for subject to allow contacting physicians and medical records to follow-up subjects who cannot be contacted; added provision if the site of the study doctor closes, and the study doctor cannot reach the subject to inform him/her, the contact information will be transferred to another site where a new study doctor will consult with family members, the subject's physicians and medical records, or public records, including the use of locator agencies as permitted by local law, to determine the subject's endpoint status.

Applicable Section(s)	Description of Change(s)
9.8 Medical Resource Utilization	Removed erroneous mention of collecting hospitalization information on MRU forms.
Rationale: The sponsor has been unblinded to the results of the analysis of the study's primary cardiovascular endpoint (MACE events), which was part of a cross-program CV meta-analysis. Originally, the cross-program CV meta-analysis results (and results from CANVAS) were only to be unblinded to the canagliflozin program Independent Data Monitoring Committee and a limited number of sponsor personnel not involved with the canagliflozin program, and then submitted to Health Authorities. Since the scope of unblinding within the sponsor organization is broader than originally planned, a more limited firewall is implemented involving individuals within the sponsor responsible for submitting events to the Endpoint Adjudication Committee.	
11.8.1. Meta-analysis Pre-Regulatory Approval	Description of the firewall to maintain data integrity has been edited.
Rationale: Study drug supplies may be supplied in bottles rather than blister packs in the future.	
14.2. Packaging	Provided for use of bottles.
Rationale: Company name and sponsorship statement updated due to the recent change in various legal entity names.	
Title Page; Attachment 4	Changed name from Johnson and Johnson Pharmaceutical Research and Development to Janssen Research and Development.

Amendment INT-4 (8 September 2011)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reasons for the amendment are (1) to remove the pre-planned adaption to re-estimate the sample size for Cohort B and (2) to specify that an interim analysis of the ongoing CANVAS (DIA3008) study will be required for reporting of safety data in the initial canagliflozin marketing applications.

Applicable Section(s)	Description of Change(s)
Rationale: In discussions between the sponsor and the CANVAS Steering Committee, a fixed sample size approach has been chosen as this is a more statistically and analytically sound approach, relative to adaptation, to re-estimate sample size.	
Synopsis; 1.2. Overall Rationale and Goals for the Study; 3. Overview of Study Design; 3.2. Study Design Rationale; 11.9. Feasibility Assessment	The pre-planned adaptation to re-estimate the sample size for Cohort B will no longer be conducted. The description of the prior adaptive design was modified to reflect the fixed sample size of the 2 sequential cohorts.

Applicable Section(s)	Description of Change(s)
Rationale: Since CANVAS (DIA3008) contributes a substantial amount of placebo-controlled, safety data in a high-risk population to the overall canagliflozin development program, health authorities will be expecting to review unblinded data from this study in order to make a determination of overall safety and efficacy of this compound and ultimately a decision on the approvability of canagliflozin.	
11.7.1. Interim Analyses for Health Authority Submissions	New section added. Text added to the protocol indicating that an unblinded interim analyses of CANVAS data will be done to prepare an interim safety report in support of the initial health authority filing.
Rationale: Recently published literature with other drugs in the SGLT2 inhibitor class suggest that the observed standard deviation with respect to HbA_{1c} change from baseline in subjects taking sulfonylureas is less than originally anticipated in the protocol. The new data would allow for an assessment of the primary substudy endpoint (ie, change in HbA_{1c} from baseline) in the sulfonylurea substudy using a smaller samples size than originally planned, ie, approximately 50 subjects per group (instead of 86 subjects per group) while retaining adequate power.	
11.10.2. Sample Size Determination; References	Added a reference to support the analysis of the sulfonylurea substudy with at least 50 subjects per group.
Rationale: An evaluation of intermediate endpoints to assess the feasibility in enrolling Cohort B involves modeling the effects on surrogate markers, such as blood pressure, body weight, and fasting lipids, in order to derive a predicted HR. Such an evaluation is beyond the current scope of the IDMC's responsibility, which is focused on ensuring the safety of subjects enrolled in the study.	
Synopsis; 4.1. General Considerations; 11.3.2. Subsequent Cohort (Cohort B); 11.7.2. Interim Analysis to Assess the Feasibility in Initiating Cohort B; 11.9. Feasibility Assessment	A CV risk factor evaluation committee was formed to evaluate the effects of canagliflozin on intermediate outcomes (eg, blood pressure, fasting lipids, body weight).
Rationale: The investigator should be allowed to retain some autonomy in their clinical diagnoses which may or may not coincide with the Adjudication Committee's clinical diagnosis.	
12. Adverse Event Reporting	Added a stipulation that any nonfatal CV event in the composite endpoint initially classified as a serious adverse event, but subsequently determined by the Endpoint Adjudication Committee as meeting the definition of a study endpoint, will be reviewed on an individual basis by the sponsor to determine whether or not such an event should be reported by the investigator on the CV events eCRF page (and removed from the adverse event/serious adverse event eCRF page).

Amendment INT-3 (11 Mar 2011)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reasons for the amendment are (1) to describe procedures associated with the use of rosiglitazone in light of recent regulatory actions and (2) to add to the follow-up provisions for subjects who discontinue double-blind study drug prior to completion of the study.

Applicable Section(s)	INT-3 Description of Change(s)
Rationale: Addition of new nonclinical study results.	
1.1.1. Brief Overview of Nonclinical Studies	The results of genotoxicity and carcinogenicity studies in rats were included.
Rationale: Rosiglitazone has been withdrawn or restrictions have been placed on its use in several markets worldwide.	
2.3. Substudies: Objectives and Hypotheses (Cohort A); 3.1. Study Design; 4.1. General Considerations; 4.2. Inclusion Criteria; 5. Treatment Allocation	Rosiglitazone was removed from the list of approved background AHAs.
4.1. General Considerations	Procedures for handling subjects taking rosiglitazone were added.
4.3. Exclusion Criteria – Medications/ Therapies	Rosiglitazone was added to the list of exclusionary medications.
Rationale: Additional follow-up measures for subjects who discontinue double-blind study drug early will allow for a more comprehensive safety dataset.	
Posttreatment Time & Events Schedule	Added new Posttreatment Time & Events Schedule for subjects who prematurely discontinue study medication.
Rationale: Additional information regarding superficial genital adverse events in men will be collected in the canagliflozin development program to better characterize this recently identified adverse drug reaction.	
3.1. Study Design; 3.2. Study Design Rationale; 12. Adverse Event Reporting	Superficial genital adverse events in men were added to the list of selected adverse events.

Applicable Section(s)	INT-3 Description of Change(s)
Rationale: The exclusion criterion related to thyroid stimulating hormone (TSH) was modified in INT-2, and measurement of TSH at Run-in is no longer necessary.	
Time & Events Schedule; Attachment 6	Thyroid stimulating hormone was removed as a procedure at the Week -2 (Run-in Start) visit.
Rationale: Pharmacogenomic samples will continue to be collected as planned; however, the analyses of those samples will not be prespecified in the statistical methods section of the protocol.	
11.11. Pharmacogenomic Analyses	This section was removed from the protocol.
Rationale: Updates need to align with other canagliflozin Phase 3 protocols.	
3.2. Study Design Rationale; 9.1.1. Overview; 9.7. Exploratory Evaluations	Description of the exploratory samples was aligned with the global canagliflozin Phase 3 protocols.
3.1. Study Design; 3.2. Study Design Rationale; 12. Adverse Event Reporting	Hypoglycemia was removed from the list of selected adverse events for editorial reasons because additional information is collected on all hypoglycemic episodes, irrespective of whether the episode is considered an adverse event.
Rationale: Flexibility for first morning void collection was needed for subjects with atypical sleep patterns.	
Time & Events Schedule; 9.4. Safety Evaluations	Added a clarification that for subjects working a night shift, or who otherwise have atypical sleep patterns, the first morning void collection should be made at the end of the subject's usual sleep period.
Rationale: Clarification of blood pressure and body weight measurements were needed.	
9.4. Safety Evaluations	Specified that blood pressure will be measured 3 times in both arms at the screening visit. Specified that if disrobing for weighing is logistically impossible, the subject must be dressed as lightly as possible, with consistency from visit to visit.
Rationale: Subjects for whom study drug is interrupted as a result of an adverse event, a life event (eg, temporary relocation to care for an ill family member), or another unforeseen circumstance may need to return to active status (ie, re-start double-blind study drug).	
10.3. Reinstitution of Subjects who Have Prematurely Discontinued Double-blind Study Drug to Active Status	New section added.

Applicable Section(s)	INT-3 Description of Change(s)
Rationale: The per-protocol analysis set definition was too restrictive based upon ICH definition of major protocol deviations.	
11.10.1. Analysis Sets	Clarified that having no major protocol deviations to be included in the per-protocol analysis set means having no deviations that may affect the interpretation of the primary efficacy endpoint.
Rationale: Follow-up telephone contact may not always be possible.	
Throughout the protocol	Noted that if a telephone contact or study visit is not possible, follow-up information may be collected via email or other electronic means.

Amendment INT-2 (27 April 2010)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reasons for the amendment are to (1) add additional data that demonstrated no clinically meaningful photosensitizing potential of canagliflozin in humans and to remove the photoprotection prohibition; and (2) add additional data of co-administration of digoxin and canagliflozin and the removal of digoxin as a prohibited medication.

Applicable Section(s)	INT-2 Description of Change(s)
Rationale: Additional studies that evaluated the photosensitizing potential of canagliflozin in humans have been completed.	
1.1.2. Clinical Studies; 3.2. Study Design Rationale	Findings of the photosensitivity studies in Caucasian subjects were added, demonstrating that canagliflozin 100 mg or 300 mg once daily, the clinical doses used in the Phase 3 studies, had no delayed photosensitizing effect at any wavebands representing the terrestrial solar spectrum.
4.4. Prohibitions and Restrictions	Instructions that subjects should use photoprotective measures were removed.
16.1. Study-Specific Design Considerations	Instructions that subjects should use photoprotective measures were removed. Text stating that the photosensitivity studies support safe participation of subjects in these Phase 3 studies without specific photoprotection precautions was added.
Rationale: A Phase 1 drug-drug interaction study with digoxin has been completed.	
1.1.2. Clinical Studies	A description of the main pharmacokinetic findings from the study was added.
4.3. Exclusion Criteria; 4.4. Prohibitions and Restrictions	Digoxin was removed as a prohibited medication and subjects will no longer be excluded for taking this medication.

Applicable Section(s)	INT-2 Description of Change(s)
Rationale: Study oversight committee structure and responsibilities were modified with input from Steering Committee.	
9.3.4. Executive Committee; throughout the protocol	Section removed. "Executive" Committee changed to "Steering" Committee throughout the protocol.
Rationale: Clarification regarding the meta-analysis for pre-regulatory approval could occur with as few as 80 events and as many as 160 events.	
11.8.1. Meta-analysis Pre-Regulatory Approval	The maximum number of expected events in the first meta-analysis for CV safety was modified from 140 to an approximate range of 140 to 160 (with the number from the CANVAS study changed from 100 to a range of 110 to 120). In no event would the meta-analysis to support regulatory approval occur with fewer than 80 events.
Rationale: Follow-up contact in other Phase 3 protocols is 30 days after last dose of study drug in accordance with requirements for SAE reporting.	
Throughout the protocol	Follow-up contact after last dose of study drug was changed from 28 to 30 days. The collection time frame after last dose of study medication for CV events for the CV analysis was changed from 28 to 30 days. The time frame for reporting SAEs after last dose of study drug was changed from 28 to 30 days.
12.2.1. All Adverse Events	Corrected the time point at which the 30-day reporting period for SAEs starts (changed to the "last dose of study medication" instead of "last follow-up contact").
Rationale: Description of events that require additional data collection was revised to be consistent with program-wide data collection.	
3.1. Study Design; 3.2. Study Design Rationale; 9.4. Safety Evaluation; 12. Adverse Events	Events of increased ALT ≥3-fold the upper limit of normal (ULN) were removed from the events that require a separate section in the eCRFs for collection of additional information. Clarification was added that investigators may be contacted and requested to provide additional information regarding such events and that subjects will be monitored and managed according to the algorithm in Attachment 7.
Rationale: Additional Phase 1 studies have been completed.	
1.1.2. Clinical Studies	The number of subjects who participated in the Phase 1/1b studies was updated.
Rationale: Single-blind placebo capsules were described as "tablets" in error.	
Synopsis; 3.1. Study Design; 4.2. Inclusion Criteria; 6.1. Study Drugs; 9.1.2. Pretreatment; 9.1.3. Double-blind Treatment	Single-blind placebo "tablets" were changed to single-blind placebo "capsules." Clarification was added that subjects are to take one single-blind capsule once daily during the 2-week run-in period.
Rationale: Hematology was not originally included at end-of-treatment/early withdrawal visit, but is needed for optimal safety monitoring.	
Time and Events Schedule	Hematology was added at end-of-treatment/early withdrawal visit.

Applicable Section(s)	INT-2 Description of Change(s)
Rationale: Input from the Steering Committee was received after further review of data from other CV outcomes trials.	
4.2. Inclusion Criteria	The blood pressure criterion was modified to clarify that the value should be an average of 3 readings recorded at the screening visit.
Rationale: The standard exclusion criteria wording has been modified in other issued canagliflozin Phase 3 protocols.	
4.3. Exclusion Criteria	Thyroid exclusion criterion was modified for consistency with the other protocols.
4.3. Exclusion Criteria	The laboratory exclusion criterion for subjects taking metformin was modified to a serum creatinine level of ≥1.4 mg/dL (124 μmol/L) for men or ≥1.3 mg/dL (115 μmol/L) for women and with no contraindication to the use of metformin (including eGFR) based on the label of the country of the investigational site.
4.3. Exclusion Criteria; 5. Treatment Allocation	The definition of a stable dose of insulin was modified from a ≤10% change to a ≤15% change.
Rationale: The standard prohibition and restrictions wording has been modified in other canagliflozin Phase 3 protocols.	
4.4. Prohibitions and Restrictions	A bullet was added with instructions that subjects should not collect first morning void during acute illness with fever.
Rationale: For consistency with standards of care for glycemic rescue in clinical trials and with other canagliflozin Phase 3 protocols.	
6.2.2. Glycemic Rescue Therapy Through Week 18 for Initial Cohort (Cohort A): Criteria and Implementation	The time points for rescue were modified: “Week 4” was changed to “Week 6.”
Rationale: Health authorities have requested that a “firewall” be established to ensure data integrity in the CANVAS study.	
11.8.1. Meta-analysis Pre-Regulatory Approval	Description of the firewall to maintain data integrity has been added.
Rationale: Additional canagliflozin Phase 3 protocols have been issued and program-wide wording and standards have been established for consistency.	
Throughout the protocol	Updates were made for consistency with the other Phase 3 protocols.
Section 1. Introduction; References	References added.

Amendment INT-1 (16 September 2009)

The overall reason for the amendment: Protocol was amended to further clarify the interim analysis and adaptation plan for the study.

Applicable Section(s)	INT-1 Description of Change(s)
Rationale: Description of the criteria for adaptation and the potential for enrollment of a second cohort of subjects was clarified. In addition, the roles of the Independent Data Monitoring Committee (IDMC) and Executive Committee in the interim analysis and adaptation of the study were clarified.	
Synopsis Overview of Study Design; 1.2. Overall Rationale; 3. Overview of Study Design; 3.1. Study Design; 3.2 Study Design Rationale; 9.3.5. IDMC; 11.3 Sample Size Determination; 11.7 Interim Analysis	Updated Text
Rationale: Description of the initial cohort (referred to as Cohort A) and the subsequent cohort (referred to as Cohort B) was modified for clarity.	
Throughout the protocol	Previously described as Cohort A and Cohort B; now described as initial cohort (Cohort A) and subsequent cohort (Cohort B).
Rationale: First morning void urine collection was added to run-in visit to provide additional baseline data for comparison with treated values.	
Time and Events Schedule	
Rationale: Description of the inclusion and exclusion criteria and prohibitions and restrictions were aligned with other Phase 3 studies in the canagliflozin development program for consistency.	
4.1. Inclusion Criteria; 4.2. Exclusion Criteria; 4.4 Prohibitions and Restrictions	Minor changes to the text were made.
Rationale: The study drug kit number will be automatically recorded.	
5. Treatment Allocation	Deleted statement that the study drug kit number will be entered in the electronic case report form (CRF) when the drug is assigned.
Rationale: Clarification regarding urinalysis by a local laboratory for safety reasons was needed.	
5. Treatment Allocation	Added a statement that if urinalysis must be performed locally for appropriate subject management (eg, to evaluate a potential infection), investigators should request microscopic rather than dipstick urinalysis (if microscopic evaluation is considered clinically sufficient).

Applicable Section(s)	INT-1 Description of Change(s)
Rationale: Consideration was needed for subjects who do not meet screening adjustment/optimization of lipid altering or blood pressure-lowering medications.	
9.1.1. Overview, 9.1.2. Pretreatment	Added text stating that if additional time in run-in is required for adjustment/optimization of lipid altering or blood pressure-lowering medications, (so as to avoid the need for adjustment of these medications after randomization), the 2-week placebo run-in may be extended by having the subject continue single-blind placebo up to 2 additional weeks (note: the single-blind placebo package contains sufficient drug supply for additional time period)
Rationale: Exploratory samples were under 2 different informed consents; modifications to the description were made to simplify the consent process and include the samples for exploratory research under a single informed consent.	
9.1.1. Overview; Attachment 4	Modified text to clarify that one set of plasma, serum, and urine samples will be collected at baseline and all 52-week intervals from subjects who consent to this component of the study to allow for exploratory research related to canagliflozin or biomarker analyses.
Rationale: Hypoglycemic events will be captured as non-serious adverse events in addition to recording the information on the hypoglycemia section of the eCRF.	
9.4. Safety evaluations; 12.2.4. Hypoglycemia	Added text stating that information on possible hypoglycemic events will be collected on a separate hypoglycemia eCRF page, and hypoglycemic events should be recorded on the adverse event eCRF, if considered an adverse event by the investigator.
Rationale: Clarification of certain procedures and corresponding analyses was needed.	
9.4. Safety evaluations; 9.5. Efficacy Evaluations; 11. Statistical Methods	• Physical examinations elaborated; estimated glomerular filtration rate (eGFR) evaluations moved from safety to efficacy; Medical Resource Utilization evaluation removed from follow-up telephone contact procedures.

SYNOPSIS

A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus (CANVAS: CANagliflozin cardioVascular Assessment Study)

EUDRACT number: 2009-012140-16

Canagliflozin (JNJ-28431754) is an orally active inhibitor of the sodium-glucose co-transporter 2 (SGLT2) that is being developed as an oral antihyperglycemic agent (AHA) for the treatment of patients with type 2 diabetes mellitus (T2DM). Canagliflozin is selective for inhibition for SGLT2 relative to sodium-glucose co-transporter 1 (SGLT1). The initial goals of this study (CANVAS) were to assess the overall safety and tolerability of canagliflozin and to demonstrate a reduction in major adverse cardiovascular events (MACE) with canagliflozin treatment.

Prior clinical studies of canagliflozin in patients with T2DM have demonstrated improvements in glycemic control (with reductions in hemoglobin A_{1c} [HbA_{1c}] and fasting plasma glucose [FPG]), reduction in body weight, and trends towards improvements in other cardiovascular (CV) disease risk factors (including increases in high-density lipoprotein cholesterol [HDL-C], decreases in triglyceride levels, and decreases in blood pressure, especially at the 300-mg dose), with generally good tolerance and appropriate safety to support continued clinical development of this medication. With improved glycemic control, which itself may provide a benefit in CV risk, and the trends towards benefit on other CV risk factors including body weight, the potential for a benefit of long-term treatment with canagliflozin on CV disease is raised.

The present study was intended to assess if treatment of subjects with T2DM with canagliflozin reduces CV risk for MACE (including CV death, nonfatal myocardial infarction [MI], and nonfatal stroke) and to achieve a number of other important goals. These include the assessment of overall safety and tolerability, glycemic efficacy (in the overall study population and in subjects on specific AHAs), long-term effects on beta-cell function, and long-term effects on renal function with canagliflozin treatment. This study also provides key support for a cross-canagliflozin program assessment of CV safety, examining a composite endpoint of MACE plus hospitalized unstable angina (pre-approval CV safety assessment) and MACE (post-approval CV safety assessment). Subsequent to the initial plan it has been necessary to modify the design of the study.

The data from this study will be combined with the data from another large-scale study of the effects of canagliflozin compared to placebo (CANVAS-R; A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects With Type 2 Diabetes Mellitus; 28431754DIA4003) in a pre-specified meta-analysis of CV safety outcomes, to satisfy post-approval United States (US) Food and Drug Administration (FDA) post-marketing requirements for canagliflozin.

OBJECTIVES AND HYPOTHESES

Primary Objectives

In subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease:

- to assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care on CV risk as measured by the hazard ratio (HR) for a composite endpoint (MACE including CV death, nonfatal MI, and nonfatal stroke)
- to assess the safety and tolerability of canagliflozin plus standard of care relative to placebo plus standard of care

The data from this study will be combined with the data from CANVAS-R in a pre-specified meta-analysis of CV safety outcomes to satisfy US FDA post-marketing requirements for canagliflozin.

Secondary Objectives

In subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease:

- to assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care on:

  - fasting measures of beta-cell function (homeostasis model assessment [HOMA]-B and the proinsulin/insulin ratio) (Note: this assessment will be conducted in a subset of subjects at sites that elect to participate, including only subjects who are not receiving insulin at randomization).
  - the proportion of subjects with progression of albuminuria (progression defined as ≥1 step increase, ie, no albuminuria to micro- or macro-albuminuria or from micro-albuminuria to macro-albuminuria)
  - the urinary albumin/creatinine ratio
  - renal function (as measured by the change from baseline in estimated glomerular filtration rate [eGFR])
- to assess the effect of canagliflozin relative to placebo after 18 weeks and at the end of the treatment period on:
  - glycemic efficacy (HbA_{1c} and FPG)
  - body weight
  - blood pressure (systolic and diastolic)
  - fasting plasma lipids (triglycerides, HDL-C, low-density lipoprotein cholesterol [LDL-C], total cholesterol, and the ratio of LDL-C to HDL-C)

Hypotheses

Primary hypothesis

In subjects with T2DM with inadequate glycemic control who have a history of or a high risk of CV disease, relative to placebo plus standard of care, canagliflozin plus standard of care reduces CV risk (as measured by the HR for a composite endpoint including CV death, nonfatal MI, and nonfatal stroke).

Secondary hypotheses

In subjects with T2DM, with inadequate glycemic control, who have a history of or a high risk of CV disease, relative to placebo plus standard of care, canagliflozin plus standard of care at the end of the treatment period:

- improves beta-cell function (change from baseline in HOMA-B)
- reduces progression of albuminuria (ie, proportion of subjects with a ≥1-step progression of albuminuria measured by the urine albumin/creatinine ratio)

(See protocol body for objectives and hypotheses for substudies examining the efficacy and safety of canagliflozin in combination with specific AHAs.)

OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, 3 parallel-group, multicenter study to evaluate the safety, tolerability, and CV risk with canagliflozin plus standard of care compared with placebo plus standard of care in subjects with T2DM, on a wide range of antihyperglycemic therapies, who have either a history or high risk of CV disease. Although the effects of canagliflozin on several CV risk factors (eg, glycemic control, body weight, blood pressure) appear favorable in short-term studies, the longer-term benefits on CV risk factors are currently unknown; in addition, Phase 3 results demonstrated a small increase in LDL-C, without a change in the LDL-C to HDL-C ratio. Note that results from this study, integrated with cross-Phase 3 program results, were included in a pre-approval meta-analysis to evaluate CV safety (as required by the US FDA Guidance for Industry: Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes) by examining the composite of MACE plus hospitalized unstable angina (referred to as the pre-approval CV safety endpoint). This CV meta-analysis was conducted in 2012 (addressing the US FDA filing requirement that the upper bound of the 2-sided 95% confidence interval (CI) around the CV HR is <1.8); this meta-analysis confirmed the requirement, showing the upper bound was <1.8.

This study was originally designed to include 2 sequential cohorts, with up to 18,500 subjects and a study duration for individual subjects of up to approximately 8 years. The study will now recruit only the initial 4,330 subjects who were randomly assigned to treatment with 1 of 2 doses of canagliflozin (100 or 300 mg)

or placebo, in a 1:1:1 ratio. The study's last subject last visit will occur when at least 688 MACE events (ie, CV death, nonfatal myocardial infarction, nonfatal stroke) are accumulated between the CANVAS and CANVAS-R studies which is projected to occur prior to April 2017.

The study was modified (as of amendment INT-5) because the cross-program meta-analysis of the pre-approval CV safety endpoint was unblinded to the sponsor to prepare regulatory submissions (originally this was to be unblinded to the study IDMC only); this was done based upon a decision by the sponsor, so that the impact of the small dose-related increase in LDL-C observed with canagliflozin treatment in Phase 3 program on the CV HR could be evaluated. Due to the unblinding of these CV endpoint results, the study Steering Committee noted that the addition to the CANVAS trial of the planned second cohort of subjects would not provide a robust assessment of the primary CV protection hypothesis.

The CANVAS study has additional objectives including the assessment of overall safety and tolerability of canagliflozin. The study also includes several substudies intended to provide additional information about the efficacy and safety of canagliflozin compared to placebo in combination with specific AHAs.

In this study, investigators will be counseled to assure appropriate management of CV risk factors (eg, blood pressure and lipids) according to standard guidelines (eg, the American Diabetes Association [ADA] or other local diabetes guidelines) for the care of patients with T2DM. In addition, after a relatively brief period during which the subject's antihyperglycemic regimen is to be kept stable (described in the section below), investigators will attempt to achieve good glycemic control, consistent with standard diabetes guidelines, individualized as considered clinically appropriate, with up-titration or stepwise addition of AHA therapies. Thus, this study will examine the impact on CV risk, and the safety and tolerability of treatment with canagliflozin along with standard of care for CV risk factor and glycemic management relative to placebo with standard of care management.

STUDY POPULATION

Men or women with T2DM who have inadequate glycemic control (HbA_{1c} ≥7.0 and ≤10.5%), not on an AHA or on an AHA in monotherapy or combination therapy, and who have known CV disease or who have 2 or more risk factors for CV events are eligible.

STRATIFICATION FOR SUBSTUDIES

Subjects will have within-subgroup balanced (1:1:1) randomization to each of the 3 treatment groups within 6 predefined strata based upon AHA medication(s) that the subject is receiving at the run-in visit and will be continuing at entry into the double-blind treatment phase (the strata are defined in the main body of the protocol).

DOSAGE AND ADMINISTRATION

Study Drugs

Upon successful completion of screening, all potentially eligible individuals will enter a 2-week run-in period, during which they will receive single-blind placebo capsules (one capsule to be administered once-daily).

Subjects will be randomly assigned in a 1:1:1 ratio to 1 of 3 treatment groups: canagliflozin 100 mg, canagliflozin 300 mg, or matching placebo. Subjects will be counseled to take their dose of canagliflozin or matching placebo once daily, before the first meal of the day, according to their randomized treatment assignment, for the duration of the study or until early discontinuation.

Concomitant Antihyperglycemic and Other Therapies

Detailed instructions are provided in the main protocol for management of (1) glycemic control and CV risk factors, and (2) glycemic rescue therapy through Week 18.

EFFICACY AND SAFETY OUTCOME DEFINITIONS/EVALUATION CRITERIA

Primary MACE Outcome

The hypothesis of CV risk reduction for canagliflozin will be evaluated based upon the events in the CV composite endpoint of MACE (CV death, nonfatal MI, nonfatal stroke). An independent Endpoint Adjudication Committee will assess all events that could potentially be in the specified CV endpoint and

only those events where the committee, using methodology and definitions defined in the committee's charter, determines a specified endpoint has occurred will be included in the primary analysis. The independent Endpoint Adjudication Committee will apply the endpoint definitions contained in its charter and classify the outcome events while blinded to treatment assignment.

Secondary Efficacy Endpoints

Secondary measures of efficacy include beta-cell function (HOMA-B; in subjects who are not receiving insulin) and progression of albuminuria (based upon categories determined by urinary albumin/creatinine ratio).

Additional efficacy endpoints of interest will include the following: changes from baseline to end-of-treatment in the proinsulin/insulin ratio (in a subset of subjects), urinary albumin/creatinine ratio, and eGFR; changes from baseline to Week 18 in HbA_{1c}, FPG, systolic and diastolic blood pressure, and body weight; and percent change from baseline to Week 18 in fasting plasma lipids (triglycerides, HDL-C, LDL-C, total cholesterol, and the ratio of LDL-C to HDL-C).

Measurements to assess HOMA-B and the proinsulin/insulin ratio will be collected in a subset of subjects of approximately 1,200 subjects (at sites that elect to participate) who are not receiving insulin at baseline.

Safety and Tolerability Assessments

The safety and tolerability assessments will include an evaluation of serious adverse events, adverse events of interest, discontinuation due to adverse events, clinical laboratory tests, vital signs (pulse, blood pressure), and body weight. Cardiovascular safety will be assessed as a part of the meta-analysis of CANVAS and CANVAS-R.

STATISTICAL METHODS

Analysis Sets

The ITT analysis set includes all subjects who are randomly assigned to a treatment group. The assessment of the primary objective will be based upon this analysis set. The primary CV analysis will be based on the time to the first occurrence of any component of the MACE composite endpoint. The modified ITT (mITT) analysis set includes the randomized subjects who receive at least one dose of study drug and their data occurring between first dose and last dose plus 30 days.

The alignment of the analysis of the secondary endpoints with the ITT and mITT analysis sets will be detailed in the study statistical analysis plan (SAP).

Sample Size Determination

The sample size for the recruitment of the initial 4,500 subjects was based upon having a sufficient number of participants to support, in concert with the other controlled clinical trials in the canagliflozin development program, a detailed pre-approval assessment of the safety and tolerability of canagliflozin. Data from this initial cohort were exported and integrated with data from other Phase 3 well-controlled studies to support a planned, pre-approval meta-analysis to demonstrate that the upper bound of the 2-sided 95% CI for the CV HR of canagliflozin relative to control in composite endpoint events (MACE and hospitalized unstable angina) was <1.8, as part of the current US regulatory requirements for filing. The FDA post-marketing requirements for canagliflozin demand a subsequent estimate of CV safety that will be performed on data from CANVAS and CANVAS-R, when sufficient events have occurred to demonstrate that the upper bound of the 95% CI HR is <1.3 based on MACE (excluding hospitalized unstable angina).

The assumed per annum event rate is 2.25% and the per annum dropout rate is 5% with an enrollment period of 1.5 years, 4,500 randomized subjects were projected to contribute sufficient CV events to support the pre-approval meta-analysis. The original phased recruitment strategy allowed for an interim assessment of study feasibility to demonstrate the primary hypothesis of CV benefit using the results of the interim analysis. Results from the interim analysis (after approximately 2 to 4 years from study initiation, eg, at approximately the time of US regulatory approval) were planned to be evaluated by a CV risk factor evaluation committee to assess the effect of canagliflozin on CV risk factors (to predict the likely effect of canagliflozin on CV events) and determine the point estimate for the HR for MACE. The data on the observed point estimate for the CV HR for MACE were to have been reviewed by the IDMC only and not

made more broadly available. Re-opening of enrollment was to have proceeded if the effects on the intermediate outcomes (ie, CV risk factors) suggested that canagliflozin compared with placebo would result in an HR of 0.85 or less (for MACE) and if the observed HR was 0.95 or less. If recruitment did proceed, an additional 14,000 subjects would have been enrolled into Cohort B. However, for the reason outlined above, this second cohort will no longer be recruited.

Without the recruitment of the second cohort of 14,000 subjects, CANVAS study power is reduced from the originally planned 90% power to detect a HR of 0.85 or less. It is now projected that at the completion of the study there will be about 400 MACE events recorded within CANVAS, which will provide 33% power to detect a HR of 0.85 or less, 55% power to detect a HR of 0.80 or less, and 76% power to detect a HR of 0.75 or less using a 2-sided test with 0.05 alpha.

Safety and Tolerability Analysis

Safety and tolerability will be evaluated by summarizing and comparing the incidence of serious adverse events and adverse events of interest, discontinuation rate due to adverse events, clinically important changes in clinical laboratory tests, vital signs (pulse, blood pressure), and body weight between randomized groups. There will be no imputation for missing values for clinical laboratory test results or vital sign measurements in the analyses.

CV Outcomes (Primary Efficacy Endpoint)

The primary endpoint for CV benefit will be time to MACE, which is calculated as the time from randomization to the first occurrence of MACE. The statistical hypothesis will be:

$H_{0(1.0)}$: the HR =1.0, versus $H_{1(1.0)}$: the HR $\neq$1.0.

The primary analysis will be based on the ITT analysis set based upon events determined by the EAC to meet prespecified criteria. The primary comparison of canagliflozin to placebo will be based on the HR estimate derived from a Cox proportional hazards model with terms for treatment and history of a previous CV event as fixed effects.

The assumption of the proportional HR will be examined. In case the assumption is deemed not reasonable, sensitivity analyses that do not rely on the constant HR assumption will be conducted to verify the results of the primary analysis. Additionally, the HR and its 2-sided 95% CIs versus placebo will be assessed for each dose of canagliflozin. For individual components of the composite CV endpoint, the HR and its 2-sided 95% CIs of canagliflozin combined doses relative to placebo will also be assessed.

Sensitivity analyses including CV endpoint events that occur within 30 days of the last dose of blinded study medication will be done.

The effects of different baseline demographic variables (eg, age, race, sex) as well as other important baseline disease characteristics (eg, history of prior CV disease, key concomitant therapy use, and region) on the primary endpoint will be explored; a detailed discussion of subgroup analyses will be provided in a SAP for this study which will be finalized before the first interim analysis.

Major Secondary Efficacy Analysis

Changes from baseline in the continuous variables of HOMA-B and the proinsulin/insulin ratio, HbA_{1c}, FPG, blood pressure, body weight, albuminuria, and eGFR, and percent change in fasting lipids will be analyzed using an analysis of covariance (ANCOVA) model with treatment (canagliflozin 100 mg, canagliflozin 300 mg, or placebo), and stratification factors as a fixed effect and the corresponding baseline value as a covariate. The treatment difference (each dose of canagliflozin minus placebo) in the least-squares means and the 2-sided 95% CI will be estimated based on this model. The analyses for beta-cell function will be conducted on subjects not receiving insulin at randomization and, for subjects who are started on insulin during the study, the last data point before the initiation of insulin will be included for these analyses.

The categorical secondary efficacy endpoint is the proportion of subjects with progression of albuminuria (defined as ≥1 step increase, ie, no albuminuria to micro- or macro-albuminuria or from micro-albuminuria to macro-albuminuria). The proportion of subjects with progression of albuminuria will be analyzed using

the logistic model with treatment (canagliflozin 100 mg, canagliflozin 300 mg or placebo) and stratification factors as a fixed effect.

Multiplicity Adjustment

To ensure the family-wise Type I error rate (alpha level) in this study is at most 5%, a gatekeeping procedure will be applied in testing the primary and secondary hypotheses.

Interim Analysis

Interim analyses of CANVAS will be done to prepare: (1) an interim safety report in support of the initial health authority filing, (2) the 18-week substudy reports, and (3) the CV safety meta-analyses (based on adjudicated data). The interim data from the CANVAS study will primarily supplement the safety and tolerability data generated from other studies in the canagliflozin development program.

TIME AND EVENTS SCHEDULE

Phase	**Pretreatment**			**Double-Blind Treatment**												
Procedures and Evaluations	**Screening**	**Run-in[a]**	**Baseline**									**13-week intervals[v]**	**26-week intervals**	**52-week intervals**		
Week[d]	-3	-2	Day 1	2, 4 (TC)[e]	6	9 (TC)[e]	12	18	26	39	52	65 to end	78 to end	104 to end[u]	**EOT or EW[b]**	**Follow-up Contact[c]** 30 days after last dose of study drug[c]
Pretreatment/Administrative																
Informed consent[f]	X															
Pharmacogenomic consent[f, q]			X													
Inclusion/exclusion criteria	X	X	X													
Medical history and demographics	X	X														
Prestudy therapy[g]	X	X	X													
Run-in compliance assessment			X													
Randomize			X													
Pretreatment Procedures																
Follicle stimulating hormone (if necessary per inclusion criteria)		X														
Counseling for diet & exercise and for hypoglycemia recognition & treatment[h]		X														
Dispense glucose testing supplies and first subject diary		X														
Study Drug																
Dispense single-blind placebo		X														
Administer/dispense double-blind study drug			X				X	X	X	X	X	X[v]	X	X		
Procedures																
Physical examination[i]		X														
Vital signs,[j] weight, foot examination[j]	X	X	X		X		X	X	X	X	X		X	X	X	
Height		X														
12-lead ECG (central reading)		X									X					
Provide container for urine collection for first morning void	X	X			X					X		X[k]	X[k]			
Medical resource utilization[l]					X		X	X	X	X	X	X	X	X	X	

NOTE: Footnotes are provided after the table.

CV=cardiovascular; EOT=end-of-treatment; EW=early withdrawal; HbA_{1c}= hemoglobin $A_{1c;}$ SMBG=self-monitored blood glucose; TC=telephone contact (Continued)

TIME AND EVENTS SCHEDULE (CONTINUED)

Phase	**Pretreatment**			**Double-Blind Treatment**												
Procedures and Evaluations	**Screening**	**Run-in[a]**	**Baseline**									**13-week intervals[v]**	**26-week intervals**	**52-week intervals**		
Week[d]	-3	-2	Day 1	2, 4 (TC)[e]	6	9 (TC)[e]	12	18	26	39	52	65 to end	78 to end	104 to end	**EOT or EW[b]**	**Follow-up Contact[c]** 30 days after last dose of study drug[c]
Clinical Laboratory Assessments																
Hematology[m]		X	X					X			X			X	X	
Urinalysis[m]		X	X					X			X			X	X	
Serum chemistry[m]	X		X		X			X		X	X		X	X	X	
HbA_{1c}	X		X				X	X	X	X	X		X	X	X	
Fasting plasma glucose[m]		X	X		X		X	X	X		X			X	X	
Fasting fingerstick glucose[m]			X													
Fasting serum C-peptide, insulin, proinsulin[m, o](subset of subjects at sites that elect to participate)			X								X			X	X	
Fasting lipids[m]	X[n]	X[n]	X					X			X			X	X	
First morning void urine for albumin/creatinine ratio[m, p]		X	X				X				X			X	X	
Plasma, serum, and urine samples for exploratory analysis[m]			X								X			X	X	
Pharmacogenomic specimen[q]			X													
Urine pregnancy test[r]		X	X													
Ongoing Review																
Review/discuss subject diary and SMBG results[s]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant therapy[t]				X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events [u]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Events in CV composite endpoint		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

NOTE: Footnotes are provided after the table.

CV=cardiovascular; EOT=end-of-treatment; EW=early withdrawal; HbA_{1c}= hemoglobin $A_{1c;}$ SMBG=self-monitored blood glucose; TC=telephone contact (Continued)

TIME AND EVENTS SCHEDULE (CONTINUED)

[a] Following the run-in visit, there will be a single-blind, placebo run-in period, during which therapy for diabetes should remain stable and therapy for CV risk factors (eg, blood pressure, fasting lipids) will be optimized as needed, at the investigator's discretion. Subjects who fail protocol-specified screening criteria for study entry may be rescreened, at the discretion of the investigator as described in Section 4.5, Rescreening.

[b] End-of-treatment/early withdrawal evaluations will be performed when the double-blind treatment phase of the study is ended or at the time the subject discontinues the double-blind study drug or is withdrawn from the study. Evaluations will be performed as soon as possible after stopping the study drug. Subjects who discontinue double-blind treatment for any reason will have a posttreatment follow-up contact and visits according to the Posttreatment Time and Events Schedule for the duration of the study, until completion of the study. It is the expectation that the investigator will make every effort to ascertain the vital status of all subjects at the end of the study, including using all reasonable means to contact the subject, family members, the subject's physicians and medical records, and the use of locator agencies and checking public records, as allowed by local law.

[c] A telephone follow-up contact (or optional study visit, at the discretion of the investigator) will be conducted for all subjects approximately 30 days (and no more than 42 days) after the last dose of study drug. If a telephone contact or study visit is not possible, follow-up information may be collected via email or other electronic or non-electronic means.

[d] After Week 65, on those occasions when the 13- 26-, and/or 52-week-interval visits overlap each other, the visit with the more comprehensive procedures will be followed.

[e] Telephone contact (or an optional, unscheduled site visit, at the discretion of the investigator) will be made at Weeks 2, 4, and 9 to check the subject's status, including discussing the subject's diary entries and any CV events or adverse events. If a telephone contact or study visit is not possible, follow-up information may be collected via email or other electronic or non-electronic means.

[f] See Section 16.2.3, Informed Consent, for details. The informed consent form must be signed before any study procedure is performed.

[g] Record as prestudy therapy any medications taken from 30 days before screening (except for AHAs; record AHAs taken within 12 months of screening).

[h] Subjects will receive information regarding the symptoms of and treatment for hypoglycemia. Signs and symptoms of hypoglycemia (and concurrent fingerstick glucose measurement, if available) should be captured in the subject diary, which should be brought to the study center for review by research study staff.

[i] Full physical examination will include a full review of body systems (vital signs, as below, head and neck, eyes, chest and lungs, breast, CV, extremities and back, abdomen, and neurological examination). A pelvic/genitourinary system examination (ie, prostate, rectal, and gynecologic examinations) should be performed if considered clinically appropriate by the investigator.

[j] Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (sitting position, after sitting for 5 minutes; record 3 consecutive blood pressure readings, at intervals of at least 1 minute apart). Consistent with standard diabetes treatment guidelines, all study participants should be provided with routine preventative foot care and early intervention for foot problems (see Section 12.2.1 All Adverse Events for further detail).

[k] Only required before a 52-week interval visit, regardless of whether the subject is coming for in-clinic visits every 13 or 26 weeks.

[l] Medical resource utilization (MRU) data should be collected in the subject diary. A sample list of MRU questions contained in the diary is provided in Attachment 9.

[m] Specific details about specimen collection, storage, packaging, and shipping will be provided in operations manuals. For fasting plasma glucose, insulin, proinsulin, C-peptide, and lipids, subjects must be fasting for at least 8 hours before blood sample collection, except for the screening visit when nonfasting blood samples may be collected. The first morning void specimens will be used to measure albumin and creatinine. A set of plasma, serum, and urine samples for exploratory analysis will be collected at each specified time point. (Specific details about specimen collection, storage, packaging, and shipping are provided in Attachment 4.) The urine collections for routine urinalyses and exploratory specimens should be obtained from a spot urine specimen in the clinic.

(Continued)

TIME AND EVENTS SCHEDULE (CONTINUED)

[n] If the subject is fasting at the screening visit, the lipid profile can be obtained at that time point; otherwise, fasting lipid profile should be obtained at the Week -2 visit.

[o] C-peptide, insulin, and proinsulin measurements will be performed on a subset of subjects (at sites that elect to participate) who are not receiving insulin at baseline; if a subject starts insulin therapy after baseline, no further assessments of these analytes will be made for that subject.

[p] The subject will provide a urine specimen from the first morning void on the morning of the clinic visit. If the subject does not provide the morning void collection on the day of the visit, the subject may bring a first morning void specimen to the investigational site during the subsequent week. For subjects working a night shift, or who otherwise have atypical sleep patterns, the collection should be made at the end of the subject's usual sleep period.

[q] Subject participation in the pharmacogenomics component of the study is optional. A 10-mL blood sample will be collected only from subjects who give informed consent for the pharmacogenomics component of the study to allow for pharmacogenomic research, as necessary (where local regulations permit). A sample may be collected at any point in time during the study if not obtained at baseline.

[r] If positive, the subject is not eligible to enter or continue in the study. A urine pregnancy test will be performed at all specified pre-randomization clinic visits, unless a serum pregnancy test is preferred at the discretion of the investigator or if required by local regulations. Serum or urine pregnancy tests may be performed in women (unless they are surgically sterile or unless there is a documented history of their postmenopausal status), as determined by the investigator or required by local regulations, to establish the absence of pregnancy at any time during the study.

[s] See Section 9.1.1, Overview, for diary procedures.

[t] Concomitant therapy includes all medications taken after the initiation of double-blind study medication (Day 1); after study drug discontinuation, use of AHA therapies will be recorded at the final visit or contact.

[u] Only serious adverse events, adverse events resulting in study drug discontinuation, and adverse events of interest will be recorded on eCRFs. Adverse events of interest include: all malignancies, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (eg, angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, male genital infections (balanitis, phimosis, events leading to circumcision), and pregnancy. Information on these events will be recorded on a supplemental eCRF or other designated forms for any event that is serious or that leads to study drug discontinuation. In addition, non-serious adverse events of malignancies, photosensitivity reactions, fractures, venous thromboembolic events, and male genital infections (balanitis, phimosis, events leading to circumcision) and amputation for which information on non-serious adverse events will also be recorded on the supplemental CRF pages or other designated forms (in addition to the information collected on serious AEs and AEs leading to study drug discontinuation). Diabetic ketoacidosis has been designated an adverse event of special interest and therefore adverse events related to DKA, ketoacidosis, metabolic acidosis or acidosis need to be reported to the sponsor within 24 hours of becoming aware of the event, which is the same timeframe for reporting of serious adverse events. These adverse events must be reported using a supplemental DKA Reporting form, to complement standard information collected on the eCRF AE/SAE page. Amputation has also been designated as an adverse event of special interest and therefore amputations need to be reported to the sponsor within 24 hours of becoming aware of the event. If adverse events of interest are identified in the future, guidance concerning the reporting of those events may be provided to investigators via appropriately-documented study communications. Details regarding adverse event collections are provided in Section 9.4, Safety Evaluations.

[v] Every 13-week in-clinic visits are no longer required and may be changed to every 26-week in-clinic visits (at the option of the investigator). Accordingly, study drug may be supplied every 13 or 26 weeks. If in-clinic visits are changed to a every 26 week frequency, a telephone contact should occur in between the 26-week in-clinic visits such that there will be a contact with the subject every 13 weeks (in-clinic visit alternating with telephone contacts). At each telephone contact, investigators should ask subjects about any foot problems and remind them about routine preventative foot care and early intervention for foot problems.

POSTTREATMENT TIME AND EVENTS SCHEDULE – SUBJECTS WHO PREMATURELY DISCONTINUE STUDY MEDICATION

Phase	**Double-Blind Visit Schedule (Posttreatment) - Starting at the nearest post-randomization week after the Follow-up Contact Visit -**									
Procedures and Evaluations									**TC or clinic visit at 26-week intervals**	**Clinic visit at 52-week intervals**
Week[a]	2, 4 (TC)[b]	6	9 (TC)[b]	12	18	26	39	52	78 to end [e]	104 to end [e]
Procedures										
Vital signs, weight, Foot examination[c]		X		X	X	X	X	X	X (foot examination only)	X
Provide container for urine collection for first morning void		X					X			
Serum creatinine		X			X		X	X		X
HbA_{1c}				X	X	X	X	X		X
Fasting serum lipids					X			X		X
First morning void urine for albumin/creatinine ratio[d]				X				X		X
Ongoing review										
Serious adverse events and adverse events of fracture	X	X	X	X	X	X	X	X	X	X
AHA agents after study drug discontinuation										At final visit or contact
Events in CV composite endpoint	X	X	X	X	X	X	X	X	X	X

[a] After Week 78, on those occasions when the 26- and/or 52-week-interval visits overlap each other, the visit with the more comprehensive procedures will be followed.

[b] Telephone contact (or an optional, unscheduled site visit, at the discretion of the investigator) will be made at Weeks 2, 4, and 9 to check the subject's status, including discussing the subject's diary entries and any CV events or adverse events. If a telephone contact or study visit is not possible, follow-up information may be collected via email or other electronic or non-electronic means.

[c] Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (sitting position, after sitting for 5 minutes; record 3 consecutive blood pressure readings, at intervals of at least 1 minute apart). At each visit or telephone contact, investigators should ask subjects about any foot problems and remind them about routine preventative foot care and early intervention for foot problems.

[d] Specific details about specimen collection, storage, packaging, and shipping will be provided in operations manuals. The first morning void specimens will be used to measure albumin and creatinine. The subject will provide a urine specimen from the first morning void on the morning of the clinic visit. If the subject does not provide the morning void collection on the day of the visit, the subject may bring a first morning void specimen to the investigational site during the subsequent week. For subjects working a night shift, or who otherwise have atypical sleep patterns, the collection should be made at the end of the subject's usual sleep period.

[e] It is the expectation that the investigator will make every effort to ascertain the vital status of all subjects at the end of the study, including using all reasonable means to contact the subject, family members, the subject's physicians and medical records, and the use of locator agencies and checking public records, as allowed by local law.

Note: Alternate follow-up provisions may be used by the investigator if necessary (see Section 9.1.4).

CV=cardiovascular; TC=telephone contact.

ABBREVIATIONS

ADA	American Diabetes Association
AHA	antihyperglycemic agent
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARO	Academic Research Organization
AST	aspartate aminotransferase
BMI	body mass index
CPK	creatine phosphokinase
CI	confidence interval
CV	cardiovascular
CYP	cytochrome P450
DKA	diabetic ketoacidosis
DPP-4	dipeptidyl peptidase 4
eCRF	electronic case report form
eDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMEA	European Medicines Agency
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP-1	glucagon-like peptide-1
GTED	global trial end date
HbA_{1c}	hemoglobin A_{1c}
HDL-C	high-density lipoprotein cholesterol
HOMA	homeostasis model assessment
HR	hazard ratio
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IVRS/IWRS	interactive voice response system/interactive web response system
LCT	Leydig cell tumor
LDL-C	low-density lipoprotein cholesterol
LOCF	last-observation-carried-forward
MACE	major adverse cardiovascular events
MDRD	Modification of Diet in Renal Disease
MI	myocardial infarction
mITT	modified intent-to-treat
MRU	Medical Resource Utilization
MSRC	Medical Safety Review Committee
NAG	N-acetyl glucosaminidase
NYHA	New York Heart Association
PG	plasma glucose
PP	per-protocol
PQC	Product Quality Complaint
SAP	statistical analysis plan
SGLT1/SGLT2	sodium-glucose co-transporter 1/sodium-glucose co-transporter 2
SMBG	self-monitored blood glucose
SU	sulphonylurea
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus

UGE	urinary glucose excretion
ULN	upper limit of normal
US	United States
UVA/UVB	ultraviolet A/ultraviolet B

1. INTRODUCTION

Over the past decades, the incidence of type 2 diabetes mellitus (T2DM) has been rapidly rising worldwide, driven primarily by an increasing incidence of obesity and sedentary lifestyles. Patients with T2DM can develop severe microvascular complications, related to persistently elevated glucose concentrations, including blindness, renal failure, or nerve damage, and have a higher incidence of atherosclerotic vascular disease with complications such as myocardial infarction (MI), stroke, and amputations due to vascular insufficiency. Improved glucose control reduces the incidence of microvascular complications in patients with both type 1 diabetes mellitus (T1DM) and T2DM. The impact of improved glycemic control on macrovascular events is less well-established.

Despite the availability of a range of therapeutic options, many patients with T2DM do not achieve or maintain glycemic control. Many of these treatments are associated with safety or tolerability issues, including hypoglycemia, edema, or gastrointestinal adverse experiences which can limit dose and hence therapeutic benefit. Further, some of the current antihyperglycemic agents (AHAs) are associated with weight gain, and only a few agents (eg, metformin and glucagon-like peptide-1 [GLP-1] analogues) lead to weight loss, an important advantage in a patient population that is often obese. Most patients with T2DM are initially managed with single-agent therapy, usually metformin. Over time, patients often require more intensive regimens, combinations of 2 or 3 agents, and eventually require insulin to maintain target glycemic control. Underlying this need for increasingly intensive treatment is a progressive loss of beta-cell mass and function, with consequent diminished insulin secretion. There remains a substantial unmet medical need for new medications to treat patients with T2DM that are well tolerated and efficacious, provide good durability, beneficially impact beta-cell function and insulin secretion, and are associated with weight loss.

In healthy individuals, glucose is freely filtered through the renal glomerulus and then reabsorbed in the proximal tubules. The renal threshold for glucose (RT_G) is the glucose plasma concentration above which glucose reabsorption by the proximal renal tubules is incomplete and glucose is excreted into the urine. A typical RT_G level in healthy individuals is approximately 180 mg/dL (10 mmol/L) (Ganong 2005; Rave 2006; Seifter 2005). Glucose reabsorption in the renal tubules, determining the renal threshold is largely due to 2 key glucose transporters: sodium glucose co-transporter 2 (SGLT2) and sodium glucose co-transporter 1 (SGLT1). Sodium glucose co-transporter 2 is a high-capacity and low-affinity glucose transporter exclusively expressed at the luminal membrane of the S1 and S2 segments of the proximal renal tubules. Sodium glucose co-transporter 2 is responsible for the majority of filtered glucose reabsorption from the lumen. Sodium-glucose co-transporter 1 expressed in the S3 segment, a low capacity and high-affinity transporter, is also involved in reabsorption of filtered glucose from the lumen (Wright 2001). Sodium-glucose co-transporter 1 is also highly expressed in the intestine and is responsible for intestinal glucose and galactose absorption.

Pharmacologic inhibition of SGLT2 is a novel mechanism to decrease renal glucose reabsorption, as it lowers the RT_G and leads to an increase in urinary glucose excretion (UGE), thereby directly lowering plasma glucose in individuals with elevated glucose concentrations. Canagliflozin is an orally active inhibitor of SGLT2. This agent has much higher potency for SGLT2 relative to SGLT1; at the plasma drug concentrations achieved with the doses in this study, canagliflozin would be expected to provide significant systemic inhibition of SGLT2 and not of SGLT1. In addition to lowering plasma glucose concentrations, the increased renal glucose excretion with SGLT2 inhibition also translates to a loss of calories, leading to a net negative energy balance and the potential for weight loss.

The canagliflozin clinical program was designed to assess the safety and efficacy of canagliflozin in subjects with T2DM. As of 01 May 2013, approximately 1,840 subjects (including healthy subjects, non-diabetic subjects with specific diseases [eg, renal or hepatic disease], and subjects with T2DM), have completed studies in the Phase 1 program conducted by the sponsor. In addition, 1,106 subjects in three Phase 2 studies and 10,961 subjects in 10 Phase 3 studies have completed or are participating in clinical studies conducted by the sponsor.

A Phase 3 development program provided evidence for the effectiveness of canagliflozin both as monotherapy and in combination with approved, commonly prescribed AHA therapies in T2DM. These 9 studies spanned a range of clinical uses (as monotherapy or as combination therapy) to treat T2DM. Three of the Phase 3 studies evaluated canagliflozin in special populations, including older adults with T2DM, subjects with T2DM who had moderate renal impairment, and subjects with T2DM who had or were at high risk for cardiovascular (CV) disease. Results of the extensive Phase 3 clinical development program indicate that canagliflozin has the potential to be a useful addition to currently available AHAs.

Canagliflozin was approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in the United State (29 March 2013), Australia (12 September 2013) and Mexico (23 October 2013). On 19 September 2013, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorization for canagliflozin.

An ongoing clinical program designed to continue research on the effects of the agent on renal and CV outcomes is underway. The goal of this study is to assess the effects of canagliflozin compared to placebo on CV events.

The term “sponsor” used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

For more detailed and current information regarding the preclinical characterization of canagliflozin pharmacokinetics (PK) (ie, absorption, distribution, metabolism and excretion) and toxicology, and clinical study results, refer to the current version of the Investigator's Brochure for canagliflozin (IB JNJ-28431754).

1.1.1. Brief Overview of Nonclinical Studies

For a complete review of the findings and discussions regarding implications for human risk, please refer to the current version of the canagliflozin Investigator's Brochure.

1.1.2. Clinical Studies

Pharmacokinetics

Canagliflozin exhibits similar PK in healthy subjects and subjects with T2DM. The mean absolute oral bioavailability of canagliflozin was 65% following single-dose administration of the canagliflozin 300 mg tablet in healthy subjects. In healthy subjects (25 to 1,600 mg once-daily [QD]) and subjects with T2DM (50 mg to 300 mg QD and 300 mg twice-daily [BID]), after oral administration of single and multiple doses, mean canagliflozin $AUC_{0-\infty}$ increased in an approximately dose-proportional manner whereas mean maximum plasma concentration (C_{max}) increased in an approximately dose-proportional manner up to 1,200 mg. Following oral administration of canagliflozin, the median time to reach maximum plasma concentration (t_{max}) was approximately 1 to 2 hours. The mean terminal plasma elimination half-life ($t_{1/2}$) of canagliflozin was 10 and 13 hours with canagliflozin doses of 100 and 300 mg, respectively. The t_{max} was independent of dose. After repeated dosing with 50 to 300 mg canagliflozin, steady state was reached by 4 to 5 days. Minimal accumulation of canagliflozin was observed at steady-state across 50, 100, and 300 mg doses with mean accumulation ratios ranging from 1.3 to 1.4 in subjects with T2DM. Bioavailability of canagliflozin was not affected after co-administration of canagliflozin 300 mg with food in healthy subjects indicating that the canagliflozin tablet formulation may be taken without regard to meals.

O-glucuronidation is the major metabolic elimination pathway for canagliflozin in humans. In human plasma, 2 non-pharmacologically active *O*-glucuronide conjugates of unchanged drug, M5 (formed by UGT2B4) and M7 (formed by UGT1A9), were present. Co-administration with rifampin, a nonselective inducer of several UGT enzymes, decreased canagliflozin area under the curve (AUC) by 51%, which may decrease efficacy. There was an increase in the AUC and C_{max} of digoxin when co-administered with canagliflozin 300 mg. Subjects taking concomitant digoxin should be monitored appropriately. The C_{max} of canagliflozin was not meaningfully altered by renal impairment.

Based on in vitro data and the clinical drug-drug interaction studies conducted to date, the potential for clinically significant CYP450 based PK interactions appears to be low.

Pharmacodynamics

In subjects with T2DM following single and multiple oral doses (30 to 600 mg QD and 300 mg BID), canagliflozin treatment dose dependently increased $UGE_{0\text{-}24h}$, with mean $UGE_{0\text{-}24h}$ of approximately 100 g/day typically observed with doses of 100 mg/day or higher.

In subjects with T2DM, canagliflozin treatment with 100 mg and 300 mg once daily lowered RT_G to approximately 70 to 90 mg/dL (3.9 to 5.0 mmol/L), respectively. Because RT_G remains above PG levels associated with hypoglycemia and because very little UGE occurs whenever plasma glucose (PG) is below the RT_G, canagliflozin, itself, is not expected to pose a risk for hypoglycemia.

Efficacy

In the Phase 3 studies, canagliflozin has been assessed as monotherapy, as add-on therapy with metformin, sulphonylurea (SU), metformin and SU, metformin and a peroxisome proliferator-activated receptor (PPARγ) agonist (pioglitazone), and as add-on therapy with insulin (with or without other AHAs). The Phase 3 program also includes studies in special populations of patients with T2DM: subjects with renal impairment (estimated glomerular filtration rate [eGFR] ≥30 to <50 mL/min/1.73 m^2); subjects with or at high risk for CV complications; and older subjects. The latter 2 studies also included subjects on incretin-based therapies, including dipeptidyl peptidase 4 (DPP-4) inhibitors and GLP-1 agonists.

Glycemic Efficacy

Results of the Phase 3 studies demonstrated the efficacy of canagliflozin in reducing hemoglobin A_{1c} (HbA_{1c}) in a broad range of subjects with T2DM, both with recent onset as well as long-standing diabetes and on a range of different background AHAs. A clinically meaningful improvement in glycemic control was seen when canagliflozin was given as monotherapy and when given in dual combinations (add-on to metformin or to SU agents), in triple oral AHA combinations (add-on to metformin plus an SU agent or metformin plus pioglitazone), in combination with insulin (alone or in combination with other agents), or as an add-on to existing diabetes therapy (any approved oral or parenteral therapy). In the monotherapy study, HbA_{1c} reductions of -0.91% and -1.16% relative to placebo for canagliflozin 100 mg and 300 mg, respectively, were observed. In the studies examining specific add-on combination uses, the efficacy of canagliflozin in lowering HbA_{1c}, relative to placebo, was generally consistent ranging from -0.62% to -0.74% with the 100 mg dose and from -0.73% to -0.92% with the 300 mg dose. Across all studies, the 300 mg dose consistently provided greater HbA_{1c} lowering relative to the 100 mg dose; since reduction in diabetic microvascular complications is continuous with improvements in glycemic control, the additional glucose-lowering efficacy with the 300 mg dose is considered likely to be clinically relevant (UKPDS 1998, DCCT 1993).

Results of subgroup analyses performed in a pooled population of the placebo-controlled Phase 3 studies found no important differences when comparing the effect of canagliflozin in change from baseline in HbA_{1c} based on baseline demographic characteristics (age, sex, race, ethnicity), body mass index (BMI), or geographic region. Greater reductions in HbA_{1c} relative to placebo were observed with canagliflozin among subjects with higher baseline HbA_{1c} and higher eGFR values compared with subjects with lower baseline values. In subjects with moderate renal impairment (ie, baseline eGFR's between 30 to 60 mL/min/1.73m^2), the mean, placebo-subtracted reduction in HbA_{1c} was 0.38% and 0.47% on canagliflozin 100 mg and 300 mg respectively. A total of 24% and 32% of subjects achieved a target HbA_{1c} <7% at the end-of-treatment on canagliflozin 100 mg and 300 mg respectively compared to 17% of subjects on placebo.

With regard to other glycemic endpoints, canagliflozin provided improvements in fasting plasma glucose (FPG) as well as in the post-prandial glucose (PPG) excursion. Canagliflozin also provided improvements in beta-cell function and a reduction in beta-cell stress as reflected by a decrease in the proinsulin/C-peptide ratio. The improvement in beta-cell function and reduction in beta-cell stress is consistent with the sustained effect of canagliflozin on both HbA_{1c} and FPG observed in the 52-week studies.

Weight and Blood Pressure Effects

In addition to the observed glycemic improvements, treatment with canagliflozin resulted in consistent, statistically significant reductions in total body weight relative to placebo. Weight loss with canagliflozin appeared dose-related (with -1.4% to -2.7% reductions with 100 mg and -1.8% to -3.7% reductions with 300 mg, relative to placebo). Results of specialized body composition investigations using dual energy X-ray absorptiometry (DXA) in 2 of the Phase 3 studies showed that the body weight reduction with canagliflozin was attributable to a greater decrease in body fat mass relative to lean body mass.

Reductions in SBP were observed with canagliflozin in Phase 3 studies (ranging from -2.2 to -5.7 mm Hg of SBP with canagliflozin 100 mg dose, and -1.6 to -7.9 mm Hg with the 300 mg dose, relative to placebo, in placebo-controlled 26-week studies), and were generally statistically significantly greater for both doses relative to placebo, and also greater relative to comparator agents (glimepiride and sitagliptin).

Safety

For a complete review of the adverse drug reactions (ADRs) and laboratory findings associated with canagliflozin, please refer to the current version of the canagliflozin Investigator's Brochure (IB JNJ-28431754).

The safety and tolerability profile that emerges from the development program for canagliflozin shows a medication that is overall well tolerated. The incidence of

discontinuations due to adverse events was slightly higher than seen in the control group, though generally low. The small increase in discontinuations due to adverse events were generally related to specific ADRs, described below, with each particular ADR infrequently leading to discontinuations; there was no increase in serious adverse events or deaths in the canagliflozin treatment groups relative to control groups.

Adverse drug reactions associated with canagliflozin include genital mycotic infections, urinary tract infections, adverse events related to osmotic diuresis, and adverse events related to reduced intravascular volume, as well as constipation, and a low incidence of rash or urticaria.

In men, the genital mycotic infections (including balanitis and balanoposthitis) occurred predominantly in uncircumcised individuals and in those with a past history of genital mycotic infections, generally did not lead to discontinuation from the study. Circumcision was performed in 17/3569 (0.5%) and 3/1924 (0.2%) of men treated with canagliflozin and control, respectively. In women, genital mycotic infections (including candidal vulvovaginitis) occurred more commonly in women with a prior history of genital mycotic infections and did not generally lead to discontinuation. A modest increase in the incidence of adverse events of urinary tract infection (mostly lower tract infections) was observed with canagliflozin relative to control, without an increase in serious adverse events of urinary tract infection.

Adverse drug reactions were observed that relate to the osmotic diuretic effect of canagliflozin, with increases in UGE leading to a diuretic action; this included ADRs of pollakiuria (increased urinary frequency), polyuria (increased urinary volume), and thirst. Adverse drug reactions related to reduced intravascular volume were observed including postural dizziness, orthostatic hypotension, and hypotension. Risk factors for volume-related adverse events on canagliflozin treatment were ≥75 years of age, eGFR of 30 to 60 ml/min/1.73m^2 and use of loop diuretics. These adverse events were generally considered as mild or moderate in intensity, and infrequently led to discontinuation. No increase in serious adverse events related to reduced intravascular volume were seen with canagliflozin treatment. The reduction in intravascular volume also led to reversible reductions in eGFR that generally attenuated with continued treatment.

Based on the observations from the 2-year rat carcinogenicity study (findings of renal tubular cell cancers, Leydig cell tumors [LCTs], and pheochromocytomas), an extensive preclinical toxicology program was conducted that demonstrated that these tumors related to effects of canagliflozin in rats, not seen in humans (including rises in luteinizing hormone [LH] associated with LCT, and carbohydrate malabsorption leading to associated metabolic effects, including marked hypercalciuria, inducing renal tubular tumors and pheochromocytomas). In the clinical program, there were no reports of LCT or pheochromocytoma and there was a low incidence across treatment groups of renal cell cancers without imbalance.

In preclinical studies in rats, hyperostosis (increased trabecular bone) was observed; mechanistic toxicology studies demonstrated that hyperostosis, like the tumors discussed above, related to carbohydrate malabsorption in rats treated with canagliflozin, with consequent marked hypercalciuria (which is not seen in human). A detailed analysis of bone safety was conducted in the Phase 3 program, including an assessment using DXA in a dedicated Phase 3 study (a study conducted in older subjects [ages ≥55 and ≤80 years] with T2DM) and a cross-program assessment of fracture incidence. Bone mineral density (BMD) was examined at 4 sites: at the lumbar spine, total hip, distal radius, and femoral neck. Minimal changes in BMD from baseline to Week 104 were seen in the lumbar spine (a cancellous bone region), femoral neck (a mixed cancellous and cortical bone region), and distal forearm. A decrease in BMD from baseline to Week 104 in the total hip, a site comprised of mixed cortical and cancellous bone (like the femoral neck), was observed for both canagliflozin treatment groups (0.9% and 1.2% in the canagliflozin 100 mg and 300 mg groups, respectively, placebo adjusted). In a cardiovascular study of 4,327 subjects with known or at high risk for cardiovascular disease (Study DIA3008), the incidence rates of bone fracture were 1.6, 1.6, and 1.1 per 100 subject-years of exposure to canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively, with the fracture imbalance initially occurring within the first 26 weeks of therapy. In other T2DM studies with canagliflozin, which enrolled a general diabetes population of approximately 5,800 subjects, no difference in fracture risk was observed relative to control (Investigator's Brochure).

Increases in low-density lipoprotein cholesterol (LDL-C) were observed with canagliflozin: in a pooled analysis of placebo-controlled 26-week studies, increases in LDL-C relative to placebo were 4.4 mg/dL (0.11 mmol/L) and 8.2 mg/dL (0.21 mmol/L) at the 100 mg and 300 mg doses, respectively. Relative increases in Apo B, non-HDL-C, and LDL particle number were approximately half as large as the rise in LDL-C. The changes in the CV risk profile with canagliflozin include reductions in SBP and increases in LDL-C, both established CV risk factors, and validated as surrogate endpoints. Improvements in other endpoints associated with CV risk, but not established as surrogate endpoints for CV benefit, such as body weight, glycemic control, HDL-C, and TG were also observed with canagliflozin. The cross-program CV meta-analysis (including results from the dedicated CV safety study) observed a hazard ratio (HR) of 0.91 for a pre-specified composite endpoint of CV death, non-fatal MI, non-fatal stroke, and hospitalized unstable angina (95% confidence interval [CI]: 0.68, 1.22), showing no signal for an increase in the CV risk.

As of 11 May 2015, in the T2DM clinical development program, incidence rates of unblinded serious adverse events of DKA, ketoacidosis, metabolic acidosis, and acidosis were 0.0522 (0.07%, 4/5337), 0.0763 (0.11%, 6/5350), and 0.0238 (0.03%, 2/6909) per 100 subject-years with canagliflozin 100 mg, canagliflozin 300 mg, and comparator, respectively. Of the 12 subjects with serious adverse events of DKA, ketoacidosis, metabolic acidosis, or acidosis (all of whom were hospitalized), 6 subjects on

canagliflozin (3 on canagliflozin 100 mg and 3 on canagliflozin 300 mg), and none on comparator were reported to have autoimmune diabetes (latent autoimmune diabetes of adulthood [LADA] or type 1 diabetes) or tested positive for GAD65 antibodies after being diagnosed with a serious DKA-related event. Eight of the 10 subjects on canagliflozin were receiving insulin therapy. The blood glucose values around the time of admission in 9 of 10 subjects on canagliflozin ranged from 347 to 571 mg/dL (9.3 to 31.7 mmol/L). The remaining subject had blood glucose values ranging from 148 to 320 mg/dL (8.2 to 17.8 mmol/L). Diabetic ketoacidosis has also been reported during post-marketing surveillance and has occurred in patients with blood glucose values less than 250 mg/dL (13.9 mmol/L). As a result, DKA is considered a rare adverse drug reaction.

During a routine review of unblinded interim data from the ongoing CANVAS study, the Independent Data Monitoring Committee observed a non-dose-dependent increase in the incidence of non-traumatic, lower-extremity amputations (mostly of the toes) in the canagliflozin 100 mg and 300 mg groups compared to placebo. With a mean duration of follow-up in CANVAS of approximately 4.5 years, the annualized incidence of lower-extremity amputation was 0.73, 0.54, and 0.30 events per 100 patient-years in the canagliflozin 100 mg, canagliflozin 300 mg, and placebo groups, respectively. Overall, treatment with canagliflozin was associated with an approximately 2-fold increase in amputation event rates (relative risk [RR] 2.15; 95% CI: 1.3- 3.5). The CANVAS/CANVAS-R IDMC, which has access to unblinded CV outcomes data, notified the sponsor that "after consideration of all outcomes, the IDMC feels the study should continue." Infections were the events most commonly associated with amputations, and most amputations were of the toe. The factors associated with the greatest risk for amputation included prior amputation, peripheral vascular disease, and neuropathy.

1.2. Overall Rationale and Goals for the Study

Patients with T2DM have an increased risk of both microvascular and macrovascular complications which lead to morbidity and mortality. New therapies are needed that can provide improved glycemic control—which has been shown to reduce microvascular complications—and lower the risk of macrovascular complications.

Prior clinical studies of canagliflozin in patients with T2DM have demonstrated improvements in glycemic control (with reductions in HbA_{1c} and FPG), reduction in body weight, and trends towards improvements in other CV disease risk factors (including increases in HDL-C, decreases in triglyceride levels, and decreases in blood pressure, especially at the 300-mg dose), with generally good tolerance and appropriate safety to support continued clinical development of this medication. With improved glycemic control, which itself may provide a benefit in CV risk (Ray 2009), and the trends towards benefit on other CV risk factors including body weight, the potential for a benefit of long-term treatment with canagliflozin on CV disease is raised.

The present study was intended to determine if treatment of subjects with T2DM with canagliflozin reduces CV risk for major adverse cardiovascular events (MACE, including CV death, nonfatal MI, and nonfatal stroke) and also was intended to achieve a number of other important goals. These include the assessment of overall safety and tolerability, glycemic efficacy (in the overall study population and in subjects on specific AHAs), long-term effects on beta-cell function, and long-term effects on renal function with canagliflozin treatment. This study also provides key support for a cross-canagliflozin program assessment of CV safety, examining a composite endpoint of MACE plus hospitalized unstable angina (pre-approval CV safety assessment) and MACE (post-approval CV safety assessment). Subsequent to the initial plan it was necessary to modify the design of the study.

To evaluate the effect of canagliflozin on CV risk, this study was to recruit up to 18,500 subjects with T2DM who are at increased risk for CV events, in 2 separate cohorts, including an initial cohort of 4,500 subjects and a subsequent cohort of 14,000 subjects (recruited after an interim analysis of results from the initial cohort). The study will now continue with the initial 4,330 randomized subjects.

The study was modified (as of amendment INT-5) because the cross-program meta-analysis of the pre-approval CV safety endpoint was unblinded to the sponsor to prepare regulatory submissions (originally this was to be unblinded to the study IDMC only); this was done based upon a decision by the sponsor, so that the impact of the small dose-related increase in LDL-C observed with canagliflozin treatment in Phase 3 program on the CV HR could be evaluated. Due to the unblinding of these CV endpoint results, the study Steering Committee noted that the addition to the CANVAS study of the planned second cohort of subjects would not provide a robust assessment of the primary CV protection hypothesis.

As part of the safety and tolerability objective, the study was originally designed to be able to show, within 4 years of marketing approval in the US, that the upper bound of the CV HR for MACE plus unstable angina events was <1.3. Upon approval of canagliflozin for marketing, the US FDA required that the 1.3 requirement be met with MACE events (ie, CV death, nonfatal MI, and nonfatal stroke, and excluding hospitalized unstable angina), and that additional subjects with high CV risk be recruited to explore events occurring within the first 30 days after initiation of therapy. Accordingly, it was not possible to fulfill these requirements solely with the ongoing CANVAS study within the 4 year post-approval timeframe required by FDA, and therefore another large-scale study of the effects of canagliflozin compared to placebo (CANVAS-R; 28431754DIA4003) with 5,700 subjects is being initiated to meet the FDA CV safety requirement.

The primary objective of the CANVAS-R study is to evaluate the effects of canagliflozin relative to placebo on albuminuria progression. The CANVAS and CANVAS-R studies will share similar inclusion and exclusion criteria and will enroll similar patient

populations. Both studies will require a standardized collection and evaluation of MACE endpoint events by the same Endpoint Adjudication Committee (see Section 9.3.5).

The original CANVAS cohort of 4,330 subjects who were randomly assigned to treatment with 1 of 2 doses of canagliflozin (100 or 300 mg) or placebo, in a 1:1:1 ratio will continue to be followed. The data from CANVAS will be combined with the data from CANVAS-R in a pre-specified meta-analysis of CV safety outcomes to satisfy US FDA post-marketing requirements for canagliflozin. The details of the meta-analysis are described in a separate statistical analysis plan (SAP).

The study's last subject last visit is targeted to occur when at least 688 MACE events (ie, CV death, nonfatal myocardial infarction, nonfatal stroke) are accumulated between the CANVAS and CANVAS-R studies, which is projected to occur prior to April 2017. In both studies, the effects of canagliflozin are being evaluated against a background of standard of care for the treatment of hyperglycemia and CV risk factors with study investigators counseled to assure appropriate management according to applicable national guidelines for the care of patients with T2DM with treatment individualized as clinically appropriate.

Assessment of glycemic efficacy of canagliflozin – overall and in key subgroups

The present study is also intended to provide important information on the glycemic efficacy of this medication. To achieve this goal, subjects will enter an 18-week AHA regimen stable period to provide an opportunity to characterize the glycemic efficacy of canagliflozin relative to placebo in this high CV risk population, and support important analyses aimed at understanding the response to this medication in patient subgroups defined by key demographic and anthropometric components, disease characteristics, and concomitant AHA treatments. After this 18-week AHA regimen stable period, and for the remainder of the double-blind treatment phase, investigators will adjust the subject's AHA regimen with the goal of achieving individualized, target glycemic control.

Embedded within this study are 3 substudies which will compare the glycemic efficacy and assess the safety of canagliflozin relative to placebo in subjects receiving regimens with (1) insulin as monotherapy or in combination therapy, (2) sulfonylurea monotherapy, or (3) pioglitazone and metformin combination therapy. These substudies are being conducted to better characterize the safety, tolerability, and efficacy profile of canagliflozin when used in conjunction with these specific glucose-lowering therapies.

Assessment of long-term effects of canagliflozin on beta-cell function and renal function

Patients with T2DM usually have a progressive deterioration in glycemic control, with the need for stepwise added therapies. Underlying this progressively worse glucose control is a progressive deterioration in beta-cell function. Canagliflozin, by increasing UGE and possibly improving insulin sensitivity through weight loss, may "unload" the beta-cells, lowering secretory demand and potentially improving function over time, and

potentially providing good durability. In addition, improved glycemic control itself, through reversal of so-called "glucotoxicity," may also improve beta-cell function. Analysis of results from a Phase 1 study in subjects with T2DM did show an improvement in a model-based assessment of beta-cell function, and HOMA-B, a measure of fasting beta-cell insulin secretion, was improved in the Phase 2b study of subjects with T2DM. To assess the effect on beta-cell function over time in the present study, standard fasting measures of beta-cell function (HOMA-B, proinsulin/insulin ratio) will be evaluated.

Another key issue in patients with T2DM is the potential for hyperglycemia to lead to progressive damage to the kidney. Early on, this damage is reflected by micro-albuminuria that may progress to macro-albuminuria and eventually loss of renal function. By virtue of its improvement in glycemic control, which has been shown to reduce micro-albuminuria progression in prior studies (ADVANCE 2008), and possible effects to reduce blood pressure (if confirmed in larger studies), canagliflozin may slow the progression of diabetic nephropathy. Additionally, proximal tubule inhibition of SGLT2 by canagliflozin is predicted to increase the distal delivery of sodium which could, via the macula densa, lead to a reduction in intraglomerular pressure and a decrease in glomerular damage (Vallon 1999). For these reasons, the study will also examine the potential benefit of canagliflozin on albuminuria.

2. OBJECTIVES AND HYPOTHESES

2.1. Objectives

2.1.1. Primary Objectives

In subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease:

- to assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care on CV risk as measured by the HR for a composite endpoint (MACE including CV death, nonfatal MI, and nonfatal stroke)
- to assess the safety and tolerability of canagliflozin plus standard of care relative to placebo plus standard of care

The data from this study will be combined with the data from CANVAS-R in a pre-specified meta-analysis of CV safety outcomes to satisfy US FDA post-marketing requirements for canagliflozin.

2.1.2. Secondary Objectives

In subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease:

- to assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care on:

  - fasting measures of beta-cell function (HOMA-B and the proinsulin/insulin ratio) (note: this assessment will be conducted in a subset of subjects at sites that elect to participate, including only subjects who are not receiving insulin at randomization)
  - the proportion of subjects with progression of albuminuria (progression defined as ≥1 step increase, ie, no albuminuria to micro- or macro-albuminuria or from micro-albuminuria to macro-albuminuria)
  - the urinary albumin/creatinine ratio
  - renal function (as measured by the change from baseline in eGFR)
- to assess the effect of canagliflozin relative to placebo after 18 weeks and at the end of the treatment period on:
  - glycemic efficacy (HbA_{1c} and FPG)
  - body weight
  - blood pressure (systolic and diastolic)
  - fasting plasma lipids (triglycerides, HDL-C, low-density lipoprotein cholesterol [LDL-C], total cholesterol, and the ratio of LDL-C to HDL-C)

2.2. Hypotheses

2.2.1. Primary Hypothesis

In subjects with T2DM, with inadequate glycemic control, who have a history of or a high risk of CV disease, relative to placebo plus standard of care, canagliflozin plus standard of care reduces CV risk (as measured by the HR for a composite endpoint including CV death, nonfatal MI, and nonfatal stroke).

2.2.2. Secondary Hypotheses

In subjects with T2DM, with inadequate glycemic control, who have a history of or a high risk of CV disease, relative to placebo plus standard of care, canagliflozin plus standard of care at the end of the treatment period:

- improves beta-cell function (change from baseline in HOMA-B)
- reduces progression of albuminuria (ie, proportion of subjects with a ≥1-step progression of albuminuria measured by the urine albumin/creatinine ratio)

2.3. Substudies: Objectives and Hypotheses

The three 18-week substudies will be conducted and are intended to assess the safety and tolerability and efficacy of canagliflozin in subjects with T2DM, with inadequate glycemic control in each of the 3 specific subgroups of subjects receiving (1) insulin ≥20 units/day monotherapy or in combination with other AHA(s), (2) sulfonylurea monotherapy at protocol-specified doses (Attachment 1), or (3) pioglitazone ≥30 mg/day plus metformin ≥2,000 mg/day (or at least 1,500 mg/day for subjects who have a history of not being able to tolerate higher metformin doses) and no other AHA. The following

objectives and hypotheses will apply to each of these substudies. These are separate and distinct from the main study hypothesis testing.

Primary Substudy Objectives

In subjects with T2DM, with inadequate glycemic control, who have a history of or a high risk of CV disease:

- to assess the HbA_{1c}-lowering efficacy (change from baseline in HbA_{1c}) of canagliflozin relative to placebo after 18 weeks of treatment
- to assess the safety and tolerability of canagliflozin

Primary Substudy Hypothesis

In subjects with T2DM, with inadequate glycemic control, who have a history of or a high risk of CV disease, after 18 weeks of treatment, canagliflozin provides a greater improvement in HbA_{1c} relative to placebo (change from baseline in HbA_{1c}).

Secondary Substudy Objectives and Hypotheses

Objectives

In subjects with T2DM, with inadequate glycemic control, who have a history of or a high risk of CV disease:

- to assess the effect of canagliflozin relative to placebo after 18 weeks on:
  - body weight
  - FPG-lowering efficacy
  - proportion of subjects reaching HbA_{1c} <7.0%
  - systolic and diastolic blood pressure
  - fasting plasma lipids (triglycerides, HDL-C, LDL-C, total cholesterol, and the ratio of LDL-C to HDL-C)
- to assess the effect of canagliflozin relative to placebo after 52 weeks on:
  - glycemic efficacy (HbA_{1c} and FPG)
  - body weight
  - systolic and diastolic blood pressure
  - fasting plasma lipids (triglycerides, HDL-C, LDL-C, total cholesterol, and the ratio of LDL-C to HDL-C)

Hypotheses

After 18 weeks, in subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease, relative to placebo, canagliflozin:

- reduces body weight

- reduces FPG
- leads to a greater proportion of subjects achieving HbA_{1c} <7%
- reduces systolic blood pressure
- increases HDL-C concentrations
- lowers triglyceride concentrations

2.4. Medical Resource Utilization Objective

To collect medical resource utilization (MRU) data that may be used in future economic modeling (the construction and reporting of the economic model will be conducted separately from this protocol).

3. OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, 3 parallel-group, multicenter study to evaluate the safety, tolerability, and CV risk with canagliflozin plus standard of care compared with placebo plus standard of care in subjects with T2DM, on a wide range of antihyperglycemic therapies, who have either a history or high risk of CV disease. Although the effects of canagliflozin on several CV risk factors (eg, glycemic control, body weight, blood pressure) appear favorable in short-term studies, the longer-term benefits on CV risk factors are currently unknown; in addition, Phase 3 results demonstrated a small increase in LDL-C, without a change in the LDL-C to HDL-C ratio.

Note that results from this study, integrated with cross-Phase 3 program results, were included in a pre-approval meta-analysis to evaluate CV safety (as required by the US FDA Guidance for Industry: Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes) by examining the composite of MACE-plus hospitalized unstable angina (referred to as the pre-approval CV safety endpoint). This CV meta-analysis was conducted in 2012 (addressing the US FDA filing requirement that the upper bound of the 2-sided 95% CI around the CV HR is <1.8); this meta-analysis confirmed the requirement, showing the upper bound was <1.8.

This study was originally designed to include 2 sequential cohorts, with up to 18,500 subjects and a study duration for individual subjects of up to approximately 8 years. The study will now recruit only the initial 4,330 subjects who were randomly assigned to treatment with 1 of 2 doses of canagliflozin (100 or 300 mg) or placebo, in a 1:1:1 ratio.

The study's last subject last visit will occur when at least 688 MACE events (ie, CV death, nonfatal myocardial infarction, nonfatal stroke) are accumulated between the CANVAS and CANVAS-R studies, which is projected to occur prior to April 2017.

The study was modified because the cross-program meta-analysis of the pre-approval CV safety endpoint was unblinded to the sponsor to prepare regulatory submissions (originally this was to be unblinded to the study IDMC only); this was done based upon a decision by the sponsor, so that the impact of the small dose-related increase in LDL-C observed with canagliflozin treatment in the Phase 3 program on the CV HR could be evaluated. Due to the unblinding of these CV endpoint results, the study Steering Committee noted that the addition to the CANVAS trial of the planned second cohort of subjects would not provide a robust assessment of the primary CV protection hypothesis.

The CANVAS study has additional objectives including the assessment of overall safety and tolerability of canagliflozin.

The study also includes several substudies intended to provide additional information about the efficacy and safety of canagliflozin compared to placebo in combination with specific AHAs.

In this study, investigators will be counseled to assure appropriate management of CV risk factors (eg, blood pressure and lipids) according to standard guidelines (eg, the American Diabetes Association [ADA] or other local diabetes guidelines) for the care of patients with T2DM. In addition, after a relatively brief period during which the subject's antihyperglycemic regimen is to be kept stable (described in the section below), investigators will attempt to achieve good glycemic control, consistent with standard diabetes guidelines, individualized as considered clinically appropriate, with up-titration or stepwise addition of AHA therapies. Thus, this study will examine the impact on CV risk, and the safety and tolerability of treatment with canagliflozin along with standard of care for CV risk factor and glycemic management relative to placebo with standard of care management.

3.1. Study Design

The following section provides an overview of subject management including screening, run-in, and double-blind treatment.

Screening/Run-in Period Management

Subjects will undergo a screening visit for a preliminary determination of eligibility. Men or women with T2DM who have inadequate glycemic control (HbA_{1c} ≥7.0 and ≤10.5%), not on an AHA or on an AHA in monotherapy or combination therapy, and who have known CV disease or who have 2 or more risk factors for CV events are eligible (refer to Section 4.2, Inclusion Criteria).

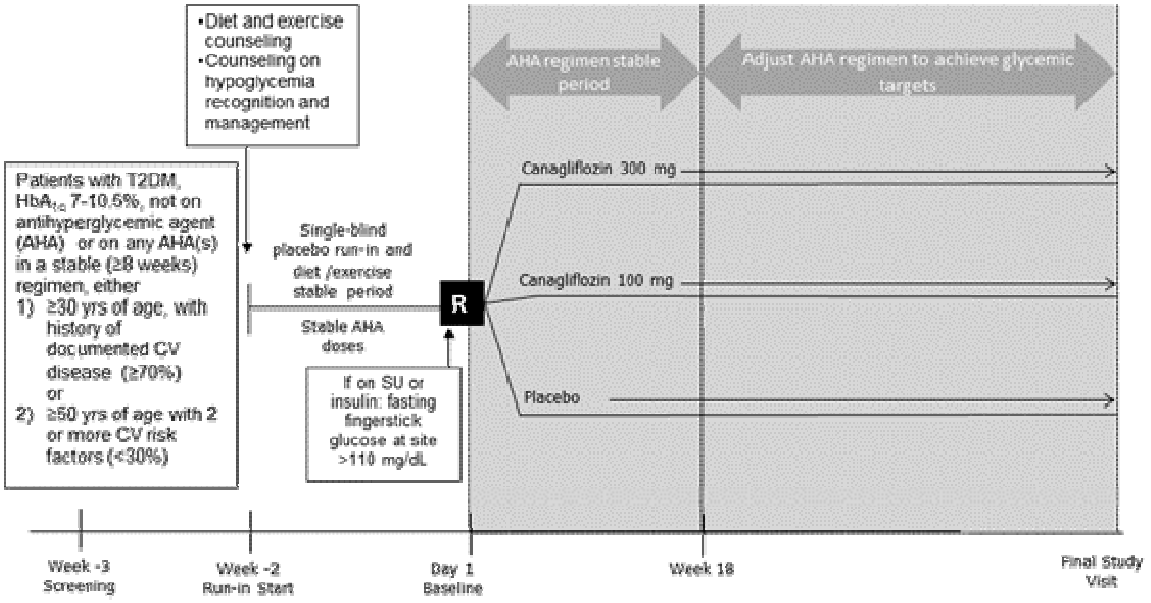
A subject meeting initial enrollment criteria at the screening visit will return to the investigational site at Week -2 (single-blind run-in start visit) to complete the evaluation of enrollment criteria. At this visit, subjects continuing to be eligible will enter a 2-week single-blind placebo, diet/exercise, and CV risk factor (eg, blood pressure and lipids) management optimization period. All subjects will receive diet/exercise counseling *at*

entry into the 2-week single-blind run-in period, be counseled on hypoglycemia recognition and management, be dispensed single-blind placebo capsules, and be given a monitor and materials for self-monitored blood glucose (SMBG) measurements. If additional time in run-in is required for adjustment/optimization of lipid-altering or blood pressure-lowering medications (so as to avoid the need for adjustment of these medications after randomization), the 2-week placebo run-in may be extended by having the subject continue single-blind placebo up to 2 additional weeks.

Subjects meeting all inclusion and none of the exclusion criteria, and successfully completing the 2-week run-in period, will be randomized to treatment with canagliflozin 100 mg, 300 mg, or matching placebo administered once daily (in a 1:1:1 ratio). Approximately 4,500 subjects will be randomized. Subjects will remain on a stable regimen (medications and doses) of their current AHA regimen (if on AHA) from screening entry until the Week 18 visit of the double-blind treatment phase (see "Double-blind Treatment Phase Management" below for details).

An overview of the study design is illustrated in Figure 1.

Figure 1: Study Design Outline



AHA=antihyperglycemic agent; CV=cardiovascular; R = randomization; SU=sulfonylurea; T2DM= type 2 diabetes mellitus

Double-blind Treatment Phase Management

Subjects will remain on a stable regimen (medications and doses) of their current AHA regimen through Week 18 of the double-blind treatment phase, unless down-titration is required to manage or avoid hypoglycemia, or unless glycemic rescue criteria are met (refer to Section 6.2.2, Glycemic Rescue Therapy Through Week 18: Criteria and Implementation). After the AHA regimen stable period is completed at Week 18, the investigator should adjust the subject's AHA regimen so as to achieve target glycemic control, per standard diabetes care guidances, individualized as considered appropriate by the investigator. *Adjustments in the AHA regimen should be carefully implemented throughout the study to avoid events of hypoglycemia.*

Planned Meta-analyses (CANVAS and Other Canagliflozin Studies)

As described in Section 11.8, Meta-analyses to Support Regulatory Requirements, during the conduct of this study, data from CANVAS will be exported and integrated with data from other large, well-controlled, double-blind, randomized studies of canagliflozin to support meta-analysis to assess the rate of important CV events in a prespecified composite endpoint.

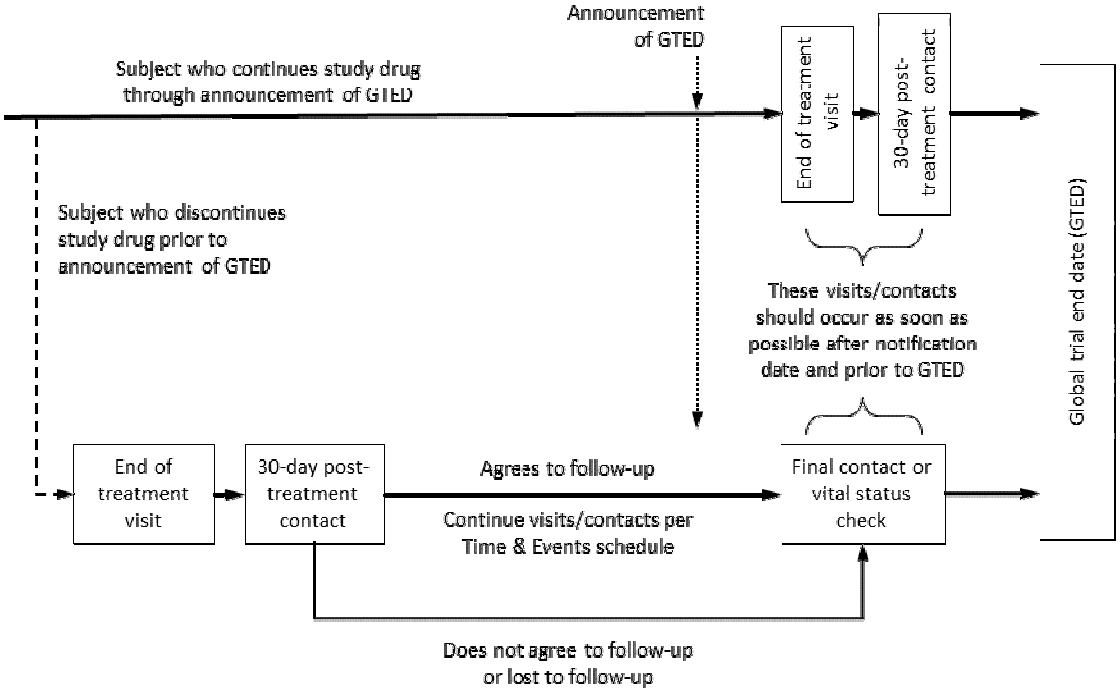
Study Duration

Subjects are expected to be followed for a maximum of approximately 7.25 years with the last visit for the last subject targeted to occur when at least 688 MACE events are accumulated between the CANVAS and CANVAS-R studies. All sites will be notified of the projected global trial end date (GTED) which is projected to occur prior to April 2017. The GTED is the stopping date of the study (ie, targeted date when the last subject completes last study visit), which will be announced to investigators at a time point when the actual accrual of events approaches the number of events required for the analysis; the announcement of the GTED may occur approximately 3 months prior to the GTED. Immediately after the projected GTED notification is sent, for subjects who remain on double-blind study drug, sites will be required to schedule the last on treatment visits and the 30-day off drug follow-up visits as per the Time and Events Schedule; for subjects who prematurely discontinue study drug, sites will be required to make a final contact (eg, schedule the last follow-up visit) or vital status check as soon as possible after announcement of GTED.

All visits (including the 30-day off drug follow-up visit) will need to be completed prior to the GTED.

Figure 2 shows the intended follow-up of randomized subjects with respect to the GTED.

Figure 2: Follow-up of Randomized Subjects With Respect to the GTED



Collection of Study Endpoints and Safety Measures

Events in the CV composite endpoint: Investigators will be counseled to report any event that they assess as potentially to be a component of the study CV composite endpoint (refer to Section 9.2, Reporting/Adjudication of Events in the CV Composite Endpoint and Other Events for Adjudication).

Collection of Information After Early Withdrawal: Early withdrawal (for subjects prematurely discontinued)/end-of-treatment (for subjects completing the study) evaluation will be performed at the time the subject discontinues double-blind study drug or when the study ends (refer to Sections 9.1.4, End-of-Treatment/Early Withdrawal, and 9.1.5, Posttreatment Phase [Follow-Up] for collection of information on CV events and other assessments). In subjects that prematurely discontinue study drug, events in the CV composite endpoint, all deaths, serious adverse events and adverse events of fractures should continue to be collected until study completion.

Safety Evaluations and Adverse Events Requiring Collection of Additional Information: See Section 3.2, Safety Evaluations, for details around safety assessments and adverse events requiring collection of additional information. Investigators may also be asked to provide additional information on other adverse events, based upon review by the Medical Safety Review Committee (MSRC) or the study IDMC (refer to Sections 9.3.3, Medical Safety Review Committee, and 9.3.4, Independent Data Monitoring Committee).

Pharmacogenomic Blood Sample: A pharmacogenomic blood sample should be collected on Day 1 (or at a subsequent visit if not collected on Day 1) from subjects who consent separately to the pharmacogenomic component of the study to allow for pharmacogenomic research, as necessary (where local regulations permit). Subject participation in pharmacogenomic research is optional. Refusal to consent for this component does not exclude a subject from participation in the clinical study.

Substudies – Add-on Use with Specific AHAs

Randomized subjects on specific concomitant AHAs, listed below, will be included in 3 substudies. These substudies will assess the glycemic efficacy and safety of canagliflozin in subjects on one of the following concomitant AHAs: insulin ≥20 units per day as monotherapy or in combination with other AHA(s); sulfonylurea monotherapy (at doses specified in Attachment 1); or pioglitazone ≥30 mg plus metformin ≥2,000 mg/day (or at least 1,500 mg/day for subjects who have a history of not being able to tolerate higher metformin doses) and no other AHAs. These subjects will follow the same procedures and assessments as described for the overall study (refer to the Time and Events Schedule that follows the Synopsis); no additional procedures or assessments are required for subjects in these substudies. Results from subjects in these substudies will be analyzed based upon prespecified objectives and hypotheses (refer to Section 2.4, Substudies: Objectives and Hypotheses).

Section 9.3, Study Management: Committees, provides details regarding the committees commissioned to provide oversight for the management of this study.

3.2. Study Design Rationale

Overall Design, Blinding, Control, Study Phases/Periods, Treatment Groups

This study was designed in general accordance with the FDA and European Medicines Agency (EMEA) guidances on the development of medications and clinical investigations for the treatment and prevention of diabetes mellitus (FDA 2008; EMEA 2002, 2008), and will contribute CV events (for a prespecified meta-analysis) to meet the requirements of the FDA guidance for industry on evaluating CV risk in new AHAs to treat type 2 diabetes issued in December 2008 (Guidance for Industry: Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes).

The study was to have 2 sequential cohorts, with the decision to recruit further subjects (ie, re-open enrollment) based upon a protocol-specified interim analysis of results from the initial cohort planned approximately 4 years after study initiation, around the time of US regulatory agency approval. However, the study will now only recruit the initial 4,330 subjects randomized for the reason discussed in Section 3. Randomization and blinding will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups. Blinded

treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints. A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of the active treatment.

The 2-week single-blind placebo period before randomization allows sufficient time for investigators to assess whether subjects demonstrate compliance with study procedures, and to study medication, and provides an opportunity to adjust treatment for other CV risk factors, by titration or addition of background medications at the investigator's discretion, before randomization.

The stable AHA regimen period of 18 weeks was chosen because it is sufficiently long to evaluate the effect of canagliflozin on HbA_{1c}. Maintaining stable background AHAs, permits an assessment of the effect of canagliflozin not confounded by changes in other agents, and hence supports the determination of glycemic efficacy of this potentially valuable medication across the entire study population as well as in the substudies.

Study Population

The study population includes subjects on a variety of different AHAs, with a range of baseline glycemic control−from mildly elevated to more moderately elevated HbA_{1c} values−and at higher risk of or having documented CV disease. This population was selected to provide a broad experience with canagliflozin so as to enhance the characterization of this new medications efficacy, safety, and tolerability profile, and to support assessment of the effect of treatment with this agent on CV risk. The substudy populations were selected to provide information on concurrent use of canagliflozin with important AHAs that are not being assessed in separate Phase 3 studies.

Dosage Selection, Route of Administration, Dose Interval, Treatment Period

The once daily oral therapy is an acceptable dosage regimen given the half-life of canagliflozin.

Based on findings from the Phase 2b diabetes study, 100 mg once daily is deemed to be the lowest dose providing clearly sufficient efficacy in terms of HbA_{1c}-lowering for approval as an AHA and 300 mg once daily is deemed to provide an incremental improvement in glycemic efficacy and possibly weight loss and blood pressure lowering, greater than that achieved with the 100 mg once daily regimen. The safety and tolerability profile of these 2 doses appeared to be generally similar. In Phase 1 studies of canagliflozin, at doses above 200 mg, a decrease in incremental glucose and an increase in the time to peak glucose were observed after a meal challenge when study drug was administered before the meal. The mechanism of this reduction in post-meal glucose is not known, but could relate to inhibition of SGLT1 gut glucose transport based upon transiently high gut concentrations of canagliflozin after dose administration. If this effect on post-meal glucose is established, it may provide an additional mechanism of

glucose-lowering benefit. In the present study, double-blind study drug is to be taken before the first meal of the day so as to obtain this potential benefit of canagliflozin. Additional studies in the canagliflozin program will evaluate this effect on post-meal glucose.

Both the 100 and 300 mg doses of canagliflozin are being evaluated in this study.

Collection of Additional Information for Selected Adverse Events

The safety profile of canagliflozin has been well-established in the Phase 3 program, which included approximately 10,000 subjects from randomized, controlled clinical trials. As a condition of approval certain health authorities (eg, US FDA) are requesting enhanced pharmacovigilance on selected adverse events of interest (see Section 9.4, Safety Evaluations, for additional details).

Choice of Cardiovascular Outcome Composite Endpoint

To evaluate the study's primary hypothesis of CV benefit (ie, a reduction in CV risk), the endpoint of MACE (CV death, nonfatal MI, nonfatal stroke) will be used. This has become the standard composite endpoint utilized for this purpose, and hence was selected for use in the current study. The effect of canagliflozin relative to placebo on the HR of the individual components of these endpoints will also be characterized. To support the planned meta-analysis of integrated results from this and other large, well-controlled, double-blind, randomized studies of canagliflozin), the pre-approval composite endpoint included MACE *and* hospitalized unstable angina. This endpoint was utilized to support the pre-approval CV safety of canagliflozin, evaluating the hypothesis (in the separate meta-analysis SAP) of no unacceptable increase in CV risk (ie, rule out an upper bound of 1.8 or greater). The event of hospitalized unstable angina was included in this composite to cast a wider net, given the importance of such events, and their close relationship to, and prediction of, progression of coronary artery disease.

Choice of Renal Efficacy Measures

The onset and progression of nephropathy is a major morbidity outcome in diabetic patients. Hyperglycemia, possibly through production of advanced glycation endproducts (Diabetes Control and Complications Trial [DCCT], Brownlee 2001), systemic hypertension (DCCT), and increases in intraglomerular pressure (Anderson 1986; ADA 2004) are known to be risk factors for the onset and progression of diabetic nephropathy.

In the Phase 2b diabetes study, canagliflozin improved glycemic control, with a trend towards reduced blood pressure in the 300 mg once daily group. By virtue of its mechanism, canagliflozin will reduce the increased glucose flux across the proximal tubule and through the interstitium to be reabsorbed into the bloodstream. The reduced glucose flux within the kidney could lead to a reduction in renal advanced glycation endproduct accumulation resulting in a delay in the onset and/or progression of diabetic

nephropathy. Because SGLT2 in the proximal tubule cotransports both sodium and glucose, SGLT2 inhibition by canagliflozin will increase the distal delivery of sodium, which could lead to a reduction in intraglomerular pressure via the macula densa and a decrease in glomerular damage (Vallon 1999).

The development and progression of renal disease in people with diabetes follows a clearly defined pathway starting with micro-albuminuria, progressing to macro-albuminuria, then to reduced renal function (lower glomerular filtration rate), and finally to renal failure with the need for dialysis or transplantation. To assess the effects of canagliflozin on the progression of diabetic nephropathy, the proportion of subjects with categorical progression of albuminuria based upon the albumin/creatinine ratio in the first morning void was selected as a key secondary endpoint and will be assessed according to the categorizations defined in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Guideline #1 (KDOQI 2007): the definition of micro-albuminuria is albumin/creatinine ratio of 30 to 300 mg/g, and the definition of macro-albuminuria is albumin/creatinine ratio greater than 300 mg/g.

In diabetes, the onset of urinary albumin excretion is a strong signal for progression of diabetic nephropathy (ADA 2004), and is associated with an increase in CV events (de Zeeuw 2004). In the present study, first morning void urine collections are being used. These collections have been shown to be more accurate than spot urine collections (Witte 2009) because they are less influenced by urinary albumin changes associated with physical activity.

Choice of Beta-cell Function Measures

Type 2 diabetes mellitus (T2DM) is a progressive disease characterized by the progressive loss of beta-cell function and insulin secretory capacity (UKPDS 1998). In large clinical trials, HOMA-B is a well-accepted means of assessing fasting beta-cell function (Wallace 2004). Homeostasis model assessment (HOMA)-B is calculated using fasting insulin or C-peptide and glucose levels (Wallace 2004). Because C-peptide is not, but insulin is, extracted by the liver, the use of C-peptide to calculate HOMA-B is not confounded by increased hepatic extraction such as that which can occur in conditions of improved hepatic insulin sensitivity. Given that canagliflozin is predicted to cause weight loss, which could lead to improved hepatic insulin sensitivity, C-peptide was chosen to be used for HOMA-B calculations, which will be assessed in a subset of subjects who are not receiving insulin at baseline; if a subject starts insulin therapy after baseline, no further assessments of these analytes will be made for that subject. Approximately 1,200 subjects (400 per treatment group) will be studied in this subset, at sites that elect to participate.

In this subset of subjects, fasting proinsulin and insulin will also be measured to assess beta-cell function. Elevated proinsulin/insulin ratios reflect increasing degrees of impairment in beta-cell function in T2DM (Roder 1998).

DNA Collection

It is recognized that genetic variation can be an important contributory factor to interindividual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to a drug. The goal of the pharmacogenomic component is to collect DNA to allow the identification of genetic factors that may influence glucose and lipid metabolism, and supporting interpretation of dynamic effects measured in the study or to characterize genes potentially affecting drug absorption, distribution, metabolism, or excretion of canagliflozin. DNA samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies in the future. Details are provided in Section 9.6, Pharmacogenomic Evaluations.

Archive Samples for Exploratory Research and Specimens for Biomarker Assessment

Numerous biomarkers have been studied as potentially important surrogate measures of CV and overall health in subjects with T2DM (Ridker 2004). Fasting plasma, serum, and urine archive samples will be collected (where local regulations permit) to allow for the analysis of important biomarkers (not prespecified) that could help to further explain and examine the efficacy and safety findings in this study. See Attachment 4 for details of specimen collection.

Medical Resource Utilization

Should canagliflozin reduce the risk of CV events, the risk of onset and progression of nephropathy and improve beta-cell function, the utilization of medical resources such as physician visits (outside of protocol-specified), hospitalizations, and medication requirements may be lower in the canagliflozin group than in the standard care group. To assess this, information will be collected in order to characterize differences in the need for additional medical interactions (eg, physician visits, hospitalizations).

4. STUDY POPULATION

4.1. General Considerations

The study will include subjects with a diagnosis of T2DM and a history or high risk of CV disease. Approximately 4,500 subjects will be randomized.

Subjects must have inadequate glycemic control (as defined by HbA_{1c} ≥7.0 to ≤10.5% at screening) and be either (1) not currently on AHA therapy or (2) on AHA monotherapy or combination therapy with any approved agent: eg, sulfonylurea, metformin, pioglitazone, alpha-glucosidase inhibitor, GLP-1 analogue, DPP-4 inhibitor, or insulin. Subjects receiving AHA therapy must be on a stable dose of that therapy for at least 8 weeks before the screening visit. Subjects taking rosiglitazone within 8 weeks before the prescreening or screening visit may not enter the study. Subjects taking rosiglitazone

who are already in screening are not eligible for randomization. Subjects who have been randomized before implementation of Protocol 28431754DIA3008 Amendment INT-3 and are taking rosiglitazone should be evaluated in a timely manner to determine how to modify their rosiglitazone-containing antihyperglycemic regimen, if clinically appropriate and in accordance with local regulatory requirements.

As noted, subjects must also either have a prior history of documented CV disease or be at high risk of CV disease (on the basis of 2 or more specific CV risk factors). For details, refer to Section 4.2, Inclusion Criteria, below.

Subjects will be recruited from centers in Asia-Pacific, North America, Latin America, Europe, and possibly other regions for this study.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling the subject in the study.

4.2. Inclusion Criteria

Potential subjects must satisfy all of the following criteria to be enrolled in the study:

Inclusion Criteria at Screening Visit

- Man or woman with a diagnosis of T2DM with HbA_{1c} level ≥7.0% to ≤10.5% at screening and be either (1) not currently on AHA therapy or (2) on AHA monotherapy or combination therapy with any approved agent: eg, sulfonylurea, metformin, pioglitazone, alpha-glucosidase inhibitor, GLP-1 analogue, DPP-4 inhibitor, or insulin.
- History or high risk of CV disease defined on the basis of either:
  - Age ≥30 years with documented symptomatic atherosclerotic CV disease: including stroke; MI; hospital admission for unstable angina; coronary artery bypass graft; percutaneous coronary intervention (with or without stenting); peripheral revascularization (angioplasty or surgery); symptomatic with documented hemodynamically-significant carotid or peripheral vascular disease; or amputation secondary to vascular disease
  - Age ≥50 years with 2 or more of the following risk factors determined at the screening visit: duration of T2DM of 10 years or more, systolic blood pressure >140 mmHg (average of 3 readings) recorded at the Screening Visit, while the subject is on at least one blood pressure-lowering treatment, current daily cigarette smoker, documented micro- or macro-albuminuria (see Section 3.2, Study Design Rationale, for definition), or documented HDL-C of <1 mmol/L (<39 mg/dL).

    ***Note**: An overall 70%:30% target ratio for CV history (first category): risk factors (second category) will be implemented (with a maximum of approximately 40% in the second category). This ratio is intended to be a global ratio and may*

vary by region. The proportion of subjects in these categories will be monitored centrally.

- Women must be:
  - postmenopausal, defined as
    - ◊ >45 years of age with amenorrhea for at least 18 months, or
    - ◊ >45 years of age with amenorrhea for at least 6 months and less than 18 months and a serum follicle stimulating hormone (FSH) level >40 IU/L, or
  - surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal ligation), or otherwise be incapable of pregnancy, or
  - heterosexually active *and* practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (eg, condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), or male partner sterilization, consistent with local regulations regarding use of birth control methods for subjects participating in clinical trials, for the duration of their participation in the study, or
  - not heterosexually active.

  Note: subjects who are not heterosexually active at screening must agree to utilize a highly effective method of birth control if they become heterosexually active during their participation in the study.
- Women of childbearing potential must have a negative urine β-human chorionic gonadotropin (β-hCG) pregnancy test at screening and baseline (predose, Day 1).
- Willing and able to adhere to the prohibitions and restrictions specified in this protocol.
- Subjects must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.
- To participate in the optional pharmacogenomic component of this study, subjects must have signed the informed consent form for pharmacogenomic research indicating willingness to participate in the pharmacogenomic component of the study (where local regulations permit). Refusal to give consent for this component does not exclude a subject from participation in the clinical study.

Inclusion Criterion for Randomization

- Subjects must have taken ≥80% of their single-blind placebo capsules during the 2-week run-in period at Day 1 to be eligible for randomization.

4.3. Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

Diabetes-Related/Metabolic

- History of DKA, T1DM, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy
- On an AHA and not on a stable regimen (ie, agents and doses) for at least 8 weeks before the screening visit and through the screening/run-in period

  Note: a stable dose of insulin is defined as no change in the insulin regimen (ie, type[s] of insulin) and ≤15% change in the total daily dose of insulin (averaged over 1 week to account for day to day variability).
- Fasting fingerstick glucose at home or at investigational site >270 mg/dL (>15 mmol/L) at Baseline/Day 1
- *For patients on a sulfonylurea agent or on insulin*: fasting fingerstick glucose at home or at investigational site <110 mg/dL (<6 mmol/L) at Baseline/Day 1

  Note: at the investigator's discretion, based upon an assessment of recent SMBG values, subjects meeting either of these fingerstick glucose exclusion criteria may continue the single-blind placebo and return to the investigational site within 14 days and may be randomized if the repeat fasting fingerstick value no longer meets the exclusion criterion. Subjects with fingerstick glucose >270 mg/dL (>15 mmol/L) may have their AHA regimen adjusted, and be rescreened once on a stable regimen for at least 8 weeks.
- History of one or more severe hypoglycemic episode within 6 months before screening

  Note: a severe hypoglycemic episode is defined as an event that requires the help of another person. Refer to Attachment 2, Hypoglycemia: Definitions, Symptoms, and Treatment, for a definition of severe hypoglycemia.
- History of hereditary glucose-galactose malabsorption or primary renal glucosuria
- Ongoing, inadequately controlled thyroid disorder

  Note: subjects on thyroid hormone replacement therapy must be on a stable dose for at least 6 weeks before Day 1.

Renal/Cardiovascular

- Renal disease that required treatment with immunosuppressive therapy or a history of chronic dialysis or renal transplant. **Note**: subjects with a history of treated childhood renal disease, without sequelae, may participate.
- Myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident within 3 months before screening, or a planned revascularization procedure, or history of New York Heart Association (NYHA) Class IV cardiac disease; refer to Attachment 3, New York Heart Association Classification of Cardiac Disease, for a description of the classes

- Findings on 12-lead ECG that would require urgent diagnostic evaluation or intervention (eg, new clinically important arrhythmia or conduction disturbance)

Gastrointestinal

- History of hepatitis B surface antigen or hepatitis C antibody positive (unless associated with documented persistently stable/normal range aspartate aminotransferase [AST] and ALT levels), or other clinically active liver disease
- Any history of or planned bariatric surgery

Laboratory

- Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 at screening (provided by the central laboratory)
- *For subjects taking metformin*: at screening, serum creatinine ≥1.4 mg/dL (124 μmol/L) for men or ≥1.3 mg/dL (115 μmol/L) for women; no contraindication to the use of metformin (including eGFR) based on the label of the country of investigational site
- ALT levels >2.0 times the ULN or total bilirubin >1.5 times the ULN at screening, unless in the opinion of the investigator and as agreed upon by the sponsor's medical officer, the findings are consistent with Gilbert's disease

Other conditions

- History of malignancy within 5 years before screening (exceptions: squamous and basal cell carcinomas of the skin and carcinoma of the cervix in situ, or a malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence)
- History of human immunodeficiency virus (HIV) antibody positive
- Subject has a current clinically important hematological disorder (eg, symptomatic anemia, proliferative bone marrow disorder, thrombocytopenia)
- Investigator's assessment that the subject's life expectancy is less than 1 year, or any condition that in the opinion of the investigator would make participation not in the best interest of the subject, or could prevent, limit, or confound the protocol-specified safety or efficacy assessments
- Major surgery (ie, requiring general anesthesia) within 3 months of the screening visit or any surgery planned during the subject's expected participation in the study (except minor surgery, ie, outpatient surgery under local anesthesia)
- Any condition that, in the opinion of the investigator, would compromise the well being of the subject or prevent the subject from meeting or performing study requirements

Medications/Therapies

- Current use of other SGLT2 inhibitor; use of rosiglitazone within 8 weeks of screening. (Note: subjects taking rosiglitazone who are already in screening are not eligible for randomization.)

- Known allergies, hypersensitivity, or intolerance to canagliflozin or its excipients (refer to Section 14.1, Physical Description of Study Drug[s])
- Current use of a corticosteroid medication or immunosuppressive agent, or likely to require treatment with a corticosteroid medication (for longer than 2 weeks in duration) or an immunosuppressive agent. **Note**: subjects using inhaled, intranasal, intra-articular, or topical corticosteroids, or corticosteroids in therapeutic replacement doses may participate
- Received an active investigational drug (including vaccines) or used an investigational medical device within 3 months before Day 1/baseline or received at least one dose of canagliflozin in a prior study

General

- History of drug or alcohol abuse within 3 years before screening
- Pregnant or breast-feeding or planning to become pregnant or breast-feed during the study
- Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator

Note: Investigators should assure that all study enrollment criteria have been met and determine that the subject has not had any interval change in clinical status since screening. Before randomization, subjects whose status changes after screening, such that they now meet an exclusion criterion, should be excluded from participation.

4.4. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

- Women of childbearing potential who are heterosexually active must use a highly effective method of birth control throughout their participation in the study (refer to Section 4.2, Inclusion Criteria)(refer to Section 12.2.3, Pregnancy, for instructions in cases of a positive pregnancy test)
- Prohibited medications include other SGLT2 inhibitors; subjects must not take any other investigational agents during the study (if a subject prematurely discontinues from the study medication but continues in the posttreatment follow-up phase, entering another investigational trial is discouraged but is not prohibited; however, entering another canagliflozin trial is prohibited)
- Strenuous exercise may affect urine protein excretion and other safety laboratory results; for this reason, strenuous exercise should be avoided within 72 hours before planned study visits
- Subjects should not collect first morning void during acute illness with fever. The collection and respective visit should be postponed until the subject is recovered from the acute illness.

4.5. Rescreening

Subjects who do not meet all inclusion criteria or who meet an exclusion criterion may, at the discretion of the investigator, be rescreened one time if the reason for non-eligibility relates to duration (eg, time from an MI, or duration on a stable dose of thyroid hormone, or duration on a stable AHA regimen), or appropriate clinical management leads to study eligibility (eg, HbA_{1c} >10.5% that prompts adjustment of the subject's AHA regimen, or subject is on a medication not allowed per local prescribing information [eg, on metformin with eGFR below level permitted per label], and the subject's treatment regimen is being adjusted as clinically appropriate to be consistent with local prescribing information).

Rescreening for an abnormal laboratory value is only allowed as indicated for the specific laboratory exclusion criterion. Typically, rescreening will require that all screening and/or run-in parameters be repeated. However, with the concurrence of the sponsor's Medical Monitor, a non-qualifying laboratory test may be repeated one time, without completely rescreening the subject, in situations where there is a clinical reason to do so.

5. TREATMENT ALLOCATION

To ensure sufficient experience in subjects with documented, pre-existing CV disease–the highest risk group–approximately 70% (minimum of 60%) of subjects (globally) are targeted to be in this group.

Stratification for Substudies

Subjects will have within-subgroup balanced (1:1:1) randomization to each of the 3 treatment groups within the following 6 predefined strata, which are based upon AHA medication(s) that the subject is receiving at the run-in visit and will be continuing at entry into the double-blind treatment phase:

- Stratum 1: insulin monotherapy ≥20 units per day, on stable doses at least 10 weeks before the run-in visit
- Stratum 2: insulin ≥20 units per day plus metformin, on stable doses at least 10 weeks before the run-in visit, and no other background AHA therapy
- Stratum 3: insulin ≥20 units per day plus any other AHA(s) on stable dose(s) for at least 10 weeks before the run-in visit
- Stratum 4: sulfonylurea monotherapy (at doses specified in Attachment 1), on stable doses at least 10 weeks before the run-in visit
- Stratum 5: pioglitazone ≥30 mg/day plus metformin ≥2,000 mg/day (or at least 1,500 mg/day for subjects who have a history of not being able to tolerate higher metformin doses) and no other background AHA therapy, on stable doses at least 10 weeks before the run-in visit
- Stratum 6: subjects not in one of the above AHA subgroups

Note: a stable dose of insulin is defined as no change in the insulin regimen (ie, type[s] of insulin) and ≤15% change in the average total daily dose of insulin (as averaged over one week).

The stratification process will be handled via queries in the Interactive Voice Response System (IVRS) or after logging on to the Interactive Web Response System (IWRS) being used for the study, described below.

Randomization and Blinding Procedures

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 3 treatment groups based on a computer-generated randomization schedule prepared by or under the supervision of the sponsor before the study. The randomization will be balanced by using randomly permuted blocks and will be stratified based on the use of specific concomitant antihyperglycemic medications at baseline (as noted above). Based on this randomization schedule, the study drug will be packaged and labeled. Medication numbers will be preprinted on the study drug labels and assigned as subjects qualify for the study and are assigned to double-blind treatment.

At baseline (Day 1), the randomization number and medication numbers, the treatment code, which is linked to the randomization schedule, will be assigned after telephoning into the IVRS or after logging on to the IWRS designated by the sponsor. The requestor must use his/her own user identification (ID) and personal identification number (PIN) when contacting the IVRS/IWRS, and will then give the relevant subject details to uniquely identify the subject. Based on this information, the IVRS/IWRS will assign a unique treatment code, which will dictate the treatment assignment and study drug kit for the subject. As subjects are randomly assigned to treatment, the IVRS/IWRS will assign a study drug kit to be dispensed at that visit. New medication numbers will be assigned each time the IVRS/IWRS is contacted for dispensing additional study drug. The randomization (or initial subject allocation) number at baseline will be the identifying number linking all subsequent kits to the individual subject.

The study drugs will be identical in appearance and will be packaged in identical containers.

The randomization code that links the randomization number assigned to the subject with a treatment group assignment will be maintained within the IVRS/IWRS. This randomization code will not be provided to the investigator unless required, as described below, for unblinding in emergency situations.

The treatment blind should be broken to provide unblinded information to the site only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment through the IVRS or IWRS. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the

particular situation, before breaking the blind. The reason for unblinding is not captured through IVRS. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the appropriate section of the eCRF and in the source documents. The documentation received from the IVRS indicating the code break must be retained with the subject's source documents in a secure manner (eg, sealed envelope) so as not to unblind the treatment assignment to the study site or sponsor personnel. The investigator is also advised not to reveal the study treatment assignment to the study site or sponsor personnel.

Subjects who have had their treatment assignment unblinded by the investigator will be discontinued (refer to Section 10.2, Withdrawal from the Study).

Randomization codes will be released based upon protocol-specified interim or meta-analyses, and after completion of the study. At the time of these analyses, the translation of randomization codes into treatment and control groups will be disclosed only to those authorized and only for those subjects included in the interim analysis (refer to Section 11.7, Interim Analyses of CANVAS and Section 11.8, Meta-analysis to Meet Regulatory Requirements).

To maintain the treatment blind, the FPG and HbA_{1c} values after baseline and before Week 18 will be masked to the study sites unless: (1) the FPG meets specific glycemic criteria for the initiation of rescue therapy (as described in Section 6.2.2, Glycemic Rescue Therapy Through Week 18: Criteria and Implementation), or (2) glycemic rescue therapy has been initiated.

Urine glucose measurements will not be performed on first morning void urine specimens, or on urinalyses during the study, as an additional step to ensure the maintenance of the treatment blind. Unless required by urgent subject management, investigators should obtain all urinalyses through the central laboratory and not by a local laboratory so as to avoid potential for unblinding related to urine glucose results (which will not be reported by the central laboratory). If a urinalysis must be performed locally for appropriate subject management (eg, to evaluate a potential infection), investigators should request microscopic rather than dipstick urinalysis (if microscopic evaluation is considered clinically sufficient).

6. DOSAGE AND ADMINISTRATION

6.1. Study Drugs

Run-in Period Single-Blind Placebo

Upon successful completion of screening, all potentially eligible individuals will enter a 2-week run-in period, during which they will receive single-blind placebo capsules (one capsule to be administered once daily).

Double-Blind Study Medication

Subjects will be randomly assigned in a 1:1:1 ratio to 1 of 3 treatment groups: canagliflozin 100 mg, canagliflozin 300 mg, or matching placebo.

Subjects will be counseled to take their dose of canagliflozin or matching placebo, one capsule once daily, before the first meal of the day for the duration of the study or until early discontinuation. Subjects will take the first dose of study drug at the study center on Day 1.

On the days of study visits when fasting blood samples are collected (refer to the Time and Events Schedule that follows the Synopsis), subjects will be instructed to refrain from taking the study drug before the clinic visit. The subject will be instructed to take the dose of study drug before the subject's next meal.

The study drug must be swallowed whole with liquid and not chewed, divided, dissolved, or crushed. If the subject does not take the study drug within 12 hours after the first meal of the day, the dose of study drug should be skipped for that day and the subject should be instructed to take the study drug on the following day before the first meal of the day.

Study-site personnel will instruct subjects on how to store study drug for at-home use as indicated for this protocol.

Study drug treatment may be interrupted (eg, for safety and/or tolerability reasons such as hospitalizations for major surgical procedure or serious medical illness). Study drug treatment interruptions, occurring for any reason and lasting 7 days or longer, will be documented in source documents at the site. Study drug may be reinstituted at the investigator's discretion once the subject has recovered and the safety and/or tolerability concern is no longer present (provided the subject has not been off study drug for >90 days).

For subjects who develop conditions that are associated with amputations, such as a lower-extremity infection, skin ulcer, osteomyelitis, gangrene, or critical limb ischemia, study drug should be interrupted until the condition has resolved in the opinion of the investigator. In the event of an amputation, restarting of dosing with canagliflozin should only be done after careful consideration of the individual risk:benefit and following discussion with the sponsor.

6.2. Concomitant Antihyperglycemic and Other Therapies

6.2.1. Management of Glycemic Control and CV Risk Factors

Run-in Period Management

Subjects will receive diet/exercise counseling at entry into the 2-week run-in period and will remain on a stable regimen (medications and doses) of their current AHA regimen (if on an AHA[s]), except as described below. During the run-in period, investigators will

counsel subjects to perform regular fasting SMBG determinations, in general at least 2 measurements per week, with additional measurements as considered clinically appropriate by the investigator.

Double-blind Treatment Phase Glycemic Management

Subjects should remain on a stable AHA regimen (doses and medications) from screening to Week 18, unless a down-titration is considered necessary to manage or avoid hypoglycemia, or if glycemic rescue criteria are met (refer to Section 6.2.2, Glycemic Rescue Therapy Through Week 18: Criteria and Implementation). From Week 18, the AHA regimen should be adjusted to achieve glycemic goals, using standard guidances, and as considered appropriate by the investigator for the individual subject. *Adjustment to the AHA regimen (from Week 18) should be carefully implemented so as to avoid events of hypoglycemia.*

Adjustment of AHA therapy will be performed by the investigator, consistent with standard diabetes guidances: no specific AHA treatment algorithm is utilized in this study. Treatment may include reinforcement of lifestyle counseling, up-titration to maximum labeled doses of current AHAs, the addition of oral AHAs, addition of GLP-1 analogue, or the initiation and up-titration of insulin (intermediate or long-acting insulin and subsequent short-acting, pre-meal insulin, if needed). Investigators should make all reasonable efforts to achieve and maintain the subject's individualized target glycemic control, and may add unscheduled visits, if clinically appropriate, to monitor glycemic control, and adjust the subject's regimen. All adjustments to the AHA regimen should be documented in the appropriate eCRF.

Use of AHAs and adjustments to the AHA regimen (dose or agents) should be consistent with the labeled use of the AHA within the country of the investigational site.

During the double-blind treatment period, investigators will counsel subjects to perform regular fasting SMBG determinations; in general, the guidance should be for subjects to perform at least 2 measurements per week, with additional measurements as considered clinically appropriate by the investigator, although it is recognized that subjects may not always be compliant with this guidance for various reasons.

Therapeutic Management of CV Risk Factors

Before randomization and throughout the study, investigators will be expected to manage the subject's diet/exercise and medication regimens so as to achieve goals for CV risk factors (eg, lipid levels, blood pressure) based upon standard guidances for the care of patients with T2DM.

During the 2-week single-blind placebo run-in period, investigators should adjust the subject's regimen as needed to optimize the subject's CV risk factors and thereby to reduce the need for adjustments of medications after randomization. If additional time in

run-in is required for adjustment/optimization of lipid-altering or blood pressure-lowering medications (so as to avoid the need for adjustment of these medications after randomization), the 2-week placebo run-in may be extended by having the subject continue single-blind placebo up to 2 additional weeks.

6.2.2. Glycemic Rescue Therapy Through Week 18 Criteria and Implementation

So as to avoid poorer glycemic control during the 18-week AHA dose-stable period, glycemic rescue criteria will be applied. After Week 18, investigators will determine subject's glycemic goals and the need for adjustments in the AHA regimen.

From Day 1 to Week 18, the criteria for starting glycemic rescue therapy are based on an FPG value exceeding the glucose cutpoints shown in the table below. Subjects should be counseled to contact the site if their SMBG consistently exceeds these values and an FPG measurement (ie, venous blood collection) to determine eligibility for initiation of glycemic rescue therapy should be obtained.

Rescue Criteria Through Week 18

Time point	Glucose
After Day 1 through Week 6	>270 mg/dL (15 mmol/L)
After Week 6 through Week 12	>240 mg/dL (13.3 mmol/L)
After Week 12 through Week 18	>200 mg/dL (11.1 mmol/L)

Glycemic rescue therapy should be as determined to be clinically appropriate by the investigator: either up-titration of current AHA medications or the stepwise addition of non-insulin antihyperglycemic agent(s) and then insulin therapies. After initiation of rescue therapy, the glycemic goals will be based upon standard diabetes guidances, individualized for the subject, as considered appropriate by the investigator.

Investigators must complete the appropriate eCRF page (documenting initiation of therapy) for subjects starting on rescue medication. From Week 18, adjustment of the subject's diabetes treatment regimen is permitted per protocol, and hence such adjustments are not considered as rescue (and therefore the eCRF for rescue therapy does not need to be completed).

Double-blind study drug is to be continued after initiation of rescue therapy.

7. TREATMENT COMPLIANCE

The investigator or designated study research staff will maintain a log of all drug dispensed and returned (including a count of capsules dispensed and returned). Drug supplies for each subject will be inventoried and accounted for throughout the study. Subjects who are poorly compliant with taking the study drug (based on capsule counts) should receive counseling on the importance of dosing compliance and may continue in the study, at the investigator's discretion.

Subjects will receive clear instructions on compliance with study procedures at the screening visit. During the course of the study, the investigator or designated study research staff will be responsible for providing additional instructions to reeducate any subject who is not compliant with taking the study drug or with completing the diary, as required.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy therapy includes any therapy used before the first dose of double-blind study medication. Concomitant therapy is any therapy used after the first dose of double-blind study drug.

Prestudy therapies administered up to 30 days before screening (and up to 12 months before screening for AHA) and up to the time of the first dose of double-blind study drug must be recorded.

Concomitant therapies must be recorded throughout the study beginning with start of the first dose of study drug to 30 days after the last dose of study drug.

All therapies (prescriptions or over-the-counter medications, including vitamins and herbal supplements; nonpharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study drug must be recorded as prestudy therapy (before the first dose of double-blind study drug) or as concomitant therapy (after the first dose of double-blind study drug) on the eCRF.

Concomitant therapies will not be provided or reimbursed by the sponsor.

Disallowed Therapies

Other SGLT2 inhibitors may not be used concurrently, and subjects should not take any other investigational agents during the study (however, please note the guidance for subjects in posttreatment follow-up in Section 4.4).

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule that follows the Synopsis summarizes the frequency and timing of efficacy, safety, and other measurements applicable to this study.

Visit Schedules and Visit Windows

A screening visit should occur 1 to 2 weeks before the run-in start visit. The single-blind placebo run-in period should be 2 weeks in length (with a recommended visit window of ±4 days). If additional time in run-in is required for adjustment/optimization of

lipid-altering or blood pressure-lowering medications (so as to avoid the need for adjustment of these medications after randomization), the 2-week placebo run-in may be extended by having the subject continue single-blind placebo up to 2 additional weeks.

Subsequent scheduled study visits during the first year of the study should occur at Day 1 (baseline, the day of randomization), Weeks 6, 12, 18, 26, 39, and 52. After the first year, scheduled (in-clinic) study visits may occur at 13-week or 26-week intervals (at the option of the investigator). If in-clinic visits are changed to an every 26-week frequency, a telephone contact should occur in between the 26-week interval in-clinic visits such that there will be contact with the subject every 13 weeks (in-clinic visits alternating with telephone contacts) (see the Time and Events Schedule). For each post-baseline visit up through Week 26, the recommended visit window is ±7 days. After Week 26, the recommended visit window is ±14 days. After Week 65, on those occasions when the 26- and/or 52-week-interval visits overlap, the visit with the more comprehensive procedures (as outlined in the Time and Events Schedule that follows the Synopsis) will be followed.

Telephone contacts, or optional site visits, should be conducted at Weeks 2, 4, and 9. Refer to the Time and Events Schedule that follows the Synopsis for further details. If a telephone contact or study visit is not possible, follow-up information may be collected via email or other electronic or non-electronic means.

For study visits that are unable to be held within the protocol-recommended visit windows, the visit should be conducted as closely as possible to the protocol-specified study visit timing. All subsequent visits should be scheduled based on the date of randomization, not the date of the rescheduled visit. The study visits at Week 52, and annual visits, should occur as closely as possible to this scheduled time.

Pregnancy Testing

Serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the study (refer to the Time and Events Schedule that follows the Synopsis for further details regarding urine pregnancy testing).

Subject Diary: Collection of Self-Monitoring of Blood Glucose (SMBG), Possible Hypoglycemic Event Information, Medical Resource Utilization Information

A standard, protocol-specified diary will be provided to each subject. Routine SMBG measurements may be recorded in the diary, and all events of possible hypoglycemia that are serious adverse events or that lead to study drug discontinuation should be documented as well as associated fingerstick glucose measurements, if available.

The diary may also be used to keep track of medications and/or medication changes at the investigator's discretion. In addition, the diary should be used for the subject to record

health-care provider visits (other than protocol-specified study visits), emergency care, and hospital visits (refer to Section 9.8, Medical Resource Utilization).

The diary should be reviewed by study research staff at each scheduled visit.

Collection of Other Endpoints: Optional Specimens for Exploratory Research

A set of fasting plasma, serum, and urine samples will be collected at the time points specified in the Time and Events Schedule from subjects who consent to this component of the study to allow for exploratory research related to canagliflozin and biomarker analyses that may provide further understanding regarding the diagnosis and treatment of T2DM or obesity (where local regulations permit). Subject participation in this component of the study is optional. Refusal to consent for this component does not exclude a subject from participation in the clinical study. Refer to Section 9.7, Exploratory Evaluations, for further details. Refer to Attachment 4, Optional Specimens for Exploratory Research - Sample Collection and Handling, for further information regarding the collection and handling of exploratory blood and urine samples.

Pharmacogenomic Testing

A blood sample will be collected on Day 1 (or any time after Day 1 if the specimen is inadvertently missed on Day 1) from subjects who have consented to participate in the pharmacogenomic component of the study. Refer to Attachment 5, Pharmacogenomic Sample Collection and Shipment Procedures, for details on collecting and handling blood samples for pharmacogenomic research. In the event of DNA extraction failure, a replacement pharmacogenomic blood sample may be requested from the subject. Signed informed consent will be required to obtain a replacement sample.

9.1.2. Pretreatment Phase

Screening Visit (Week -3)

Potential subjects will be seen at a screening visit, approximately 3 weeks before scheduled randomization, at which informed consent will be obtained and an initial assessment of eligibility will be performed.

At the screening visit, a focused medical history and initial screening assessment of inclusion/exclusion criteria will be performed and key laboratory studies (including serum chemistry and HbA_{1c}, and fasting lipids [if subject is fasting at the screening visit]) will be obtained.

Run-in Visit (Week -2)

At the Week –2 run-in visit, a complete medical history will be obtained and a physical examination and additional laboratory evaluations (including hematology, urinalysis, FPG, fasting lipids [if not obtained at screening visit]), and an ECG will be performed, per the Time and Events Schedule that follows the Synopsis.

At this visit, subjects who continue to meet enrollment criteria may then be dispensed single-blind placebo capsules (through IVRS or IWRS, refer to Section 5, Treatment Allocation) and enter the 2-week single-blind placebo run-in period. An assessment of the subjects' adherence to protocol procedures during the run-in will be made at the end of the period, before randomization, and will provide investigators with an opportunity to assess subjects' compliance with taking the single-blind study drug (by counting capsules), and having a stable diet and exercise regimen.

Subjects who do not meet all inclusion criteria or meet a study exclusion criterion based upon the results of the screening or run-in visit laboratory studies should be excluded from the study, and discontinue single-blind placebo.

At the run-in visit and during the 2-week run-in period (ie, at additional visits as considered appropriate), investigators should evaluate CV risk factors (eg, blood pressure, and fasting lipid levels) and adjust therapies, if necessary (refer to Section 6.2.1, Management of Glycemic Control and CV Risk Factors). At the run-in visit (Week -2), subjects who continue to be eligible will be provided with a glucose meter and testing supplies and instructed on the performance of SMBG. In addition, a standard, protocol-specified diary will be provided to each subject. Subjects will also receive counseling regarding diet and exercise consistent with standard diabetes guidance recommendations (eg, ADA), and will be counseled regarding recognition and management of hypoglycemia, including recording of possible hypoglycemic events on the subject diary along with concurrent fingerstick glucose measurements. Subjects should be counseled by the study research personnel regarding the importance of good compliance with all study procedures throughout the study.

9.1.3. Double-Blind Treatment Phase

Day 1/Day of Randomization

Potential subjects who return for the Day 1 (baseline), who have taken ≥80% of the scheduled single-blind placebo capsules during the run-in period, and who meet the enrollment criteria will be randomly assigned in a 1:1:1 ratio to once daily treatment with canagliflozin 100 mg, canagliflozin 300 mg, or matching placebo. Subjects will continue treatment until the study completes or the subject is prematurely withdrawn from double-blind study medication (refer to Section 10.2, Withdrawal From the Study, for reasons for withdrawal).

In addition, pharmacogenomic informed consent will be obtained (only from those subjects who agree to participate in this component).

Visits Following Randomization

Subjects will be seen in the clinic at visits or contacted by telephone as described in Section 9.1.1, Overview, and in the Time and Events Schedule. Procedures and clinical

laboratory assessments for each visit or contact are outlined in the Time and Events Schedule.

Subjects who experience nonfatal events in the CV composite endpoint (ie, nonfatal MI, nonfatal stroke) during the double-blind treatment phase will continue in the study, continuing to receive double-blind study drug and complete all assessments at all scheduled visits, as appropriate.

9.1.4. End-of-Treatment/Early Withdrawal

The end-of-treatment/early withdrawal evaluation will be performed when the double-blind treatment phase of the study is ended or at the time the subject is withdrawn from the study. The evaluation should be performed as soon as possible after stopping the study drug.

Refer to the Time and Events Schedule that follows the Synopsis for procedures at the End-of-Treatment/Early Withdrawal evaluation.

Subjects who prematurely discontinue double-blind treatment will have follow-up contact as described in Section 9.1.5, Posttreatment Phase (Follow-Up) and in the Posttreatment Time and Events Schedule. If it becomes no longer possible for a subject to continue to make site visits for posttreatment measurement of vital signs and laboratory specimen collection, the investigator may revert to telephone contacts (with the subject or, as a last resort, with relatives or a family physician) or other available medical records to assess and collect information regarding serious adverse events, CV events, and fractures on the timelines described in the Time and Events Schedule, and forego the clinic visits. Alternately, at the investigator's discretion, less frequent in-clinic visits may be interspersed with other forms of contact, including telephone, email, letters, social media sources, fax, or other electronic or non-electronic means.

9.1.5. Posttreatment Phase (Follow-Up)

All subjects should have a follow-up telephone contact (or optional study visit, at the discretion of the investigator) (if a telephone contact or study visit is not possible, follow-up information may be collected via email or other electronic or non-electronic means) approximately 30 days (but no more than 42 days) after the last dose of study drug to collect:

- Nonfatal CV events in the primary composite endpoint (nonfatal MI, nonfatal stroke)
- Death from any cause
- Nonfatal serious adverse events
- Adverse events of fracture

Subjects who discontinue treatment early for any reason (other than withdrawal of consent for follow-up contacts) will be contacted according to the Posttreatment Time and Events Schedule (or more frequently if necessary based on the investigator's knowledge of the subject) until completion of the overall study, with the goal of collecting any CV outcome events (ie, nonfatal events in the CV composite endpoint), deaths from any cause, adverse events of fracture, and any serious adverse events. Subjects who discontinue treatment less than 26 weeks before the completion of the study will be contacted by telephone at the end of the study to collect any of the events in the list above.

9.2. Reporting/Adjudication of Events in the CV Composite Endpoint and Other Events for Adjudication

Investigators will be counseled to report any event that they assess as potentially being a component of the study CV composite endpoints: CV death, nonfatal MI, and nonfatal stroke. In addition, all deaths (to determine cause of death) as well as events of hospitalized heart failure, will be submitted for adjudication.

For events of hospitalized unstable angina, adjudication will conclude with implementation of amendment INT-6. However, investigators will continue to report such events that are serious or that lead to study drug discontinuation on the eCRF.

Investigators will complete a separate eCRF for potential events in the CV composite endpoints and must provide a specific package of information to be submitted for adjudication evaluation that will be provided in a procedural manual. An independent Endpoint Adjudication Committee will assess all events that could potentially contribute to the specified CV endpoints and only those events that the committee, using methodology defined in the committee's charter, determines are prespecified endpoint events will be included in the analysis. The Endpoint Adjudication Committee will classify the outcome events while blinded to treatment assignment. The same Endpoint Adjudication Committee will adjudicate events from all of the studies that will contribute to the meta-analysis of the pooled large, well-controlled, randomized studies of canagliflozin (including CANVAS).

Note that events assessed by the investigator as an event in the CV composite endpoint, with the exception of CV death, should not be reported as adverse events/serious adverse events (refer to Section 12, Adverse Event Reporting). If the event is adjudicated by the Endpoint Adjudication Committee as **not** meeting the event definition, *then the event should be reported as an adverse event/serious adverse event* (with reporting timelines starting at the time of notification of this by the Endpoint Adjudication Committee).

With the implementation of INT-6, hospitalized unstable angina events should now be reported as adverse events/serious adverse events (see Section 9.4, Safety Evaluations).

9.3. Study Management: Committees

9.3.1. Academic Research Organization

An Academic Research Organization (ARO) will provide scientific and academic oversight of the study. The ARO will also have a role in site monitoring for a portion of the sites.

9.3.2. Steering Committee

A Steering Committee, made up of external scientific experts will provide scientific advice regarding the study design, conduct, and data collection. The Steering Committee is responsible for providing input on study design, academic leadership to study sites, reviewing study progress, and reviewing study results before publication. Details of the composition, roles, and responsibilities will be documented in its charter.

9.3.3. Medical Safety Review Committee

An MSRC will be established to ensure that the safety of subjects participating in the study is not compromised. The MSRC will include, but will not be limited to, at least one medical expert and at least one statistician. The MSRC will include members from the sponsor organization and may include ARO representatives. The MSRC will monitor the progress of the study by reviewing blinded data on a regular basis and will refer safety concerns to the IDMC.

Details of the composition, roles, and responsibilities will be documented in its charter.

9.3.4. Independent Data Monitoring Committee

An IDMC will be commissioned for this study to review accumulated, unblinded safety information during the study. Details of the composition, roles, and responsibilities will be documented in its charter.

The IDMC will also have responsibility for review of the primary CV endpoints for this study as well as across the canagliflozin clinical development program.

9.3.5. Endpoint Adjudication Committee

An independent Endpoint Adjudication Committee composed of external specialists, blinded to treatment assignment, will be commissioned to review case information on potential MACE events. The operations, processes, and endpoint definitions to be employed by the committee will be defined in its charter.

9.4. Safety Evaluations

Only serious adverse events, non-serious adverse events resulting in study drug discontinuation, and adverse events of interest (see below) will be recorded on eCRFs.

Safety and tolerability will include an evaluation of serious adverse events, adverse events of interest, discontinuation due to adverse events, clinical laboratory tests, vital

signs (pulse, blood pressure), and body weight. Cardiovascular safety will be assessed as part of the meta-analysis of CANVAS and CANVAS-R.

Refer to Section 9.2, Reporting/Adjudication of Events in the CV Composite Endpoint and Other Events for Adjudication, for reporting and adjudication of events in the CV composite endpoint.

Adverse Events of Interest

Adverse events of interest include: all malignancies, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (eg, angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, male genital infections (balanitis, phimosis, events leading to circumcision), and pregnancy. Information on these events will be recorded on supplemental eCRFs or other designated forms for any event that is serious or that leads to study drug discontinuation. In addition, non-serious adverse events of malignancies, photosensitivity reactions, fractures, venous thromboembolic events, male genital infections (balanitis, phimosis, events leading to circumcision), and amputations for which information on non-serious adverse events will also be recorded on the supplemental CRF pages or other designated forms (in addition to the information collected on serious AEs and AEs leading to study drug discontinuation). Diabetic ketoacidosis has been designated as an adverse event of special interest and therefore adverse events related to DKA, ketoacidosis, metabolic acidosis or acidosis need to be reported to the sponsor within 24 hours of becoming aware of the event, which is the same timeframe for reporting of serious adverse events. These adverse events must be reported using a supplemental DKA Reporting form, to complement standard information collected on the eCRF AE/SAE page. Amputation has also been designated as an adverse event of special interest and therefore amputations need to be reported to the sponsor within 24 hours of becoming aware of the event. If adverse events of interest are identified in the future, guidance concerning the reporting of those events may be provided to investigators via appropriately-documented study communications. (see Table 1)

Table 1: Adverse Event Collection Requirements

Collect all (serious or non-serious):	Collect if serious or if adverse event causes discontinuation:
• Malignancies (especially renal cell cancer, pheochromocytoma, Leydig cell tumor) • Photosensitivity • Venous thromboembolic events • Fractures • Male genital infections (balanitis phimosis, events leading to circumcision) • Amputations • Diabetic ketoacidosis • Any pregnancy	• Fatal pancreatitis and hemorrhagic/necrotizing pancreatitis • Severe hypersensitivity reactions (eg, angioedema, anaphylaxis, Stevens-Johnson syndrome) • Serious adverse events of hepatic injury • Nephrotoxicity/acute kidney injury • Any other event

Detailed collection of information on serious adverse events of hypoglycemia or adverse events of hypoglycema that lead to study drug discontinuation will be performed on supplemental eCRFs. For selected specific adverse events (ie, vulvovaginal adverse events, superficial genital adverse events in men, and adverse events of urinary tract infection), investigators will be asked to provide additional information, on separate eCRFs, so as to support more detailed analyses for events that are serious or that lead to study drug discontinuation.

All deaths will undergo adjudication by the Endpoint Adjudication Committee to determine cause of death and whether CV disease was a proximate or underlying cause.

Events with characteristics of DKA will be adjudicated by an ad hoc adjudication committee, to verify whether or not the event meets a specified definition of DKA. Other categories of events (eg, renal) may undergo adjudication as necessary based on regulatory agency requests or to supplement data analyses.

Adverse Events

Adverse events as noted above will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally-acceptable representative) for the duration of the study, beginning when the informed consent is signed. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

For purposes of reporting serious adverse events for this study, the components of the CV composite endpoints (with the exception of CV death) will not be considered adverse events or serious adverse events. Events in the CV composite endpoints will not be considered as unexpected but as disease-related, and as such will not be

unblinded. Refer to Section 12, Adverse Event Reporting, for details regarding the handling of components of the CV composite endpoints (note: hospitalized unstable angina, previously considered a component of the CV composite endpoint, will now be considered as a serious adverse event and should be recorded on the adverse event/serious adverse event eCRF page).

Information for all adverse events will be collected in source documents (eg, progress notes) retained at the investigative sites.

Follow-Up Collection of Safety Information

Any clinically significant abnormalities persisting at the time of end-of-treatment or early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached, or until further follow-up is no longer considered by the investigator to be clinically meaningful. For details on the end-of-treatment or early withdrawal evaluations, and posttreatment follow-up collection of information, see Section 9.1.4, End-of-Treatment/Early Withdrawal, and Section 9.1.5, Posttreatment Phase (Follow-Up).

Clinical Safety Laboratory Tests

Subjects will be monitored with safety laboratory measurements (hematology, chemistry, and urinalysis [with urine glucose not measured to avoid unblinding]) as described in Attachment 6.

In subjects with elevations in ALT ≥3-fold ULN, subjects will be monitored and managed using the algorithm in Attachment 7.

Alerts will be provided to investigators by the central laboratory identifying important laboratory changes or key out-of-range values, so the investigator can follow up as necessary. For creatine phosphokinase (CPK) elevations, the investigator should determine if follow-up evaluation is clinically appropriate to exclude a potential cardiac event. The review of such alerts should be documented by the investigator as soon as possible after receipt of the results.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF.

Urine samples from first morning void on day of designated visits will be collected for urine albumin and creatinine determinations. If the subject does not provide the morning void collection on the day of the visit, the subject may bring a first morning void specimen to the investigational site during the subsequent week. For subjects working a night shift, or who otherwise have atypical sleep patterns, the collection should be made at the end of the subject's usual sleep period.

The urine collections for exploratory analysis, as well as the routine urinalyses, should be obtained from a spot urine specimen in the clinic.

Urine glucose will not be measured in the first morning void urine specimens or urinalyses.

For SMBG monitoring during the study, see Section 6.2.1, Management of Glycemic Control and CV Risk Factors.

Vital Signs (pulse, blood pressure)

Vital signs will consist of pulse and blood pressure measurements and will be obtained after the subject has been in the sitting position for 5 minutes and before blood sample collection for laboratory tests. Pulse rate will be measured once at each clinic visit. Blood pressure will be assessed manually with a mercury sphygmomanometer, or a properly calibrated automated blood pressure monitor; if neither of these is available, a high-quality aneroid sphygmomanometer calibrated according to manufacturer specifications will be acceptable. Three consecutive blood pressure readings will be taken and recorded, at intervals of at least 1 minute apart, as specified in the Time and Events Schedule.

In addition, blood pressure will be measured 3 times in both arms at the screening visit; if there is a difference between arms of >10 mmHg in either the mean systolic or diastolic pressure, the arm with the higher pressure should be used to measure blood pressure and *should be used for all subsequent blood pressure measurements during the study*. If possible, if blood pressure is measured manually, it should be measured by the same individual, using the same equipment, at each clinic visit to reduce variability.

Body Weight

Body weight will be measured using the same calibrated scale at each visit. The study center will be responsible for calibrating the scale before the first subject enrolled in the study at the site is weighed and then at approximately 12-week intervals during the study. Calibration must be documented in a calibration log. Subjects should be weighed at approximately the same time of day on the same scale, wearing underwear and a gown and without shoes (note: if disrobing for weighing is logistically impossible, the subject must be dressed as lightly as possible, with consistency from visit to visit); subjects will be asked to urinate before being weighed.

Urine Pregnancy Testing

Serum or urine pregnancy tests may be performed in women (unless they are surgically sterile or unless there is a documented history of their postmenopausal status), as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the study (refer to Section 12.2.3, Pregnancy, for

instructions in cases of a positive pregnancy test). Supplies for urine and serum pregnancy testing will be provided by the central laboratory, where possible.

9.5. Measures of Efficacy/Efficacy Endpoints

The primary measure of efficacy is the HR of the composite endpoint of MACE (CV death, nonfatal MI, nonfatal stroke). Secondary measures of efficacy include beta-cell function (HOMA-B; in subjects who are not receiving insulin) and progression of albuminuria (based upon categories determined by urinary albumin/creatinine ratio).

The primary efficacy endpoint, the hypothesis of CV benefit for canagliflozin, will be evaluated based upon the events in the CV composite endpoint of MACE (CV death, nonfatal MI, nonfatal stroke). As previously described, an independent Endpoint Adjudication Committee will assess all events that could potentially be in the specified CV endpoint and only those events where the committee, using methodology and definitions defined in the committee's charter, determines a specified endpoint has occurred will be included in the analysis. The independent Endpoint Adjudication Committee (refer to Section 9.3.5) will apply the endpoint definitions contained in its charter and classify the outcome events while blinded to treatment assignment.

The secondary efficacy endpoint of change in HOMA-B will be assessed in a subset of subjects (approximately 1,200 subjects at sites that elect to participate) who are not receiving insulin at baseline. Homeostasis model assessment-B will be assessed based upon C-peptide and fasting glucose; for subjects who initiate therapy with insulin during the study, data from the last proinsulin, insulin, and C-peptide measurement before initiation of insulin will be utilized for beta-cell function analyses.

The categorical secondary efficacy endpoint of the proportion of subjects with progression of albuminuria (defined as ≥1 step increase in category [as defined below] of albuminuria [ie, none to micro- or macro-, or micro- to macroalbuminuria]) will be assessed from first morning void urine collections according to the categorizations defined in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Guideline #1 (KDOQI 2007). The definition of micro-albuminuria is albumin/creatinine ratio of 30 to 300 mg/g and the definition of macro-albuminuria is albumin/creatinine ratio greater than 300 mg/g.

Additional efficacy endpoints of interest will include the following: changes from baseline to end-of-treatment in the proinsulin/insulin ratio (in a subset of subjects), urinary albumin/creatinine ratio, and eGFR; changes from baseline to Week 18 in HbA_{1c}, FPG, systolic and diastolic blood pressure, and body weight; and percent change from baseline to Week 18 in fasting plasma lipids (triglycerides, HDL-C, LDL-C, total cholesterol, and the ratio of LDL-C to HDL-C). The eGFR will be calculated using the Modification of Diet in Renal Disease [MDRD] equation (Levey 2006).

Refer to Section 11.5, CV Outcomes and Efficacy Analyses, for the evaluation of efficacy criteria.

9.6. Pharmacogenomic Evaluations

There are 2 parts to the pharmacogenomic component of this study.

Analysis Related to the Study (Part 1)

Part 1 of pharmacogenomic research allows for the analysis of genes that may be relevant to help to better understand canagliflozin, or T2DM or obesity. Candidate genes will only be genotyped, if it is hypothesized that this may help resolve issues with the clinical data. Analyses may involve the analysis of known candidate genes or the analysis of genetic variants throughout the genome (genome-wide association analysis), both in relation to canagliflozin, or T2DM or obesity (provided in Attachment 8). Genotyping of any of these candidate genes would be performed on identifiable samples.

Additional genes may be analyzed on identifiable samples if these genes are hypothesized to be relevant to canagliflozin, or T2DM or obesity between the time that the clinical protocol has been issued and the samples have been made nonidentifiable.

DNA Storage for Future Research (Part 2)

Part 2 of the pharmacogenomic research allows for the storage of DNA samples for future genetic research related to canagliflozin or the indication(s) for which it is developed. Stored DNA samples and relevant clinical data will be made nonidentifiable after the Clinical Study Report has been issued. This involves removing personal identifiers and replacing the study subject identifier with a new number to limit the possibility of linking genetic data to a subject's identity.

Subjects will be given the option to participate in Part 1 only, Part 2 only, both parts, or neither part of the pharmacogenomic component of this study (where local regulations permit).

9.7. Exploratory Evaluations

A set of fasting plasma, serum, and urine samples will be collected (where local regulations permit) at the time points specified in the Time and Events Schedule for the following:

- exploratory analysis that may be done to provide insight into the actions of canagliflozin or assist in understanding of adverse events possibly associated with the compound. Samples may also be used for future exploratory research to improve understanding of the pathophysiology of T2DM or obesity or to assess other pharmacodynamic effects of canagliflozin, and
- to develop biomarkers that may provide further understanding regarding the risk of development of diabetes-related complications.

This exploratory evaluation is optional and will only be performed in subjects who give informed consent for this specific component of the study.

9.8. Medical Resource Utilization

Subjects will be requested to collect information in a protocol-specified diary on information related to their utilization of medical resources (see Attachment 9). This MRU data from the subject diaries will then be documented in the eCRF by the investigator and study research staff for all subjects at each visit throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses.

No cost data will be collected in this study.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

A subject will be considered to have completed the study if he or she has experienced a clinical endpoint that precludes further study (eg, early mortality due to CV event) or when the study ends. Note that occurrence of a nonfatal event in the CV composite endpoint (ie, nonfatal MI, nonfatal stroke) is not a study withdrawal criteria. Subjects with these events should be continued in the study, on study drug, unless they meet a study withdrawal criterion (see Section 10.2, Withdrawal From the Study). Subjects who prematurely discontinue study treatment for any reason before completion of the double-blind treatment phase will not be considered to have completed the study.

10.2. Withdrawal From Study Drug

A subject will be withdrawn from the study drug for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent (subject withdrew consent for treatment and refuses any further follow-up)
- Subject is persistently in poor compliance with study treatment or procedures
- The investigator believes that for safety or tolerability reasons (eg, an adverse event) it is in the best interest of the subject to stop treatment
- The subject becomes pregnant (study therapy should be immediately discontinued based upon a positive urinary hCG, and permanently discontinued if confirmed by a serum β-hCG test)
- The subject's eGFR is <15 mL/min/1.73m^2 (as reported by the central laboratory).

  Note: the central laboratory will alert the investigator for eGFR values <15 mL/min/1.73m^2. A repeat determination should be performed within 2 weeks, and study treatment discontinued if the repeat eGFR is <15 mL/min/1.73m^2 (unless a reversible cause is identified [eg, short-term illness or transient volume depletion] in

which case an additional repeat determination can be performed after resolution of the short-term illness).

- Subject requires dialysis or renal transplantation
- Subject has liver function test abnormalities meeting criteria for permanent discontinuation of study drug as outlined in Attachment 7
- The investigator formally unblinds the subject's treatment allocation
- Subject initiates disallowed therapy (refer to Section 8, Prestudy and Concomitant Therapy)
- The subject experiences a serious adverse event of biochemically-confirmed (eg, pH, serum ketones, anion gap) DKA.

The end-of-treatment evaluations should be performed as soon as possible after stopping the study drug (see Section 9.1.4, End-of-Treatment/Early Withdrawal, and the Time and Events Schedule that follows the Synopsis for procedures to be performed). For posttreatment follow-up contacts, refer to Section 9.1.5, Posttreatment Phase (Follow-up).

Subjects who decide to withdraw from double-blind study drug must be interviewed by the investigator so as to determine if a specific reason for withdrawal can be identified. If the subject elects to withdraw due to an adverse event, the event should be recorded as the reason for withdrawal, even if the investigator's assessment is that the adverse event would not require study drug withdrawal.

When a subject withdraws from double-blind study drug before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source documentation. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

A subject who elects to withdraw consent for the biomarker specimen collections will not have further collections made after withdrawing consent, and has the following options:

- to allow the previously collected specimens to remain for biomarker analysis, or
- to request that the previously collected specimens be destroyed.

A subject who withdraws from the main part of the study will have the following options regarding pharmacogenomic research:

- The DNA extracted from the subject's blood will be retained and used in accordance with the subject's original pharmacogenomic informed consent.
- The subject may withdraw consent for pharmacogenomic research, in which case the DNA sample will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor site contact to request sample destruction. The sponsor site contact will, in turn, contact the pharmacogenomics representative to execute sample destruction. If requested, the

investigator will receive written confirmation from the sponsor that the sample has been destroyed.

Withdrawal from Pharmacogenomic Research Only

The subject may withdraw consent for pharmacogenomic research while remaining in the clinical study. In such a case, any DNA extracted from the subject's blood will be destroyed. The sample destruction process will proceed as described above. However, all samples will be made nonidentifiable after the Clinical Study Report is issued and thereafter cannot be identified for destruction. If the sample has already undergone conversion to the nonidentifiable format, the sponsor will notify the investigator in writing.

10.3. Reinstitution of Subjects Who Have Prematurely Discontinued Double-Blind Study Drug to Active Status

Subjects for whom study drug is interrupted as a result of an adverse event, a life event (eg, temporary relocation to care for an ill family member), or other unforeseen circumstance may return to active status (ie, re-start double-blind study drug) in the study at the discretion of the investigator, with concurrence from the sponsor's medical monitor, even if previously withdrawn from the study or off study drug for up to 90 days. Subjects off study drug for more than 90 days, or subjects who meet the conditions that require withdrawal (eg, unblinding), should not be returned to active status. If the subject had previously withdrawn consent but decides to retract that withdrawal, the subject will be reconsented. The investigator will be responsible for making all required notifications to the IRB or Ethical Committee.

10.4. Measures to Re-establish Contact in Subjects Lost to Follow-up

If a subject is lost to follow-up, **all possible efforts must be made by the study site personnel to contact the subject and to determine endpoint status and the reason for discontinuation/withdrawal.** The measures taken to follow-up must be documented. The informed consent form will stipulate that even if a subject decides to discontinue double-blind study drug, he/she will agree to be contacted periodically by the investigator to assess his/her endpoint status (refer to the Posttreatment Time and Events Schedule for subjects that prematurely discontinue double-blind study drug). Furthermore, the subject will be asked to agree to grant permission for the investigator to consult family members, the subject's physicians and medical records, or public records, including the use of locator agencies as permitted by local law, to determine the subject's endpoint status, in the event the subject is not reachable by conventional means (eg, office visit, telephone, email, or certified mail). The subject is informed that if the site of the study doctor closes, and the study doctor cannot reach the subject to inform him/her, the contact information will be transferred to another site where a new study doctor will consult with family members, the subject's physicians and medical records, or public records, including the use of locator agencies as permitted by local law, to determine the subject's endpoint status.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the SAP.

11.1. Analysis Sets

The ITT analysis set includes all subjects who are randomly assigned to a treatment group. The assessment of the primary objective will be based upon this analysis set. The primary CV analysis will be based on the time to the first occurrence of any component of the CV composite endpoint.

The modified intent-to-treat (mITT) analysis set includes randomized subjects who receive at least one dose of study drug and their data occurring between first dose and last dose plus 30 days.

The alignment of the analysis of the secondary endpoints with the ITT and mITT analysis sets will be detailed in the study SAP.

11.2. Handling of Dose in Analysis

The primary comparison, to assess CV risk reduction, will be between canagliflozin (100 and 300 mg groups combined) versus placebo. Additionally, the HR and its 2-sided 95% CIs versus placebo will be assessed for each dose of canagliflozin.

11.3. Sample Size Determination

The sample size for the recruitment of the initial 4,500 subjects was based upon having a sufficient number of participants to support, in concert with the other controlled clinical trials in the canagliflozin development program, a detailed pre-approval assessment of the safety and tolerability of canagliflozin. Data from this initial cohort were exported and integrated with data from other Phase 3 well-controlled studies to support a planned pre-approval meta-analysis to demonstrate that the upper bound of the 2-sided 95% CI for the CV HR of canagliflozin relative to control in composite endpoint events (MACE and hospitalized unstable angina) was <1.8; the current US regulatory requirements for filing. The FDA post-marketing requirements for canagliflozin demand a subsequent estimate of CV safety that will be performed on data from CANVAS and CANVAS-R, when sufficient events have occurred to demonstrate that the upper bound of the 95% CI HR is <1.3 based on MACE (excluding hospitalized unstable angina).

The assumed per annum event rate is 2.25% and the per annum dropout rate is 5%. With an enrollment period 1.5 years, 4,500 randomized subjects were projected to contribute sufficient CV events to support the pre-approval CV meta-analysis.

The original phased recruitment strategy allowed for an interim assessment of study feasibility to demonstrate the primary hypothesis of CV benefit using the results of the interim analysis. Results from the interim analysis (conducted after approximately 2 to

4 years from study initiation, eg, at approximately the time of US regulatory approval) were planned to be evaluated by a CV risk factor evaluation committee to assess the effect of canagliflozin on CV risk factors (to predict the likely effect of canagliflozin on CV events) and determine the point estimate for the HR for MACE. The data on the observed point estimate for the CV HR for MACE were to have been reviewed by the IDMC only and would not have been made more broadly available. Re-opening of enrollment was to have proceeded if the effects on the intermediate outcomes (ie, CV risk factors) as determined by appropriate models (to be prespecified before the interim analysis) that canagliflozin compared to placebo would result in an HR of 0.85 or less (for MACE) and if the observed HR (for MACE) is 0.95 or less. If recruitment did proceed, an additional 14,000 subjects would have been enrolled into Cohort B. However, for the reason outlined above (see Section 3), this second cohort will no longer be recruited.

Without the recruitment of the second cohort of 14,000 subjects, CANVAS study power is reduced from the originally planned 90% power to detect a HR of 0.85 or less. It is now projected that at the completion of the study there will be about 400 MACE events recorded within CANVAS, which will provide 33% power to detect a HR of 0.85 or less, 55% power to detect a HR of 0.80 or less, and 76% power to detect a HR of 0.75 or less using a 2-sided test with 0.05 alpha.

11.4. Safety Analyses

The safety analysis will be based on the mITT analysis set. The mITT analysis set includes all subjects who are randomly assigned to a treatment group and have received at least one dose of study drug and their data occurring between first dose and last dose plus 30 days. There will be no imputation for missing values for clinical laboratory test results or vital sign measurements in the analyses.

Safety and tolerability will be evaluated by summarizing and comparing the incidence of serious adverse events and adverse events of interest, discontinuation rate due to adverse events, clinically important changes in clinical laboratory tests, vital signs (pulse, blood pressure), and body weight between randomized groups. There will be no imputation for missing values for clinical laboratory test results or vital sign measurements in the analyses.

Adverse Events

The verbatim terms used in the eCRFs by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported serious adverse events, adverse events resulting in study drug discontinuation, and adverse events of interest with onset during the treatment phase (ie, treatment-emergent adverse events) will be included in the analysis. For each adverse event, the percentage of subjects who experienced at least one occurrence of the given event will be summarized by treatment group. An adverse event will be considered to be a treatment-emergent

event if it occurs within 30 days of the last date of blinded study medication. The percentage of subjects with specific treatment-emergent adverse events will be summarized by severity and relationship to study drug, as classified by the investigators, for each treatment group.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, who experience a serious adverse event, or who experience an adverse event of interest.

Further analyses, described in the SAP for this study, will be conducted on the prespecified adverse events for which additional information is collected from the investigators (refer to Section 9.4, Safety Evaluations).

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Normal reference ranges will be provided. Criteria for markedly abnormal laboratory values will be prespecified in the SAP. The percentage of subjects with markedly abnormal results will be summarized for each laboratory analyte. Descriptive statistics will be reported for each laboratory analyte at baseline and at each scheduled time point and for change from baseline.

Vital Signs

Descriptive statistics for pulse and sitting blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

11.5. CV Outcomes and Efficacy Analyses

11.5.1. CV Outcomes (Primary Efficacy Endpoint)

The primary endpoint for CV benefit will be time to MACE, which is calculated as the time from randomization to the first occurrence of MACE. The statistical hypothesis will be:

$H_{0(1.0)}$: the HR =1.0, versus $H_{1(1.0)}$: the HR $\neq$1.0.

The primary analysis will be based on the ITT analysis set and the MACE events determined by the EAC to meet prespecified criteria. The primary comparison of canagliflozin to placebo will be based on the HR estimate derived from Cox proportional hazards model with terms for treatment, history of a previous CV event as fixed effects.

The assumption of the proportional HR will be examined. In case the assumption is deemed not reasonable, sensitivity analyses that do not rely on the constant HR assumption will be conducted to verify the results of the primary analysis.

Additionally, the HR and its 2-sided 95% CIs versus placebo will be assessed for each dose of canagliflozin. For individual components of the composite CV endpoint, the HR

and its 2-sided 95% CIs of canagliflozin combined doses relative to placebo will also be assessed.

Sensitivity analyses including CV endpoint events that occur within 30 days of the last dose of blinded study medication will be done.

The effects of different baseline demographic variables (eg, age, race, sex) as well as other important baseline disease characteristics (eg, history of prior CV disease, key concomitant therapy use, and region) on the primary endpoint will be explored; a detailed discussion of subgroup analyses will be provided in a SAP for this study, which will be finalized before the first interim analysis.

11.5.2. Major Secondary Efficacy Endpoints

The continuous secondary efficacy endpoint, change from baseline in HOMA-B will be analyzed using an analysis of covariance (ANCOVA) model with treatment (canagliflozin 100 mg, canagliflozin 300 mg or placebo) and stratification factors as fixed effects and the corresponding baseline value as a covariate. The treatment difference (each dose of canagliflozin minus placebo) in the least-squares means and the 2-sided 95% CI will be estimated based on this model. The analyses for beta-cell function will be conducted on subjects not receiving insulin at randomization and, for subjects who are started on insulin during the study, the last data point before the initiation of insulin will be included for these analyses.

The categorical secondary efficacy endpoint is the proportion of subjects with progression of albuminuria (defined as ≥1 step increase, ie, no albuminuria to micro- or macro-albuminuria or from micro-albuminuria to macro-albuminuria). The proportion of subjects with progression of albuminuria will be analyzed using the logistic model with treatment (canagliflozin 100 mg, canagliflozin 300 mg or placebo), and stratification factors as a fixed effect. Albuminuria will be assessed according to the categorizations defined in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Guideline #1 (KDOQI 2007): the definition of micro-albuminuria is albumin/creatinine ratio of 30 to 300 mg/g, and the definition of macro-albuminuria is albumin/creatinine ratio greater than 300 mg/g.

For the secondary endpoints of HOMA-B and proportion of subjects with progression of albuminuria, the analyses will compare the dose groups, *combined* and *individually*, relative to placebo.

11.5.3. Multiplicity Adjustment

To ensure the family-wise Type I error rate (alpha level) in this study is at most 5%, a gatekeeping procedure will be applied in testing the primary and secondary hypotheses. The superiority of the canagliflozin combined doses over placebo in time to MACE will be tested first. If statistically significant, the procedure will proceed to test the secondary endpoints of the proportion of subjects with progression of albuminuria and HOMA-B for

each canagliflozin dose versus placebo. Details of the gatekeeping procedure will be contained in the SAP.

11.5.4. Additional Secondary Efficacy Endpoints

Additional efficacy endpoints of interest will include the following:

- changes from baseline to end-of-treatment in the proinsulin/insulin ratio (in a subset of subjects), urinary albumin/creatinine ratio, and eGFR
- changes from baseline to Week 18 in HbA_{1c}, FPG, systolic and diastolic blood pressure, and body weight
- percent change from baseline to Week 18 in fasting plasma lipids (triglycerides, HDL-C, LDL-C, total cholesterol, and the ratio of LDL-C to HDL-C)

The continuous secondary efficacy endpoints, changes from baseline in the proinsulin/insulin ratio, HbA_{1c}, FPG, body weight, blood pressure, albuminuria, and eGFR and percent change in fasting lipids will be analyzed in the same manner as the secondary efficacy endpoint, change from baseline in HOMA-B.

For the assessment of change from baseline in HbA_{1c} at Week 18, subgroup analyses (described in detail in the SAP for this study) will be conducted to enhance understanding of factors that might impact glycemic response to canagliflozin.

11.6. Medical Resource Utilization Analyses

Medical Resource Utilization data analyses will be descriptively summarized by primary outcome variable (ie, those with a CV event versus those without) regardless of treatment group. These data may be used in future economic modeling to be done outside of the protocol.

11.7. Interim Analyses of CANVAS

11.7.1. Interim Analyses for Health Authority Submissions

Interim analyses of CANVAS will be done to prepare: (1) an interim safety report in support of the initial health authority filing, (2) the 18-week substudy reports, and (3) the CV safety meta-analyses (based on adjudicated data). The interim data from the CANVAS study will primarily supplement the safety and tolerability data generated from other studies in the canagliflozin development program.

11.8. Meta-Analysis to Support Regulatory Requirements

11.8.1. Meta-Analysis Pre-Regulatory Approval

To support submissions for marketing approval, the CV event data and other safety and efficacy results in this study will be exported and integrated with the data from other large, well-controlled, double-blind, randomized studies in the canagliflozin clinical development program. A meta-analysis of the integrated CV data will be conducted to compare canagliflozin with active or placebo control (eg, current FDA guidance requires

exclusion of the upper bound of the 2-sided 95% CI around the HR of 1.8 or greater). It is projected that the meta-analysis to support regulatory approval would be conducted when an approximate range of 140 to 160 composite events of MACE (CV death, nonfatal MI, nonfatal stroke) and hospitalized unstable angina are observed across the canagliflozin clinical development program (including CANVAS). In no case would a meta-analysis to support regulatory approval occur with fewer than 80 events. Note that the primary composite endpoint to show CV risk reduction in the present study includes MACE, while the pre-approval meta-analysis to rule out harm utilizes a composite endpoint that includes MACE plus hospitalized unstable angina.

If the meta-analysis occurs with 140 to 160 events, 30 to 40 are expected to be observed in the other large, well-controlled, double-blind, randomized studies that will be included in the meta-analysis and 110 to 120 observed from the CANVAS study.

Sponsor personnel will be unblinded to the data during the submission of data from this analysis; however, blinding to the subject's treatment allocation will be maintained for the subjects, investigators, Endpoint Adjudication Committee, and sponsor site-monitoring personnel throughout the study. In order to maintain data integrity with respect to endpoint adjudication, individuals within the sponsor responsible for submitting events to the Endpoint Adjudication Committee will handle the review and submission of adjudication packages in a completely blinded fashion.

The meta-analysis will be the subject of a separate SAP in which the objectives, hypotheses, and analytic strategy are described.

11.8.2. Meta-Analysis Post-Regulatory Approval

To meet US regulatory requirements post-approval (refer to Section 1.2, Overall Rationale and Goals for the Study), results from this study will be exported and integrated with results from CANVAS-R to demonstrate that the upper bound of the 95% CI around the HR for important CV events (MACE) is <1.3. The primary objective of the CANVAS-R study is to evaluate the effects of canagliflozin relative to placebo on albuminuria progression. The CANVAS and CANVAS-R studies will share similar inclusion and exclusion criteria and will enroll similar patient populations. Both studies will require a standardized collection and evaluation of MACE endpoint events by the same Endpoint Adjudication Committee (see Section 9.3.5).

A CV meta-analysis was conducted with 201 MACE plus events. The pre-approval condition was met by demonstrating that the upper bound of the 2-sided 95% CI for the HR was <1.8. The post-approval condition for the exclusion of HR of 1.3 was then tested with 0.001 alpha, and was not met.

As part of the post-approval CV safety requirement, a meta-analysis based on the data from this study and the data from another large-scale study, CANVAS-R, will be conducted when at least 688 MACE events are accumulated in the 2 studies, which is

projected to occur prior to April 2017. With at least 688 MACE events, the power to show the HR <1.3 is about 90% with a 2-sided significance level of 0.05.

The 'Statistical Analysis Plan for the Post-Marketing Requirement for the CV Risk Assessment of Canagliflozin (CANVAS and CANVAS-R)' was finalized and submitted to FDA.

11.9. Glycemic Efficacy Substudies

11.9.1. Analysis Sets

The mITT analysis set includes all subjects who are randomly assigned to a treatment group and received at least one dose of study medication. The per-protocol (PP) analysis set will consist of all mITT subjects who completed 18 weeks of treatment, and have no protocol deviations that may affect the interpretation of the primary efficacy endpoint (to be defined in the SAP before database lock and unblinding of the treatment groups) and have not received glycemic rescue therapy. The primary efficacy analysis will be based on the mITT set. The efficacy data measured after the initiation of rescue therapy will be treated as missing. Analysis based on the PP set will also be conducted as a sensitivity analysis.

Efficacy data will be analyzed according to the randomization assignment, regardless of actual treatment received. Safety data will be analyzed according to actual treatment received. The approaches to handle study treatment deviations will be detailed in the SAP.

11.9.2. Sample Size Determination

The primary objectives of the substudies are to compare the HbA_{1c}-lowering efficacy of canagliflozin with placebo after 18 weeks of treatment, in subjects on specific AHAs.

With the exception of the sulfonylurea substudy, assuming a group difference of 0.50% and a common SD of 1.0% with respect to change in HbA_{1c}, and using a 2-sample, 2-sided t-test with Type I error rate of 0.05, it is estimated that 258 randomized subjects (86 subjects in each of the 3 treatment groups) would provide 90% power.

Recently published literature with another SGLT2 inhibitor (Strojek 2010) suggest that the observed standard deviation with respect to HbA_{1c} change from baseline in subjects taking sulfonylureas is less than originally anticipated in the protocol (ie, SD was reported to be 0.75% instead of 1.0%). These new data would allow for an assessment of the primary substudy endpoint (ie, change in HbA_{1c} from baseline) in the sulfonylurea substudy using a smaller sample size in this substudy, ie, 150 randomized subjects (50 subjects in each of the 3 treatment groups) would provide 90% power.

11.9.3. Efficacy Analyses

For each substudy, except the sulfonylurea substudy as noted above, the primary efficacy analysis will only be performed when sufficient subjects (≥258) in the subpopulation are

randomized in each of the 3 treatment groups (≥86 per group). The analysis will be conducted when the sponsor prepares for the regulatory submissions. For the sulfonylurea substudy, the primary efficacy analysis will only be performed when sufficient subjects (≥150) in the subpopulation are randomized in each of the 3 treatment groups (≥50 per group).

The primary efficacy endpoint will be the change in HbA_{1c} from baseline through Week 18. The LOCF method will be applied when the Week 18 values are missing. In subjects receiving rescue therapy, their measurements made before rescue will be used as the last observation. An ANCOVA model with treatment as a fixed effect and the corresponding baseline value as covariate will be used. The treatment difference (each dose of canagliflozin minus placebo) in the least-squares means and the 2-sided 95% CI will be estimated based on this model.

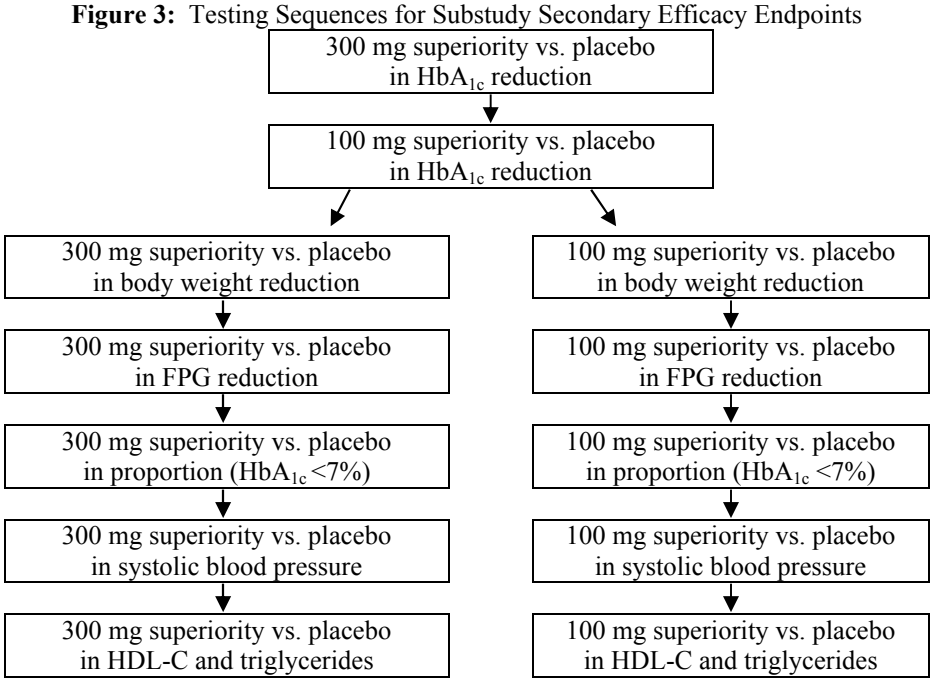
As a supportive analysis, change from baseline in HbA_{1c} will be analyzed using a restricted maximum likelihood (REML) based on repeated measures approach. The analysis will be based on observed data and will include the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. An unstructured covariance will be used to model the within-subject errors. The treatment comparisons will be made between each dose of canagliflozin and placebo at Week 18 and significance tests will be based on the difference of the least-squares means.

The secondary efficacy evaluations of change in body weight, FPG, and systolic and diastolic blood pressure, and percent change in fasting plasma lipids will be analyzed using an ANCOVA model similar to that used in the primary efficacy analysis. The percentage of subjects with HbA_{1c} <7% at Week 18 will be assessed by means of a logistic model with treatment and stratification factors as fixed effects and baseline HbA_{1c} as a covariate.

11.9.4. Multiplicity Adjustment

To ensure the family-wise Type I error rate (alpha level) in each substudy is at most 5%, a gatekeeping procedure will be applied in testing the hypotheses in the substudy. The superiority over placebo in HbA_{1c} reduction will be tested sequentially for the descending doses of canagliflozin. After the superiority of the 2 doses on HbA_{1c} is concluded, the hypothesis of the secondary endpoints will be tested via 2 testing sequences as illustrated in Figure 3. The alpha level will be split evenly for the 2 sequences.

Figure 3: Testing Sequences for Substudy Secondary Efficacy Endpoints



Testing in each sequence stops as soon as any hypothesis in the sequence is failed to be rejected. The Hochberg procedure will be applied for the 2 lipid parameters at the end of the testing sequence. Note that the alpha level in the main study and the alpha level in each substudy are separately controlled.

11.9.5. Safety Analyses

The safety analysis for the substudies will follow the methodology as outlined in Section 11.4, Safety Analyses.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures (SOPs) in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

All deaths and events that are assessed by the investigator as being one of the components of the CV composite endpoints* (ie, CV deaths, nonfatal MI, nonfatal stroke) should be handled as follows:

- Events in the CV composite endpoints will be captured on an eCRF page specifically designed to record endpoint events (note: hospitalized unstable angina events which were previously recorded on the CV eCRF page will now be recorded on the AE/SAE eCRF page) (note: with the implementation of INT-6, hospitalized unstable angina is

no longer part of the CV safety composite endpoint and should now be recorded on the adverse event/serious adverse event eCRF page. This type of event will no longer undergo adjudication as discussed in Section 9.2, Reporting/Adjudication of Events in the CV Composite Endpoint and Other Events for Adjudication).

- Because these events in the CV composite endpoint are not unexpected in this high CV risk population (and are considered part of the natural history of the disease), these events, *with the exception of CV deaths (and hospitalized unstable angina),* will *not* be reported (or recorded) as adverse events (ie, not recorded in the adverse event or serious adverse event eCRF page).
- All deaths, including CV deaths, will be reported as serious adverse events, and submitted for adjudication to the Endpoint Adjudication Committee. These events will be subject to expedited reporting to health authorities by the sponsor, *but will not be subject to unblinding* (unless it is determined by the Adjudication Committee that the death was non-CV related).

  *Note that for the study primary hypothesis of CV benefit, the post-approval CV composite endpoint includes MACE (CV death, nonfatal MI, nonfatal stroke); the composite endpoint to assess pre-approval CV safety (as part of a meta-analysis of events from pooled large, well-controlled, randomized studies including CANVAS to assess CV safety) includes MACE plus hospitalized unstable angina (refer to Section 3.2, Study Design Rationale).
- Events that are *initially* reported by the investigator as a study endpoint event, but which are determined by the Endpoint Adjudication Committee as *not* meeting the definition of a study endpoint, will be reported as an adverse event or a serious adverse event upon the sponsor's receipt of this determination by the Endpoint Adjudication Committee (with the sponsor reporting timeline starting from the time of notification by the Adjudication Committee). Such serious adverse events will be handled as per serious adverse event reporting guidelines, when the sponsor is notified by the Endpoint Adjudication Committee. The sponsor will notify the investigator to immediately report the event as a serious adverse event.
- Nonfatal CV events in the composite endpoint that, due to a reporting error or other reason, are initially classified as a serious adverse event, but which are subsequently determined by the Endpoint Adjudication Committee as meeting the definition of a study endpoint, will be reviewed on an individual basis by the sponsor regarding whether the case should be recorded only on the specific endpoint eCRF page and removed from the database as an adverse event or serious adverse event; clear and appropriate documentation of any changes will be maintained.

Deaths or events with an outcome of death will be reported as outcome events if within the composite (ie, if considered a CV death) and the cause of death will also be reported as a serious adverse event (and hence managed per serious adverse event reporting guidelines).

Investigators may also be asked to provide additional information on other adverse events, based upon review by the MSRC or the study IDMC (refer to Sections 9.3.3, Medical Safety Review Committee, and 9.3.4, Independent Data Monitoring Committee).

Refer to Section 9.4, Safety Evaluations, for additional information on the adverse events of interest.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the informed consent form (refer to Section 12.2.1, All Adverse Events, for time of last adverse event recording).

Change in Adverse Event Collection with the Implementation of INT-6

Only serious adverse events, adverse events resulting in study drug discontinuation, and adverse events of interest will be recorded on eCRFs. Details regarding adverse event collections are provided in Section 9.4, Safety Evaluations.

Serious Adverse Event

See above for handling of components of the composite CV endpoint other than CV deaths.

A serious adverse event as defined by ICH is any untoward medical occurrence that at any dose meets any of the following conditions:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

As described in the section above, nonfatal events in the CV composite endpoint (nonfatal MI and nonfatal stroke) will not be considered or reported as adverse events, but collected as study endpoints, subjected to adjudication, and only reported as adverse events if the Endpoint Adjudication Committee determines that the event does not meet the prespecified criteria for an endpoint event.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An unlisted adverse event is one for which the nature or severity of which is not consistent with the applicable product reference safety information. For an investigational product, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure. For a comparator product or baseline therapy with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the approved label for the product.

Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Not related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

Mild: Awareness of symptoms that are easily tolerated causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the intensity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Procedures

12.2.1. All Adverse Events

All adverse events, whether serious or non-serious, will be collected in source documents from the time a signed and dated informed consent form is obtained until completion of the last study-related procedure (may include contact for follow-up of safety).

Data will be collected on the eCRF for serious adverse events, adverse events that result in study drug discontinuation, and adverse events of interest described in Section 9.4, Safety Evaluations.

Serious adverse events, including those spontaneously reported to the investigator within 30 days (with the exception of those components of the clinical primary composite endpoints) after the last dose of study drug, must be reported using a Serious Adverse Event Form, which must be completed and signed by a member of the investigational staff, and transmitted to the sponsor within 24 hours. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Adverse events, as specified in Section 9.4, Safety Evaluations, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology

(eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

Study research staff should make study subjects aware of potential signs and symptoms of DKA such as difficulty breathing, nausea, vomiting, abdominal pain, feeling confused, fruity-smelling breath, and unusual fatigue or sleepiness. Study subjects should be instructed to contact the site if they experience such symptoms. If the investigator suspects these symptoms may be related to DKA (even if the subject's blood glucose levels are less than 250 mg/dL [13.9 mmol/L]), testing for urine or blood ketones should be considered.

Consistent with standard diabetes treatment guidelines, all study participants should be provided with routine preventative foot care and early intervention for foot problems. Specifically:

- Provide or ensure that all subjects have had general foot self-care education.
- Perform a comprehensive foot evaluation at each visit to identify risk factors for ulcers and amputations. The examination should include inspection of the skin, assessment of foot deformities, neurological assessment including pinprick or vibration testing or assessment of ankle reflexes, and vascular assessment including pulses in the legs and feet.
- Subjects who have a history of prior lower-extremity complications, loss of protective sensation, structural abnormalities, or peripheral arterial disease should be referred to foot care specialists for ongoing preventive care.

For all study participants, there should be a clinical evaluation at every visit to assess the presence of any sign or symptom suggestive of volume depletion (eg, hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), which if present should be adequately treated either by decreasing dose or eliminating use of diuretics or other antihypertensive medications or interrupting study drug until the condition resolves.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator all serious adverse events that are unlisted (unexpected) and associated with the use of the drug, according to standard operating procedures and the requirements outlined in this protocol. These events will be reported blinded to the investigator when and where possible. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. Subjects (or their designees, if appropriate) must be provided with a "study card" indicating the name of

the investigational study drug, the study number, the investigator's name, a 24-hour emergency contact number, and, if applicable, excluded concomitant medications.

12.2.2. Serious Adverse Events

All serious adverse events occurring during clinical studies must be reported to the appropriate sponsor contact person by investigational staff within 24 hours of their knowledge of the event. For purposes of reporting serious adverse events for this study, the components of the clinical primary composite endpoints (with the exception of CV death, which, as with all deaths, will be reported as a serious adverse event; see Section 12, Adverse Event Reporting) will not be considered adverse events or serious adverse events and will not be considered as unexpected but as disease-related, and as such will not be unblinded. These events will be captured on the eCRF as endpoint events only and will not be unblinded or subject to expedited reporting.

Events that are adjudicated as non-endpoints by the Endpoint Adjudication Committee will be subject to standard reporting requirements, but the reporting time limit will start when the sponsor learns that the event is not an endpoint as per the Endpoint Adjudication Committee.

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health-care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event.

The cause of death of a subject in a clinical study, whether or not the event is expected or associated with the investigational agent, is considered a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical study must be reported as a serious adverse event, except hospitalizations for the following:

- Related to a component of the clinical primary composite endpoints
- Social reasons in absence of an adverse event

- Surgery or procedure planned before entry into the study (must be documented in the eCRF)

12.2.3. Pregnancy

All initial reports of pregnancy must be reported to the sponsor by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must immediately discontinue further study treatment.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.3. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability of a product, including its labeling or package integrity. PQCs may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the investigational staff within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the investigational staff must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.2.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

Canagliflozin will be supplied for this study as over encapsulated 100- or 300-mg tablets in a gray-colored, hard, gelatin capsule. The over encapsulated tablet will be backfilled with microcrystalline cellulose to prevent the tablet from rattling in the capsule shell.

Matching placebo capsules will consist of microcrystalline cellulose within a gray-colored, hard, gelatin capsule.

It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

14.2. Packaging

The study drug will be packaged either as individual blister cards or individual bottles. The study drug will be packaged according to good manufacturing practices and local regulations. The study supplies will be packaged according to the randomization code and each unit will be labeled with a medication ID number.

All study drug will be dispensed in child-resistant packaging.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

All study drug must be stored at controlled temperatures ranging from 20°C to 25°C (68°F to 77°F) and kept out of reach of children. Where applicable, excursions from 15°C to 30°C (59°F to 86°F) are allowed.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject, must be documented on the drug accountability form. Subjects or their legally-acceptable representative where applicable, must be instructed to return all original containers, whether empty or containing study drug. The study drug administered to the subject must be documented on the drug accountability form. All study drug will be stored and disposed of according to the sponsor's instructions. Site staff must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited access area or in a locked cabinet under appropriate environmental conditions. Unused study drug and partially used study drug returned by the subject (if applicable), must be available for verification by the sponsor’s or sponsor-delegated site monitor during on-site monitoring visits. The return to the

sponsor of unused study drug, or partially used study drug returned for destruction, will be documented on the drug return form. When the site is an authorized destruction unit and study drug supplies are destroyed on site, this must also be documented on the drug return form.

Study drug should be dispensed under the supervision of the investigator, a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Recruitment and retention tools
- IVRS/IWRS manual and worksheets
- eCRF completion guidelines
- Study binder with all other necessary documentation (eg, protocol, IB, clinical trial agreement)
- Manual of instructions regarding endpoints, endpoint documentation required, and adjudication-related procedures
- Home blood glucose monitoring system, glucose strips, lancets, and calibration solution
- Diary card
- Materials to support diet and exercise counseling
- Standardized ECG recording devices and instruction manual
- Laboratory manual, requisition forms, sampling supplies, and equipment, if necessary
- Computer, if the study site is assessed to require a laptop computer to enter eCRF data for the study

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

The primary ethical concerns of this study are that the safety profile of canagliflozin has not been fully established so that subjects may be placing themselves at an increased risk of unexpected adverse events by participating in this study, and that subjects with T2DM who have not achieved optimal glycemic control at study entry could fail to achieve optimal glycemic control for a prolonged period. In this study, there is no requirement to discontinue prestudy medications. The investigator is asked not to change the antihyperglycemic regimen during the first 18 weeks of the study, but rescue criteria are

specified. The potential risks that are apparent in the present study include exposure to study drug, with the potential for side effects and the inherent risks associated with venipuncture and multiple blood sample collections. The study has been designed to mitigate these inherent risk factors.[1]

Based on data from clinical studies with canagliflozin and the theoretical possibilities associated with SGLT2 and intestinal SGLT1 inhibition, potential human adverse effects may occur, including osmotic diuresis due to increased UGE, alterations in serum or urine electrolytes, gastrointestinal intolerability, hypoglycemia, changes in bone formation and/or bone resorption and in the hormones controlling calcium homeostasis, abnormalities in renal function, photosensitivity, or vulvovaginal adverse events. Data from the Phase 1 studies as well as from Phase 2b studies involving over 1,200 subjects indicates that canagliflozin is generally well tolerated and serious adverse events are uncommon.

Results from the photosensitivity studies demonstrate that canagliflozin has no clinically relevant photosensitizing effect at the doses studied in the Phase 3 studies (100 mg or 300 mg once daily), and support safe participation of subjects in these Phase 3 studies without specific photo-protection precautions.

As described in Section 1.1.2, Clinical Studies, women subjects may be at an increased risk for vulvovaginal adverse events. Also, because of the modest magnitude of the observed increase of serum CTx levels and the biologic variability associated with this marker as well as it not being associated with changes in other markers of bone turnover, the increase in serum CTx levels is of uncertain significance; nonetheless, this will be monitored in Phase 3 studies by careful collection of information on any fractures and additional assessments in selected Phase 3 studies. Renal glomerular and tubular integrity were assessed using several biomarkers in Phase 2b studies. A urinary NAG increase noted could be secondary to increased flow in the proximal tubule or to glucosuria. Based on the preclinical, theoretical, and clinical experience to date, appropriate safety measures have been included to help in the selection of subjects as defined in the inclusion and exclusion criteria in Sections 4.2 and 4.3, respectively.

This study will provide scientific guidance on using canagliflozin in a T2DM subject population requiring improved glycemic control, and it should answer important questions about canagliflozin. Subjects will be randomly assigned to either canagliflozin 100 or 300 mg, both of which have shown glucose-lowering activity in Phase 1 and Phase 2b clinical studies, or placebo. The use of placebo as a comparator in this study does not represent an ethical compromise because subjects will be allowed to remain on a

[1] The study-specific design considerations are reflective of the available data at the time the protocol was originally designed. For updated information regarding canagliflozin, please refer to the current version of the Investigator's Brochure.

background of standard care for diabetes or to add other agents as the investigator considers necessary according to established treatment guidelines.

One of the objectives of this study is to demonstrate safety in subjects treated with the compound. Safety will be evaluated on a frequent and ongoing basis, and all adverse events will be treated according to standard medical practice. Hypoglycemia is considered to be a side effect of treatment in T2DM. It occurs most frequently with insulin therapy, but hypoglycemia can occur with the use of other agents as well. Because canagliflozin does not alter the regulation of glucose-dependent insulin secretion, hypoglycemia is not intrinsic to the mechanism of action of canagliflozin and should not be a frequent occurrence in subjects treated with this agent.

Clinical and laboratory evaluations will be performed throughout the study (according to the Time and Events Schedule that follows the Synopsis) to monitor the safety of subjects. HbA_{1c} will be measured approximately every 3 months. Subjects will be required to report episodes of hypoglycemia and encouraged to report any changes in their clinical condition to the investigator.

Subjects will be followed after discontinuing study drug and early withdrawal from the study by a follow-up contact to evaluate adverse events and concomitant therapy use, and to document CV events.

The investigator will be provided with detailed information about the study to ensure that the study research staff is fully informed. Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

Subjects will sign an informed consent form before any study-related procedure is performed.

The maximum blood volume that would be collected if a subject were to continue in the study for 7.25 years would be approximately 850 mL. The maximum amount that would be collected at a single visit would be approximately 80 mL. These volumes are considered to be well within the normal range for this subject population over this time frame according to blood donation standards (American Red Cross).

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board (IEC/IRB)

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved informed consent form (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the informed consent form, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the pharmacogenomic research component of the clinical study and for the pharmacogenomic informed consent form must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of approval for pharmacogenomic research.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments
- Revision(s) to informed consent form and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's Brochure amendments or new edition(s)
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted, and associated with the investigational drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report or Periodic Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or trial conduct), the amendment and applicable informed consent form revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this clinical study. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data or trial conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the

sponsor and by the reviewing IEC/IRB. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the investigational staff must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor staff without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the informed consent form the subject is authorizing such access, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, or to obtain information about his or her survival status.

The subject will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's personally dated signature. After having obtained the consent, a copy of the informed consent form must be given to the subject.

Subjects will be asked to consent to participate in a pharmacogenomic research component of the study where local regulations permit. After informed consent for the clinical study is appropriately obtained, the subject will be asked to sign and personally date a separate pharmacogenomic informed consent form indicating agreement to participate in optional pharmacogenomic research. A copy of the signed pharmacogenomic informed consent form will be given to the subject. Refusal to participate will not result in ineligibility for the clinical study.

If the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the informed consent form after the oral consent of the subject is obtained.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational study drug(s) used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator to allow direct access to his or her original medical records for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

For those subjects who gave consent to store DNA samples for future genetic research (Part 2), samples and corresponding relevant clinical data will be made nonidentifiable by the removal of personal identifiers. Samples will be stored until completely used. Only research related to the drug or the indications for which the drug is developed will be done on stored samples. For data generated on identifiable samples (Part 1), the sponsor will provide the individual raw data, through the investigator, to subjects who submit a written request. The sponsor cannot make decisions as to the significance of any findings resulting from this pharmacogenomic research, and cannot, therefore, provide genetic counseling. Genotypic data generated on nonidentifiable samples (Part 2) cannot be returned to individual subjects.

16.2.5. Country Selection

Unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations, this study will only be conducted in those countries where the intent is to help ensure access to the developed product, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for

non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor or its designee. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (refer to Contact Information pages provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the investigational site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed written IEC/IRB approval of the protocol, amendments, informed consent form, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the investigational staff is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)

- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all clinical subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject-screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: subject identification, eligibility, and study identification; study discussion and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events; and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion, and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

It is recommended that the author of an entry in the source documents be identifiable.

At a minimum, the type and level of detail of source data available for a study subject should be consistent with that commonly recorded at the site as a basis for standard

medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study personnel from the source documents onto an electronic eCRF, and transmitted in a secure manner to the sponsor within 3 working days of the subject's visit. The electronic file will be considered to be the eCRF. Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subjects' source documentation. All data relating to the study must be recorded in eCRFs prepared by the sponsor. Data must be entered into eCRFs in English. Designated site personnel must complete eCRFs as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or study-site personnel must adjust the eCRF (if applicable) and complete the query. A query is generally to be answered within 5 days of generation of the query.

If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- Site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool)
- Site manager (SM) can generate a query (field data correction form [DCF]) for resolution by the investigational staff
- Clinical data manager (CDM) can generate a query for resolution by the investigational staff

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits by the sponsor, and transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study personnel before the start of the study.

The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the clinical study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator must permit access to such reports.

17.8. Monitoring

The sponsor and ARO designated by the sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study center visit log that will be kept at the site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and investigational staff and are accessible for verification by the sponsor site contact. If electronic records

are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents will be discussed with the investigational staff. The sponsor expects that, during monitoring visits, the relevant investigational staff will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed (ie, GTED) with the last visit/contact of the last subject participating in the study. The final data from the investigational site will be sent to the sponsor (or designee) after completion of the final subject visit/contact at that site, 3 days after the subject's visit/contact (query generation and resolution excluded), or in the time frame specified in the clinical trial agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the investigational site or terminate the study at any time for any reason at the sole discretion of the sponsor. Investigational sites will be closed upon study completion. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigational site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development.

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison

with the eCRFs. Subject privacy must, however, be respected. The investigator and staff are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding canagliflozin or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the clinical study will be used by the sponsor in connection with the continued development of canagliflozin, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain eCRF data from all investigational sites that participated in the study and clinical laboratory data from a central laboratory via direct transmission into the sponsor's data base. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of pharmacogenomic analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided

to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, results may need to be published in a given sequence (eg, substudies) should not generally be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not publishing data derived from the individual site until the combined results from the completed study have been published in full, within 12 months after conclusion, abandonment, or termination of the study at all sites, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

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Attachment 1:
Sulfonylurea Monotherapy Doses for Stratification Purposes

Monotherapy consisting of one of the following:

- glipizide ≥20 mg/day
- glipizide extended release ≥10 mg/day
- glyburide/glibenclamide ≥10 mg/day
- glimepiride ≥4 mg/day
- gliclazide ≥160 mg/day
- gliclazide modified release ≥60 mg/day

Attachment 2:
Hypoglycemia: Definitions, Symptoms, and Treatment

Hypoglycemia is defined and classified as follows:

Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose (PG) concentration ≤70 mg/dL (3.9 mmol/L)

Asymptomatic hypoglycemia is defined as an event not accompanied by typical symptoms of hypoglycemia but with a measured PG concentration ≤70 mg/dL (3.9 mmol/L)

Probable symptomatic hypoglycemia is defined as an event during which symptoms of hypoglycemia are not accompanied by a PG determination.

Severe hypoglycemia is defined as an event requiring the assistance of another person to actively administer a carbohydrate, glucagon, or other resuscitative actions. A subject is considered to "require assistance" if he/she is unable to help himself/herself. An act of kindness to assist a subject when it is not necessary does not qualify as "requiring assistance". These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurologic recovery attributable to the restoration of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration.

Symptoms

Subjects will receive information regarding the symptoms of and treatment for hypoglycemia. Signs and symptoms of hypoglycemia and other specific details should be captured in the subject diary, which should be returned to the study center for review by research study staff at each visit. The following list of symptoms is not meant to be exhaustive but represents the more common symptoms associated with hypoglycemia:

- Seizure
- Loss of consciousness
- Headache
- Tremor
- Hunger
- Sweating
- Nervousness
- Palpitations
- Light headedness
- Blurred vision
- Disorientation
- Dizziness
- Feeling faint

Treatment

The treatment of hypoglycemia requires the ingestion of glucose- or carbohydrate-containing foods. The acute glycemic response correlates better with the glucose content than with the carbohydrate content of the food. Therefore, glucose (15 to 20 g) is the preferred treatment for hypoglycemia. Although pure glucose may be the preferred treatment, any form of carbohydrate that contains glucose will raise blood glucose and may be used. Adding protein to a carbohydrate does not affect the glycemic response and does not prevent subsequent hypoglycemia. However, adding fat may retard and then prolong the acute hypoglycemic response. Treatment effects should be apparent within 15 minutes although the effects may only be temporary. Therefore, PG should be retested in approximately 15 minutes, as additional treatment may be necessary.

Attachment 3:
New York Heart Association Classification of Cardiac Disease

The following table represents the NYHA classification of cardiac disease:

Functional capacity	Objective assessment
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain	A. No objective evidence of cardiovascular disease
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain	B. Objective evidence of minimal cardiovascular disease
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	C. Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	D. Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

Attachment 4:
Optional Specimens for Exploratory Research - Sample Collection and Handling

Materials and Labeling

- The central laboratory will provide the study site with blood collection tubes, storage tubes, preprinted Janssen Research and Development labels (or tubes labeled with preprinted labels), and related supplies for the collection and shipment of exploratory samples.
- The central laboratory will provide the study site with urine collection containers, storage tubes, and preprinted Janssen Research and Development labels (or tubes labeled with preprinted labels), for the collection and shipment of urine exploratory samples.
- Use of alternative materials will not result in a protocol amendment if preapproved by the Bioanalysis Scientist.
- Detailed information regarding the collection and storage containers will be provided in the laboratory manual from the central laboratory.

Preparation of Exploratory Plasma Samples

- Collect one full blood sample into the K_2EDTA-containing collection tube (eg, Vacutainer®) provided (10 mL or 5 mL) at the appropriate time point.
- Immediately after draw, gently invert the plasma tube 8 times (up-down-up=1 inversion) to completely mix tube contents. Place tubes at room temperature, 15°C to 25°C, until processed.
- Record the exact date and time of sampling in the eCRF or laboratory requisition form, as appropriate.
- Centrifuge blood sample at room temperature within 1 hour of collection in a clinical centrifuge according to the specifications in the laboratory manual.
- The following steps should be done separately for each blood sample that was collected. Do not combine the plasma. Keep aliquots separate.
- Immediately after centrifugation, transfer all separated plasma with a clean disposable plastic pipette to a prelabeled storage tube. Gently mix the tube by inversion.
- Dispense the plasma (0.5 to 1.0 mL aliquots) into two prelabeled microfuge tubes or cryovials (1.5- to 2-mL size) and securely cap.
- Store the plasma samples in an upright position in a freezer at –70°C or colder until transfer to the central laboratory. Record the exact time of storage in the eCRF or laboratory requisition form, as appropriate. Shipment on dry ice on the day of collection is acceptable if the site does not have a freezer at –70°C or colder.
- The time between blood collection and freezing the plasma must not exceed 2 hours.
- Ship specimens on dry ice according to the instructions provided by the central laboratory.
- Questions regarding handling the exploratory plasma specimens should be addressed to the contact person for the sponsor.
- Alternative procedures will not result in a protocol amendment if approved by the Bioanalysis Scientist.

Attachment 4: (Continued)
Optional Specimens for Exploratory Research - Sample Collection and Handling

Preparation of Exploratory Serum Samples

- Collect one 8.5 mL of blood into the appropriate plastic collection tube (Serum SST; SST with clot accelerator and gel barrier, also called Red & Black Tiger top) at the appropriate time point.
- Immediately after draw, gently invert the serum tube 5 times (up-down-up=1 inversion) to completely mix tube contents. Place tube at room temperature, 15°C to 25°C, for a minimum of 30 minutes or until processed.
- Record the exact date and time of sampling in the eCRF or laboratory requisition form, as appropriate.
- Centrifuge blood sample at room temperature within 45 min of collection in a clinical centrifuge according to the specifications in the laboratory manual.

The following steps should be done separately for each blood sample that was collected. Do not combine the serum. Keep aliquots separate.

- Immediately after centrifugation, transfer all separated serum with a clean disposable plastic pipette to a pre-labeled storage tube. Gently mix the tube once by inversion.
- Dispense the serum (0.5-1.0 mL aliquots) into two prelabelled microfuge tubes or cryovials (1.5 to 2 mL size) and securely cap.
- Store serum samples in an upright position in a freezer at –70° C or colder until transfer to the central laboratory. Record the exact time of storage in the eCRF or laboratory requisition form, as appropriate.
- Shipment on dry ice on the day of collection is acceptable if the site does not have a freezer at –70°C or colder.
- The time between blood collection and freezing the serum must not exceed 2 hours.
- Ship specimens on dry ice according to the instructions provided by the central laboratory.
- Questions regarding handling the exploratory serum specimens should be addressed to the contact person for the sponsor.

Alternative procedures will not result in a protocol amendment if approved by the Bioanalysis Scientist.

Preparation of Exploratory Urine Samples

- Collect voided urine in the appropriate urine collection container at the time designated in the protocol.
- Thoroughly mix the urine.
- Transfer one 3-mL aliquot into a labeled cryovial.
- Store the urine sample in an upright position in a freezer at –70°C or colder until transfer to the central laboratory. Shipment on dry ice on the day of collection is acceptable if the site does not have a freezer at –70°C or colder.
- The time between urine collection and freezing should not exceed 1 hour.
- Ship specimen on dry ice according to the instructions provided by the central laboratory.
- Questions regarding handling the exploratory urine sample should be addressed to the contact person for the sponsor.
- Alternative procedures will not result in a protocol amendment if approved by the Bioanalysis Scientist.

Attachment 5:
Pharmacogenomic Sample Collection and Shipment Procedure

Pharmacogenomic Sample Supplies and Labeling
The central laboratory will provide the investigational site with prelabeled 10 mL blood collection tubes containing potassium or sodium EDTA. Detailed information is provided in the laboratory manual from the central laboratory.

Preparation of Pharmacogenomic Samples
Pharmacogenomic samples should be prepared as follows:

- Invert the tube 10 to 15 times immediately after collection, to prevent coagulation.
- DO NOT centrifuge the sample.
- Freeze the samples at or below -20°C in an upright position immediately after collection

Pharmacogenomic Sample Shipment
Once collected, the blood samples must immediately be frozen at or below -20°C in an upright position. Samples must remain at this temperature until shipment to the central laboratory. All samples must then be shipped with sufficient dry ice to ensure samples remain frozen during shipment. Detailed information will be provided in the laboratory manual from the central laboratory.

The following guidelines should be adhered to:

- Shipment of the frozen pharmacogenomic blood samples should be arranged with other clinical study samples. If this is not possible, a separate shipment for these blood samples should be organized, using the courier recommended by the central laboratory.
- Notify the courier, at least 24 hours in advance of the planned shipment. Provide the courier with the appropriate account number to be used, if applicable.
- Package the samples in sufficient dry ice to ensure that the samples remain frozen during shipment.
- Label the package with the study number and all other information required by the central laboratory.
- Include a return address (that includes the investigator's name) on the outside of each shipping container.
- Comply with all courier regulations for shipment of biological specimens (include all paperwork).
- Retain all documents indicating date, time, and signature(s) of person(s) making the shipment, in the study files.
- The blood samples should be shipped to the name and address indicated in the central laboratory manual.

NOTE: If there are changes regarding the courier or location to which samples are shipped during the course of the clinical study, written notification will be provided to the investigator; a protocol amendment will not be required.

Attachment 6:
Clinical Laboratory Tests

Blood samples for serum chemistry and hematology and a urine sample for urinalysis will be collected for the tests listed below. The investigator must review the laboratory report, document this review, and record any clinically relevant changes (in the investigator's judgment) occurring during the study in the adverse event section of the eCRF.

The following tests will be performed by the central laboratory (the use of local laboratory studies should be limited to situations in which immediate availability of laboratory study results are necessary for appropriate care of the subject):

Hematology Panel	Chemistry Panel		Urinalysis*
Hemoglobin	Sodium, potassium, chloride, bicarbonate	Uric acid	Specific gravity
Hematocrit		Calcium	pH
RBC count	Blood urea nitrogen (BUN)	Phosphate	Protein
WBC with automated differential	Serum creatinine	Albumin	Blood
	Glucose	Total protein	Ketones
Platelet count	Aspartate aminotransferase (AST)	Magnesium	Bilirubin/ urobilinogen
	Alanine aminotransferase (ALT)	Creatine phosphokinase (CPK)	
	Gamma-glutamyl transferase (GGT)		Nitrate
	Total bilirubin		Leukocyte esterase
	Alkaline phosphatase		
	Lactic acid dehydrogenase (LDH)		

Fasting lipid profile: triglycerides, HDL-C, LDL-C (using Friedewald [1972] equation), total cholesterol (Note, C-peptide, insulin, proinsulin are collected as efficacy assessments as described in Section 9.5)

*Urine glucose will not be measured by the central laboratory

At run-in visit: Follicle stimulating hormone (FSH) only for women >45 years of age with amenorrhea for at least 6 months and <18 months before screening

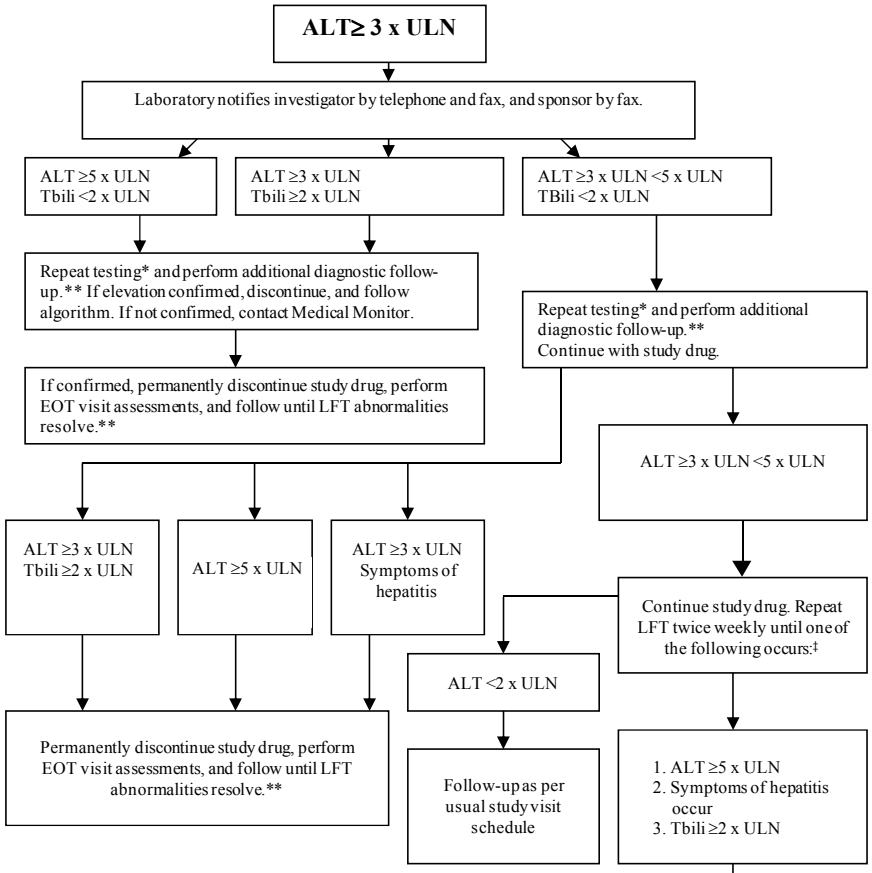
Central laboratory will report the eGFR according to the Modification of Diet in Renal Disease Study (MDRD) equation (Levey 2006) at study visits when serum creatinine is measured.

The 4-variable MDRD eGFR includes serum creatinine, age, race, and sex according to the equation below:

For creatinine in mg/dL:

eGFR (mL/min/1.73 m^2) = 175 x (serum creatinine$^{)-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.21 if black)

Attachment 7:
Algorithm for Monitoring Abnormal Liver Function Tests



If the investigator feels that the subject cannot safely continue administration of study drug regardless of algorithm, the subject should discontinue study drug and continue to the EOT visit.

* LFT (ie, ALT, AST, total bilirubin, alkaline phosphatase, GGT) within 2 to 3 days of investigator receipt of report, with earlier testing (ie, within 1 day of receipt of laboratory report) for more substantial elevations in ALT (≥5xULN) or total bilirubin (≥2xULN) levels. An alternate frequency of laboratory assessments may be considered in consultation with the sponsor's medical monitor.

** Focused medical history (including review of prior history of liver or biliary disorders, concurrent symptoms, review of all concomitant medications [eg, acetaminophen-containing medications, over-the-counter or herbal medications, nutritional supplements] including any changes in medications, detailed review of alcohol use and a complete physical examination); liver ultrasound and follow-up imaging as appropriate; hepatitis serology (anti-HAV, HBsAg, anti-HBs, anti-HB core, anti-HCV, HCV RNA, EBV and CMV screen) and autoantibodies (eg, ANA, anti-smooth muscle antibody) should be obtained as appropriate, with additional evaluation as clinically indicated. The extent of the evaluations should be made in consultation with the sponsor's medical monitor.

‡ If the subject's ALT value is ≥2XULN and <3xULN upon retest, then repeat LFT weekly until one of the subsequent events occurs. An alternate frequency of laboratory assessments may be considered in consultation with the sponsor's medical monitor.

Key: ALT=alanine aminotransferase; EOT=End of Treatment; GGT= gamma-glutamyl transferase; LFT=liver function test; Tbili=total bilirubin; ULN=upper limit of normal

Attachment 8:
Candidate Gene List for Part 1 of Pharmacogenomics

Absorption, Distribution, Metabolism, and Excretion Genes: *ABCB family, ABCC family, ABCG2, ADH family, AHR, ALDH family, AOX1, ARNT, ATP7A, ATP7B, BDH2, CDA, CHST family, COMT, CYP11A1, CYP11B1, CYP11B2, CYP17A1, CYP19A1, CYP1A1, CYP1A2, CYP1B1, CYP20A1, CYP21A2, CYP24A1, CYP26A1, CYP27A1, CYP2A13, CYP2A6, CYP2A7, CYP2B6, CYP2B7, CYP2C family, CYP2D6, CYP2E1, CYP2J2, CYP2S1, CYP39A1, CYP3A family, CYP46A1, CYP4B1, CYP4F family, CYP4Z1, CYP51A1, CYP5A1, CYP7A1, CYP7B1, CYP8A1, CYP8B1, DHRS family, DHRSX, DPYD, EPHX1, EPHX2, FMO family, FOM3, GPX family, GSR, GSS, GSTA family, GSTCD, GSTK1, GSTM family, GSTO1, GSTO2, GSTP1, GSTP2, GSTT1, GSTT2, GSTZ1, HAGH, HNMT, MAOA, MAOB, MGST1, MGST2, MGST3, MPO, NAT1, NAT2, NFE2L2, NNMT, NQO1, NR1I2, NR3C1, POR, PPARA, PPARD, PPARG, RALBP1, RLIP76, SLC10A1, SLC10A2, SLC13A1, SLC15A1, SLC15A2, SLC16A1, SLC19A1, SLC22A family, SLC28A family, SLC29A1, SLC29A2, SLC5A6, SLC7A5, SLC7A7, SLCO1A2, SLCO1B1, SLCO1B3, SLCO1C1, SLCO2A1, SLCO2B1, SLCO3A1, SLCO4A1, SLCO4C1, SLCO5A1, SLCO6A1, SPG7, STE, SULT1A1, SULT1A2, SULT1B1, SULT1C1, SULT2A1, SULT2B1, SULT4A1, TPMT, UGT1A family, UGT2A1, UGT2B family, UGT8, XDH.*

Target related genes: SGLT *gene family (SLC5 family), GLUT gene family (SLC2 family).*

Diabetes related genes: *ABCA1, ABCC8, ABCG5, ACE, ACP1, ACTN4, ADA, ADAMTS9, ADIPOQ, ADRB3, AKR1B1, ALB, ALMS1, ALX4, ANGPTL4, APOA1, APOA4, APOA5, APOB, APOC3, APOE, ARG1, ASIP, ASPN, BBS4, BCHE, CAMK1D, CAPN10, CART, CCK, CCKAR, CCL2, CD36, CD59, CDC123, CDKAL1, CDKN2A-2B, CELSR2, CETP, CIDEA, CILP2, COL2A1, CPE, CTLA4, CTNNBL1, CXCL12, CYP19A1, DF, DIANPH, DOCK7, DPP4, ENPP1, ESR1, EXT2, FABP10, FABP2, FABP4, FABP5, FADS1-3, FASN, FOLH1, FOXC2, FRZB, FTO, FXN, GAD1, GAD2, GAL, GALNT2, GCG, GCGR, GCK, GCKR, GDF8, GH1, GH2, GHRL, GIP, GIPR, GNB3, GPD2, GPKOW, GYS1, HBA1, HFE, HHEK1, HHEX-IDE, HK1, HK2, HK3, HLA-DQA1, HLA-DQB1, HMGA2, HMGCR, HNF4A, HSD11B1, HSD17B7, IAPP, IDE, IGF1, IGF1R, IGF2BP2, IKBKB, IL1R1, IL gene family, INS, INSIG2, INSR, IPF1, IRS1, IRS2, IRS4, ISL1, JAZF1, JPH3, KCNJ11, KCNJ9, KCNQ1, KIF11, LACT, LDLR, LEP, LEPR, LGR5, LIPC, LIPE, LIPG, LMNA, LPA, LPAL2, LPL, LRPAP1, MADD, MANT3, MAPK8, MAPK8IP1, MBL2, MC3R, MC4R, MIA3, MKKS, MLXIPL, MMAB, MMP13, MVK, NEGR1, NEUROD1, NEUROG3, NFKB1, NOS3, NOTCH2, NPY, NR0B2, NR3C1, NUCB2, PBX1, PCSK1, PCSK9, PDE3B, PFKP, PGC, PGR, PLG, PLIN, PNPLA3, POMC, PON1, PON2, PPARG, PPARGC1A, PPARGC1B, PPP1R1A, PPP1R3A, PRL, PSRC1, PTPN1, PTPRN, RBP4, REG1A, RETN, RPS6KB1, SCARB1, SERPINE1, SH2B1, SIM1, SLC2A1, SLC2A10, SLC2A2, SLC2A4, SLC30A8, SORBS1, SORT1, SPINK1, SREBF1, SST, TCF1, TCF2, TCF7L2, TGFB1, TH, THADA, TMEM18, TNF, TRAPPC2, TRIP1, TSPAN8, TUB, TULP2, UCN, UCP1, UCP2, UCP3, VDR, WFS1, WRN, XBP1, ZDHHC23 and ZFP36.*

Attachment 9:
Medical Resource Utilization Review

The questions below are representative but may not be exact wording of those that will be asked in the Diary.

When To Use Your Diary:

- Complete this diary any time you seek medical care that is not part of your study visit.

How To Use Your Diary:

- Do not list medical care received during an overnight hospitalization.
- Please indicate whether the medical care is planned
- Please be as accurate and complete as you can.

Sample Medical Care Visit Chart

Visit Date	Health-Care Provider Type	Planned	Location of Visit
05 February 2010	Primary Care Doctor	Yes	Home
11 March 2010	ER Doctor	No	Emergency Room
13 March 2010	Cardiologist	No	Doctor's Office

Medical Care Chart

Visit Date	Health-Care Provider Type	Planned	Location of Visit

LAST PAGE

Janssen Research & Development*

Clinical Protocol

A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects With Type 2 Diabetes Mellitus

The "CANVAS-R" Trial
(CANagliflozin cardioVascular Assessment Study-Renal)

Protocol 28431754DIA4003; Phase 4

JNJ-28431754 (canagliflozin)

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

Status:	Approved
Date:	27 September 2013
Prepared by:	Janssen Research & Development, LLC
EDMS No & Version:	EDMS-ERI-65832346
EudraCT No.:	2013-003050-25

GCP Compliance: This study will be conducted in compliance with this protocol, Good Clinical Practice, and applicable regulatory requirements.

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SYNOPSIS

A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects With Type 2 Diabetes Mellitus ("CANVAS-R")

EUDRACT number: 2013-003050-25

PREAMBLE

Canagliflozin (JNJ-28431754) is an inhibitor of the sodium-glucose co-transporter 2 (SGLT2) that has been developed as an oral antihyperglycemic agent (AHA) for the treatment of patients with type 2 diabetes mellitus (T2DM).

In March 2013, canagliflozin was approved for marketing by the United States (US) Food and Drug Administration (FDA). An ongoing clinical program designed to continue research on the effects of the agent on renal and cardiovascular outcomes is underway. The goal of this study is to assess the effects of canagliflozin compared to placebo on the progression of albuminuria, an important intermediate marker of renal injury and progression of diabetic nephropathy.

OBJECTIVES AND HYPOTHESES

Primary objective

In subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk of cardiovascular (CV) events to assess the effect of canagliflozin compared to placebo on progression of albuminuria.

Secondary objectives

In subjects with T2DM receiving standard care but with inadequate glycemic control and at elevated risk of CV events to assess the effect of canagliflozin compared to placebo on:

- Regression of albuminuria
- Change in glomerular filtration rate (eGFR) from baseline to the last off-treatment value done approximately 30 days post study drug discontinuation
- Urinary albumin/creatinine ratio (ACR)

Exploratory objectives

In subjects with T2DM receiving standard care but with inadequate glycemic control and at elevated risk of CV events to assess the effect of canagliflozin compared to placebo on:

- Change in eGFR determined from a between group comparison of the eGFR slopes using all on-treatment measures of eGFR made from the first on-treatment measurement to the final on-treatment measurement
- Changes in HbA_{1c}
- Utilization of AHA therapy

Safety objective

Cardiovascular safety data from this study will be combined with the data from the other large-scale study of the effects of canagliflozin compared to placebo (CANVAS; 28431754DIA3008; A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus; NCT01032629) in a pre-specified meta-analysis of cardiovascular safety outcomes.

Hypotheses

Primary hypothesis

In subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk of CV events canagliflozin compared to placebo reduces the rate of progression of albuminuria.

Secondary hypotheses

In subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk of CV events canagliflozin compared to placebo:

- Increases the rate of regression of albuminuria
- Slows the decline in eGFR
- Reduces albuminuria

OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the effects of canagliflozin compared to placebo on progression of albuminuria, an important intermediate marker of renal injury and progression of diabetic nephropathy. The study will be conducted in subjects with T2DM, receiving standard of care for hyperglycemia and CV risk factors, who have either a history or high risk of CV events. A total of 5,700 subjects will be recruited into the study. The study's last subject last visit is targeted to occur when the last subject randomized has approximately 78 weeks of follow-up or when 688 MACE events (ie, CV death, nonfatal myocardial infarction, nonfatal stroke) are accumulated between the CANVAS and CANVAS-R (DIA4003) studies, whichever comes later (estimated to occur between January 2017 and April 2017). The effects of canagliflozin will be evaluated against a background of standard of care for the treatment of hyperglycemia and CV risk factors with study investigators counseled to assure appropriate management according to applicable national guidelines for the care of patients with T2DM with treatment individualized as clinically appropriate.

STUDY POPULATION

Men or women with T2DM who have inadequate glycemic control (HbA_{1c} ≥7.0 and ≤10.5%) with either a history of a prior CV event or 2 or more risk factors for a CV event are eligible. Subjects can be included whether they are drug naïve to antihyperglycemic agents, using monotherapy, or using combination antihyperglycemic therapy for the control of blood glucose levels.

DOSAGE AND ADMINISTRATION

Study Drugs

Upon successful completion of screening, all potentially eligible individuals will enter a 2-week run-in period, during which they will receive single-blind placebo capsules (one capsule to be taken once-daily) to assess compliance.

Individuals that meet inclusion/exclusion criteria and that are compliant during run-in will be randomly assigned in a 1:1 ratio to canagliflozin or matching placebo to be taken once daily, before the first meal of the day. Canagliflozin will be provided at the dose of 100 mg/day through Week 13 and then increased at the discretion of the investigator at Week 13 or a subsequent visit to the dose of 300 mg/day, if the subject requires additional glycemic control and is tolerating the 100 mg dose (see Section 3.1). All study drug after randomization will be provided in a double-blind manner.

EFFICACY OUTCOME DEFINITIONS/EVALUATION CRITERIA

Primary outcomes

Progression is the development of microalbuminuria or macroalbuminuria in a subject with baseline normoalbuminuria or the development of macroalbuminuria in a subject with baseline microalbuminuria, accompanied by an ACR value increase of greater than or equal to 30% from baseline.

The primary outcome is progression of albuminuria (as defined above). If the ACR at a visit meets the definition of progression described above, a repeat ACR collection approximately 1 to 2 months later (or sooner under unusual circumstances, eg, subject is stopping study drug) must confirm progression of albuminuria (ie, confirmed progression). If the last on-treatment value meets the definition of progression and no repeat ACR collection can be made, the subject will also be deemed to have progressed.

ACR assessments will be based upon values obtained from first morning void urines analyzed by the central laboratory. In this study, duplicate urine specimens will be collected for all ACR measurements.

Secondary outcomes

The secondary outcomes are:

- Regression of albuminuria is the development of normoalbuminuria in a subject with baseline microalbuminuria or macroalbuminuria or the development of microalbuminuria in a subject with baseline macroalbuminuria, accompanied by a decrease in the urinary ACR value of greater than or equal to 30% from baseline. If the ACR at a visit meets the definition of regression described above, a repeat on-treatment ACR collection approximately 1 to 2 months later (or sooner under unusual circumstances, eg, subject is stopping study drug), must confirm regression of albuminuria (ie, confirmed regression). If the last on-treatment value meets the definition of regression and no repeat ACR collection can be made, the subject will also be deemed to have regressed.
- Change in eGFR from baseline to the last off-treatment value done approximately 30 days post study drug discontinuation.
- Urinary albumin/creatinine ratio at last on-treatment visit.

Safety outcomes

The data from this study will be combined with the data from another large-scale study of the effects of canagliflozin compared to placebo (CANVAS) in a pre-specified meta-analysis of cardiovascular safety outcomes to satisfy the US FDA Post Marketing Requirements.

STATISTICAL METHODS

Analysis Sets

The modified intent-to-treat (mITT) analysis set includes all subjects who are randomly assigned to a treatment group, receive at least one dose of double-blind study drug. The assessment of the primary and secondary endpoints will be based upon this analysis set.

Sample Size Determination

Based on the interim data from the CANVAS study, where ACR was measured periodically at scheduled visits, it is projected that the annual progression rate for CANVAS-R study is approximately 7.4%. Assuming a 22% relative risk reduction for albuminuria progression, an annual progression rate in the placebo arm of 7.4%, an 18-month accrual period, a maximum treatment period of 36 months, and an annual discontinuation (from treatment) rate of 10%, it is estimated 693 events of ACR progression will be reported. With 5,700 subjects enrolled, the power to demonstrate the superiority of canagliflozin over placebo for albuminuria progression is 90.5%, with type I error rate of 0.05 (two-sided).

Primary efficacy analysis

In this study, duplicate urine specimens will be collected for all ACR measurements. At each visit, the geometric mean of the duplicate measurements will be computed and used for all subsequent analysis unless otherwise specified.

Subjects will be classified as having normoalbuminuria (urinary ACR of <3.5 mg/mmol [<30 mg/g]), microalbuminuria (ACR ≥3.5 mg/mmol [≥30 mg/g] and ≤35 mg/mmol [≤300mg/g]), or macroalbuminuria (ACR of >35 mg/mmol [>300 mg/g]).

The primary efficacy analysis seeks to demonstrate the superiority of canagliflozin in the reduction of albuminuria progression relative to placebo.

The time from first study drug administration to first visit date observing progression (i.e., not using the visit date of the repeat sample collection) of albuminuria will be analyzed using a Cox proportional hazards regression model. The model will include treatment and baseline albuminuria status as covariates. The hazard ratio between canagliflozin and placebo will be provided, including its 95% confidence interval. The observation period for this time-to-event analysis will include all available measurements from first study drug administration to the visit date of the last on-treatment ACR was measured. Subjects with no progression will be censored at the visit date of the last on-treatment albuminuria measurement.

As a sensitivity analysis, the actual onset time of progression of albuminuria can be determined to be within an interval from a sequence of examination times (ie, data are interval censored). As a supportive analysis, the accelerated failure time (AFT) model with log normal error structure will be implemented considering interval censoring. The dependent variable in AFT model is the logarithm of time to progression of albuminuria. The model will include treatment group and baseline albuminuria status as covariates. We can use speed of progression to interpret AFT model. For any time (t), the probability of a subject on placebo progression-free beyond time t is the probability of a subject on canagliflozin progression-free beyond t/α, where α is the acceleration factor which can be estimated from the model. Additional sensitivity analyses will be specified in the study Statistical Analysis Plan (SAP).

The cumulative progression rate derived from Kaplan-Meier estimate will be displayed graphically to evaluate the timing of progression and the consistency of the treatment effect over time.

Secondary efficacy analyses

Regression of albuminuria will be analyzed in a similar fashion as the analysis for progression of albuminuria.

For change in eGFR from baseline to the off-treatment measurement (approximately 30 days after the last dose of double-blind study drug), an analysis of covariance (ANCOVA) model will be used with treatment as a fixed effect and adjusting for the baseline eGFR value. The treatment difference in the least-squares means and their 2-sided 95% CI will be estimated.

Since the distribution of ACR value is highly skewed, log transformed ACR value for the last on-treatment visit will be modeled using ANCOVA. The model will include treatment group and logarithm of baseline ACR value as covariates. The percentage treatment difference can be calculated by anti-logarithm of the estimated coefficient for the treatment group minus 1.

Exploratory efficacy analyses

For on-treatment eGFR measurements, a linear mixed effects model will be fitted to eGFR as a dependent variable, including treatment, baseline eGFR value, time (as a continuous variable), and treatment time interaction as fixed effects and including subject effect as a random intercept and time as a random slope. The parameter of interest is the coefficient for treatment and time interaction term, which measures the slope difference between canagliflozin and placebo.

The effect of canagliflozin relative to placebo on changes in HbA_{1c} over time will be evaluated using linear mixed effects model. The use of utilization of AHA therapy over time will also be summarized by treatment group.

Safety analyses

The cardiovascular safety data from this study will be evaluated in conjunction with the data from the CANVAS study according to a pre-specified meta-analysis plan.

Multiplicity adjustment

A closed testing procedure will be implemented to control the overall type I error at 5% for primary and secondary endpoints. There are no interim analyses planned.

A more detailed description of the analyses for all outcomes other than the planned CV meta-analysis will be pre-specified in the SAP for this study. The CV meta-analysis SAP will be pre-specified in a separate document.

TIME AND EVENTS SCHEDULE
PRETREATMENT AND DOUBLE-BLIND TREATMENT

	Pre-treatment		Double-blind treatment						
Procedures and Evaluations	**Screening [a]**	**Baseline**							
Time point	Week -2	Day 1	Phone/email contact at Week 6	Week 13	Week 26	Phone/email contact at Week 39	Week 52 and every 26 weeks thereafter unless otherwise indicated	Phone/email contact midway between 26-week visits until last on-treatment visit [k]	Last on-treatment visit (or after early discontinuation of treatment)[b]
Pretreatment/Administrative									
Informed consent [d]	X								
Diet, exercise, SMBG counseling	X								
Inclusion/exclusion criteria	X	X							
Medical history and demographics	X								
Prestudy therapy (drug classes of interest) [e]	X	X							
Dispense single-blind placebo	X								
Randomize		X							
Study Drug									
Administer/dispense double-blind study drug [m]		X		X	X		X		
Increase dose if subject requires additional glycemic control (see Section 3.1)				X	X		X		
Procedures									
Vital signs, weight [f]	X	X		X	X		X		X
Serum chemistry panel [g]	X	X		X	X		X		X
Hematology [g]		X					Week 52, 104 and 156		X
Fasting serum lipid profile [g]		X			X		Week 52, 104 and 156		X
HbA_{1c}	X	X		X	X		X		X
Duplicate first morning void urines for urine albumin/creatinine (provide collection containers at previous visit) [g, h]		X			X		Weeks 52, 78, 104 and 156		X
Urine pregnancy test [i]		X							
Dispense glucose testing supplies (optional per country/region)		X		X	X		X		

TIME AND EVENTS SCHEDULE
PRETREATMENT AND DOUBLE-BLIND TREATMENT

	Pre-treatment		Double-blind treatment						
Procedures and Evaluations	**Screening [a]**	**Baseline**							
Time point	Week -2	Day 1	Phone/email contact at Week 6	Week 13	Week 26	Phone/email contact at Week 39	Week 52 and every 26 weeks thereafter unless otherwise indicated	Phone/email contact midway between 26-week visits until last on-treatment visit [k]	Last on-treatment visit (or after early discontinuation of treatment)[b]
Ongoing Review									
Concomitant therapy (drug classes of interest) [j]			X	X	X	X	X	X	X
Serious adverse events, and AEs causing discontinuation; vital status; AEs of interest [k, l]		X	X	X	X	X	X	X	X
CV events		X	X	X	X	X	X	X	X

For footnotes, see below

TIME AND EVENTS SCHEDULE

Posttreatment

Procedures and Evaluations	Posttreatment Follow-up			
	All Subjects	Subjects Who Withdraw Prior to End of Study		
Time point	Final visit 30 days after last on-treatment visit (or after early discontinuation of treatment; preferably 30 days after last dose of study drug) [c]	Visit every 26 weeks after last dose until notification of global trial end date (GTED)[b]	Phone/email contact midway between 26 week visits until notification of the GTED[b]	Final phone contact, public record search or Vital status check within 3 months prior to GTED
Procedures				
Vital signs, weight [f]		X		
Serum chemistry panel [g]	X			
Hematology [g]				
Fasting serum lipid profile [g]				
HbA_{1c}				
Duplicate first morning void urines for urine albumin/creatinine (provide collection containers at previous visit) [g, h]				
Urine pregnancy test [i]				
Dispense glucose testing supplies (optional per country/region)				
Ongoing Review				
Concomitant therapy (drug classes of interest) [j]				
Serious adverse events, and AEs causing discontinuation; vital status [k,]; AEs of interest [l]	X	X	X	X
CV events	X	X	X	X

See footnotes on the following page

FOOTNOTES

[a] Subjects will receive diet/exercise counseling at the screening visit, be counseled on hypoglycemia recognition and management, and be dispensed single-blind placebo capsules. During the 2-week run-in period between screening and randomization, the investigator should adjust/optimize the subject's antihyperglycemic agents and agents to reduce CV risk (eg, lipid-altering, and blood pressure-lowering medications) as necessary. Subjects who fail protocol-specified screening criteria for study entry may be rescreened (Section 4.5), at the discretion of the investigator.

[b] Every subject who remains on study drug through the end of the double-blind treatment period will have a scheduled date for a last on-treatment visit as soon as possible after site notification of the projected global trial end date (GTED) expected to occur between January 2017 and April 2017. Early withdrawal (EW) evaluations will be performed when a subject stops the double-blind treatment prematurely prior to the site notification of the GTED. EW evaluations will be performed on the day study drug is discontinued or as soon as possible after stopping the study drug. For subjects who prematurely discontinue study drug prior to the announcement of GTED, sites will be required to make a final contact or vital status check after announcement of GTED. For subjects who prematurely discontinue double-blind study drug prior to the site notification of the GTED, the study's informed consent form will enable efforts to achieve follow-up of lost participants using all reasonable means to contact the subject, family members, the subject's physicians and medical records, and the use of locator agencies and checking public records, as allowed by local law. It is the expectation that the investigator will make every effort to ascertain the vital status of all subjects at the end of the study (ie between the notification of the GTED and the actual GTED), including using all reasonable means outlined above.

[c] A study visit will be conducted for all subjects approximately 30 days (+/- 12 days) after the last dose of study drug. (note: this applies to subjects who prematurely discontinue study drug and also those who discontinue study drug after site notification of the projected GTED) This will require a clinic visit for collection of lab specimens. If a study visit is not immediately possible, follow-up information may be collected by telephone, via email or other electronic or non-electronic means, and a subsequent study visit should be attempted.

[d] The informed consent form must be signed before any study procedure is performed.

[e] Record as prestudy therapy the classes of medications taken from 30 days before screening.

[f] Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (sitting position, after sitting for 5 minutes; record 3 consecutive blood pressure readings, at intervals of at least 1 minute apart); the average of the 3 blood pressure readings will be recorded on eCRFs.

[g] Specific details about specimen collection, storage, and processing will be provided in operations manuals. Attachment 1 lists the laboratory studies to be performed.

[h] The subject will provide first morning void (FMV) urine specimens (collection of the first urine void after the individual awakes from sleep). At each visit, the subject will bring in 2 FMV specimens: one from the morning of the visit, and one from the morning of the day prior to the visit. If the urinary albumin/creatinine result reflects progression or regression of albuminuria from the baseline (eg, progression from normoalbuminuria to microalbuminuria or macroalbuminuria accompanied by a urinary ACR value increase of ≥30% from baseline; or regression from macroalbuminuria to microalbuminuria or normoalbuminuria accompanied by a urinary ACR value decrease of ≥30% from baseline), the investigator will be notified to have the subject bring 2 additional consecutive-morning FMV specimens to the clinic approximately 1 to 2 months later. If the subject is unable to return the specimens in person, the site may engage a courier service to deliver the specimen to the site. If the subject does not provide the morning void collection on the day of the visit, the subject may bring first morning void specimens to the investigational site during the subsequent 30 days. For subjects working a night shift, or who otherwise have atypical sleep patterns, the collection should be made at the end of the subject's usual sleep period.

[i] Urine pregnancy testing will be performed locally for all women unless they are surgically sterile or unless there is a documented history of their postmenopausal status. Additional pregnancy tests may be conducted throughout the study in sufficient number, as determined by the investigator or required by local regulations, to establish the absence of pregnancy during the study. If positive, the subject is not eligible to enter the study or continue study drug. A urine pregnancy test will be performed as specified, unless a serum pregnancy test is preferred at the discretion of the investigator or if required by local regulations; in such situations, the serum pregnancy test will be performed at the screening visit instead of the baseline visit, in order to determine the subject's pregnancy status prior to randomization.

[j] Concomitant therapy includes all medications from drug classes of interest taken regularly after the initiation of double-blind study medication (Day 1).

[k] This applies only to subjects who prematurely discontinue study drug any time prior to the site notification of the GTED. As noted above, it is the expectation that the investigator will make every effort to ascertain the vital status of all subjects at the end of the study, including using all reasonable means to contact the subject, family members, the subject's physicians and medical records, or other sources, as well as the use of locator agencies and checking public records, as allowed by local law.

[l] Adverse events of interest include: all malignancies, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (eg, angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, and pregnancy. Information on these events will be recorded on a supplemental eCRF for any event that is serious or that leads to study drug discontinuation. The only exceptions are for malignancies, photosensitivity reactions, fractures, venous thromboembolic events for which information on non-serious adverse events will also be recorded on the supplemental CRF pages (in addition to the information collected on serious AEs and AEs leading to study drug discontinuation).

[m] An unscheduled visit may be used for increasing or decreasing the dose of study drug , any time after Week 13.

ABBREVIATIONS

ACR	urinary albumin/creatinine ratio
ADA	American Diabetes Association
AHA	antihyperglycemic agent
ALT	alanine aminotransferase
ARO	Academic Research Organization
AST	aspartate aminotransferase
BMI	body mass index
CI	confidence interval
CV	cardiovascular
eCRF	electronic case report form
eDC	electronic data capture
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
FMV	first morning void
FPG	fasting plasma glucose
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GTED	global trial end date
HbA_{1c}	hemoglobin A_{1c}
HDL-C	high-density lipoprotein cholesterol
IB	Investigator Brochure
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IWRS	interactive web response system
LDL-C	low-density lipoprotein cholesterol
MACE	major adverse cardiovascular events
MI	myocardial infarction
mITT	modified intent-to-treat
MSRC	Medical Safety Review Committee
NYHA	New York Heart Association
PG	plasma glucose
PQC	Product Quality Complaint
SAP	statistical analysis plan
SGLT1/SGLT2	sodium-glucose co-transporter 1/sodium-glucose co-transporter 2
SMBG	self-monitored blood glucose
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
UGE	urinary glucose excretion
ULN	upper limit of normal
US	United States
VTE	venous thromboembolic event

1. INTRODUCTION

Over the past decades, the incidence of type 2 diabetes mellitus (T2DM) has been rapidly rising worldwide, driven primarily by an increasing incidence of obesity and sedentary lifestyles. Patients with T2DM can develop severe microvascular complications, related to persistently elevated glucose concentrations, including blindness, renal failure, or nerve damage, and have a higher incidence of atherosclerotic vascular disease with complications such as myocardial infarction (MI), stroke, and amputations due to vascular insufficiency. Improved glucose control reduces the incidence of microvascular complications in patients with both type 1 diabetes mellitus (T1DM) and T2DM. The impact of improved glycemic control on macrovascular events is less well established. Despite the availability of a range of therapeutic options, many patients with T2DM do not achieve or maintain glycemic control. Many of these treatments are associated with safety or tolerability issues, including hypoglycemia, edema, or gastrointestinal adverse experiences which can limit dose and hence therapeutic benefit. Further, some of the current antihyperglycemic agents (AHAs) are associated with weight gain, and only a few agents (eg, metformin and glucagon-like peptide-1 [GLP-1] analogues) lead to weight loss, an important advantage in a patient population that is often obese. Most patients with T2DM are initially managed with single-agent therapy, usually metformin. Over time, patients often require more intensive regimens, combinations of 2 or 3 agents, and eventually require insulin to maintain target glycemic control. Underlying this need for increasingly intensive treatment is a progressive loss of beta-cell mass and function, with consequent diminished insulin secretion. There remains a substantial unmet medical need for new medications to treat patients with T2DM that are well tolerated and efficacious, provide good durability, beneficially impact beta-cell function and insulin secretion, and are associated with weight loss.

In healthy individuals, glucose is freely filtered through the renal glomerulus and then reabsorbed in the proximal tubules. The renal threshold for glucose (RT_G) is the glucose plasma concentration above which glucose reabsorption by the proximal renal tubules is incomplete and glucose is excreted into the urine. A typical RT_G level in healthy individuals is approximately 180 mg/dL (10 mmol/L) (Ganong 2005; Rave 2006; Seifter 2005). Glucose reabsorption in the renal tubules, determining the renal threshold is largely due to 2 key glucose transporters: sodium glucose co-transporter 2 (SGLT2) and sodium glucose co-transporter 1 (SGLT1). Sodium glucose co-transporter 2 is a high-capacity and low-affinity glucose transporter exclusively expressed at the luminal membrane of the S1 and S2 segments of the proximal renal tubules. Sodium glucose co-transporter 2 is responsible for the majority of filtered glucose reabsorption from the lumen. Sodium-glucose co-transporter 1 expressed in the S3 segment, a low capacity and high-affinity transporter, is also involved in reabsorption of filtered glucose from the lumen (Wright 2001). Sodium-glucose co-transporter 1 is also highly expressed in the intestine and is responsible for intestinal glucose and galactose absorption.

Pharmacologic inhibition of SGLT2 is a novel mechanism to decrease renal glucose reabsorption, as it lowers RT_G and leads to an increase in urinary glucose excretion (UGE), thereby directly lowering plasma glucose in individuals with elevated glucose concentrations. Canagliflozin is an orally active inhibitor of SGLT2. This agent has much higher potency for SGLT2 relative to SGLT1; at the plasma drug concentrations achieved with the doses in this

study, canagliflozin would be expected to provide significant systemic inhibition of SGLT2 and not of SGLT1. In addition to lowering plasma glucose concentrations, the increased renal glucose excretion with SGLT2 inhibition also translates to a loss of calories, leading to a net negative energy balance and the potential for weight loss as well as an osmotic diuretic effect, which can lead to reductions in blood pressure and osmotic diuresis- and volume depletion-related adverse events.

A Phase 3 development program including 9 controlled studies was conducted providing evidence for the effectiveness of canagliflozin both as monotherapy and in combination with approved, commonly prescribed AHA therapies in T2DM. These 9 studies spanned a range of clinical uses (as monotherapy or as combination therapy) to treat T2DM. Three of the Phase 3 studies evaluated canagliflozin in special populations, including older adults with T2DM, subjects with T2DM who had moderate renal impairment, and subjects with T2DM who had or were at high risk for cardiovascular (CV) disease. Results of the extensive Phase 3 clinical development program, involving approximately 10,285 subjects with T2DM and including nearly 6,650 subjects treated with 100 mg or 300 mg doses of canagliflozin, indicate that canagliflozin has the potential to be a useful addition to currently available antihyperglycemic agents. Across all of the studies, clinically meaningful reductions in hemoglobin A_{1c} (HbA_{1c}) and fasting plasma glucose (FPG) were seen. Statistically significant (relative to placebo) reductions in body weight (predominantly fat mass) were also achieved with canagliflozin 100 mg and 300 mg across the spectrum of T2DM patients evaluated in the Phase 3 program. Canagliflozin also showed benefit in improving other clinical endpoints associated with diabetic comorbidities, including systolic and diastolic blood pressure (SBP and DBP), and lipid parameters (high-density lipoprotein cholesterol [HDL-C], and triglyceride). Improvements in beta-cell function, presumably through an indirect effect, such as reductions in glucotoxicity and insulin secretory demand, were also seen with canagliflozin treatment.

In March 2013, canagliflozin was approved for marketing by the United States Food and Drug Administration (FDA). An ongoing clinical program designed to continue research on the effects of the agent on renal and cardiovascular outcomes is underway. The goal of this study is to assess the effects of canagliflozin compared to placebo on the progression of albuminuria, an important intermediate marker of renal injury and the progression of diabetic nephropathy.

The term “sponsor” used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

For more detailed and current information regarding the preclinical characterization of canagliflozin pharmacokinetics (PK) (ie, absorption, distribution, metabolism and excretion) and toxicology, and clinical study results, refer to the current version of the Investigator's Brochure for canagliflozin (IB JNJ-28431754).

1.1.1. Nonclinical Studies

For a complete review of the findings and discussions regarding implications for human risk, please refer to the current version of the canagliflozin IB.

1.1.2. Clinical Studies

Overview

The canagliflozin clinical program was designed to assess the safety and efficacy of canagliflozin in patients with T2DM. The program consists of 52 completed or ongoing clinical studies, including data from 10,285 subjects as of late 2012 (who received at least 1 dose of double-blind study drug) in 9 Phase 3 studies, 1,210 subjects in 3 Phase 2 studies, and 1,300 subjects in 40 Phase 1 studies.

Pharmacokinetics

Canagliflozin exhibits similar PK in healthy subjects and subjects with T2DM. The mean absolute oral bioavailability of canagliflozin was 65% following single-dose administration of the canagliflozin 300 mg tablet in healthy subjects. In healthy subjects (25 to 1,600 mg once-daily [QD]) and subjects with T2DM (50 mg to 300 mg QD and 300 mg twice-daily [BID]), after oral administration of single and multiple doses, mean canagliflozin $AUC_{0-\infty}$ increased in an approximately dose-proportional manner whereas mean maximum plasma concentration (C_{max}) increased in an approximately dose-proportional manner up to 1,200 mg. Following oral administration of canagliflozin, the median time to reach maximum plasma concentration (t_{max}) was approximately 1 to 2 hours. The mean terminal plasma elimination half-life ($t_{1/2}$) of canagliflozin was 10 and 13 hours with canagliflozin doses of 100 and 300 mg, respectively. The t_{max} was independent of dose. After repeated dosing with 50 to 300 mg canagliflozin, steady state was reached by 4 to 5 days. Minimal accumulation of canagliflozin was observed at steady-state across 50, 100, and 300 mg doses with mean accumulation ratios ranging from 1.3 to 1.4 in subjects with T2DM. Bioavailability of canagliflozin was not affected after co-administration of canagliflozin 300 mg with food in healthy subjects indicating that the canagliflozin tablet formulation may be taken without regard to meals.

O-glucuronidation is the major metabolic elimination pathway for canagliflozin in humans. In human plasma, two non-pharmacologically active O-glucuronide conjugates of unchanged drug, M5 (formed by UGT2B4) and M7 (formed by UGT1A9), were present. Co-administration with rifampin, a nonselective inducer of several UGT enzymes, decreased canagliflozin area under the curve (AUC) by 51%, which may decrease efficacy. There was an increase in the AUC and C_{max} of digoxin when co-administered with canagliflozin 300 mg. Subjects taking concomitant digoxin should be monitored appropriately. The C_{max} of canagliflozin was not meaningfully altered by renal impairment.

Based on in vitro data and the clinical drug-drug interaction studies conducted to date, the potential for clinically significant CYP450 based PK interactions appears to be low.

Pharmacodynamics

In subjects with T2DM following single and multiple oral doses (30 to 600 mg QD and 300 mg BID), canagliflozin treatment dose dependently increased UGE_{0-24h}, with mean UGE_{0-24h} of approximately 100 g/day typically observed with doses of 100 mg/day or higher.

In subjects with T2DM, canagliflozin treatment with 100 mg and 300 mg once daily lowered RT_G to approximately 70 to 90 mg/dL (3.9 to 5.0 mmol/L), respectively. Because RT_G remains above PG levels associated with hypoglycemia and because very little UGE occurs whenever plasma glucose (PG) is below the RT_G, canagliflozin, itself, is not expected to pose a risk for hypoglycemia.

Efficacy

In the Phase 3 studies, canagliflozin has been assessed as monotherapy, as add-on therapy with metformin, sulphonylurea (SU), metformin and SU, metformin and a peroxisome proliferator-activated receptor (PPARγ) agonist (pioglitazone), and as add-on therapy with insulin (with or without other AHAs). The Phase 3 program also includes studies in special populations of patients with T2DM: subjects with renal impairment (estimated glomerular filtration rate [eGFR] ≥30 to <50 mL/min/1.73 m^2); subjects with or at high risk for CV complications; and older subjects. The latter 2 studies also included subjects on incretin-based therapies, including DPP-4 inhibitors and GLP-1 agonists.

Glycemic Efficacy

Results of the Phase 3 studies demonstrated the efficacy of canagliflozin in reducing HbA_{1c} in a broad range of subjects with T2DM, both with recent onset as well as long-standing diabetes and on a range of different background AHAs. A clinically meaningful improvement in glycemic control was seen when canagliflozin was given as monotherapy and when given in dual combinations (add-on to metformin or to SU agents), in triple oral AHA combinations (add-on to metformin plus an SU agent or metformin plus pioglitazone), in combination with insulin (alone or in combination with other agents), or as an add-on to existing diabetes therapy (any approved oral or parenteral therapy). In the monotherapy study, HbA_{1c} reductions of -0.91% and -1.16% relative to placebo for canagliflozin 100 mg and 300 mg, respectively, were observed. In the studies examining specific add-on combination uses, the efficacy of canagliflozin in lowering HbA_{1c}, relative to placebo, was generally consistent ranging from -0.62% to -0.74% with the 100 mg dose and from -0.73% to -0.92% with the 300 mg dose. Across all studies, the 300 mg dose consistently provided greater HbA_{1c} lowering relative to the 100 mg dose; since reduction in diabetic microvascular complications is continuous with improvements in glycemic control, the additional glucose-lowering efficacy with the 300 mg dose is considered likely to be clinically relevant (UKPDS 1998, DCCT 1993).

Results of subgroup analyses performed in a pooled population of the placebo-controlled Phase 3 studies found no important differences when comparing the effect of canagliflozin in change from baseline in HbA_{1c} based on baseline demographic characteristics (age, sex, race, ethnicity), body mass index (BMI), or geographic region. Greater reductions in HbA_{1c} relative to placebo were observed with canagliflozin among subjects with higher baseline HbA_{1c} and higher eGFR values compared with subjects with lower baseline values. In subjects with moderate renal impairment (ie, baseline eGFR's between 30 to 60 mL/min/1.73m^2), the mean, placebo-subtracted reduction in HbA_{1c} was 0.38% and 0.47% on canagliflozin 100 mg and 300 mg respectively. A total of 24% and 32% of subjects achieved a target HbA_{1c} <7% at the end

of treatment on canagliflozin 100 mg and 300 mg respectively compared to 17% of subjects on placebo.

With regard to other glycemic endpoints, canagliflozin provided improvements in FPG as well as in the PPG excursion. Canagliflozin also provided improvements in beta-cell function and a reduction in beta cell stress as reflected by a decrease in the proinsulin/C-peptide ratio. The improvement in beta-cell function and reduction in beta-cell stress is consistent with the sustained effect of canagliflozin on both HbA_{1c} and FPG observed in the 52-week studies.

Weight and Blood Pressure Effects

In addition to the observed glycemic improvements, treatment with canagliflozin resulted in consistent, statistically significant reductions in total body weight relative to placebo. Weight loss with canagliflozin appeared dose-related (with -1.4% to -2.7% reductions with 100 mg and -1.8% to -3.7% reductions with 300 mg, relative to placebo). Results of specialized body composition investigations using dual energy X-ray absorptiometry (DXA) in 2 of the Phase 3 studies showed that the body weight reduction with canagliflozin was attributable to a greater decrease in body fat mass relative to lean body mass.

Reductions in SBP were observed with canagliflozin in Phase 3 studies (ranging from -2.2 to -5.7 mm Hg of SBP with canagliflozin 100 mg dose, and -1.6 to -7.9 mm Hg with the 300 mg dose, relative to placebo, in placebo-controlled 26-week studies), and were generally statistically significantly greater for both doses relative to placebo, and also greater relative to comparator agents (glimepiride and sitagliptin).

Safety

For a complete review of the adverse drug reactions (ADRs) and laboratory findings associated with canagliflozin, please refer to the current version of the canagliflozin Investigator's Brochure (IB JNJ-28431754).

The safety and tolerability profile that emerges from the development program for canagliflozin shows a medication that is overall well tolerated. The incidence of discontinuations due to adverse events was slightly higher than seen in the control group, though generally low. The small increase in discontinuations due to adverse events were generally related to specific ADRs, described below, with each particular ADR infrequently leading to discontinuations; there was no increase in serious adverse events or deaths in the canagliflozin treatment groups relative to control groups.

Adverse drug reactions associated with canagliflozin include genital mycotic infections, urinary tract infections (UTIs), adverse events related to osmotic diuresis, and adverse events related to reduced intravascular volume, as well as constipation, and a low incidence of rash or urticaria.

In men, the genital mycotic infections (including balanitis and balanoposthitis) occurred predominantly in uncircumcised individuals and in those with a past history of genital mycotic infections, generally did not lead to discontinuation from the study. Circumcision was performed in 17/3569 (0.5%) and 3/1924 (0.2%) of men treated with canagliflozin and control, respectively.

In women, genital mycotic infections (including candidal vulvovaginitis) occurred more commonly in women with a prior history of genital mycotic infections and did not generally lead to discontinuation. A modest increase in the incidence of adverse events of UTI (mostly lower tract infections) was observed with canagliflozin relative to control, without an increase in serious adverse events of UTI.

Adverse drug reactions were observed that relate to the osmotic diuretic effect of canagliflozin, with increases in UGE leading to a diuretic action; this included ADRs of pollakiuria (increased urinary frequency), polyuria (increased urinary volume), and thirst. Adverse drug reactions related to reduced intravascular volume were observed including postural dizziness, orthostatic hypotension, and hypotension. Risk factors for volume-related adverse events on canagliflozin treatment were ≥75 years of age, eGFR of 30 to 60 ml/min/1.73m^2 and use of loop diuretics. These adverse events were generally considered as mild or moderate in intensity, and infrequently led to discontinuation. No increase in serious adverse events related to reduced intravascular volume were seen with canagliflozin treatment. The reduction in intravascular volume also led to reversible reductions in eGFR that generally attenuated with continued treatment.

Based on the observations from the 2-year rat carcinogenicity study (findings of renal tubular cell cancers, Leydig cell tumors [LCTs], and pheochromocytomas), an extensive preclinical toxicology program was conducted that demonstrated that these tumors related to effects of canagliflozin in rats, not seen in humans (including rises in luteinizing hormone [LH] associated with LCT, and carbohydrate malabsorption leading to associated metabolic effects, including marked hypercalciuria, inducing renal tubular tumors and pheochromocytomas). In the clinical program, there were no reports of LCT or pheochromocytoma and no imbalance in the low incidence across groups of renal cell cancers.

In preclinical studies in rats, hyperostosis (increased trabecular bone) was observed; mechanistic toxicology studies demonstrated that hyperostosis, like the tumors discussed above, related to carbohydrate malabsorption in rats treated with canagliflozin, with consequent marked hypercalciuria (which is not seen in human). A detailed analysis of bone safety was conducted in the Phase 3 program, including an assessment using dual-energy X-ray absorptiometry (DXA) in a dedicated Phase 3 study (a study conducted in older subjects [ages ≥55 and ≤80 years] with T2DM) and a cross-program assessment of fracture incidence. The results of the DXA assessment at Week 104 showed small decreases in bone density at the lumbar spine and total hip, with trends towards increases seen at the femoral neck and distal forearm. The small reductions in bone density seen at the lumbar spine and total hip are likely related to the weight loss seen with canagliflozin (weight loss is known to be associated with reductions in bone mineral density [BMD]). In a pool of 8 clinical trials with a longer mean duration of exposure, the incidence rate of bone fracture was 14.2, 18.7, and 17.6 per 1,000 patient-years of exposure to comparator, canagliflozin 100 mg, and canagliflozin 300 mg, respectively.

Increases in low-density lipoprotein-cholesterol (LDL-C) were observed with canagliflozin: in a pooled analysis of placebo-controlled 26-week studies, increases in LDL-C relative to placebo were 4.4 mg/dL (0.11 mmol/L) and 8.2 mg/dL (0.21 mmol/L) at the 100 mg and 300 mg doses,

respectively. Relative increases in Apo B, non-HDL-C, and LDL particle number were approximately half as large as the rise in LDL-C. The changes in the CV risk profile with canagliflozin include reductions in SBP and increases in LDL-C, both established CV risk factors, and validated as surrogate endpoints. Improvements in other endpoints associated with CV risk, but not established as surrogate endpoints for CV benefit, such as body weight, glycemic control, HDL-C, and TG were also observed with canagliflozin. The cross-program CV meta-analysis (including results from the dedicated CV safety study) observed a hazard ratio of 0.91 for a pre-specified composite endpoint of CV death, non-fatal MI, non-fatal stroke, and hospitalized unstable angina (95% CI: 0.68, 1.22), showing no signal for an increase in the CV risk.

1.2. Overall Rationale and Goals for the Study

Patients with T2DM have an increased risk of both microvascular and macrovascular complications which lead to morbidity and mortality. A key issue in patients with T2DM is the potential for hyperglycemia to lead to progressive damage to the kidney. Early on, this damage is reflected by microalbuminuria that may progress to macroalbuminuria and eventually loss of renal function. Hyperglycemia, possibly through production of advanced glycation end products (Diabetes Control and Complications Trial [DCCT]; Brownlee 2001) and systemic hypertension (DCCT) are known to be risk factors for the onset and progression of diabetic nephropathy. By virtue of its improvement in glycemic control, which has been shown to reduce albuminuria progression in prior studies (ADVANCE 2008; DCCT 1993; UKPDS 1998), and effects to reduce blood pressure, canagliflozin may slow the progression of diabetic nephropathy.

Hyperglycemia increases glucose levels delivered to the proximal tubule, which is reabsorbed, predominantly via an SGLT-2-dependent mechanism (Vallon 1999). Increased proximal tubule resorption of glucose results in increases in the proximal tubule reabsorption of sodium and reduces the delivery of sodium to the distal tubule. Decreases in sodium levels in the distal tubule reduce macula densa-dependent tubuloglomerular feedback, which results in afferent glomerular arteriole vasodilation and increases in glomerular pressure (Vallon 1999). Increases in glomerular pressure are believed to be an important factor in the onset and progression of diabetic nephropathy (Anderson 1986; American Diabetes Association [ADA] 2004). ACEI and ARB decrease glomerular pressure by stimulating efferent glomerular arteriole vasodilation and reduce albuminuria and the progression of diabetic nephropathy (IDNT, Lewis 2001, and RENAAL, deZeeuw 2004).

In preclinical diabetic rodent models, SGLT2 inhibition increases tubuloglomerular feedback and reduces single nephron glomerular filtration rates, consistent with an increase in tubuloglomerular feedback leading to a decrease in glomerular pressure (Vallon 2011). In a Phase 1 study in subjects with T1DM who exhibited glomerular hyperfiltration (eGFR 172 ml/min/1.73 m^2), an 8-week treatment with empagliflozin, a selective SGLT2 inhibitor, significantly reduced glomerular hyperfiltration (eGFR 139 ml/min/1.73 m^2) (Cherney 2013 ADA poster). The reduction in hyperfiltration was associated with increases in renal vascular resistance and reductions in renal blood flow, both consistent with an increase in afferent glomerular arteriole tone. Thus, in preclinical and clinical models, SGLT2 inhibition reduces

glomerular pressure, a factor known to be associated with the onset and progression of diabetic nephropathy.

In the clinical program, clinically-important, favorable changes were observed with canagliflozin compared to placebo in the progression of albuminuria. In a post hoc analysis performed in CANVAS (28431754DIA3008; A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus), after approximately 20 months of mean follow-up, 253/1390 (18.2%) of placebo-treated subjects showed albuminuria progression (defined by albuminuria status change and 30% increase in ACR from baseline) relative to baseline versus 221/1406 (15.7%) with canagliflozin 100 mg, 191/1397 (13.7%) with canagliflozin 300 mg, and 412/2803 (14.7%) with canagliflozin overall. In a pooled analysis of subjects with moderate renal impairment (defined as a baseline eGFR of ≥30 mL/min/1.73 m^2 and ≤60 mL/min/1.73 m^2) that included subjects from the CANVAS study and other studies in the Phase 3 program, the observed mean change from baseline in the albumin/creatinine ratio was 28 mg/g, -22 mg/g, and -41 mg/g for placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. The corresponding observed median changes from baseline in the 3 groups respectively were 1.2 mg/g, -0.6 mg/g, and -0.7 mg/g.

In the Phase 3 program, treatment with canagliflozin was associated with a dose-dependent, reversible reduction in eGFR that was maximal at the first post baseline visit and was either stable or attenuated with continued treatment. The time course of eGFR changes over a 104-week, active comparator study and over a 52-week week study in subjects with moderate renal impairment are shown in Figure 1 and Figure 2 below.

Figure 1: Mean Change in eGFR Over Time (DIA3009)

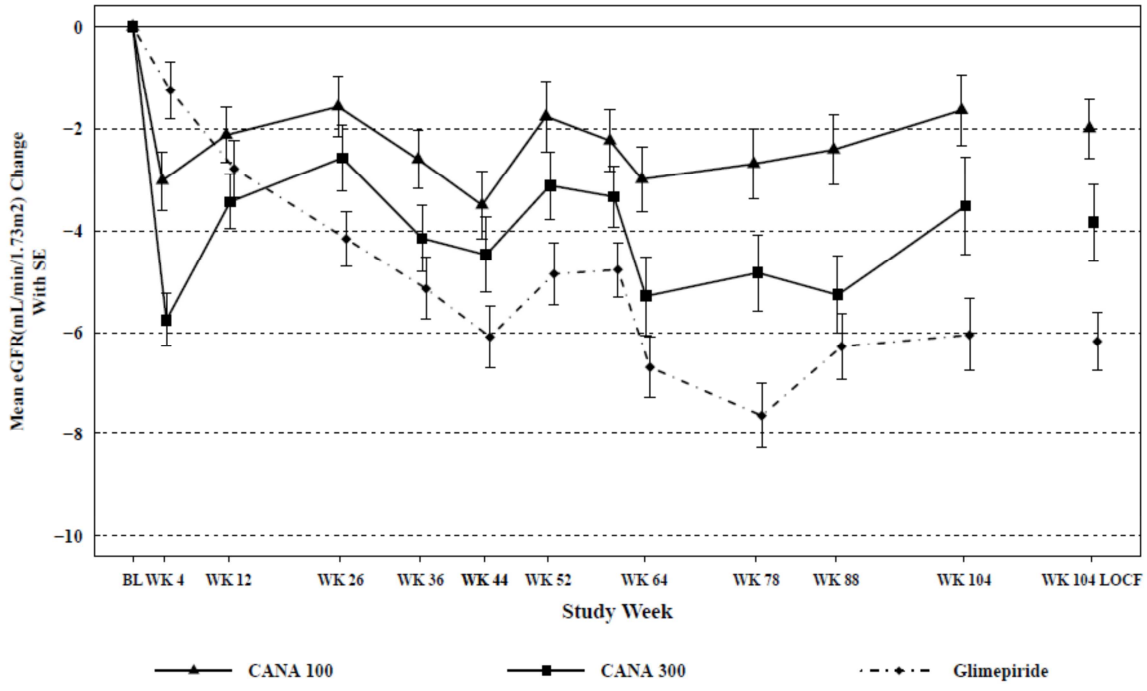
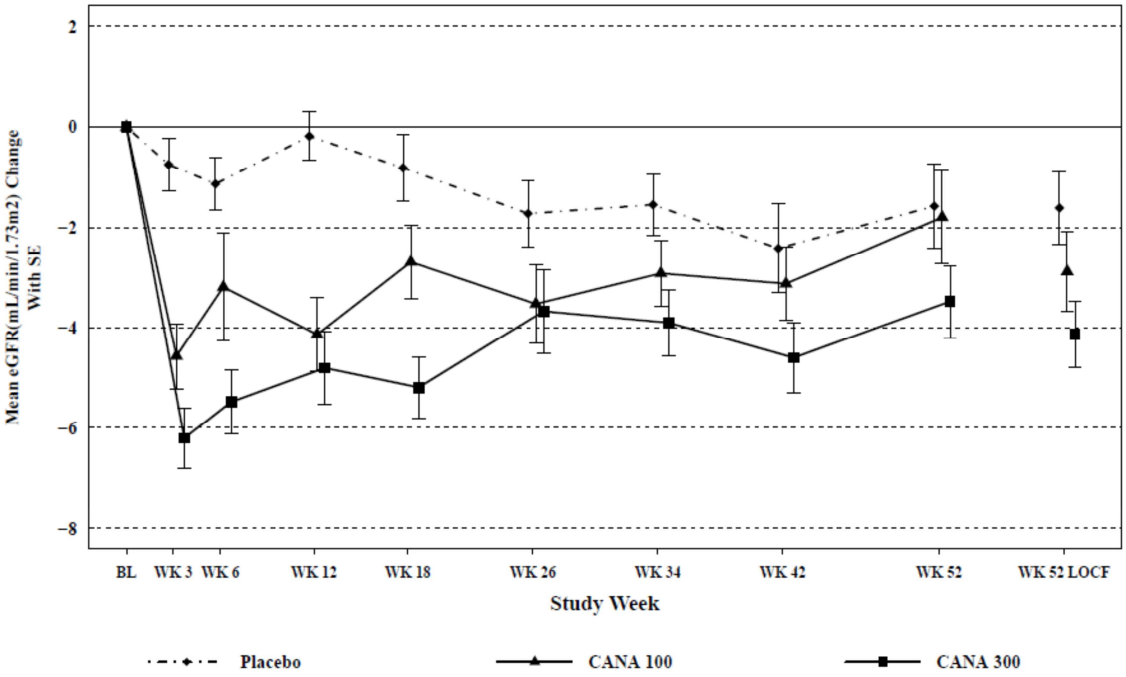
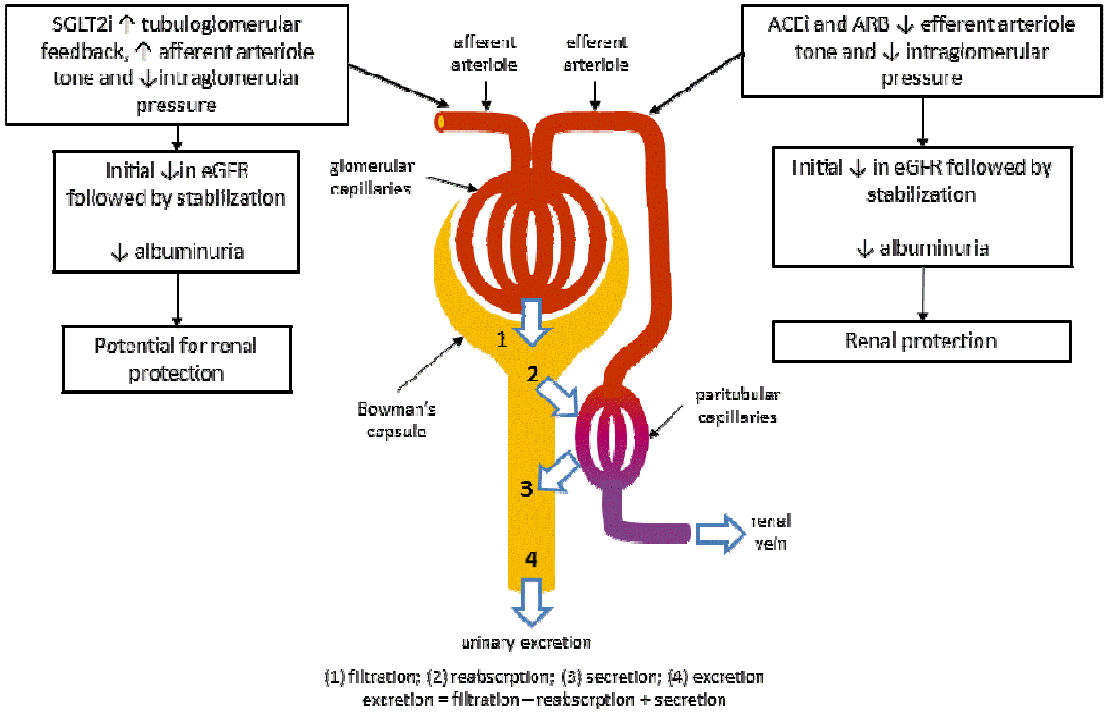


Figure 2: Mean Change in eGFR Over Time (DIA3004)



Based on these data, it is hypothesized that SGLT2 inhibition with canagliflozin will reduce glomerular pressure by increasing afferent glomerular arteriole tone, which will lead to a hemodynamically mediated decrease in glomerular pressure, as reflected by an acute, mild decrease in GFR. The reduction in glomerular pressure is hypothesized to mediate the reduction in albuminuria seen with canagliflozin treatment and to potentially lead to a reduction in progression of diabetic nephropathy. A schematic of these hypotheses and the effect of ACEI and ARBs on the progression of diabetic nephropathy is shown in Figure 3, below.

Figure 3: Hypotheses Regarding the Effect of ACEI and ARBs on the Progression of Diabetic Nephropathy



The present study is intended to determine if treatment of subjects with T2DM with canagliflozin reduces the progression of albuminuria, a biomarker for renal injury and for progression of diabetic nephropathy. The study will also explore the effects of canagliflozin on the regression of albuminuria, and changes in eGFR.

Data from this study will also be used for a pre-specified meta-analysis with data from CANVAS for the assessment of CV safety, examining a composite endpoint of the major adverse cardiovascular events (MACE) of cardiovascular death, nonfatal MI, and nonfatal stroke. The details of the meta-analysis are described in a separate statistical analysis plan (SAP).

2. OBJECTIVES AND HYPOTHESES

2.1. Objectives

Primary Objective

In subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk of CV events, to assess the effect of canagliflozin compared to placebo on progression of albuminuria.

Secondary Objectives

In subjects with T2DM receiving standard care but with inadequate glycemic control and at elevated risk of CV events, to assess the effect of canagliflozin compared to placebo on:

- Regression of albuminuria

- Change in eGFR from baseline to the last off-treatment value done approximately 30 days post study drug discontinuation.
- Urinary albumin/creatinine ratio

Exploratory objective

In subjects with T2DM receiving standard care but with inadequate glycemic control and at elevated risk of CV events to assess the effect of canagliflozin compared to placebo on:

- Change in eGFR determined from a between group comparison of the eGFR slopes using all on-treatment measures of eGFR made from the first on-treatment measurement to the final on-treatment measurement
- Changes in HbA_{1c}
- Utilization of AHA therapy

Safety Objective

Cardiovascular safety data from this study will be combined with the data from the other large-scale study of the effects of canagliflozin compared to placebo (CANVAS) in a pre-specified meta-analysis of cardiovascular safety outcomes.

2.2. Hypotheses

2.2.1. Primary Hypothesis

In subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk of CV events, canagliflozin compared to placebo reduces the rate of progression of albuminuria.

2.2.2. Secondary Hypotheses

In subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk of CV events, canagliflozin compared to placebo:

- Increases the rate of regression of albuminuria
- Slows the decline in eGFR
- Reduces albuminuria

3. OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the effects of canagliflozin compared to placebo on progression of albuminuria, an important intermediate marker of renal injury and progression of diabetic nephropathy. The study will be conducted in subjects with T2DM, receiving standard of care for hyperglycemia and CV risk factors, who have either a history or high risk of CV events. A total of 5,700 subjects will be recruited into the study. The study's last subject last visit is targeted to occur when the last subject randomized has approximately 78 weeks of follow-up or when 688 MACE events are accumulated between the CANVAS and CANVAS-R (DIA4003) studies,

whichever comes later (estimated to occur between January 2017 and April 2017). The effects of canagliflozin will be evaluated against a background of standard of care for the treatment of hyperglycemia and CV risk factors with study investigators counseled to assure appropriate management according to applicable national guidelines for the care of patients with T2DM with treatment individualized as clinically appropriate.

3.1. Study Design

The following section provides an overview of subject management including screening, run-in, and double-blind treatment.

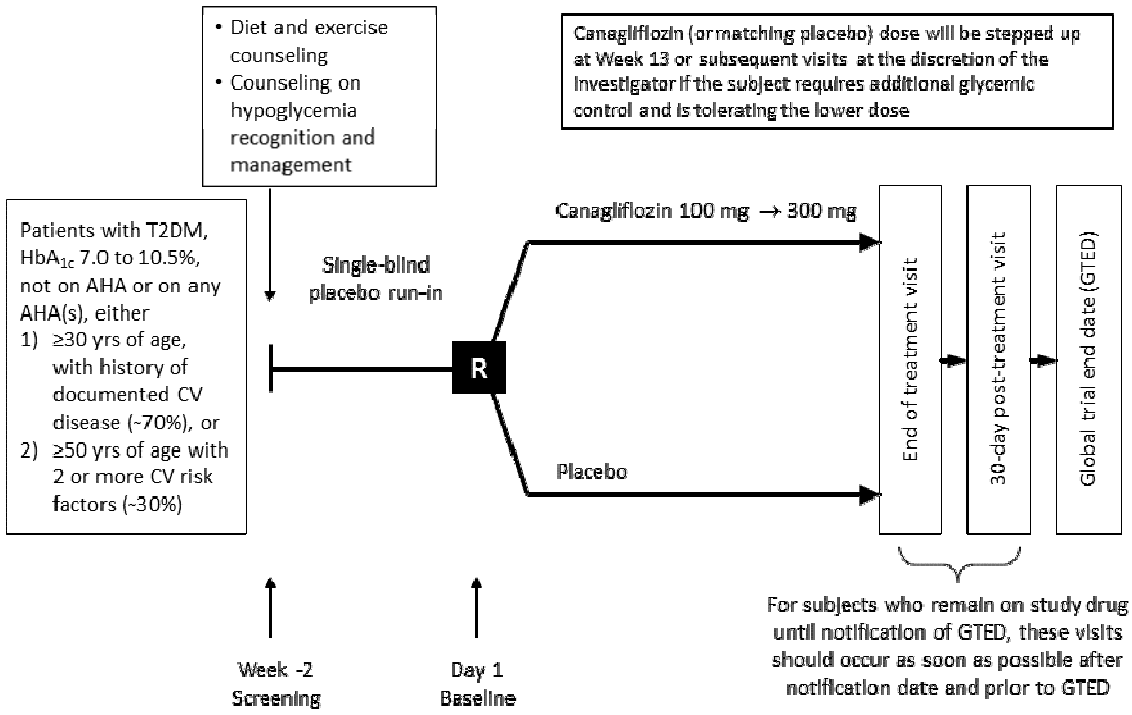
Screening Period

Subjects will undergo a screening visit for a preliminary determination of eligibility. Men or women with T2DM who are known to have inadequate glycemic control (HbA_{1c} ≥7.0 and ≤10.5%), not on an AHA, or on an AHA (oral or injectable [eg, insulin or GLP-1 analogue] in monotherapy or combination therapy, and who have known CV events or who have 2 or more risk factors for CV events are eligible (refer to Section 4.2, Inclusion Criteria).

At this visit, potentially-eligible subjects will enter a 2-week single-blind placebo run-in period. All subjects should receive diet/exercise counseling at the screening visit, be counseled on hypoglycemia recognition and management, and be dispensed single-blind placebo capsules. During this period, the investigator should also adjust/optimize the subject's medications to reduce CV risk (eg, anti-hyperglycemic, lipid-altering or blood pressure-lowering medications) as necessary. If in the investigator's opinion additional time is required for adjustment/optimization of these medications, the 2-week period between screening and randomization may be extended by having the subject continue single-blind placebo up to 2 additional weeks. Subjects should be counseled to perform fasting self-monitored blood glucose (SMBG) determinations, according to standard guidelines. This counseling, as well as the counseling regarding diet/exercise and hypoglycemia recognition/management, should begin with a focus during the screening phase and be reinforced as needed throughout the study.

An overview of the study design is illustrated in Figure 4.

Figure 4: Study Design Outline



AHA=antihyperglycemic agent; CV=cardiovascular; R = randomization; SU=sulfonylurea; T2DM= type 2 diabetes mellitus

Double-Blind Treatment Phase

Subjects meeting all inclusion and none of the exclusion criteria, and successfully completing the 2-week run-in period, will be randomly allocated to initial treatment with canagliflozin 100 mg or matching placebo administered once daily (in a 1:1 ratio). A total of 5,700 subjects will be randomized. After 13 weeks, the dose of canagliflozin (or matching placebo) may be increased from 100 mg to 300 mg if the subject requires additional glycemic control, provided the 100 mg dose is well tolerated. The dose should be increased if the subject requires additional glycemic control (eg, ≥50% of the subject's glucose determinations from the fasting SMBG [finger stick] readings [a minimum of 3 readings recommended] are >110 mg/dL [6 mmol/L] during the 2 weeks preceding the clinic visit or telephone contact) and the subject had no events of hypoglycemia or volume depletion in the preceding 2-week interval that in the opinion of the investigator would preclude dose titration. After increasing the dose to 300 mg, the dose should remain at 300 mg; however, if necessary, in the investigator's judgment, the dose may be decreased to 100 mg at any time point (eg, due to an adverse event of reduced intravascular volume). In addition, if there is need for additional glycemic control, the investigator should adjust the subject's AHA regimen as, per standard diabetes care guidelines, individualized as considered appropriate by the investigator. Adjustments in the AHA regimen should be carefully implemented throughout the study to minimize the risk of hypoglycemia. The investigator should optimize agents to reduce CV risk (eg, antihyperglycemic, lipid-altering and blood pressure-lowering medications) as required during the course of the trial to assure appropriate control consistent with standard care guidelines.

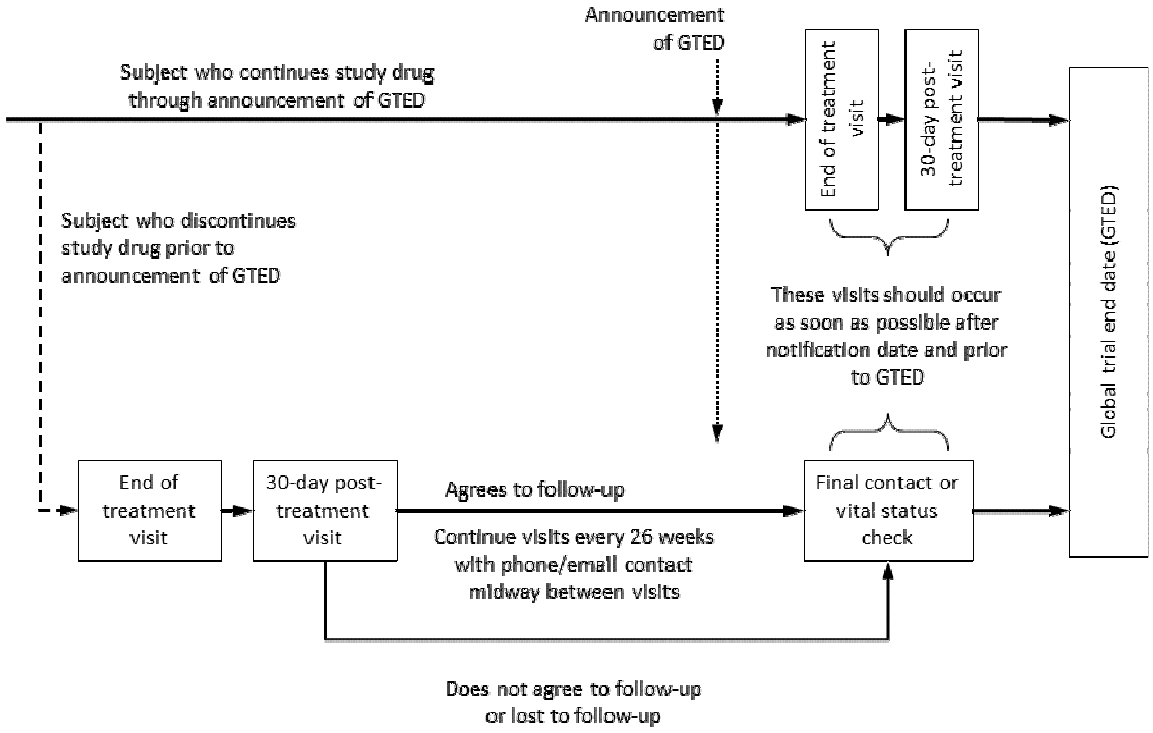
Study Duration

Subjects are expected to be followed for a maximum of about 3.5 years with the last visit for the last subject targeted to occur when all subjects have approximately 78 weeks of follow-up or when 688 MACE events are accumulated between the CANVAS and CANVAS-R (DIA4003) studies, whichever comes later. All sites will be notified of the projected global trial end date (GTED) (projected to occur between January 2017 and April 2017). Immediately after the projected GTED notification is sent, for subjects who remain on double-blind study drug, sites will be required to schedule the last on treatment visits and the 30-day off drug follow-up visits as per the Time and Events schedule; for subjects who prematurely discontinue study drug, sites will be required to make a final contact (eg, schedule the last follow-up visit) or vital status check as soon as possible after announcement of GTED.

All visits (including the 30-day off drug follow-up visit) will need to be completed prior to the GTED.

Figure 5 shows the intended follow-up of randomized subjects with respect to the GTED.

Figure 5: Follow-up of Randomized Subjects With Respect to the GTED



Collection of data about Cardiovascular Safety Outcomes

Investigators will be required to report any cardiovascular (CV) event that they consider could possibly be a nonfatal MI or nonfatal stroke (refer to Section 9.2, Reporting/Adjudication of Events in the CV Composite Endpoint and Other Events for Adjudication), as well as all deaths. Additional information and documentation will be requested from investigators for all such

events to support a detailed assessment of these outcomes by an Endpoint Adjudication Committee.

Collection of Information After Early Discontinuation of Randomized Treatment

It is the intent that subjects who discontinue treatment with the study drug will continue in the study according to the visit schedule described in the Post-treatment Time & Events Schedule. After early discontinuation of randomized treatment, subjects will continue to be followed up for specific data collection, including any MACE events, vital signs, serious adverse events, and adverse events of interest.

Participants who prematurely discontinue study drug will require an immediate follow-up assessment (either on the day of study drug discontinuation or as soon as possible following study drug discontinuation) as well as a follow-up assessment approximately 30 days (±12 days) after last dose after which they should then continue to be followed for the full originally scheduled follow-up period through to study completion. If for some reason the subject is unable to be seen shortly after discontinuing study drug, the end of treatment visit may be omitted, but the 30-day off-drug follow-up visit should be performed. The follow-up regimen for these individuals will require 26-week visits interspersed with phone/email contact exactly as for those individuals that continue with randomized therapy (refer to Section 9.1.4, End-of-Treatment/Early Withdrawal, and Section 9.1.5, Posttreatment Phase [Follow-Up] for collection of information on CV events and other assessments).Safety Evaluations and Adverse Events of Interest

Safety evaluations will include the monitoring of serious adverse events, adverse events resulting in discontinuation, adverse events of interest, clinical laboratory tests, vital sign measurements, and measurement of body weight. For adverse events of interest, investigators will be asked to provide additional information, on separate electronic case report forms (eCRFs), so as to support more detailed analyses. Adverse events of interest include: all malignancies, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (eg, angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, and pregnancy. Information on these events will be recorded on a supplemental eCRF for any event that is serious or that leads to study drug discontinuation. The only exceptions are for malignancies, photosensitivity reactions, fractures, venous thromboembolic events for which information on non-serious adverse events will also be recorded on the supplemental CRF pages (in addition to the information collected on serious AEs and AEs leading to study drug discontinuation). Investigators may also be asked to provide additional information on other adverse events, based upon review by the Medical Safety Review Committee (MSRC) or the study Independent Data Monitoring Committee (IDMC) (Sections 9.3.3, Medical Safety Review Committee, and Section 9.3.4, Independent Data Monitoring Committee). Refer to Section 3.2, Study Design Rationale, for review of rationale for collection of additional information on these selected adverse events.

Section 9.3, Study Management: Committees, provides details regarding the committees commissioned to provide oversight for the management of this study.

3.2. Study Design Rationale

Overall Design, Blinding, Control, Study Phases/Periods, Treatment Groups

This study was based upon the design of CANVAS and developed both to address the primary renal hypothesis and to meet the post-marketing requirements for canagliflozin defined by the US FDA. Broadly, the pretreatment phase allows sufficient time for study-related procedures to be performed, for subject eligibility to be determined and for optimization of background therapy by the investigators. Randomization, placebo control, and blinding will be used to minimize bias in the assignment of subjects to treatment groups and throughout data collection, and to maximize the likelihood that the study precisely and reliably addresses the questions it is designed to answer.

Study Population

The study population includes a broad spectrum of subjects on a variety of different AHAs with a range of different levels of baseline glycemic control and background risks of vascular and renal disease. The ratio of subjects with a history of CV events versus a high risk of CV events will be approximately 70% to 30%, respectively. Conducting the trial in this population will ensure broad generalizability of the trial results upon study completion.

Dosage Selection, Route of Administration, Dose Interval, Treatment Period

Both the 100 mg and 300 mg doses of canagliflozin are being used in this study. These are the doses that have been filed with health agencies for approval based on the results of the clinical program, and have been approved for marketing in some countries.

Choice of Renal Efficacy Measures

The development and progression of renal disease in people with diabetes follows a clearly defined pathway starting with microalbuminuria, progressing to macroalbuminuria, then to reduced renal function (lower glomerular filtration rate), and finally to renal failure with the need for dialysis or transplantation. To assess the effects of canagliflozin on the progression of diabetic nephropathy, the proportion of subjects with categorical progression of albuminuria based upon the urinary albumin/creatinine ratio in the first morning void is the primary endpoint and will be assessed according to the categorizations defined in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Guideline #1 (KDOQI 2007): the definition of microalbuminuria is urinary albumin/creatinine ratio of 30 to 300 mg/g, and the definition of macroalbuminuria is urinary albumin/creatinine ratio greater than 300 mg/g.

In diabetes, the onset of urinary albumin excretion is a strong signal for progression of diabetic nephropathy (ADA 2004), and is associated with an increase in CV events (de Zeeuw 2004). In the present study, duplicate first morning void urine collections on consecutive days, made by subjects at home (collection of the first urine void after the individual awakes from sleep), are being used. These collections have been shown to be more accurate than spot urine collections (Witte 2009) because they are less influenced by urinary albumin changes associated with physical activity. In addition to the progression and regression of albuminuria, changes in eGFR

will be analyzed in this study, since it is the basic measurement of renal function and is used to assess progression of renal disease (ADA 2004).

4. STUDY POPULATION

4.1. General Considerations

The study will include subjects with a diagnosis of T2DM and a history or high risk of CV events; the ratio of subjects with a history of versus high risk of CV events will be approximately 70% to 30%, respectively. The inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling the subject in the study.

4.2. Inclusion Criteria

Potential subjects must satisfy all of the following criteria to be enrolled in the study:

Inclusion Criteria at Screening Visit

- Man or woman with a diagnosis of T2DM with HbA_{1c} level ≥7.0% to ≤10.5% at screening and be either (1) not currently on AHA therapy or (2) on AHA monotherapy or combination therapy with any approved agent: eg, sulfonylurea, metformin, pioglitazone, alpha-glucosidase inhibitor, GLP-1 analogue, DPP-4 inhibitor, or insulin.
- History or high risk of CV events defined on the basis of either:
  - Age ≥30 years with documented symptomatic atherosclerotic CV events: including stroke; MI; hospital admission for unstable angina; coronary artery bypass graft; percutaneous coronary intervention (with or without stenting); peripheral revascularization (angioplasty or surgery); symptomatic with documented hemodynamically-significant carotid or peripheral vascular disease; or amputation secondary to vascular disease.
  - Age ≥50 years with 2 or more of the following risk factors determined at the screening visit: duration of T2DM of 10 years or more, systolic blood pressure >140 mmHg (average of 3 readings) recorded at the Screening Visit, while the subject is on at least one blood pressure-lowering treatment, current daily cigarette smoker, documented micro- or macroalbuminuria (see Section 3.2, Study Design Rationale, for definition) within one year of screening, or documented HDL-C of <1 mmol/L (<39 mg/dL) within one year of screening.

    Note: An overall target ratio of approximately 70%:30% for CV history (first category):risk factors (second category) will be implemented (with a maximum of approximately 40% in the second category). This target is intended to be a global ratio and may vary by region. The proportion of subjects in these categories will be monitored centrally.

    Note: the term "documented" in the above paragraphs refers to the required information being clearly noted in hospital/clinical records or in physician-referral documents, copies of which should be retained in the subject's study files.

- Women must be:
  - postmenopausal, defined as
    - >45 years of age with amenorrhea for at least 18 months, or
    - >45 years of age with amenorrhea for at least 6 months and less than 18 months and a known serum follicle stimulating hormone (FSH) level >40 IU/L, or
  - surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal occlusion), or otherwise be incapable of pregnancy, or
  - heterosexually active *and* practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (eg, condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), or male partner sterilization, consistent with local regulations regarding use of birth control methods for subjects participating in clinical trials, for the duration of their participation in the study, or
  - not heterosexually active.

    Note: subjects who are not heterosexually active at screening must agree to utilize a highly effective method of birth control if they become heterosexually active during their participation in the study.
- Women of childbearing potential (ie, those subjects who do not meet the postmenopausal definition above, regardless of age) must have a negative urine pregnancy test at baseline (Day 1) and at screening if required by local regulations (Note: a serum pregnancy test is acceptable in lieu of a urine pregnancy test if required by local regulations).
- Willing and able to adhere to the prohibitions and restrictions specified in this protocol
- Subjects must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study

Inclusion Criterion for Randomization

- Subjects must have taken ≥80% of their single-blind placebo doses during the 2-weeks prior to randomization on Day 1 to be eligible for randomization.

4.3. Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

Diabetes-Related/Metabolic

- History of diabetic ketoacidosis, T1DM, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy
- History of one or more severe hypoglycemic episodes within 6 months before screening

  Note: a severe hypoglycemic episode is defined as an event that requires the help of another person.

- History of hereditary glucose-galactose malabsorption or primary renal glucosuria
- Ongoing, inadequately controlled thyroid disorder

  Note: subjects on thyroid hormone replacement therapy must be on a stable dose for at least 6 weeks before Day 1.

Renal/Cardiovascular

- Renal disease that required treatment with immunosuppressive therapy or a history of chronic dialysis or renal transplant. Note: subjects with a history of treated childhood renal disease, without sequelae, may participate.
- Myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident within 3 months before screening, or a planned revascularization procedure, or history of New York Heart Association (NYHA) Class IV cardiac disease (The Criteria Committee of the New York Heart Association).
- Known ECG findings within 3 months before screening that would require urgent diagnostic evaluation or intervention (eg, new clinically important arrhythmia or conduction disturbance)

Gastrointestinal

- Known history of hepatitis B surface antigen or hepatitis C antibody positive (unless known to be associated with documented persistently stable/normal range aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels), or other clinically active liver disease
- Any history of or planned bariatric surgery

Laboratory

- eGFR <30 mL/min/1.73m^2 at screening visit
- ALT levels >2.0 times the upper limit of normal (ULN) or total bilirubin >1.5 times the ULN, unless in the opinion of the investigator and as agreed upon by the sponsor's medical officer, the findings are consistent with Gilbert's disease

Other conditions

- History of malignancy within 5 years before screening (exceptions: squamous and basal cell carcinomas of the skin and carcinoma of the cervix in situ, or a malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence)
- History of human immunodeficiency virus (HIV) antibody positive
- Subject has a current clinically important hematological disorder (eg, symptomatic anemia, proliferative bone marrow disorder, thrombocytopenia)
- Investigator's assessment that the subject's life expectancy is less than 1 year, or any condition that in the opinion of the investigator would make participation not in the best interest of the subject, or could prevent, limit, or confound the protocol-specified safety or efficacy assessments

- Major surgery (ie, requiring general anesthesia) within 3 months of the screening visit or any surgery planned during the subject's expected participation in the study (except minor surgery, ie, outpatient surgery under local anesthesia)
- Any condition that, in the opinion of the investigator, would compromise the well-being of the subject or prevent the subject from meeting or performing study requirements

Medications/Therapies

- Current or prior use of an SGLT2 inhibitor.
- Prior or current participation in another canagliflozin study.
- Known allergies, hypersensitivity, or intolerance to canagliflozin or its excipients (refer to Section 14.1, Physical Description of Study Drug[s])
- Current use of a corticosteroid medication or immunosuppressive agent, or likely to require treatment with a corticosteroid medication (for longer than 2 weeks in duration) or an immunosuppressive agent. **Note**: subjects using inhaled, intranasal, intra-articular, or topical corticosteroids, or corticosteroids in therapeutic replacement doses may participate
- Received an active investigational drug (including vaccines) or used an investigational medical device within 3 months before Day 1/baseline

General

- History of drug or alcohol abuse within 3 years before screening
- Pregnant or breast-feeding or planning to become pregnant or breast-feed during the study
- Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator

  Note: Investigators should assure that all study enrollment criteria have been met and determine that the subject has not had any interval change in clinical status since screening. Before randomization, subjects whose status changes after screening, such that they now meet an exclusion criterion, should be excluded from participation.

4.4. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

- Prohibited medications include other SGLT2 inhibitors (including commercially available canagliflozin); subjects must not take any other investigational agents during the study (if a subject prematurely discontinues from the study medication but continues in the posttreatment follow-up phase, entering another investigational trial is discouraged but is not prohibited; however, entering another canagliflozin trial is prohibited)
- Strenuous exercise may affect urine protein excretion and other safety laboratory results; for this reason, strenuous exercise should be avoided within 72 hours before planned study visits

- Subjects should not collect first morning void urine specimens during acute illness with fever. The collection and respective visit should be postponed until the subject is recovered from the acute illness.

4.5. Rescreening

Subjects who do not meet all inclusion criteria or who meet an exclusion criterion may, at the discretion of the investigator, be rescreened if appropriate clinical management leads to study eligibility (eg, HbA_{1c} >10.5% that prompts adjustment of the subject's AHA regimen). Generally, a subject may only be rescreened once, but an additional rescreening may be allowed with concurrence of the sponsor's Medical Monitor.

Typically, rescreening will require that all screening parameters be repeated. However, with the concurrence of the sponsor's Medical Monitor, a non-qualifying laboratory test may be repeated one time, without completely rescreening the subject, in situations where there is a clinical reason to do so.

5. TREATMENT ALLOCATION

To ensure sufficient experience in subjects with a documented history of CV events – the highest risk group – approximately 70% of subjects (globally) are targeted to be in this group. The proportion of subjects in these categories will be monitored centrally.

Randomization and Blinding Procedures

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared under the supervision of the sponsor before the study. The randomization will be balanced by using randomly permuted blocks. Based on this randomization schedule, the study drug will be packaged and labeled. Medication numbers will be preprinted on the study drug labels and assigned as subjects qualify for the study and are assigned to double-blind treatment.

At baseline (Day 1), the randomization number and medication numbers, the treatment code, which is linked to the randomization schedule, will be assigned after logging on to the interactive web response system (IWRS) designated by the sponsor. The requestor must use his/her own user identification (ID) and personal identification number (PIN) when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject. Based on this information, the IWRS will assign a unique treatment code, which will dictate the treatment assignment and study drug kit for the subject. As subjects are randomly assigned to treatment, the IWRS will assign a study drug kit to be dispensed at that visit. New medication numbers will be assigned each time the IWRS is contacted for dispensing additional study drug. The randomization (or initial subject allocation) number at baseline will be the identifying number linking all subsequent kits to the individual subject.

The study drugs, whether canagliflozin or placebo, will be identical in appearance and will be packaged accordingly to maintain the blind. The randomization code that links the randomization number assigned to the subject with a treatment group assignment will be maintained within the

IWRS. This randomization code will not be provided to the investigator unless required, as described below, for unblinding in emergency situations.

The treatment blind may be broken to provide unblinded information to the site only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment through IWRS. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. The reason for unblinding is not captured through IWRS. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the appropriate section of the electronic case report form (eCRF) and in the source documents. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner (eg, in a sealed envelope) so as not to unblind the treatment assignment to the study site or sponsor personnel. The investigator is also advised not to reveal the study treatment assignment to the study site or sponsor personnel.

All randomization codes will be released after completion of the study. The translation of randomization codes into treatment and control groups will be disclosed only to those authorized.

Urine glucose measurements will not be performed on first morning void urine specimens, as an additional step to ensure the maintenance of the treatment blind. If a urinalysis must be performed locally for appropriate subject management (eg, to evaluate a potential infection), investigators should request microscopic rather than dipstick urinalysis (if microscopic evaluation is considered clinically sufficient).

6. DOSAGE AND ADMINISTRATION

6.1. Study Drugs

Two-week Single-Blind Placebo period following Screening

Upon completion of initial screening, all potentially eligible individuals will receive single-blind placebo capsules (one capsule to be administered once-daily) for 2-weeks to assess compliance.

Double-Blind Study Medication

On Day 1, subjects will be randomly assigned in a 1:1 ratio to 1 of 2 treatment groups: canagliflozin or matching placebo. Initially, canagliflozin will be provided at a dose of 100 mg daily, but at Week 13 (or any time thereafter) the dose of canagliflozin (or matching placebo) may be increased from 100 mg to 300 mg if the subject requires additional glycemic control, provided the 100 mg dose is well tolerated. The dose of study drug should be increased if the subject requires additional glycemic control (for example, ≥50% of the subject's glucose determinations from the fasting SMBG [finger stick] readings [a minimum of 3 readings recommended] are >110 mg/dL [6 mmol/L] during the 2 weeks preceding the clinic visit or telephone contact) and the subject had no events of hypoglycemia or volume depletion in the

preceding 2-week interval that in the opinion of the investigator would preclude dose titration. After increasing the dose to 300 mg, the dose should remain at 300 mg; however, if necessary, in the investigator's judgment, the dose may be decreased to 100 mg at any time point (eg, due to an adverse event of reduced intravascular volume).

Subjects will be counseled to take their dose of canagliflozin or matching placebo, one capsule once daily, before the first meal of the day for the duration of the study or until early discontinuation. Subjects should take the first dose of study drug at the study center on Day 1.

The study drug must be swallowed whole with liquid and not chewed, divided, dissolved, or crushed. If the subject does not take the study drug within 12 hours after the first meal of the day, the dose of study drug should be skipped for that day and the subject should be instructed to take the study drug on the following day before the first meal of the day.

Study drug may be interrupted (eg, for safety and/or tolerability reasons). Study drug interruptions, occurring for any reason and lasting 7 days or longer, will be documented on the eCRF.

6.2. Concomitant Antihyperglycemic and Other Therapies

6.2.1. Management of Glycemic Control and CV Risk Factors

Screening Management

Subjects will receive diet/exercise counseling at entry into the screening period. During this visit, subjects should also be counseled to perform fasting self-monitored blood glucose (SMBG) determinations, according to standard guidelines.

Double-blind Treatment Phase Glycemic Management

The background AHA regimen may be adjusted at any time during the study to achieve glycemic goals, using standard guidelines, and as considered appropriate by the investigator for the individual subject. Adjustment to the AHA regimen should be carefully implemented so as to avoid events of hypoglycemia.

Adjustment of AHA therapy after randomization will be performed by the investigator. The preferred initial option for enhancing glucose control is to increase the dose of canagliflozin/placebo, so if possible, after Week 13 the investigator should increase the dose of canagliflozin/placebo from 100 mg to 300 mg (see Section 6.1). If increasing the dose of canagliflozin/placebo is not effective, there is no specific AHA treatment algorithm required for this study and the responsible clinician is free to adjust therapy as appropriate. Treatment may include reinforcement of lifestyle counseling, addition of or up-titration to maximum labeled doses of oral and/or injectable AHAs as locally applicable, **except the use of any other approved SGLT2 inhibitor**. Investigators should make all reasonable efforts to achieve and maintain the subject's individualized target glycemic control, and may add unscheduled visits, if clinically appropriate, to monitor glycemic control, and adjust the subject's regimen. Adjustments to the AHA regimen should be documented in the appropriate eCRF.

During the double-blind treatment period, investigators should counsel subjects to perform fasting SMBG determinations according to standard guidelines.

Therapeutic Management of CV Risk Factors

Before randomization and throughout the study, investigators will be expected to manage the subject's diet/exercise and other medication regimens so as to achieve goals for CV risk factors (eg, HbA_{1c}, lipid levels, blood pressure) based upon standard guidelines for the care of subjects with T2DM.

The 2-week period between screening and randomization provides investigators with the opportunity to adjust the subject's regimen as needed to optimize the subject's CV risk factors. If in the investigator's opinion additional time is required for adjustment/optimization of agents to reduce CV risk (eg, anti-hyperglycemia, lipid-altering or blood pressure-lowering medications) prior to randomization, the 2-week period pre-randomization may be extended by having the subject continue single-blind placebo up to 2 additional weeks. Additional amendments can also be made to background therapy at any time during the course of follow-up.

7. TREATMENT COMPLIANCE

The investigator or designated study research staff will maintain a log of all drug dispensed and returned (including a count of capsules dispensed and returned). Drug supplies for each subject will be inventoried and accounted for throughout the study. Subjects who are poorly compliant with the study drug (based on capsule counts) should receive counseling on the importance of dosing compliance and should continue in the study.

Subjects will receive clear instructions on compliance with study procedures at the screening visit. During the course of the study, the investigator or designated study research staff will be responsible for providing additional instructions to reeducate any subject who is not compliant with taking the study drug or with making required clinic visits.

Study drug interruptions, occurring for any reason and lasting 7 days or longer, will be documented on the eCRF.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy therapy is defined as any therapy used before the first dose of double-blind study medication. Concomitant therapy is defined as any therapy used after the first dose of double-blind study drug.

Selected classes of prestudy therapies administered up to 30 days before screening and up to the time of the first dose of double-blind study drug will be documented. Likewise, selected classes of concomitant therapies taken after the first dose of double-blind study drug will be documented. Examples of the classes of interest may include AHAs such as sulfonylureas, metformin, pioglitazone, alpha-glucosidase inhibitors, GLP-1 analogs, DPP-4 inhibitors, all forms of insulin, as well as non-AHAs such as renin angiotensin aldosterone system (RAAS) inhibitors, diuretics, beta-blockers, calcium channel blockers, statins, and anti-thrombotics. Checkboxes may be used on eCRFs to capture the required information on prestudy and

concomitant agents. Details will be provided in the eCRF completion guidelines regarding the specific types of medications that fall in the categories of interest and what information will be collected.

Concomitant therapies will not be provided or reimbursed by the sponsor.

Disallowed Therapies

Other SGLT2 inhibitors (including canagliflozin) may <u>not</u> be used concurrently, and subjects should not take any other investigational agents during the study. If the use of another SGLT2 inhibitor or investigational agent is reported during the study, the subject's physician should be contacted, the other agent discontinued, and the subject should continue in the study.

The sponsor must be notified as soon as possible of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule that follows the Synopsis summarizes the frequency and timing of efficacy, safety, and other measurements applicable to this study.

Visit Schedules and Visit Windows

Single-blind pre-randomization period - The recommended visit window for the initial single-blind placebo phase of the study is 2 weeks ±4 days. If in the investigator's opinion additional screening time is required for adjustment/optimization of agents to reduce CV risk (eg, anti-hyperglycemia, lipid-altering, blood pressure-lowering or other medications), the screening period may be extended by having the subject continue single-blind placebo therapy for up to 2 additional weeks.

Post-randomization period - Subsequent scheduled in-clinic study visits during the first year of the study should occur at Day 1 (baseline, the day of randomization) and Weeks 13, 26, and 52. After the first year, scheduled in-clinic study visits should occur at 26-week intervals with telephone contacts approximately midway between visits. For the Week 13 and Week 26 visits, the recommended visit window is ±7 days. After Week 26, the recommended visit window is ±14 days. Phone/email contacts will occur at approximately 26-week intervals in between the scheduled in-clinic visits. Similar windows are proposed for the phone/email contacts made between visits.

In the event that it is impossible for a subject to make a scheduled clinic visit, telephone contacts may be conducted at the time of the missed visit, but a clinic visit should be scheduled as soon as possible thereafter. If a telephone contact or study visit is not possible, follow-up information may be collected via email or any other appropriate means. Details regarding discussions via

telephone, email, or other such contacts must be properly documented in source records, including responses by the subject.

For study visits that are unable to be held within the protocol-recommended visit windows, the visit should be conducted as close as possible to the protocol-specified study visit timing. All subsequent visits should be scheduled based on the date of randomization, not the date of the rescheduled visit.

For subjects who complete double-blind study drug through the time of site notification of the projected GTED, it will be important for sites to schedule the last on-treatment visit as soon as possible after the notification date and the 30-day off drug visit prior to the GTED.

For subjects who prematurely discontinue study drug, sites will be required to make a final contact (eg, schedule the last follow-up visit) or vital status check as soon as possible after announcement of GTED.

Pregnancy Testing

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the study (refer to the Time and Events Schedule that follows the Synopsis for further details regarding urine pregnancy testing).

9.1.2. Pretreatment Phase

Screening Visit (Week -2)

Potential subjects will be seen at a screening visit, approximately 2 weeks before scheduled randomization, at which informed consent will be obtained and an initial assessment of eligibility will be performed.

At the screening visit, a focused medical history and initial screening assessment of inclusion/exclusion criteria will be performed and samples for required laboratory tests will be collected. Laboratory specimens will be obtained as described in the Time and Events Schedule. An operations manual will be provided to describe collection, processing, and shipping procedures for the duration of the study.

At this visit, subjects who appear to meet enrollment criteria may then be dispensed single-blind placebo capsules and enter the 2-week single-blind placebo run-in period. An assessment of the subjects' adherence to protocol procedures during this period will be made at the end of the period, before randomization, and will provide investigators with an opportunity to assess subjects' compliance with taking the single-blind study drug (by counting capsules).

Subjects who do not meet all inclusion criteria or meet a study exclusion criterion should be excluded from the study.

The screening visit and the 2-week run-in period provide investigators with the opportunity to evaluate and optimize management of CV risk factors prior to randomization as required (refer to

Section 6.2.1, Management of Glycemic Control and CV Risk Factors) and to provide subjects with counseling regarding diet and exercise consistent with applicable local guidelines.

9.1.3. Double-Blind Treatment Phase

Day 1/Day of Randomization

Potential participants who return for the Day 1 (baseline) visit, who have taken ≥80% of the scheduled single-blind placebo capsules during the period between screening and randomization, and who meet the enrollment criteria will be randomly assigned to once-daily treatment with canagliflozin or matching placebo. Subjects will continue treatment until the study completes or the subject is prematurely withdrawn from double-blind study medication (refer to Section 10.2, Withdrawal From the Study, for reasons for withdrawal).

At the randomization visit, in some countries or regions (at the option of local sponsor representatives), subjects will be given a glucose meter and materials for SMBG measurements and instructed on the performance of SMBG.

Visits Following Randomization

Subjects will be seen in the clinic at visits as described in Section 9.1.1, Overview, and in the Time and Events Schedule. Procedures and clinical laboratory assessments for each visit or contact are outlined in the Time and Events Schedule.

Subjects who experience nonfatal CV events (ie, nonfatal MI, nonfatal stroke) during the double-blind treatment phase will continue in the study, continuing to receive double-blind study drug and complete all assessments at all scheduled visits, as appropriate.

On designated visits (see the Time and Events Schedule that follows the Synopsis), subjects will bring to the clinic duplicate first morning void urine specimens (collection of the first urine void after the individual awakes from sleep), one from the morning of the visit, and one from the morning of the day prior to the visit. If the urinary albumin/creatinine result reflects a stage change from an earlier measurement (eg, progression from normoalbuminuria to microalbuminuria, or regression from macroalbuminuria to microalbuminuria), the subject will be contacted to bring 2 additional consecutive-morning first morning void urine specimens to the clinic approximately 1 to 2 months later (or sooner under unusual circumstances, eg, subject is discontinuing study drug). If the subject is unable to return the specimens in person, the site may engage a courier service to deliver the specimen to the site. If the subject does not provide the morning void collections on the day of the visit, the subject may bring a first morning void specimen to the investigational site during the subsequent week. For subjects working a night shift, or who otherwise have atypical sleep patterns, the collection should be made at the end of the subject's usual sleep period. Collection containers and directions will be provided to subjects at prior visits. The site staff should call subjects a few days prior to visits to remind them to make the consecutive urine collections and bring them to the clinic.

9.1.4. Post-Treatment Follow-up for Participants who Withdraw from Randomized Treatment Early

Early withdrawal from randomized treatment will require the immediate collection of key data as soon as possible after stopping the study drug as well as an off-drug clinic visit approximately 30 days (+/- 12 days) after discontinuation. The Time and Events Schedule that follows the Synopsis describes the evaluation required. It is important to note that subjects who discontinue randomized treatment early will be required, wherever possible, to continue with scheduled visits. While the data collection required for participants who discontinue randomized treatment early will be somewhat modified, comprehensive follow-up, as described in the Time and Events Schedule will be essential for every randomized subject.

For subjects who prematurely discontinue study drug, sites will be required to make a final contact (eg, schedule the last follow-up visit) or vital status check as soon as possible after announcement of GTED.

9.1.5. Post-Treatment Follow-up for Participants that Complete Randomized Treatment as Initially Scheduled

Subjects who complete double-blind study drug through the time of notification of the projected GTED will have a final on-treatment visit as soon as possible followed by a 30-day off-drug visit to occur no later than the GTED. At this visit, a blood specimen for laboratory measurement will be collected as well as assessments of any serious adverse event, CV event, or adverse events of interest.

9.1.6. Post-Randomization Follow-up for Participants Unable to Attend Scheduled Visits

Subjects who are no longer able to continue to attend clinic visits for scheduled follow-up must have an alternate follow-up plan put in place. The options for this follow-up include:

- Less frequent clinic visits (eg, annual or to coincide with other care)
- Telephone, e-mail, letter, social media, fax, or other contact with the subject
- Telephone, e-mail, letter, social media, fax, or other contact with relatives of the subject
- Telephone, e-mail, letter, social media, fax, or other contact the subject's physicians (family or specialist)
- Review of any available medical records

These alternate follow-up methods should be planned to coincide with the visit times outlined in Time and Events schedule. Wherever possible follow-up should be made at least once each year and in very rare cases where this cannot be achieved arrangements must be made to follow-up with the participant at the scheduled completion of the study. Details regarding discussions via telephone, email, or other such contacts must be properly documented in source records, including responses by the subject.

If all means of follow-up fail, at a minimum, the site must attempt to collect vital status data, as noted in Section 10.5, Circumstances for Reduced Follow-up, by consulting family members, the

subject's physicians and medical records, or public records, including the use of locator agencies as permitted by local law.

In the rare instance that a site closes for operational, financial or other reasons and subjects are unable to be contacted regarding site closure, data from that site will be transferred to another site for a check of public records and/or vital status (at a minimum).

9.2. Reporting/Adjudication of MACE and Other Events for Adjudication

Investigators will be counseled to report any event that they assess as potentially being a MACE (CV death, nonfatal MI, nonfatal stroke). In addition, all deaths (to determine cause of death) will be submitted for adjudication.

Investigators must provide a specific package of information to be submitted for adjudication evaluation that will be provided in a procedural manual. An independent Endpoint Adjudication Committee will assess these events according to the committee's charter. The Endpoint Adjudication Committee will classify the events while blinded to treatment assignment.

Note that events assessed by the investigator as nonfatal MI or nonfatal stroke (ie, nonfatal MACE) are not immediately subject to expedited serious adverse experiences reporting requirements (refer to Section 12, Adverse Event Reporting). If the event is adjudicated by the Endpoint Adjudication Committee as not meeting the nonfatal MACE definition, then the event will then be subject to expedited serious adverse experiences reporting requirements, (with reporting timelines starting at the time of notification of this by the Endpoint Adjudication Committee).

9.3. Study Management: Committees

9.3.1. Academic Research Organization

An Academic Research Organization (ARO) will provide scientific and academic oversight of the study. The ARO will also have a role in site management and monitoring for a portion of the sites.

9.3.2. Steering Committee

The Steering Committee responsible for monitoring the CANVAS study will also be responsible for monitoring the current study, CANVAS-R. This Steering Committee, made up of external scientific experts, will provide scientific advice regarding the study design, conduct, and data collection. The Steering Committee is responsible for providing input on study design, academic leadership to study sites, reviewing study progress, and reviewing study results before publication. Details of the composition, roles, and responsibilities of the Steering Committee are documented in its charter.

9.3.3. Medical Safety Review Committee

An MSRC will be established to ensure that the safety of subjects participating in the study is not compromised. The MSRC will include, but will not be limited to, at least one medical expert and at least one statistician. The MSRC will include members from the sponsor organization and may

also involve ARO representatives. The MSRC will monitor the progress of the study by reviewing blinded data on a regular basis and will refer safety concerns to the IDMC.

Details of the composition, roles, and responsibilities will be documented in its charter.

9.3.4. Independent Data Monitoring Committee

The IDMC responsible for monitoring the CANVAS study to periodically review accumulating unblinded safety information during the study will also be responsible for monitoring the current study, CANVAS-R. Details of the composition, roles, and responsibilities are documented in its charter.

The IDMC will have responsibility for review of serious adverse events, events resulting in study drug discontinuation, CV events, and adverse events of interest for this study as well as across the broader canagliflozin clinical trials program.

9.3.5. Endpoint Adjudication Committee

The independent Endpoint Adjudication Committee (EAC) responsible for adjudicating CV events in the CANVAS study will also be responsible for adjudicating CV events in the current study, CANVAS-R. The EAC is composed of external specialists, blinded to treatment assignment. The operations, processes, and endpoint definitions to be employed by the committee are defined in its charter.

9.4. Safety Evaluations

Safety and tolerability will be evaluated on the basis of the overall incidence of serious adverse events, adverse events that lead to study drug discontinuation, adverse events of interest, the incidence of MACE events (overall and within the first 30 days of study drug treatment), vital signs (pulse, blood pressure), and body weight. Adverse events that do not meet the definitions above will not be collected.

The safety data from this study will be combined with the data from the other large-scale study of the effects of canagliflozin compared to placebo (CANVAS) in a pre-specified meta-analysis of cardiovascular safety outcomes to meet regulatory requirements set at the time marketing authorization for canagliflozin was granted. The CV meta-analysis will be described in a separate document with a specific statistical analysis plan.

Serious Adverse Events and Adverse Events Leading to Discontinuation

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally-acceptable representative) for the duration of the study, beginning from when informed consent is provided. Information about all adverse events (serious or not) should be recorded in source documents (eg, progress notes) according to good clinical practice, and retained at the investigative sites. Only serious adverse events, nonserious adverse events that result in study drug discontinuation, and adverse events of interest will be recorded on eCRFs.

For purposes of reporting serious adverse events for this study, nonfatal MI and nonfatal stroke events (ie, nonfatal MACE) will not immediately be subject to expedited serious adverse event

reporting requirements. Refer to Section 12, Adverse Event Reporting, for details regarding the handling of MACE.

Collection of Additional Information for Adverse Events of Interest

Adverse events of interest include: all malignancies, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (eg, angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, and pregnancy. Information on these events will be recorded on a supplemental eCRF for any event that is serious or that leads to study drug discontinuation. The only exceptions are for malignancies, photosensitivity reactions, fractures, venous thromboembolic events for which information on non-serious adverse events will also be recorded on the supplemental CRF pages (in addition to the information collected on serious AEs and AEs leading to study drug discontinuation).

Investigators will be asked to provide additional information so as to support more detailed analyses. Investigators may also be asked to provide additional information on other adverse events, based upon review by the MSRC or the IDMC (refer to Sections 9.3.3, Medical Safety Review Committee, and Section 9.3.4, Independent Data Monitoring Committee).

Follow-Up Collection of Safety Information

Any clinically significant abnormalities persisting at the time treatment is discontinued (either prematurely or at completion of the study) will be followed by the investigator until resolution or until a clinically stable outcome is reached, or until further follow-up is no longer considered by the investigator to provide clinically meaningful information. (see Sections 9.1.4, 9.1.5, and 12.2.2 for additional details regarding follow-up).

Clinical Safety Laboratory Tests

Subjects will be monitored with safety laboratory measurements as described in Attachment 1.

The investigator must review the laboratory reports, document this review, and record any serious adverse changes occurring during the study in the adverse event section of the eCRF.

Vital Signs (pulse, blood pressure)

Vital signs will consist of pulse and blood pressure measurements and will be obtained after the subject has been in the sitting position for 5 minutes and before blood sample collection for laboratory tests. Pulse rate will be measured once at each clinic visit. Blood pressure will be assessed manually with a mercury sphygmomanometer, or an automated blood pressure monitor; if neither of these is available, a high-quality aneroid sphygmomanometer will be acceptable. Calibration of the blood pressure measuring device is not required for this trial, but if the institution has a calibration policy, compliance with this policy is expected. Three consecutive blood pressure readings will be taken and recorded, at intervals of at least 1 minute apart, as specified in the Time and Events Schedule; the average of the 3 readings will be recorded in the eCRFs.

For each subject, a consistent arm should be used for blood pressure measurements across the course of the study. If possible, if blood pressure is measured manually, it should be measured by the same individual, using the same equipment, at each clinic visit to reduce variability.

Body Weight

Body weight will be measured using a consistent scale at each visit. Scale calibration is not required for this trial, but if the institution has a scale calibration policy, compliance with this policy is expected. As far as possible, subjects should be weighed at approximately the same time of day on the same scale, wearing underwear and a gown and without shoes (note: if disrobing for weighing is logistically impossible, the subject should be dressed as lightly as possible, with consistency from visit to visit); subjects will be asked to urinate before being weighed.

Urine Pregnancy Testing

Urine pregnancy testing will be performed on all women unless they are surgically sterile or unless there is a documented history of their postmenopausal status. A urine pregnancy test will be performed at the baseline visit unless a serum pregnancy test is preferred at the discretion of the investigator or if required by local regulations (if a serum pregnancy test is required, it will be performed at the screening visit). Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the study (refer to Section 12.2.3, Pregnancy, for instructions in cases of a positive pregnancy test).

9.5. Measures of Efficacy/Efficacy Endpoints

The categorical efficacy endpoint of the proportion of subjects with progression of albuminuria (defined as ≥1 step increase in category of albuminuria [ie, none to micro- or macro, or micro- to macroalbuminuria]) will be assessed from urine collections according to the categorizations defined in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Guideline #1 (KDOQI 2007). The definition of microalbuminuria is urinary albumin/creatinine ratio of 30 to 300 mg/g and the definition of macroalbuminuria is urinary albumin/creatinine ratio greater than 300 mg/g.

On designated visits, subjects will bring to the clinic duplicate first morning void urine specimens (collection of the first urine void after the individual awakes from sleep), one from the morning of the visit, and one from the morning of the day prior to the visit. If the urinary albumin/creatinine result reflects progression or regression of albuminuria from the baseline (eg, progression from normoalbuminuria to microalbuminuria or macroalbuminuria accompanied by a urinary ACR value increase of ≥30% from baseline; or regression from macroalbuminuria to microalbuminuria or normoalbuminuria accompanied by a urinary ACR value decrease of ≥30% from baseline), the subject will be contacted to bring 2 additional consecutive-morning first morning void urine specimens to the clinic approximately 1 to 2 months later (or sooner under unusual circumstances, eg, subject is discontinuing study drug). If the subject is unable to return the specimens in person, the site may engage a courier service to deliver the specimen to the site. If the subject does not provide the morning void collections on the day of the visit, the

subject may bring a first morning void specimen to the investigational site during the subsequent week. For subjects working a night shift, or who otherwise have atypical sleep patterns, the collection should be made at the end of the subject's usual sleep period. Collection containers and directions will be provided to subjects at prior visits. The site staff should call subjects a few days prior to visits to remind them to make the consecutive urine collections and bring them to the clinic.

10. SUBJECT COMPLETION, PREMATURE DISCONTINUATION OF TREATMENT, LOSS TO FOLLOW-UP AND WITHDRAWAL OF CONSENT

10.1. Subject Completion

A subject will be considered as having completed the study, regardless of whether the subject is on or off study drug, if the subject is followed until a time point between the notification of the GTED and the GTED (eg, subjects who complete the treatment need to have a final posttreatment follow-up visit; subjects who withdraw early from the treatment need to have a final contact after the notification of the GTED), or at the time of death for subjects who die prior to the GTED. The occurrence of a nonfatal MI, nonfatal stroke or any other safety of efficacy outcome does not comprise study completion and is not a criterion for withdrawal from the study or study drug.

10.2. Premature Discontinuation of Study Medication

A subject will discontinue study medication for any of the following reasons:

- The investigator believes that for safety or tolerability reasons it is essential for the subject to stop treatment
- The investigator formally unblinds the subject's treatment allocation
- The subject becomes pregnant (study therapy should be immediately discontinued based upon a positive urinary hCG, and permanently discontinued if confirmed by a serum β-hCG test)
- The subject's eGFR is <15 mL/min/1.73m^2 (as reported by the central laboratory).

  Note: the central laboratory will alert the investigator for eGFR falls to <15 mL/min/1.73m^2. A repeat determination should be performed within 2 weeks, and study treatment discontinued if the repeat eGFR is <15 mL/min/1.73m^2 (unless a reversible cause is identified [eg, short-term illness or transient volume depletion] in which case an additional repeat determination can be performed after resolution of the short-term illness).
- Subject requires dialysis or renal transplantation
- Subject requires disallowed therapy (refer to Section 8, Prestudy and Concomitant Therapy)

Premature discontinuation of study treatment does not comprise study completion and is not a criterion for withdrawal from the study. All subjects who prematurely discontinue study treatment should continue study follow-up, although the nature of follow-up may be modified (see Section 9.1.4 and the Time and Events Schedule). Treatment should be recommenced wherever possible and routinely considered at every visit following discontinuation.

Subjects who decide to withdraw from double-blind study drug must be interviewed by the investigator so as to determine if a specific reason for withdrawal can be identified. Withdrawing subjects should be explicitly asked about the contribution of possible adverse events to their decision to withdraw consent, and any adverse event information elicited should be documented. If the subject elects to withdraw due to an adverse event, the event should be recorded as the reason for withdrawal, even if the investigator's assessment is that the adverse event would not require study drug withdrawal. The reason for withdrawal is to be documented in the eCRF and in the source documentation. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

10.3. Reinstitution of Treatment for Subjects Who Have Prematurely Discontinued Double-Blind Study Drug to Active Status

Subjects for whom study drug is interrupted as a result of an adverse event, a life event (eg, temporary relocation to care for an ill family member), or other unforeseen circumstance should be encouraged to recommence study drug unless there is a clear contraindication at the discretion of the investigator, with concurrence from the sponsor's medical monitor.

Study drug interruptions, occurring for any reason and lasting 7 days or longer, will be documented on the eCRF.

10.4. Lost to Follow-up

If a subject is lost to follow-up, all possible efforts must be made by the study site personnel to contact the subject and to achieve as complete follow-up as possible until after the site notification of the GTED. The measures taken to achieve follow-up are discussed in Section 10.5, Circumstances for Reduced Follow-up, and must be documented. The informed consent form will stipulate that even if double-blind study drug is discontinued, he/she will agree to continue follow-up.

10.5. Circumstances for Reduced Follow-up

There may be circumstances in which a reduced follow-up schedule is required and the options for this are described in Section 9.1.6, Post-Randomization Follow-up for Participants Unable to Attend Scheduled Visits. If one of these regimens is not possible, it will be necessary for the site investigator to contact the Sponsor representative to indicate the reasons why no further follow-up is necessary. It is important to note that a subject declining further follow-up does not constitute withdrawal of consent and the alternate follow-up mechanisms that the participant agreed to when signing the consent form will still apply (eg, searches of databases, use of locator agencies at study completion) as permitted by local regulations.

In this regard, the subject will be asked as a condition of entry into the study to agree to grant permission for the investigator to consult family members, the subject's physicians and medical records, or public records, including the use of locator agencies as permitted by local law, to determine the subject's status with respect to the CV safety composite endpoint, in the event the subject is not reachable by conventional means (eg, office visit, telephone, e-mail, or certified mail). The subject is also to be advised that if the site of the study doctor closes, and the study

doctor cannot reach the subject to inform him/her, the contact information will be transferred to another site where a new study doctor will consult with family members, the subject's physicians and medical records, or public records, including the use of locator agencies as permitted by local law, to determine the subject's endpoint status.

10.6. Withdrawal of Consent

Withdrawal of consent should be a very unusual occurrence in a clinical trial. The investigator should make every effort to maintain a good relationship with subjects to avoid this occurrence. In many instances where withdrawal of consent could potentially be recorded, the subject could be expected to be followed-up through one of the alternative follow-up mechanisms discussed in Section 10.5, Circumstances for Reduced Follow-up.

Withdrawal of consent in this trial may only be logged in the eCRF after a discussion between the investigator and the appropriate sponsor representative.

For subjects truly requesting withdrawal of consent, it is recommended that the subject withdraw consent in writing; if the subject or the subject's representative refuses or is physically unavailable, the site should document and sign the reason for the subject's failure to withdraw consent in writing.

If a subject had previously withdrawn consent but decides to retract that withdrawal, the subject will be reconsented. The investigator will be responsible for making all required notifications to the IRB or Ethical Committee.

11. STATISTICAL METHODS

11.1. Analysis Sets

The modified intent-to-treat (mITT) analysis set includes all subjects who are randomly assigned to a treatment group, receive at least one dose of double-blind study. The assessment of the primary and secondary objectives will be based upon this analysis set.

Efficacy data will be analyzed according to the initial randomization assignment regardless of actual treatment received.

11.2. Sample Size Determination

Based on the interim data from the CANVAS study, where ACR was measured periodically at scheduled visits, it is projected that the annual progression rate for CANVAS-R study is approximately 7.4%. Assuming a 22% relative risk reduction for albuminuria progression, an annual progression rate in the placebo arm of 7.4%, an 18-month accrual period, a maximum treatment period of 36 months, and an annual discontinuation (from treatment) rate of 10%, it is estimated 693 progression events will be reported. With 5,700 subjects enrolled, the power to demonstrate the superiority of canagliflozin over placebo for albuminuria progression is 90.5%, with type I error rate of 0.05 (two-sided).

11.3. Efficacy Analyses

11.3.1. Primary Efficacy Analysis

In this study, duplicate urine specimens will be collected for all ACR measurements. At each visit, the geometric mean of the duplicate measurements will be computed and used for all subsequent analysis unless otherwise specified.

Subjects will be classified as having normoalbuminuria (urinary ACR of <3.5 mg/mmol [<30 mg/g]), microalbuminuria (ACR ≥3.5 mg/mmol [≥30 mg/g] and ≤35 mg/mmol [≤300mg/g]), or macroalbuminuria (ACR of >35 mg/mmol [>300 mg/g]).

The primary efficacy analysis seeks to demonstrate the superiority of canagliflozin in the reduction of albuminuria progression relative to placebo.

The time from first study drug administration to first visit date observing progression (ie, not using the visit date of the repeat sample collection) of albuminuria will be analyzed using a Cox proportional hazards regression model. The model will include treatment and baseline albuminuria status as covariates. The hazard ratio between canagliflozin and placebo will be provided, including its 95% confidence interval. The observation period for this time-to-event analysis will include all available measurements from first study drug administration to the visit date of the last on-treatment ACR was measured. Subjects with no progression will be censored at the visit date of the last on-treatment albuminuria measurement.

As a sensitivity analysis, the actual onset time of progression of albuminuria can be determined to lie within an interval from a sequence of examination times (ie, data are interval censored). As a supportive analysis, the accelerated failure time (AFT) model with log normal error structure will be implemented considering interval censoring. The dependent variable in AFT model is logarithm of time to progression of albuminuria. The model will include treatment group and baseline albuminuria status as covariates. We can use speed of progression to interpret AFT model. For any time (t), the probability of a subject on placebo progression-free beyond time t is the probability of a subject on canagliflozin progression-free beyond t/α, where α is the acceleration factor which can be estimated from the model. Additional sensitivity analyses will be specified in the study SAP.

The cumulative progression rate derived from Kaplan-Meier estimate will be displayed graphically to evaluate the timing of progression and the consistency of the treatment effect over time.

11.3.2. Secondary Efficacy Analyses

Regression of albuminuria will be analyzed in a similar fashion as the analysis for progression of albuminuria.

For change in eGFR from baseline to the off-treatment measurement (approximately 30 days after the last dose of double-blind study drug), an analysis of covariance (ANCOVA) model will

be used with treatment as a fixed effect and adjusting for the baseline eGFR value. The treatment difference in the least-squares means and their 2-sided 95% CI will be estimated.

Since the distribution of ACR value is highly skewed, log transformed ACR value for the last on-treatment visit will be modeled using ANCOVA. The model will include treatment group and logarithm of baseline ACR value as covariates. The percentage treatment difference can be calculated by anti-logarithm of the estimated coefficient for the treatment group minus 1.

11.3.3. Exploratory Efficacy Analyses

For on-treatment eGFR measurements, a linear mixed effects model will be fitted to eGFR as a dependent variable, including treatment, baseline eGFR value, time (as a continuous variable), and treatment time interaction as fixed effects and including subject effect as a random intercept and time as a random slope. The parameter of interest is the coefficient for treatment and time interaction term, which measures the slope difference between canagliflozin and placebo.

The effect of canagliflozin relative to placebo on changes in HbA_{1c} over time will evaluated using linear mixed effects model. The use of AHA therapy over time will also be summarized by treatment group.

11.3.4. Multiplicity Adjustment

A closed testing procedure will be implemented to control the overall type I error at 5% for primary and secondary endpoints. There are no interim analyses planned.

A more detailed description of the analyses for all outcomes (other than the CV meta-analysis) will be pre-specified in the Statistical Analysis Plan.

11.4. Safety Analyses

The safety analysis will be based on all randomized subjects who receive at least one dose of double-blind study medication (ie the same as the mITT analysis set). There will be no imputation for missing values for clinical laboratory test results and vital sign measurements.

The study objective regarding safety and tolerability will be assessed based upon a review of the incidence of overall and specific adverse events, discontinuations due to adverse events, laboratory results, and other safety and tolerability measurements.

Adverse Events

The original terms used in the eCRFs by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the treatment phase (ie, treatment-emergent adverse events) will be included in the analysis. For each adverse event, the percentage of subjects who experienced at least one occurrence of the given event will be summarized by treatment group. An adverse event will be considered to be a treatment-emergent event if it occurs within 30 days of the last date of blinded study medication. The percentage of subjects with specific treatment-emergent adverse events will be summarized by severity and relationship to study drug, as classified by the investigators, for each treatment group.

Further analyses, described in the SAP for this study, will be conducted on the prespecified adverse events for which additional information is collected from the investigators (refer to Section 9.4, Safety Evaluations).

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Normal reference ranges will be provided. Criteria for markedly abnormal laboratory values will be prespecified in the SAP. The percentage of subjects with markedly abnormal results will be summarized for each laboratory analyte. Descriptive statistics will be reported for each laboratory analyte at baseline and at each scheduled time point and for change from baseline.

Vital Signs, Weight

Descriptive statistics for pulse and sitting blood pressure (systolic and diastolic), weight values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures (SOPs) in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

All deaths and events that are assessed by the investigator as being one of the components of the CV safety composite endpoints (ie, CV deaths, nonfatal MI, nonfatal stroke) should be handled as follows:

Investigator Responsibilities:

All SAEs must be reported to the sponsor within 24 hours of knowledge of the event. This reporting timeline is also applicable to CV events. The investigator will record the event on the AE eCRF and will submit an SAE report to the Sponsor. For CV events, an adjudication package will also be submitted; details on assembly and submission of adjudication packages will be provided in an Adjudication Manual.

Sponsor Responsibilities:

Nonfatal MACE Events (ie, nonfatal stroke, nonfatal myocardial infarction):

- The sponsor will submit non-fatal MACE events for adjudication to the Endpoint Adjudication Committee.
- Nonfatal events that are adjudicated to be components of the primary endpoint will not be unblinded or reported to either Health Authorities (HAs) or investigators as safety reports. These events will be included in the final analysis which will be unblinded and submitted to HAs.

- Non-fatal events that are adjudicated NOT to be components of the primary endpoint, and are considered possibly, probably or definitely related by the investigator will be unblinded and subject to reporting requirements to both HAs and investigators. The reporting timeline starts when the Adjudication Committee notifies the sponsor of the decision.

Fatal Events:

- The sponsor will submit all deaths for adjudication to the Endpoint Adjudication Committee.
- Fatal events will be submitted to HAs but to protect the integrity of the trial, the event will not be unblinded prior to review of the death by the EAC. The US FDA has agreed to receive these fatal cases blinded. These will also be submitted blinded to other HAs worldwide, if allowed by local regulation (eg, where local regulations do not allow for submission of blinded safety reports, those regulations should be followed).
- Fatal events that are adjudicated to be a component of the primary endpoint (ie, CV death) will remain blinded and will not be reported to either HAs or investigators as safety reports. These events will be included in the final analysis which will be unblinded and submitted to HAs.
- Fatal events that are adjudicated NOT to be a component of the primary endpoint (ie, non-CV death) and considered possibly, probably or definitely related will be unblinded and subject to reporting requirements to both HAs and investigators. The reporting timeline starts when the Adjudication Committee notifies the sponsor of the adjudication decision.

For specific adverse events of interest, investigators will be asked to provide additional information so as to support more detailed analyses. Adverse events of interest include: all malignancies, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (eg, angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, and pregnancy. Information on these events will be recorded on a supplemental eCRF for any event that is serious or that leads to study drug discontinuation. The only exceptions are for malignancies, photosensitivity reactions, fractures, venous thromboembolic events for which information on non-serious adverse events will also be recorded on the supplemental CRF pages (in addition to the information collected on serious AEs and AEs leading to study drug discontinuation). Additional information and documentation will be requested from investigators to support a detailed assessment and all deaths. Investigators may also be asked to provide additional information on other adverse events, based upon review by the MSRC or the IDMC (refer to Sections 9.3.3, Medical Safety Review Committee, and 9.3.4, Independent Data Monitoring Committee). Refer to Section 3.2, Study Design Rationale, for review of rationale for collection of additional information on these selected adverse events.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonization [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the informed consent form (refer to Section 12.2.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

See above for handling of components of the composite CV endpoint other than CV deaths.

A serious adverse event as defined by ICH is any untoward medical occurrence that at any dose meets any of the following conditions:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An unlisted adverse event is one for which the nature or severity of which is not consistent with the applicable product reference safety information. For an investigational product, the

expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Not related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

Mild: Awareness of symptoms that are easily tolerated causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the intensity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Procedures

12.2.1. All Adverse Events

For this study, all serious adverse events, nonserious adverse events that result in study drug discontinuation and other selected adverse events as specified later in this section are to be reported from the time a signed and dated informed consent form is obtained until completion of the study (including subjects who withdraw prematurely). For specific adverse events of interest, a supplemental eCRF page will be used to collect additional information. Adverse events of interest include: all malignancies, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (eg, angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, and pregnancy. Information on these events will be recorded on the supplemental eCRF for any event that is serious or that leads to study drug discontinuation. The only exceptions are for malignancies, photosensitivity reactions, fractures, venous thromboembolic events for which information on non-serious adverse events will also be recorded on the supplemental CRF pages (in addition to the information collected on serious AEs and AEs leading to study drug discontinuation). All deaths will also be recorded.

Data will be collected in source documents and on the eCRF for these adverse events.

Serious adverse events, including those spontaneously reported to the investigator must be reported using a Serious Adverse Event Form, which must be completed and signed by a member of the investigational staff, and transmitted to the sponsor within 24 hours. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Adverse events, regardless of severity or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator all serious adverse events that are unlisted (unexpected) and associated with the use of the drug, according to standard operating procedures and the requirements outlined in this protocol. These events will be reported blinded to the investigator when and where possible. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

Subjects (or their designees, if appropriate) will be provided with a "study card" indicating the name of the investigational study drug, the study number, the investigator's name, a 24-hour emergency contact number, and, if applicable, excluded concomitant medications.

12.2.2. Serious Adverse Events

All serious adverse events occurring during clinical studies must be reported to the appropriate sponsor contact person by investigational staff within 24 hours of their knowledge of the event.

Nonfatal MI and nonfatal stroke events will be reported on the AE eCRF pages; the entry must be completed within 24 hours of the investigator staff's knowledge of the event. Events that are adjudicated as not meeting with charter-specified event definitions by the Endpoint Adjudication Committee will be subject to standard reporting requirements, but the reporting time limit will start when the sponsor learns that the event is not a CV safety event as per the Endpoint Adjudication Committee.

All serious adverse events that have not resolved by the end of the study, or that have not resolved after a reasonable time following the discontinuation of study drug, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The cause of death of a subject in a clinical study, whether or not the event is expected or associated with the investigational agent, is considered a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical study must be reported as a serious adverse event, except hospitalizations for the following:

- Social reasons in absence of an adverse event
- Surgery or procedure planned before entry into the study or a procedure to treat or explore a non-worsened pre-existing condition (eg, elective knee replacement, routine coronary angiogram without intervention, elective bariatric surgery); the non-worsening of the pre-existing condition must be documented in the source documents and the eCRF.

12.2.3. Pregnancy

All initial reports of pregnancy must be reported to the sponsor by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes are considered serious adverse events and must be reported using

the Serious Adverse Event Form. Any subject who becomes pregnant during the study must immediately discontinue further study treatment. If a subject's partner becomes pregnant any time between the start of study drug and 30 days after the last dose, the subject must inform the investigator as soon as possible.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.3. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability of a product, including its labeling or package integrity. PQCs may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the investigational staff as soon as possible after being made aware of the event.

If the defect is combined with a serious adverse event, the investigational staff must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.2.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

Canagliflozin will be supplied for this study as over encapsulated 100- or 300-mg tablets in a gray-colored, hard, gelatin capsule. The over encapsulated tablet will be backfilled with microcrystalline cellulose to prevent the tablet from rattling in the capsule shell.

Matching placebo capsules will consist of microcrystalline cellulose within a gray-colored, hard, gelatin capsule.

14.2. Packaging

The study drug will be packaged as individual bottles. The study drug will be packaged according to good manufacturing practices and local regulations. The study supplies will be packaged according to the randomization code and each unit will be labeled with a medication ID number.

All study drug will be dispensed in child-resistant packaging.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

All study drug must be stored at controlled temperatures ranging from 15°C to 30°C (59°F to 86°F) and kept out of reach of children.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject, must be documented on the drug accountability form. Subjects, or their legally-acceptable representative where applicable, must be instructed to return all original containers, whether empty or containing study drug. Study drug returned by study subjects will be stored and disposed of according to the sponsor's instructions. Site staff must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label and will be stored in a limited access area or in a locked cabinet under appropriate environmental conditions. Unused study drug and partially used study drug returned by the subject (if applicable), must be available for verification by the sponsor's or sponsor-delegated site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or partially used study drug returned for destruction, will be documented on the Drug Return Form. When the site is an authorized destruction unit and study drug supplies are destroyed on site, this must also be documented on the Drug Return Form.

Study drug should be dispensed under the supervision of the investigator, a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Recruitment and retention tools
- IWRS manual and worksheets
- eCRF completion guidelines
- Study binder with all other necessary documentation (eg, protocol, IB, clinical trial agreement)
- Manual of instructions regarding CV events, documentation required, and adjudication-related procedures
- Home blood glucose monitoring system, glucose strips, lancets, and calibration solution (optional by country/region)
- Materials to promote healthy dietary and exercise habits
- Laboratory operations manual, requisition forms, sampling supplies, and equipment, if necessary
- Computer, if the study site is assessed to require a laptop computer to enter eCRF data for the study

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

This study is being conducted under U.S. FDA IND regulations as part of a post-approval commitment. The protocol was submitted to and reviewed by the FDA prior to implementation.

The primary ethical concern of this study is that, though the safety profile of canagliflozin has been demonstrated in a clinical program involving more than 10,000 subjects, long-term safety data under conditions of extensive market use have not yet been established. Thus, subjects may be placing themselves at an increased risk of unexpected adverse events by participating in this study, and that subjects with T2DM who have not achieved optimal glycemic control at study entry could fail to achieve optimal glycemic control for a prolonged period. The investigator is asked to appropriately manage glycemic control and CV risk according to standard guidelines across the study. The potential risks in the present study include exposure to study drug, with the potential for side effects (Section 1.1.2, “Safety”) and the inherent risks associated with venipuncture and multiple blood sample collections. The study has been designed to mitigate these inherent risk factors. As per Section 9.3.4, an IDMC is commissioned for this study to review unblinded safety information on a periodic basis during the study.

Based on data from clinical studies with canagliflozin and the theoretical possibilities associated with SGLT2 and intestinal SGLT1 inhibition, potential human adverse effects may occur (Section 1.1.2, “Safety”). The following adverse of interest have been identified for follow-up in post-marketing studies by the US FDA: all malignancies, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (eg, angioedema,

anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, and pregnancy. Information on these events will be recorded on a supplemental eCRF for any event that is serious or that leads to study drug discontinuation. The only exceptions are for malignancies, photosensitivity reactions, fractures, venous thromboembolic events for which information on non-serious adverse events will also be recorded on the supplemental CRF pages (in addition to the information collected on serious AEs and AEs leading to study drug discontinuation). These events will be recorded and analyzed in this study, as will all serious adverse events, adverse events that result in study drug discontinuation, all deaths, nonfatal MI and nonfatal stroke.

Clinical and laboratory evaluations will be performed throughout the study (according to the Time and Events Schedule that follows the Synopsis) to monitor the safety of subjects. HbA_{1c} will be measured approximately every 6 months.

Subjects will be followed after prematurely discontinuing study drug until scheduled study completion in line with the Time and Event Schedule to obtain comprehensive information about their health and well-being. The investigator will be provided with detailed information about the study to ensure that the study research staff is fully informed. Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

Subjects will sign an informed consent form before any study-related procedure is performed.

The maximum blood volume that would be collected if a subject were to continue in the study for about 3.5 years would be approximately 300 mL. The maximum amount that would be collected at a single visit would be approximately 30 mL. These volumes are considered to be well within the normal range for this subject population over this time frame according to blood donation standards (American Red Cross).

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of

study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board (IEC/IRB)

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents:

- Final protocol and, if applicable, amendments
- Sponsor-approved informed consent form (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any), the informed consent form, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments
- Revision(s) to informed consent form and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's Brochure amendments or new edition(s)
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted, and associated with the investigational drug

- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Annual Safety Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or trial conduct), the amendment and applicable informed consent form revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this clinical study. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data or trial conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the sponsor and by the reviewing IEC/IRB. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the investigational staff must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor staff without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the informed consent form the subject is authorizing such access, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, or to obtain information about his or her survival status.

The subject will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's personally dated signature. After having obtained the consent, a copy of the informed consent form must be given to the subject.

If the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the informed consent form after the oral consent of the subject is obtained.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational study drug(s) used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator to allow direct access to his or her original medical records for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

16.2.5. Country Selection

Unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations, this study will only be conducted in those countries where the intent is to help ensure access to the developed product.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be

promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor or its designee. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (refer to Contact Information pages provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the investigational site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed written IEC/IRB approval of the protocol, amendments, informed consent form, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee.
- Name and address of the IEC/IRB including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the investigational staff is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement

- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all clinical sub-investigators
- Documentation of sub-investigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by initials and assigned number only.

The investigator must also complete a subject-screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: subject identification, eligibility, and study identification; study discussion and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events; and follow-up of adverse events; concomitant medications of interest; drug receipt/dispensing/return records; study drug administration information; and date of study completion, and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

It is recommended that the author of an entry in the source documents be identifiable.

At a minimum, the type and level of detail of source data available for a study subject should be consistent with that commonly recorded at the site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study personnel from the source documents onto an eCRF, and transmitted in a secure manner to

the sponsor within 3 working days of the subject's visit or in the time frame specified in the clinical trial agreement. The electronic file will be considered to be the eCRF. Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subjects' source documentation. All data relating to the study must be recorded in eCRFs prepared by the sponsor. Data must be entered into eCRFs in English. Designated site personnel must complete eCRFs as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or an authorized member of the investigational staff must adjust the eCRF (if applicable) and complete the query. A query is generally to be answered within 5 days of generation of the query or in the time frame specified in the clinical trial agreement.

If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- Site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool)
- Site manager (SM) can generate a query (field data correction form [DCF]) for resolution by the investigational staff
- Clinical data manager (CDM) can generate a query for resolution by the investigational staff

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits by the sponsor, and transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, preparation, and shipment of blood, plasma, and urine samples.

Guidelines for eCRF completion will be provided and reviewed with study personnel before the start of the study.

The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the clinical study database they will be verified for accuracy.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s).

The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator must permit access to such reports.

17.8. Monitoring

The sponsor and ARO designated by the sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study center visit log that will be kept at the site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and investigational staff and are accessible for verification by the sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents will be discussed with the investigational staff. The sponsor expects that, during monitoring visits, the relevant investigational staff will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed with the last visit/contact of the last subject participating in the study. The final data from the investigational site will be sent to the sponsor (or designee) after completion of the final subject visit/contact at that site, 3 days after the subject's

visit/contact (query generation and resolution excluded), or in the time frame specified in the clinical trial agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the investigational site or terminate the study at any time for any reason at the sole discretion of the sponsor. Investigational sites will be closed upon study completion. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigational site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further drug development.

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the eCRFs. Subject privacy must, however, be respected. The investigator and staff are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding canagliflozin or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the clinical study will be used by the sponsor in connection with the continued development of canagliflozin, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain eCRF data from all investigational sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of pharmacogenomic analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of pharmacogenomic results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

The sponsor shall have the right to publish such data and information without approval from the investigator. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, results may need to be published in a given sequence (eg, substudies) should not generally be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not publishing data derived from the individual site until the combined results from the completed study have been published in full, within 12 months after conclusion, abandonment, or termination of the study at all sites, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

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Attachment 1: Clinical Laboratory Tests

Blood samples for serum chemistry and hematology, and a random urine sample for urinalysis will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF and take appropriate action (eg, repeating abnormal laboratory result or further evaluation as considered clinically appropriate). The following tests will be performed by the central laboratory.

- Hematology Panel

  -hemoglobin
  -hematocrit
  -red blood cell (RBC) count
  -white blood cell (WBC) count with differential
  -platelet count

- Serum Chemistry Panel

  -sodium
  -potassium
  -chloride
  -bicarbonate
  -blood urea nitrogen (BUN)
  -creatinine
  -aspartate aminotransferase (AST)
  -alanine aminotransferase (ALT)
  -gamma-glutamyltransferase (GGT)
  -total bilirubin
  -alkaline phosphatase
  -creatine phosphokinase (CPK)
  -lactic acid dehydrogenase (LDH)
  -uric acid
  -calcium
  -phosphate
  -albumin
  -total protein
  -magnesium

- Fasting serum lipid profile (triglycerides, LDL-C, HDL-C, total cholesterol).
- HbA_{1c}

Central laboratory will report the estimated glomerular filtration rate (eGFR) according to the Modification of Diet in Renal Disease Study (MDRD) equation (Levey 2006) at study visits when serum creatinine is measured. The 4-variable MDRD eGFR includes serum creatinine, age, race, and sex according to the equation below:

For creatinine in mg/dL:

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203}$$

$$\times (0.742 \text{ if female}) \times (1.21 \text{ if black})$$

For creatinine in µmol/L:

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{serum creatinine} \times 0.0113)^{-1.154} \times (\text{age})^{-0.203}$$

$$\times (0.742 \text{ if female}) \times (1.21 \text{ if black})$$

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Mehul Desai, MD

Institution: [redacted] & Development

Signature: [redacted] Date: 26 September 2013

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

LAST PAGE

Janssen Research & Development, LLC*

Clinical Protocol

A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects With Type 2 Diabetes Mellitus

The "CANVAS-R" Trial
(CANagliflozin cardioVascular Assessment Study-Renal)

Protocol 28431754DIA4003; Phase 4**
AMENDMENT INT-5

JNJ-28431754 (canagliflozin)

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

**This is a Phase 4 postmarketing study required by the US Food & Drug Administration but may be considered a Phase 3 study in some countries in which canagliflozin has not been approved.

Status:	Approved
Date:	1 September 2016
Prepared by:	Janssen Research & Development, LLC
EDMS No & Version:	EDMS-ERI-65832346, 8.0
EudraCT No.:	2013-003050-25

GCP Compliance: This study will be conducted in compliance with this protocol, Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	27 September 2013
INT-1	16 October 2013
INT-2	20 December 2013
INT-3	17 September 2015
INT-4	05May 2016
INT-5	01 September 2016

Amendments are listed beginning with the most recent amendment.

Amendment INT-5 (01 September 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The primary reason to amend the study protocol is to add secondary cardiovascular objectives and exploratory renal objectives.

Applicable Section(s)	Description of Change(s)
Rationale: Added secondary cardiovascular objectives to assess cardioprotective effects of canagliflozin and added exploratory renal objectives.	
Synopsis Section 2. Objectives and Hypotheses, Section 11.3.2. Secondary Efficacy Analyses Section 11.3.3. Exploratory Efficacy Analyses Section 11.3.4. Multiplicity Adjustment Section 11.4. Safety Analyses	Added secondary cardiovascular objectives of the composite endpoint of cardiovascular death or hospitalization for heart failure, and cardiovascular death. Added exploratory renal composite endpoints. Under 'Multiplicity Adjustment', removed statements about CV meta-analysis being pre-specified in the SAP for this study, and that the CV meta-analysis SAP will be pre-specified in a separate document, since these statements are not necessary and unrelated to the multiplicity adjustment.
Rationale: Added checkmark for foot care guidance that was erroneously omitted.	
Time and Events Schedule; footnote "n"	Added checkmark for foot care discussion/assessment and provision of foot care guidance during phone/email contact midway between 26-week visits until last on-treatment visit.
Rationale: Added rationale for expanded secondary CV objectives.	
Section 1.2: Overall rationale and goals for the study	Added rationale for expanded CV secondary objectives and exploratory renal objectives, including a brief summary of EMPA-REG OUTCOME data with empagliflozin.

Amendment INT-4 (05 May 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The primary reason to amend the study protocol is to include new safety information and guidance regarding subject management surrounding the event of lower extremity amputations.

Applicable Section(s)	Description of Change(s)
Rationale: Include guidance regarding subject management surrounding the event of lower extremity amputations.	
Time and Events Schedule footnote "f"; footnote "n" Section 12.2.1. All Adverse Events	Added foot examination to be consistent with standard diabetes treatment guidelines. Added guidance regarding foot care and reducing risk of amputation.
Rationale: To address a request from a Health Authority	
Time and Events Schedule (posttreatment)	Added collection of AHAs after study drug discontinuation
Rationale: To address a request from a Health Authority.	
Section 9.4. Safety Evaluations	Events with characteristics of DKA will be adjudicated by an ad hoc adjudication committee, to verify whether or not the event meets a specified definition of DKA.
Rationale: Include new safety information and guidance regarding subject management surrounding the event of lower extremity amputations.	
Section 1.1.2. Clinical Studies; Section 6.1. Study Drug;	Added amputation data from IDMC. Added statement that study drug should be interrupted for subjects who develop conditions that are associated with or leading to amputation.
Time and Events Schedule footnote "l" Section 3.1. Study Design; Section 9.4. Safety Evaluations Section 12. Adverse Event Reporting Section 12.2.1. All Adverse Events Section 16.1. Study-Specific Design Considerations	An additional AE of special interest was added, "amputations".
Rationale: Minor errors were noted.	
Throughout the protocol.	Minor grammatical, formatting, or spelling changes were made.

Amendment INT-3 (17 September 2015)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: In response to Agence Nationale de Securite de Medicament et des Produits de Sante (ANSM)- France IB addendum 2 - Canagliflozin - where a request to amend the study protocol to include diabetic ketoacidosis (DKA) safety information and handling of subjects surrounding this event.

Applicable Section(s)	Description of Change(s)
Rationale: To provide clarification of the urinary albumin/creatinine ratio (ACR) analysis and expand analysis scope for ACR to cover all the post-baseline data.	
Synopsis: Efficacy Outcome/Evaluation Criteria Primary Outcomes Secondary Outcomes Primary Efficacy Analysis Secondary Efficacy Analyses Section 2.1 Secondary Objectives Section 11.3.2 Efficacy Analysis	Additional wording and more detailed descriptions added
Rationale: To expand analysis scope for post-treatment eGFR to cover all the post-treatment data	
Synopsis: Secondary Objective Secondary Outcomes Secondary Efficacy Analyses Section 2.1 Secondary Objectives Section 11.3.2 Efficacy Analysis	Additional wording and more detailed descriptions added
Rationale: To remove a previously introduced error in the footnotes	
Time & Events Schedule Footnote "k"	Footnote was removed from the double-blind treatment period.
Rationale:. Balanitis was added as an AE of interest and DKA as an AE of special interest to obtain and collect safety information surrounding these events.	
Time & Events Schedule Footnote "l"; Section 3.1 Study Design; Section 9.4 Safety Evaluations; Section 12 Adverse Event Reporting; Section 12.2.1 All Adverse Events; Section 16.1 Study-Specific Design Considerations	An AE of interest "male genital infections (balanitis, phimosis, events leading to circumcision)"and AE of special interest "Diabetic ketoacidosis has been designated an adverse event of special interest and therefore adverse events related to diabetic ketoacidosis, ketoacidosis, metabolic acidosis or acidosis need to be reported to Janssen within 24 hours of becoming aware of the event, which is the same timeframe for reporting of serious adverse events. These adverse events must be reported using a supplemental DKA Reporting form, to complement standard information collected on the eCRF AE/SAE page" were added; the statement "If adverse events of interest are identified in the future, guidance concerning the reporting of those events may be provided to investigators via appropriately-documented study communications." was added.
Rationale: To provide the most up to date data results of safety findings.	
Section 1.1.2. Clinical Studies	Additional paragraph added stating additional AE results as of 11, May 2015.

Applicable Section(s)	Description of Change(s)
Rationale: To provide clarification on study drug interruption	
Section 6.1 Study Drugs	Additional wording added to last paragraph to clarify study drug interruption requirements.
Rationale: To include an experience of a serious confirmed adverse event of diabetic DKA to the list of reasons for premature discontinuation of study drug.	
Section 10.2 Premature Discontinuation of Study Medication	The sentence "The subject experiences a serious adverse event of biochemically-confirmed (eg, pH, serum ketones, anion gap) DKA" was added.
Rationale: To preserve the original randomization, the analysis set for primary analysis of all efficacy endpoints is intent-to-treat (ITT) and secondary is modified intent-to-treat (mITT/On-treatment) if applicable.	
Synopsis: Analysis Set Section 11.1 Analysis Set	ITT set is added and analysis sets for primary and secondary efficacy analysis are clarified.
Rationale: To provide guidance on the monitoring and management of DKA.	
Section 12.2.1 All Adverse Events	A paragraph was added: "Study research staff should make study subjects aware of potential signs and symptoms of diabetic ketoacidosis such as difficulty breathing, nausea, vomiting, abdominal pain, feeling confused, fruity-smelling breath, and unusual fatigue or sleepiness. Study subjects should be instructed to contact the site if they experience such symptoms. If the investigator suspects these symptoms may be related to diabetic ketoacidosis (even if the subject's blood glucose levels are less than 250 mg/dL [13.9 mmol/L]), testing for urine or blood ketones should be considered."
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical or formatting changes were made.

Amendment INT-2 (20 December 2013)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: The overall reason for the amendment is to add a baseline (Day 1) urinalysis measurement to provide baseline health status information and safety data.

Applicable Section(s)	Description of Change(s)
Rationale: A baseline (Day 1) urinalysis measurement was added to provide baseline health status information and safety data.	
Time & Events Schedule	A spot urine collection at the clinic was added at Day 1. (Footnote "g" was also modified to add this procedure.)
Rationale: An inconsistency between a footnote and the text was noted.	
Time & Events Schedule footnote "h"	The timeframe to return a first morning void specimen to the site (if not provided on the day of the visit) was corrected to 7 days (previously 30 days).

Applicable Section(s)	Description of Change(s)
Rationale: A baseline (Day 1) urinalysis measurement was added to provide baseline health status information and safety data.	
Rationale: New canagliflozin protocols have added additional bone mineral density data.	
Section 1.1.2. Clinical Studies	Further clarification of the bone mineral density data in the 28431754DIA3010 study at Week 104 was made to ensure consistency in the description with other canagliflozin protocols.
Rationale: An update to Attachment 1 was needed to align with updates in the Time & Events schedule for urinalysis.	
Attachment 1: Clinical Laboratory Tests	Baseline (Day 1) urinalysis was added.

Amendment INT-1 (16 October 2013)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: The overall reason for the amendment is to ensure consistency with the standard protocol template text in the sections listed below.

Applicable Section(s)	Description of Change(s)
Section 12.2.3, Pregnancy	Was removed: *"If a subject's partner becomes pregnant any time between the start of study drug and 30 days after the last dose, the subject must inform the investigator as soon as possible."*
Section 14.5, Drug Accountability	*'Study drug returned…"* was replaced with *"All study drug…"* Was added: *"Returned study drug must not be dispensed again, even to the same subject."*
Section 16.2.2, Independent Ethics Committee or Institutional Review Board (IEC/IRB)	Was added throughout the section: *"…excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct…"*
Section 17.3, Subject Identification, Enrollment, and Screening Logs	"*…by initials and assigned number only…"* was replaced with *"…by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used."*
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical or formatting changes were made.

SYNOPSIS

A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects With Type 2 Diabetes Mellitus ("CANVAS-R")

EUDRACT number: 2013-003050-25

PREAMBLE

Canagliflozin (JNJ-28431754) is an inhibitor of the sodium-glucose co-transporter 2 (SGLT2) that has been developed as an oral antihyperglycemic agent (AHA) for the treatment of patients with type 2 diabetes mellitus (T2DM).

In March 2013, canagliflozin was approved for marketing by the United States (US) Food and Drug Administration (FDA). An ongoing clinical program designed to continue research on the effects of the agent on renal and cardiovascular outcomes is underway. The goal of this study is to assess the effects of canagliflozin compared to placebo on the progression of albuminuria, an important intermediate marker of renal injury and progression of diabetic nephropathy.

OBJECTIVES AND HYPOTHESES

Primary objective

In subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk of cardiovascular (CV) events to assess the effect of canagliflozin compared to placebo on progression of albuminuria.

Secondary objectives

In subjects with T2DM receiving standard care, but with inadequate glycemic control and at elevated risk of CV events, to assess the effect of canagliflozin compared to placebo on:

- The composite endpoint of death from CV causes or hospitalization for heart failure
- Death from CV causes

Exploratory objectives

In subjects with T2DM receiving standard care, but with inadequate glycemic control and at elevated risk of CV events, to assess the effect of canagliflozin compared to placebo on:

- Regression of albuminuria. Regression of albuminuria is the development of normoalbuminuria in a subject with baseline microalbuminuria or macroalbuminuria or the development of microalbuminuria in a subject with baseline macroalbuminuria, accompanied by a decrease in the urinary albumin creatinine ratio (ACR) value of greater than or equal to 30% from baseline. If the ACR at a visit meets the definition of regression described above, a repeat ACR collection approximately 1 to 2 months later (or sooner under unusual circumstances, eg, subject is stopping study drug) should be done. If the last value meets the definition of regression and no repeat ACR collection can be made, the subject will also be deemed to have regressed Analyses using single ACR, as well as duplicate ACR assays will be performed.
- Change in estimated glomerular filtration rate (eGFR) from baseline to the last off-treatment value
- Urinary albumin/creatinine ratio (ACR)
- Change in eGFR determined from a between-group comparison of the eGFR slopes using all on-treatment measures of eGFR made from the first on-treatment measurement to the final on-treatment measurement
- Changes in HbA_{1c}

- Utilization of AHA therapy
- The composite endpoint of 40% reduction in eGFR, renal death, or requirement for renal replacement therapy
- The composite endpoint of doubling of serum creatinine, renal death, or requirement for renal replacement therapy
- The composite endpoint of 40% reduction in eGFR, renal death, requirement for renal replacement therapy, or death due to CV cause
- The composite endpoint of doubling of serum creatinine, renal death, requirement for renal replacement therapy, or death due to CV cause
- The composite endpoint of 40% reduction in eGFR, conversion to macroalbuminuria, renal death, or requirement for renal replacement therapy
- The composite endpoint of doubling of serum creatinine, conversion to macroalbuminuria, renal death, or requirement for renal replacement therapy

Safety objective

Cardiovascular safety data from this study will be combined with the data from the other large-scale study of the effects of canagliflozin compared to placebo (CANVAS; 28431754DIA3008; A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus; NCT01032629) in a pre-specified meta-analysis of CV safety outcomes.

Hypotheses

Primary hypothesis

In subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk of CV events canagliflozin compared to placebo reduces the rate of progression of albuminuria.

Secondary hypotheses

In subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk of CV events canagliflozin compared to placebo:

- Reduces the composite endpoint of death from CV causes or hospitalization for heart failure
- Reduces death from CV causes

OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the effects of canagliflozin compared to placebo on progression of albuminuria, an important intermediate marker of renal injury and progression of diabetic nephropathy. The study will be conducted in subjects with T2DM, receiving standard of care for hyperglycemia and CV risk factors, who have either a history or high risk of CV events. A total of 5,700 subjects will be recruited into the study. The study's last subject last visit is targeted to occur when the last subject randomized has approximately 78 weeks of follow-up or when 688 major adverse cardiovascular events (MACE) events (ie, CV death, nonfatal myocardial infarction, nonfatal stroke) are accumulated between the CANVAS and CANVAS-R (DIA4003) studies (estimated to occur between January 2017 and April 2017). The effects of canagliflozin will be evaluated against a background of standard of care for the treatment of hyperglycemia and CV risk factors with study investigators counseled to assure appropriate management according to applicable national guidelines for the care of patients with T2DM with treatment individualized as clinically appropriate.

STUDY POPULATION

Men or women with T2DM who have inadequate glycemic control (HbA_{1c} ≥7.0 and ≤10.5%) with either a history of a prior CV event or 2 or more risk factors for a CV event are eligible. Subjects can be included whether they are drug naïve to antihyperglycemic agents, using monotherapy, or using combination antihyperglycemic therapy for the control of blood glucose levels.

DOSAGE AND ADMINISTRATION

Study Drugs

Upon successful completion of screening, all potentially eligible individuals will enter a 2-week run-in period, during which they will receive single-blind placebo capsules (one capsule to be taken once-daily) to assess compliance.

Individuals that meet inclusion/exclusion criteria and that are compliant during run-in will be randomly assigned in a 1:1 ratio to canagliflozin or matching placebo to be taken once daily, before the first meal of the day. Canagliflozin will be provided at the dose of 100 mg/day through Week 13 and then increased at the discretion of the investigator at Week 13 or a subsequent visit to the dose of 300 mg/day, if the subject requires additional glycemic control and is tolerating the 100 mg dose (see Section 3.1). All study drug after randomization will be provided in a double-blind manner.

EFFICACY OUTCOME DEFINITIONS/EVALUATION CRITERIA

Primary outcomes

Progression is the development of microalbuminuria or macroalbuminuria in a subject with baseline normoalbuminuria or the development of macroalbuminuria in a subject with baseline microalbuminuria, accompanied by an ACR value increase of greater than or equal to 30% from baseline.

The primary outcome is progression of albuminuria (as defined above). If the ACR at a visit meets the definition of progression described above, a repeat ACR collection approximately 1 to 2 months later (or sooner under unusual circumstances, eg, subject is stopping study drug) should be done. If the last value meets the definition of progression and no repeat ACR collection can be made, the subject will also be deemed to have progressed. Analyses using single ACR, as well as duplicate ACR assays will be performed. Detail about the primary and sensitivity analysis approaches will be specified in the SAP.

ACR assessments will be based upon values obtained from first morning void urines analyzed by the central laboratory. In this study, duplicate urine specimens will be collected for all ACR measurements.

Secondary outcomes

The secondary outcomes are:

- Composite endpoint of death from CV causes or hospitalization for heart failure
- Death from CV causes

Safety outcomes

The data from this study will be combined with the data from another large-scale study of the effects of canagliflozin compared to placebo (CANVAS) in a pre-specified meta-analysis of CV safety outcomes to satisfy the US FDA Post Marketing Requirements.

STATISTICAL METHODS

Analysis Sets

The intent-to-treat (ITT) analysis set includes all subjects who are randomized via the Interactive Web Response System (IWRS). The assessment of the primary and most of the secondary objectives will be based upon this analysis set.

The modified intent-to-treat (mITT) or On-Treatment analysis set includes all subjects who are randomly assigned to a treatment group and receive at least one dose of double-blind study. It will be used in the analyses assessing on-treatment effects, e.g. time slope of on-treatment eGFR.

Sample Size Determination

Based on the interim data from the CANVAS study, where ACR was measured periodically at scheduled visits, it is projected that the annual progression rate for the CANVAS-R study will be approximately 7.4%. Assuming a 22% relative risk reduction for albuminuria progression, an annual progression rate in the placebo arm of 7.4%, an 18-month accrual period, a maximum treatment period of 36 months, and an annual discontinuation (from treatment) rate of 10%, it is estimated that 693 events of ACR progression will be reported. With 5,700 subjects enrolled, the power to demonstrate the superiority of canagliflozin over placebo for albuminuria progression is 90.5%, with type I error rate of 0.05 (two-sided).

Primary efficacy analysis

In this study, duplicate urine specimens will be collected for all ACR measurements. At each visit, the geometric mean of the duplicate measurements will be computed and used for all subsequent analysis unless otherwise specified.

Subjects will be classified as having normoalbuminuria (urinary ACR of <3.5 mg/mmol [<30 mg/g]), microalbuminuria (ACR ≥3.5 mg/mmol [≥30 mg/g] and ≤35 mg/mmol [≤300mg/g]), or macroalbuminuria (ACR of >35 mg/mmol [>300 mg/g]).

The primary efficacy analysis seeks to demonstrate the superiority of canagliflozin in the reduction of albuminuria progression relative to placebo.

The time from first study drug administration to first visit date observing progression (i.e., not using the visit date of the repeat sample collection) of albuminuria will be analyzed using a Cox proportional hazards regression model. The model will include treatment and baseline albuminuria status as covariates. The hazard ratio between canagliflozin and placebo will be provided, including its 95% confidence interval. The observation period for this time-to-event analysis will include all available measurements from first study drug administration to the visit date of the last ACR measurement. Subjects with no progression will be censored at the visit date of the last albuminuria measurement.

As a sensitivity analysis, the actual onset time of progression of albuminuria can be determined to be within an interval from a sequence of examination times (ie, data are interval censored). As a supportive analysis, the accelerated failure time (AFT) model with log normal error structure will be implemented considering interval censoring. The dependent variable in AFT model is the logarithm of time to progression of albuminuria. The model will include treatment group and baseline albuminuria status as covariates. We can use speed of progression to interpret AFT model. For any time (t), the probability of a subject on placebo progression-free beyond time t is the probability of a subject on canagliflozin progression-free beyond t/α, where α is the acceleration factor which can be estimated from the model. Additional sensitivity analyses will be specified in the study Statistical Analysis Plan (SAP).

The cumulative progression rate derived from Kaplan-Meier estimate will be displayed graphically to evaluate the timing of progression and the consistency of the treatment effect over time.

Secondary efficacy analyses

The secondary efficacy analysis seeks to demonstrate the superiority of canagliflozin in the reduction of the following CV events relative to placebo.

- Composite of CV death or hospitalization for heart failure
- CV death

The analysis of these CV endpoints will be based on the time to first occurrence of the events using the ITT analysis set. The hazard ratio of all canagliflozin compared to placebo and its 95% CI will be estimated using a stratified Cox proportional hazards regression model with treatment (all canagliflozin and placebo) as the explanatory variable and prior CV disease subgroup (secondary prevention and primary prevention) as the stratification factor.

Exploratory efficacy analyses

Regression of albuminuria will be analyzed in a similar fashion as the analysis for progression of albuminuria.

For change in eGFR from baseline to the off-treatment measurement, an analysis of covariance (ANCOVA) model will be used with treatment as a fixed effect and adjusting for the baseline eGFR value. The treatment difference in the least-squares means and their 2-sided 95% CI will be estimated.

Since the distribution of ACR is highly skewed, the log-transformed ACR values for all the post-baseline and scheduled visits will be modeled using a linear mixed effect model. The model will include treatment group and logarithm of baseline ACR value, visit, and treatment-by-visit interaction as fixed effects. The percentage treatment difference can be calculated by taking the anti-logarithm of the estimated coefficient for the treatment group and subtracting 1.

For on-treatment eGFR measurements, a linear mixed effects model will be fitted to eGFR as a dependent variable, including treatment, baseline eGFR value, time (as a continuous variable), and treatment time interaction as fixed effects and including subject effect as a random intercept and time as a random slope. The parameter of interest is the coefficient for treatment and time interaction term, which measures the slope difference between canagliflozin and placebo.

The effect of canagliflozin relative to placebo on changes in HbA_{1c} over time will be evaluated using a linear mixed effects model. The use of AHA therapy over time will also be summarized by treatment group.

Safety analyses

The CV safety data from this study will be evaluated in conjunction with the data from the CANVAS study according to a pre-specified meta-analysis plan.

Multiplicity adjustment

A closed testing procedure will be implemented to control the overall type I error at 5% for primary (progression of albuminuria) and secondary endpoints (composite of CV death or hospitalization for heart failure, and death). There are no interim analyses planned.

TIME AND EVENTS SCHEDULE: PRETREATMENT AND DOUBLE-BLIND TREATMENT

	Pre-treatment		Double-blind treatment						
Procedures and Evaluations	**Screening [a]**	**Baseline**							
Time point	Week -2	Day 1	Phone/email contact at Week 6	Week 13	Week 26	Phone/email contact at Week 39	Week 52 and every 26 weeks thereafter unless otherwise indicated	Phone/email contact midway between 26-week visits until last on-treatment visit	Last on-treatment visit (or after early discontinuation of treatment)[b]
Pretreatment/Administrative									
Informed consent [d]	X								
Diet, exercise, SMBG counseling	X								
Inclusion/exclusion criteria	X	X							
Medical history and demographics	X								
Prestudy therapy (drug classes of interest) [e]	X	X							
Dispense single-blind placebo	X								
Randomize		X							
Study Drug									
Administer/dispense double-blind study drug [m]		X		X	X		X		
Increase dose if subject requires additional glycemic control (see Section 3.1)				X	X		X		
Procedures									
Vital signs, weight, foot examination[f]	X	X		X	X		X	X[n] (ask about foot problems and provide foot care guidance)	X
Serum chemistry panel [g]	X	X		X	X		X		X
Hematology [g]		X					Week 52, 104 and 156		X
Fasting serum lipid profile [g]		X			X		Week 52, 104 and 156		X
HbA_{1c}	X	X		X	X		X		X
Duplicate first morning void urines for urine albumin/creatinine (provide collection containers at previous visit) [g, h]		X			X		Weeks 52, 78, 104 and 156		X
Urinalysis [g]		X							

	Pre-treatment		Double-blind treatment						
Procedures and Evaluations	**Screening** [a]	**Baseline**							
Time point	Week -2	Day 1	Phone/email contact at Week 6	Week 13	Week 26	Phone/email contact at Week 39	Week 52 and every 26 weeks thereafter unless otherwise indicated	Phone/email contact midway between 26-week visits until last on-treatment visit	Last on-treatment visit (or after early discontinuation of treatment)[b]
Urine pregnancy test [i]		X							
Dispense glucose testing supplies (optional per country/region)		X		X	X		X		
Ongoing Review									
Concomitant therapy (drug classes of interest) [j]			X	X	X	X	X	X	X
Serious adverse events, and AEs causing discontinuation; vital status; AEs of interest [l]		X	X	X	X	X	X	X	X
CV events		X	X	X	X	X	X	X	X

For footnotes, see below

TIME AND EVENTS SCHEDULE: POSTTREATMENT

Posttreatment

Procedures and Evaluations	Posttreatment Follow-up			
	All Subjects	Subjects Who Withdraw Prior to End of Study		
Time point	Final visit 30 days after last on-treatment visit (or after early discontinuation of treatment; preferably 30 days after last dose of study drug) [c]	Visit every 26 weeks after last dose until notification of global trial end date (GTED)[b]	Phone/email contact midway between 26 week visits until notification of the GTED[b,n]	Final phone contact, public record search or Vital status check within 3 months prior to GTED
Procedures				
Vital signs, weight, foot examination[f]		X	X (ask about foot problems and provide foot care guidance)	
Serum chemistry panel [g]	X			
Hematology [g]				
Fasting serum lipid profile [g]				
HbA_{1c}				
Duplicate first morning void urines for urine albumin/creatinine (provide collection containers at previous visit) [g, h]				
Urine pregnancy test [i]				
Dispense glucose testing supplies (optional per country/region)				
Ongoing Review				
Concomitant AHA therapy [j]				X
Serious adverse events, and AEs causing discontinuation; vital status [k,]; AEs of interest [l]	X	X	X	X
CV events	X	X	X	X

See footnotes on the following page

FOOTNOTES

[a] Subjects will receive diet/exercise counseling at the screening visit, be counseled on hypoglycemia recognition and management, and be dispensed single-blind placebo capsules. During the 2-week run-in period between screening and randomization, the investigator should adjust/optimize the subject's antihyperglycemic agents and agents to reduce CV risk (eg, lipid-altering, and blood pressure-lowering medications) as necessary. Subjects who fail protocol-specified screening criteria for study entry may be rescreened (Section 4.5), at the discretion of the investigator.

[b] Every subject who remains on study drug through the end of the double-blind treatment period will have a scheduled date for a last on-treatment visit as soon as possible after site notification of the projected global trial end date (GTED) expected to occur between January 2017 and April 2017. Early withdrawal (EW) evaluations will be performed when a subject stops the double-blind treatment prematurely prior to the site notification of the GTED. EW evaluations will be performed on the day study drug is discontinued or as soon as possible after stopping the study drug. For subjects who prematurely discontinue study drug prior to the announcement of GTED, sites will be required to make a final contact or vital status check after announcement of GTED. For subjects who prematurely discontinue double-blind study drug prior to the site notification of the GTED, the study's informed consent form will enable efforts to achieve follow-up of lost participants using all reasonable means to contact the subject, family members, the subject's physicians and medical records, and the use of locator agencies and checking public records, as allowed by local law. It is the expectation that the investigator will make every effort to ascertain the vital status of all subjects at the end of the study (ie between the notification of the GTED and the actual GTED), including using all reasonable means outlined above.

[c] A study visit will be conducted for all subjects approximately 30 days (+/- 12 days) after the last dose of study drug. (note: this applies to subjects who prematurely discontinue study drug and also those who discontinue study drug after site notification of the projected GTED) This will require a clinic visit for collection of lab specimens. If a study visit is not immediately possible, follow-up information may be collected by telephone, via email or other electronic or non-electronic means, and a subsequent study visit should be attempted.

[d] The informed consent form must be signed before any study procedure is performed.

[e] Record as prestudy therapy the classes of medications taken from 30 days before screening.

[f] Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (sitting position, after sitting for 5 minutes; record 3 consecutive blood pressure readings, at intervals of at least 1 minute apart); the average of the 3 blood pressure readings will be recorded on eCRFs. Consistent with standard diabetes treatment guidelines, all study participants should be provided with routine preventative foot care and early intervention for foot problems (see Section 12.2.1 for further detail).

[g] Specific details about specimen collection, storage, and processing will be provided in operations manuals. Attachment 1 lists the laboratory studies to be performed. Urinalysis will be performed from a spot urine collection in the clinic on Day 1.

[h] The subject will provide first morning void (FMV) urine specimens (collection of the first urine void after the individual awakes from sleep). At each visit, the subject will bring in 2 FMV specimens: one from the morning of the visit, and one from the morning of the day prior to the visit. If the urinary albumin/creatinine result reflects progression or regression of albuminuria from the baseline (eg, progression from normoalbuminuria to microalbuminuria or macroalbuminuria accompanied by a urinary ACR value increase of ≥30% from baseline; or regression from macroalbuminuria to microalbuminuria or normoalbuminuria accompanied by a urinary ACR value decrease of ≥30% from baseline), the investigator will be notified to have the subject bring 2 additional consecutive-morning FMV specimens to the clinic approximately 1 to 2 months later. If the subject is unable to return the specimens in person, the site may engage a courier service to deliver the specimen to the site. If the subject does not provide the morning void collection on the day of the visit, the subject may bring first morning void specimens to the investigational site during the subsequent 7 days. For subjects working a night shift, or who otherwise have atypical sleep patterns, the collection should be made at the end of the subject's usual sleep period.

[i] Urine pregnancy testing will be performed locally for all women unless they are surgically sterile or unless there is a documented history of their postmenopausal status. Additional pregnancy tests may be conducted throughout the study in sufficient number, as determined by the investigator or required by local regulations, to establish the absence of pregnancy during the study. If positive, the subject is not eligible to enter the study or continue study drug. A urine pregnancy test will be performed as specified, unless a serum pregnancy test is preferred at the discretion of the investigator or if required by local regulations; in such situations, the serum pregnancy test will be performed at the screening visit instead of the baseline visit, in order to determine the subject's pregnancy status prior to randomization.

[j] Concomitant therapy includes all medications from drug classes of interest taken regularly after the initiation of double-blind study medication (Day 1); after study drug discontinuation, use of AHA therapies will be recorded at the final visit or contact..

[k] This applies only to subjects who prematurely discontinue study drug any time prior to the site notification of the GTED. As noted above, it is the expectation that the investigator will make every effort to ascertain the vital status of all subjects at the end of the study, including using all reasonable means to contact the subject, family members, the subject's physicians and medical records, or other sources, as well as the use of locator agencies and checking public records, as allowed by local law.

[l] Adverse events of interest include: all malignancies, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (eg, angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, male genital infections (balanitis, phimosis, events leading to circumcision), and pregnancy. Information on these events will be recorded on the supplemental eCRFs or other designated forms for any event that is serious or that leads to study drug discontinuation. In addition, non-serious adverse events of malignancies, photosensitivity reactions, fractures, amputations, and venous thromboembolic events will also be recorded on the supplemental CRF pages or other designated forms (in addition to the information collected on serious AEs and AEs leading to study drug discontinuation). Diabetic ketoacidosis has been designated an adverse event of special interest and therefore adverse events related to diabetic ketoacidosis, ketoacidosis, metabolic acidosis or acidosis need to be reported to Janssen within 24 hours of becoming aware of the event, which is the same timeframe for reporting of serious adverse events. These adverse events must be reported using a supplemental DKA Reporting form, to complement standard information collected on the eCRF AE/SAE page. Amputations have also been designated as adverse events of special interest and therefore amputations need to be reported to the sponsor within 24 hours of becoming aware of the event. If adverse events of interest are identified in the future, guidance concerning the reporting of those events may be provided to investigators via appropriately-documented study communications..

[m] An unscheduled visit may be used for increasing or decreasing the dose of study drug , any time after Week 13.

[n] At each telephone contact, investigators should ask subject about any foot problems and remind them about routine preventative foot care and early intervention for foot problems.

ABBREVIATIONS

ACR	urinary albumin/creatinine ratio
ADA	American Diabetes Association
AHA	antihyperglycemic agent
ALT	alanine aminotransferase
ARO	Academic Research Organization
AST	aspartate aminotransferase
BMI	body mass index
CI	confidence interval
CV	cardiovascular
eCRF	electronic case report form
eDC	electronic data capture
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
FMV	first morning void
FPG	fasting plasma glucose
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GTED	global trial end date
HbA_{1c}	hemoglobin A_{1c}
HDL-C	high-density lipoprotein cholesterol
IB	Investigator Brochure
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IWRS	interactive web response system
LDL-C	low-density lipoprotein cholesterol
MACE	major adverse cardiovascular events
MI	myocardial infarction
mITT	modified intent-to-treat
MSRC	Medical Safety Review Committee
NYHA	New York Heart Association
PG	plasma glucose
PQC	Product Quality Complaint
SAP	statistical analysis plan
SGLT1/SGLT2	sodium-glucose co-transporter 1/sodium-glucose co-transporter 2
SMBG	self-monitored blood glucose
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
UGE	urinary glucose excretion
ULN	upper limit of normal
US	United States
VTE	venous thromboembolic event

1. INTRODUCTION

Over the past decades, the incidence of type 2 diabetes mellitus (T2DM) has been rapidly rising worldwide, driven primarily by an increasing incidence of obesity and sedentary lifestyles. Patients with T2DM can develop severe microvascular complications, related to persistently elevated glucose concentrations, including blindness, renal failure, or nerve damage, and have a higher incidence of atherosclerotic vascular disease with complications such as myocardial infarction (MI), stroke, and amputations due to vascular insufficiency. Improved glucose control reduces the incidence of microvascular complications in patients with both type 1 diabetes mellitus (T1DM) and T2DM. The impact of improved glycemic control on macrovascular events is less well established. Despite the availability of a range of therapeutic options, many patients with T2DM do not achieve or maintain glycemic control. Many of these treatments are associated with safety or tolerability issues, including hypoglycemia, edema, or gastrointestinal adverse experiences which can limit dose and hence therapeutic benefit. Further, some of the current antihyperglycemic agents (AHAs) are associated with weight gain, and only a few agents (eg, metformin and glucagon-like peptide-1 [GLP-1] analogues) lead to weight loss, an important advantage in a patient population that is often obese. Most patients with T2DM are initially managed with single-agent therapy, usually metformin. Over time, patients often require more intensive regimens, combinations of 2 or 3 agents, and eventually require insulin to maintain target glycemic control. Underlying this need for increasingly intensive treatment is a progressive loss of beta-cell mass and function, with consequent diminished insulin secretion. There remains a substantial unmet medical need for new medications to treat patients with T2DM that are well tolerated and efficacious, provide good durability, beneficially impact beta-cell function and insulin secretion, and are associated with weight loss.

In healthy individuals, glucose is freely filtered through the renal glomerulus and then reabsorbed in the proximal tubules. The renal threshold for glucose (RT_G) is the glucose plasma concentration above which glucose reabsorption by the proximal renal tubules is incomplete and glucose is excreted into the urine. A typical RT_G level in healthy individuals is approximately 180 mg/dL (10 mmol/L) (Ganong 2005; Rave 2006; Seifter 2005). Glucose reabsorption in the renal tubules, determining the renal threshold is largely due to 2 key glucose transporters: sodium glucose co-transporter 2 (SGLT2) and sodium glucose co-transporter 1 (SGLT1). Sodium glucose co-transporter 2 is a high-capacity and low-affinity glucose transporter exclusively expressed at the luminal membrane of the S1 and S2 segments of the proximal renal tubules. Sodium glucose co-transporter 2 is responsible for the majority of filtered glucose reabsorption from the lumen. Sodium-glucose co-transporter 1 expressed in the S3 segment, a low capacity and high-affinity transporter, is also involved in reabsorption of filtered glucose from the lumen (Wright 2001). Sodium-glucose co-transporter 1 is also highly expressed in the intestine and is responsible for intestinal glucose and galactose absorption.

Pharmacologic inhibition of SGLT2 is a novel mechanism to decrease renal glucose reabsorption, as it lowers RT_G and leads to an increase in urinary glucose excretion (UGE), thereby directly lowering plasma glucose in individuals with elevated glucose concentrations. Canagliflozin is an orally active inhibitor of SGLT2. This agent has much higher potency for SGLT2 relative to SGLT1; at the plasma drug concentrations achieved with the doses in this

study, canagliflozin would be expected to provide significant systemic inhibition of SGLT2 and not of SGLT1. In addition to lowering plasma glucose concentrations, the increased renal glucose excretion with SGLT2 inhibition also translates to a loss of calories, leading to a net negative energy balance and the potential for weight loss as well as an osmotic diuretic effect, which can lead to reductions in blood pressure and osmotic diuresis- and volume depletion-related adverse events.

A Phase 3 development program including 9 controlled studies was conducted providing evidence for the effectiveness of canagliflozin both as monotherapy and in combination with approved, commonly prescribed AHA therapies in T2DM. These 9 studies spanned a range of clinical uses (as monotherapy or as combination therapy) to treat T2DM. Three of the Phase 3 studies evaluated canagliflozin in special populations, including older adults with T2DM, subjects with T2DM who had moderate renal impairment, and subjects with T2DM who had or were at high risk for cardiovascular (CV) disease. Results of the extensive Phase 3 clinical development program, involving approximately 10,285 subjects with T2DM and including nearly 6,650 subjects treated with 100 mg or 300 mg doses of canagliflozin, indicate that canagliflozin has the potential to be a useful addition to currently available antihyperglycemic agents. Across all of the studies, clinically meaningful reductions in hemoglobin A_{1c} (HbA_{1c}) and fasting plasma glucose (FPG) were seen. Statistically significant (relative to placebo) reductions in body weight (predominantly fat mass) were also achieved with canagliflozin 100 mg and 300 mg across the spectrum of T2DM patients evaluated in the Phase 3 program. Canagliflozin also showed benefit in improving other clinical endpoints associated with diabetic comorbidities, including systolic and diastolic blood pressure (SBP and DBP), and lipid parameters (high-density lipoprotein cholesterol [HDL-C], and triglyceride). Improvements in beta-cell function, presumably through an indirect effect, such as reductions in glucotoxicity and insulin secretory demand, were also seen with canagliflozin treatment.

In March 2013, canagliflozin was approved for marketing by the United States Food and Drug Administration (FDA). An ongoing clinical program designed to continue research on the effects of the agent on renal and cardiovascular outcomes is underway. The goal of this study is to assess the effects of canagliflozin compared to placebo on the progression of albuminuria, an important intermediate marker of renal injury and the progression of diabetic nephropathy.

The term “sponsor” used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

For more detailed and current information regarding the preclinical characterization of canagliflozin pharmacokinetics (PK) (ie, absorption, distribution, metabolism and excretion) and toxicology, and clinical study results, refer to the current version of the Investigator's Brochure for canagliflozin (IB JNJ-28431754).

1.1.1. Nonclinical Studies

For a complete review of the findings and discussions regarding implications for human risk, please refer to the current version of the canagliflozin IB.

1.1.2. Clinical Studies

Overview

The canagliflozin clinical program was designed to assess the safety and efficacy of canagliflozin in patients with T2DM. The program consists of 52 completed or ongoing clinical studies, including data from 10,285 subjects as of late 2012 (who received at least 1 dose of double-blind study drug) in 9 Phase 3 studies, 1,210 subjects in 3 Phase 2 studies, and 1,300 subjects in 40 Phase 1 studies.

Pharmacokinetics

Canagliflozin exhibits similar PK in healthy subjects and subjects with T2DM. The mean absolute oral bioavailability of canagliflozin was 65% following single-dose administration of the canagliflozin 300 mg tablet in healthy subjects. In healthy subjects (25 to 1,600 mg once-daily [QD]) and subjects with T2DM (50 mg to 300 mg QD and 300 mg twice-daily [BID]), after oral administration of single and multiple doses, mean canagliflozin $AUC_{0-\infty}$ increased in an approximately dose-proportional manner whereas mean maximum plasma concentration (C_{max}) increased in an approximately dose-proportional manner up to 1,200 mg. Following oral administration of canagliflozin, the median time to reach maximum plasma concentration (t_{max}) was approximately 1 to 2 hours. The mean terminal plasma elimination half-life ($t_{1/2}$) of canagliflozin was 10 and 13 hours with canagliflozin doses of 100 and 300 mg, respectively. The t_{max} was independent of dose. After repeated dosing with 50 to 300 mg canagliflozin, steady state was reached by 4 to 5 days. Minimal accumulation of canagliflozin was observed at steady-state across 50, 100, and 300 mg doses with mean accumulation ratios ranging from 1.3 to 1.4 in subjects with T2DM. Bioavailability of canagliflozin was not affected after co-administration of canagliflozin 300 mg with food in healthy subjects indicating that the canagliflozin tablet formulation may be taken without regard to meals.

O-glucuronidation is the major metabolic elimination pathway for canagliflozin in humans. In human plasma, two non-pharmacologically active O-glucuronide conjugates of unchanged drug, M5 (formed by UGT2B4) and M7 (formed by UGT1A9), were present. Co-administration with rifampin, a nonselective inducer of several UGT enzymes, decreased canagliflozin area under the curve (AUC) by 51%, which may decrease efficacy. There was an increase in the AUC and C_{max} of digoxin when co-administered with canagliflozin 300 mg. Subjects taking concomitant digoxin should be monitored appropriately. The C_{max} of canagliflozin was not meaningfully altered by renal impairment.

Based on in vitro data and the clinical drug-drug interaction studies conducted to date, the potential for clinically significant CYP450 based PK interactions appears to be low.

Pharmacodynamics

In subjects with T2DM following single and multiple oral doses (30 to 600 mg QD and 300 mg BID), canagliflozin treatment dose dependently increased UGE_{0-24h}, with mean UGE_{0-24h} of approximately 100 g/day typically observed with doses of 100 mg/day or higher.

In subjects with T2DM, canagliflozin treatment with 100 mg and 300 mg once daily lowered RT_G to approximately 70 to 90 mg/dL (3.9 to 5.0 mmol/L), respectively. Because RT_G remains above PG levels associated with hypoglycemia and because very little UGE occurs whenever plasma glucose (PG) is below the RT_G, canagliflozin, itself, is not expected to pose a risk for hypoglycemia.

Efficacy

In the Phase 3 studies, canagliflozin has been assessed as monotherapy, as add-on therapy with metformin, sulphonylurea (SU), metformin and SU, metformin and a peroxisome proliferator-activated receptor (PPARγ) agonist (pioglitazone), and as add-on therapy with insulin (with or without other AHAs). The Phase 3 program also includes studies in special populations of patients with T2DM: subjects with renal impairment (estimated glomerular filtration rate [eGFR] ≥30 to <50 mL/min/1.73 m^2); subjects with or at high risk for CV complications; and older subjects. The latter 2 studies also included subjects on incretin-based therapies, including DPP-4 inhibitors and GLP-1 agonists.

Glycemic Efficacy

Results of the Phase 3 studies demonstrated the efficacy of canagliflozin in reducing HbA_{1c} in a broad range of subjects with T2DM, both with recent onset as well as long-standing diabetes and on a range of different background AHAs. A clinically meaningful improvement in glycemic control was seen when canagliflozin was given as monotherapy and when given in dual combinations (add-on to metformin or to SU agents), in triple oral AHA combinations (add-on to metformin plus an SU agent or metformin plus pioglitazone), in combination with insulin (alone or in combination with other agents), or as an add-on to existing diabetes therapy (any approved oral or parenteral therapy). In the monotherapy study, HbA_{1c} reductions of -0.91% and -1.16% relative to placebo for canagliflozin 100 mg and 300 mg, respectively, were observed. In the studies examining specific add-on combination uses, the efficacy of canagliflozin in lowering HbA_{1c}, relative to placebo, was generally consistent ranging from -0.62% to -0.74% with the 100 mg dose and from -0.73% to -0.92% with the 300 mg dose. Across all studies, the 300 mg dose consistently provided greater HbA_{1c} lowering relative to the 100 mg dose; since reduction in diabetic microvascular complications is continuous with improvements in glycemic control, the additional glucose-lowering efficacy with the 300 mg dose is considered likely to be clinically relevant (UKPDS 1998, DCCT 1993).

Results of subgroup analyses performed in a pooled population of the placebo-controlled Phase 3 studies found no important differences when comparing the effect of canagliflozin in change from baseline in HbA_{1c} based on baseline demographic characteristics (age, sex, race, ethnicity), body mass index (BMI), or geographic region. Greater reductions in HbA_{1c} relative to placebo were observed with canagliflozin among subjects with higher baseline HbA_{1c} and higher eGFR values compared with subjects with lower baseline values. In subjects with moderate renal impairment (ie, baseline eGFR's between 30 to 60 mL/min/1.73m^2), the mean, placebo-subtracted reduction in HbA_{1c} was 0.38% and 0.47% on canagliflozin 100 mg and 300 mg respectively. A total of 24% and 32% of subjects achieved a target HbA_{1c} <7% at the end

of treatment on canagliflozin 100 mg and 300 mg respectively compared to 17% of subjects on placebo.

With regard to other glycemic endpoints, canagliflozin provided improvements in FPG as well as in the PPG excursion. Canagliflozin also provided improvements in beta-cell function and a reduction in beta cell stress as reflected by a decrease in the proinsulin/C-peptide ratio. The improvement in beta-cell function and reduction in beta-cell stress is consistent with the sustained effect of canagliflozin on both HbA_{1c} and FPG observed in the 52-week studies.

Weight and Blood Pressure Effects

In addition to the observed glycemic improvements, treatment with canagliflozin resulted in consistent, statistically significant reductions in total body weight relative to placebo. Weight loss with canagliflozin appeared dose-related (with -1.4% to -2.7% reductions with 100 mg and -1.8% to -3.7% reductions with 300 mg, relative to placebo). Results of specialized body composition investigations using dual energy X-ray absorptiometry (DXA) in 2 of the Phase 3 studies showed that the body weight reduction with canagliflozin was attributable to a greater decrease in body fat mass relative to lean body mass.

Reductions in SBP were observed with canagliflozin in Phase 3 studies (ranging from -2.2 to -5.7 mm Hg of SBP with canagliflozin 100 mg dose, and -1.6 to -7.9 mm Hg with the 300 mg dose, relative to placebo, in placebo-controlled 26-week studies), and were generally statistically significantly greater for both doses relative to placebo, and also greater relative to comparator agents (glimepiride and sitagliptin).

Safety

For a complete review of the adverse drug reactions (ADRs) and laboratory findings associated with canagliflozin, please refer to the current version of the canagliflozin Investigator's Brochure (IB JNJ-28431754).

The safety and tolerability profile that emerges from the development program for canagliflozin shows a medication that is overall well tolerated. The incidence of discontinuations due to adverse events was slightly higher than seen in the control group, though generally low. The small increase in discontinuations due to adverse events were generally related to specific ADRs, described below, with each particular ADR infrequently leading to discontinuations; there was no increase in serious adverse events or deaths in the canagliflozin treatment groups relative to control groups.

Adverse drug reactions associated with canagliflozin include genital mycotic infections, urinary tract infections (UTIs), adverse events related to osmotic diuresis, and adverse events related to reduced intravascular volume, as well as constipation, and a low incidence of rash or urticaria.

In men, the genital mycotic infections (including balanitis and balanoposthitis) occurred predominantly in uncircumcised individuals and in those with a past history of genital mycotic infections, generally did not lead to discontinuation from the study. Circumcision was performed in 17/3569 (0.5%) and 3/1924 (0.2%) of men treated with canagliflozin and control, respectively.

In women, genital mycotic infections (including candidal vulvovaginitis) occurred more commonly in women with a prior history of genital mycotic infections and did not generally lead to discontinuation. A modest increase in the incidence of adverse events of UTI (mostly lower tract infections) was observed with canagliflozin relative to control, without an increase in serious adverse events of UTI.

Adverse drug reactions were observed that relate to the osmotic diuretic effect of canagliflozin, with increases in UGE leading to a diuretic action; this included ADRs of pollakiuria (increased urinary frequency), polyuria (increased urinary volume), and thirst. Adverse drug reactions related to reduced intravascular volume were observed including postural dizziness, orthostatic hypotension, and hypotension. Risk factors for volume-related adverse events on canagliflozin treatment were ≥75 years of age, eGFR of 30 to 60 ml/min/1.73m^2 and use of loop diuretics. These adverse events were generally considered as mild or moderate in intensity, and infrequently led to discontinuation. No increase in serious adverse events related to reduced intravascular volume were seen with canagliflozin treatment. The reduction in intravascular volume also led to reversible reductions in eGFR that generally attenuated with continued treatment.

Based on the observations from the 2-year rat carcinogenicity study (findings of renal tubular cell cancers, Leydig cell tumors [LCTs], and pheochromocytomas), an extensive preclinical toxicology program was conducted that demonstrated that these tumors related to effects of canagliflozin in rats, not seen in humans (including rises in luteinizing hormone [LH] associated with LCT, and carbohydrate malabsorption leading to associated metabolic effects, including marked hypercalciuria, inducing renal tubular tumors and pheochromocytomas). In the clinical program, there were no reports of LCT or pheochromocytoma and no imbalance in the low incidence across groups of renal cell cancers.

In preclinical studies in rats, hyperostosis (increased trabecular bone) was observed; mechanistic toxicology studies demonstrated that hyperostosis, like the tumors discussed above, related to carbohydrate malabsorption in rats treated with canagliflozin, with consequent marked hypercalciuria (which is not seen in human). A detailed analysis of bone safety was conducted in the Phase 3 program, including an assessment using DXA in a dedicated Phase 3 study (a study conducted in older subjects [ages ≥55 and ≤80 years] with T2DM) and a cross-program assessment of fracture incidence. Bone mineral density (BMD) was examined at 4 sites: at the lumbar spine, total hip, distal radius, and femoral neck. Minimal changes in BMD from baseline to Week 104 were seen in the lumbar spine (a cancellous bone region), femoral neck (a mixed cancellous and cortical bone region), and distal forearm. A decrease in BMD from baseline to Week 104 in the total hip, a site comprised of mixed cortical and cancellous bone (like the femoral neck), was observed for both canagliflozin treatment groups (-0.9% and -1.2% in the canagliflozin 100 mg and 300 mg groups, respectively, placebo adjusted). In a pool of 8 clinical trials with a longer mean duration of exposure, the incidence rate of bone fracture was 14.2, 18.7, and 17.6 per 1,000 patient-years of exposure to comparator, canagliflozin 100 mg, and canagliflozin 300 mg, respectively.

Increases in low-density lipoprotein-cholesterol (LDL-C) were observed with canagliflozin: in a pooled analysis of placebo-controlled 26-week studies, increases in LDL-C relative to placebo were 4.4 mg/dL (0.11 mmol/L) and 8.2 mg/dL (0.21 mmol/L) at the 100 mg and 300 mg doses, respectively. Relative increases in Apo B, non-HDL-C, and LDL particle number were approximately half as large as the rise in LDL-C. The changes in the CV risk profile with canagliflozin include reductions in SBP and increases in LDL-C, both established CV risk factors, and validated as surrogate endpoints. Improvements in other endpoints associated with CV risk, but not established as surrogate endpoints for CV benefit, such as body weight, glycemic control, HDL-C, and TG were also observed with canagliflozin. The cross-program CV meta-analysis (including results from the dedicated CV safety study) observed a hazard ratio of 0.91 for a pre-specified composite endpoint of CV death, non-fatal MI, non-fatal stroke, and hospitalized unstable angina (95% CI: 0.68, 1.22), showing no signal for an increase in the CV risk.

As of 11 May 2015, in the T2DM clinical development program, incidence rates of unblinded serious adverse events of DKA, ketoacidosis, metabolic acidosis, and acidosis were 0.0522 (0.07%, 4/5337), 0.0763 (0.11%, 6/5350), and 0.0238 (0.03%, 2/6909) per 100 subject-years with canagliflozin 100 mg, canagliflozin 300 mg, and comparator, respectively. Of the 12 subjects with serious adverse events of DKA, ketoacidosis, metabolic acidosis, or acidosis (all of whom were hospitalized), 6 subjects on canagliflozin (3 on canagliflozin 100 mg and 3 on canagliflozin 300 mg), and none on comparator were reported to have autoimmune diabetes (latent autoimmune diabetes of adulthood [LADA] or type 1 diabetes) or tested positive for GAD65 antibodies after being diagnosed with a serious DKA-related event. Eight of the 10 subjects on canagliflozin were receiving insulin therapy. The blood glucose values around the time of admission in 9 of 10 subjects on canagliflozin ranged from 347 to 571 mg/dL (9.3 to 31.7 mmol/L). The remaining subject had blood glucose values ranging from 148 to 320 mg/dL (8.2 to 17.8 mmol/L). Diabetic ketoacidosis has also been reported during post-marketing surveillance and has occurred in patients with blood glucose values less than 250 mg/dL (13.9 mmol/L). As a result, diabetic ketoacidosis is considered a rare adverse drug reaction.

During a routine review of unblinded interim data from the ongoing CANVAS study (DIA3008), the Independent Data Monitoring Committee observed a non-dose-dependent increase in the incidence of non-traumatic, lower-extremity amputations (mostly of the toes) in the canagliflozin 100 mg and 300 mg groups compared with placebo. With a mean duration of follow-up in CANVAS of approximately 4.5 years, the annualized incidence of lower-extremity amputation was 0.73, 0.54, and 0.30 events per 100 patient-years in the canagliflozin 100 mg, canagliflozin 300 mg, and placebo groups, respectively. Overall, treatment with canagliflozin was associated with an approximately 2-fold increase in amputation event rates (relative risk [RR] 2.15; 95% CI: 1.3- 3.5). The CANVAS/CANVAS-R IDMC, which has access to unblinded CV outcomes data, notified the sponsor that “after consideration of all outcomes, the IDMC feels the study should continue.” Infections were the events most commonly associated with amputations, and most amputations were of the toe. The factors associated with the greatest risk for amputations include prior amputation, peripheral vascular disease, and neuropathy.

1.2. Overall Rationale and Goals for the Study

Patients with T2DM have an increased risk of both microvascular and macrovascular complications which lead to morbidity and mortality. A key issue in patients with T2DM is the potential for hyperglycemia to lead to progressive damage to the kidney. Early on, this damage is reflected by microalbuminuria that may progress to macroalbuminuria and eventually loss of renal function. Hyperglycemia, possibly through production of advanced glycation end products (Diabetes Control and Complications Trial [DCCT]; Brownlee 2001) and systemic hypertension (DCCT) are known to be risk factors for the onset and progression of diabetic nephropathy. By virtue of its improvement in glycemic control, which has been shown to reduce albuminuria progression in prior studies (ADVANCE 2008; DCCT 1993; UKPDS 1998), and effects to reduce blood pressure, canagliflozin may slow the progression of diabetic nephropathy.

Hyperglycemia increases glucose levels delivered to the proximal tubule, which is reabsorbed, predominantly via an SGLT-2-dependent mechanism (Vallon 1999). Increased proximal tubule resorption of glucose results in increases in the proximal tubule reabsorption of sodium and reduces the delivery of sodium to the distal tubule. Decreases in sodium levels in the distal tubule reduce macula densa-dependent tubuloglomerular feedback, which results in afferent glomerular arteriole vasodilation and increases in glomerular pressure (Vallon 1999). Increases in glomerular pressure are believed to be an important factor in the onset and progression of diabetic nephropathy (Anderson 1986; American Diabetes Association [ADA] 2004). ACEI and ARB decrease glomerular pressure by stimulating efferent glomerular arteriole vasodilation and reduce albuminuria and the progression of diabetic nephropathy (IDNT, Lewis 2001, and RENAAL, de Zeeuw 2004).

In preclinical diabetic rodent models, SGLT2 inhibition increases tubuloglomerular feedback and reduces single nephron glomerular filtration rates, consistent with an increase in tubuloglomerular feedback leading to a decrease in glomerular pressure (Vallon 2011). In a Phase 1 study in subjects with T1DM who exhibited glomerular hyperfiltration (eGFR 172 ml/min/1.73 m^2), an 8-week treatment with empagliflozin, a selective SGLT2 inhibitor, significantly reduced glomerular hyperfiltration (eGFR 139 ml/min/1.73 m^2) (Cherney 2013 ADA poster). The reduction in hyperfiltration was associated with increases in renal vascular resistance and reductions in renal blood flow, both consistent with an increase in afferent glomerular arteriole tone. Thus, in preclinical and clinical models, SGLT2 inhibition reduces glomerular pressure, a factor known to be associated with the onset and progression of diabetic nephropathy.

In the clinical program, clinically-important, favorable changes were observed with canagliflozin compared to placebo in the progression of albuminuria. In a post hoc analysis performed in CANVAS (28431754DIA3008; A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus), after approximately 20 months of mean follow-up, 253/1390 (18.2%) of placebo-treated subjects showed albuminuria progression (defined by albuminuria status change and 30% increase in albumin/creatinine ratio (ACR) from baseline) relative to baseline versus 221/1406 (15.7%) with canagliflozin 100 mg, 191/1397 (13.7%) with

canagliflozin 300 mg, and 412/2803 (14.7%) with canagliflozin overall. In a pooled analysis of subjects with moderate renal impairment (defined as a baseline eGFR of ≥30 mL/min/1.73 m^2 and ≤60 mL/min/1.73 m^2) that included subjects from the CANVAS study and other studies in the Phase 3 program, the observed mean change from baseline in the albumin/creatinine ratio was 28 mg/g, -22 mg/g, and -41 mg/g for placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. The corresponding observed median changes from baseline in the 3 groups respectively were 1.2 mg/g, -0.6 mg/g, and -0.7 mg/g.

In the Phase 3 program, treatment with canagliflozin was associated with a dose-dependent, reversible reduction in eGFR that was maximal at the first post baseline visit and was either stable or attenuated with continued treatment. The time course of eGFR changes over a 104-week, active comparator study and over a 52-week week study in subjects with moderate renal impairment are shown in Figure 1 and Figure 2 below.

Figure 1: Mean Change in eGFR Over Time (DIA3009)

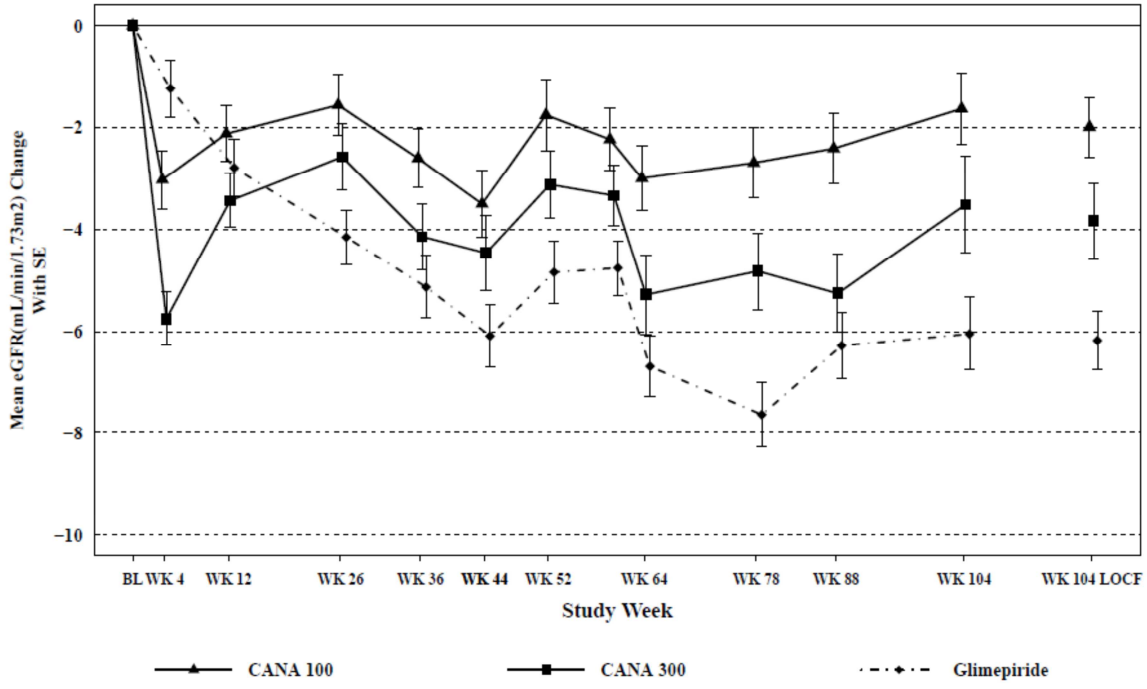
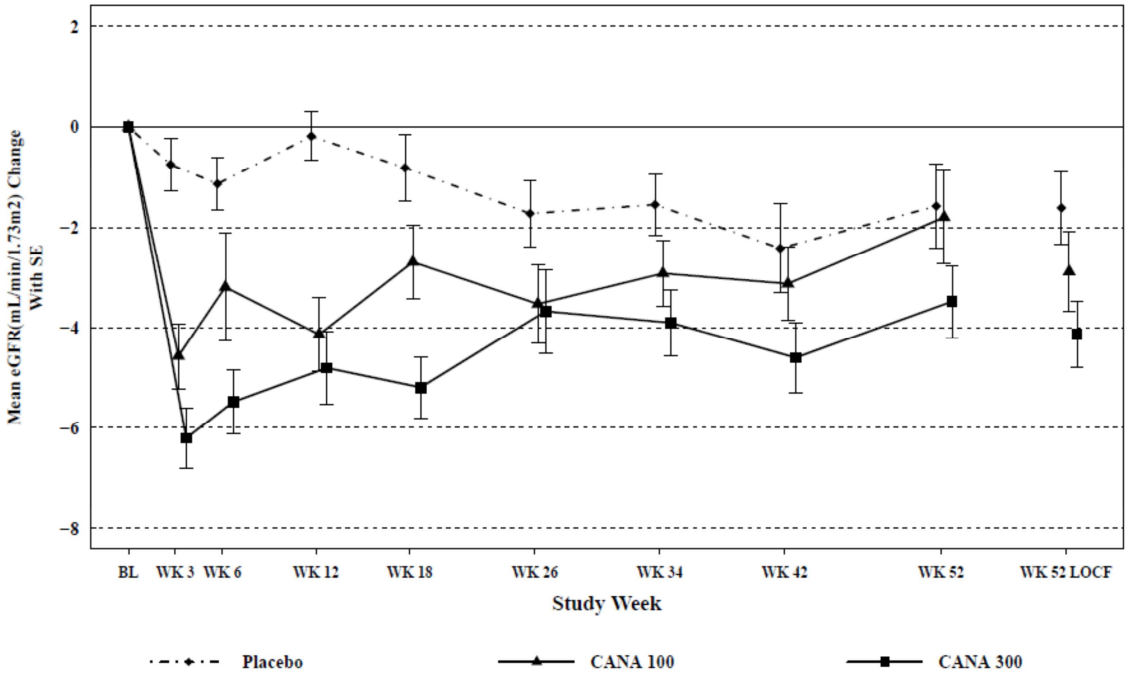
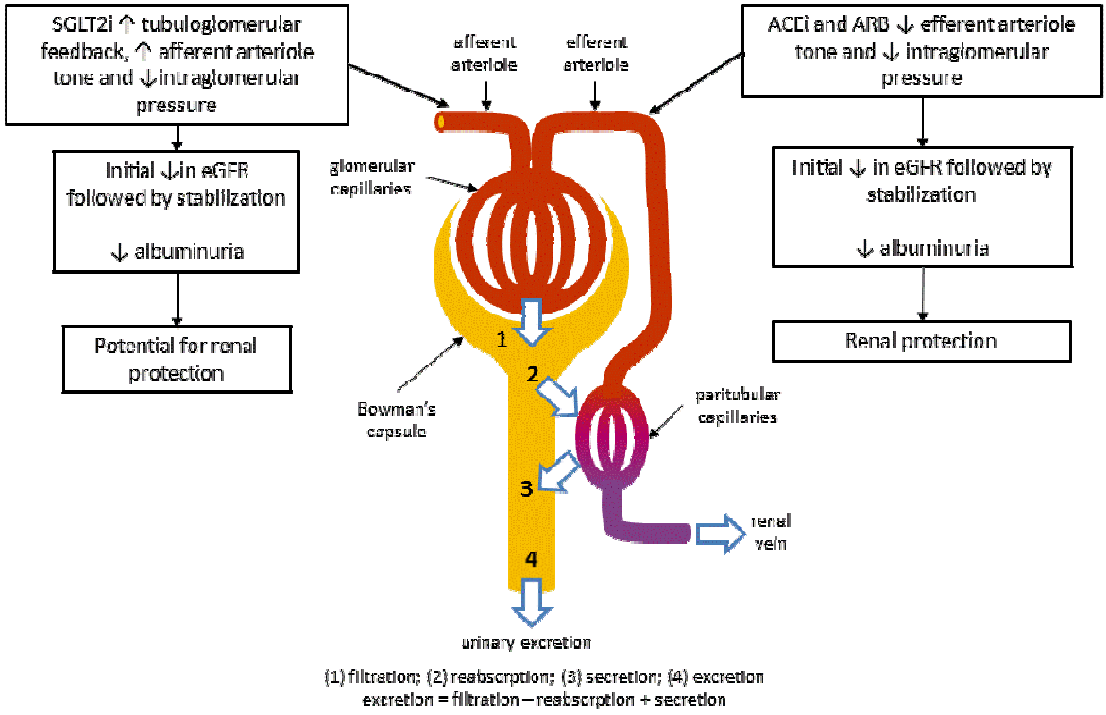


Figure 2: Mean Change in eGFR Over Time (DIA3004)



Based on these data, it is hypothesized that SGLT2 inhibition with canagliflozin will reduce glomerular pressure by increasing afferent glomerular arteriole tone, which will lead to a hemodynamically mediated decrease in glomerular pressure, as reflected by an acute, mild decrease in GFR. The reduction in glomerular pressure is hypothesized to mediate the reduction in albuminuria seen with canagliflozin treatment and to potentially lead to a reduction in progression of diabetic nephropathy. A schematic of these hypotheses and the effect of ACEI and ARBs on the progression of diabetic nephropathy is shown in Figure 3, below.

Figure 3: Hypotheses Regarding the Effect of ACEI and ARBs on the Progression of Diabetic Nephropathy



The present study is intended to determine if treatment of subjects with T2DM with canagliflozin reduces the progression of albuminuria, a biomarker for renal injury and for progression of diabetic nephropathy. The study will also explore the effects of canagliflozin on the regression of albuminuria, and changes in eGFR.

Data from this study will also be used for a pre-specified meta-analysis with data from CANVAS for the assessment of CV safety, examining a composite endpoint of the major adverse cardiovascular events (MACE) of cardiovascular death, nonfatal MI, and nonfatal stroke. The details of the meta-analysis are described in a separate statistical analysis plan (SAP).

Results of a CV outcomes trial with another SGLT2 inhibitor were recently reported. EMPA-REG OUTCOME was a randomized, double-blind, placebo-controlled CV outcome trial to examine the long-term effects of empagliflozin versus placebo, in addition to standard of care, on CV outcomes in patients with T2DM and established CV disease, ie, EMPA-REG was a secondary prevention study (Zinman 2015). This study had a median observation time of 3.1 years and was conducted in 7,020 subjects. In this study, empagliflozin, compared to placebo, was associated with a reduction in the MACE primary outcome (CV death, nonfatal MI, and nonfatal stroke; hazard ratio 0.86 [0.74, 0.99], p=0.04), but the key secondary outcome of MACE-Plus (CV death, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina; hazard ratio 0.89 [0.78, 1.01], p=0.08) did not achieve statistical significance. The effect on the primary MACE outcome was numerically smaller than the effects on the secondary endpoints of CV death (hazard ratio 0.62 [0.49, 0.77], p<0.001), and the composite endpoint of CV death and hospitalization for heart failure (hazard ratio 0.66 [0.55, 0.79] , p<0.001). The reductions in CV

death and hospitalization for heart failure with empagliflozin treatment were apparent within 3 months after randomization. No statistical differences were seen relative to placebo on non-fatal MI and non-fatal stroke. In order to assess whether these effects are specific to the SGLT2 inhibitor class, the composite event of death from CV causes or hospitalization for heart failure and the event of death from CV causes are being added as secondary endpoints to CANVAS-R.

Post-hoc analysis of data from EMPA-REG OUTCOME also demonstrated a benefit on renal endpoints, particularly on the composite endpoint of doubling of serum creatinine, initiation of renal replacement therapy, or death due to renal cause. These and other renal events are being added as exploratory endpoints to CANVAS-R.

2. OBJECTIVES AND HYPOTHESES

2.1. Objectives

Primary Objective

In subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk of CV events, to assess the effect of canagliflozin compared to placebo on progression of albuminuria.

Secondary Objectives

In subjects with T2DM receiving standard care but with inadequate glycemic control and at elevated risk of CV events, to assess the effect of canagliflozin compared to placebo on:

- The composite endpoint of death from CV causes or hospitalization for heart failure
- Death from CV causes

Exploratory objective

In subjects with T2DM receiving standard care, but with inadequate glycemic control and at elevated risk of CV events, to assess the effect of canagliflozin compared to placebo on:

- Regression of albuminuria
- Change in eGFR from baseline to the last off-treatment value.
- Urinary ACR
- Change in eGFR determined from a between group comparison of the eGFR slopes using all on-treatment measures of eGFR made from the first on-treatment measurement to the final on-treatment measurement
- Changes in HbA_{1c}
- Utilization of AHA therapy
- The composite endpoint of 40% reduction in eGFR, renal death or requirement for renal replacement therapy
- The composite endpoint of doubling of serum creatinine, renal death, or requirement for renal replacement therapy

- The composite endpoint of 40% reduction in eGFR, renal death, requirement for renal replacement therapy, or death due to CV cause
- The composite endpoint of doubling of serum creatinine, renal death, requirement for renal replacement therapy, or death due to CV cause
- The composite endpoint of 40% reduction in eGFR, conversion to macroalbuminuria, renal death, or requirement for renal replacement therapy
- The composite endpoint of doubling of serum creatinine, conversion to macroalbuminuria, renal death, or requirement for renal replacement therapy

Safety Objective

Cardiovascular safety data from this study will be combined with the data from the other large-scale study of the effects of canagliflozin compared to placebo (CANVAS) in a pre-specified meta-analysis of cardiovascular safety outcomes.

2.2. Hypotheses

2.2.1. Primary Hypothesis

In subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk of CV events, canagliflozin compared to placebo reduces the rate of progression of albuminuria.

2.2.2. Secondary Hypotheses

In subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk of CV events, canagliflozin compared to placebo:

- Reduces the composite endpoint of death from CV causes or hospitalization for heart failure
- Reduces death from CV causes

3. OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the effects of canagliflozin compared to placebo on progression of albuminuria, an important intermediate marker of renal injury and progression of diabetic nephropathy. The study will be conducted in subjects with T2DM, receiving standard of care for hyperglycemia and CV risk factors, who have either a history or high risk of CV events. A total of 5,700 subjects will be recruited into the study. The study's last subject last visit is targeted to occur when the last subject randomized has approximately 78 weeks of follow-up or when 688 MACE events are accumulated between the CANVAS and CANVAS-R (DIA4003) studies(estimated to occur between January 2017 and April 2017). The effects of canagliflozin will be evaluated against a background of standard of care for the treatment of hyperglycemia and CV risk factors with study investigators counseled to assure appropriate management according to applicable national guidelines for the care of patients with T2DM with treatment individualized as clinically appropriate.

3.1. Study Design

The following section provides an overview of subject management including screening, run-in, and double-blind treatment.

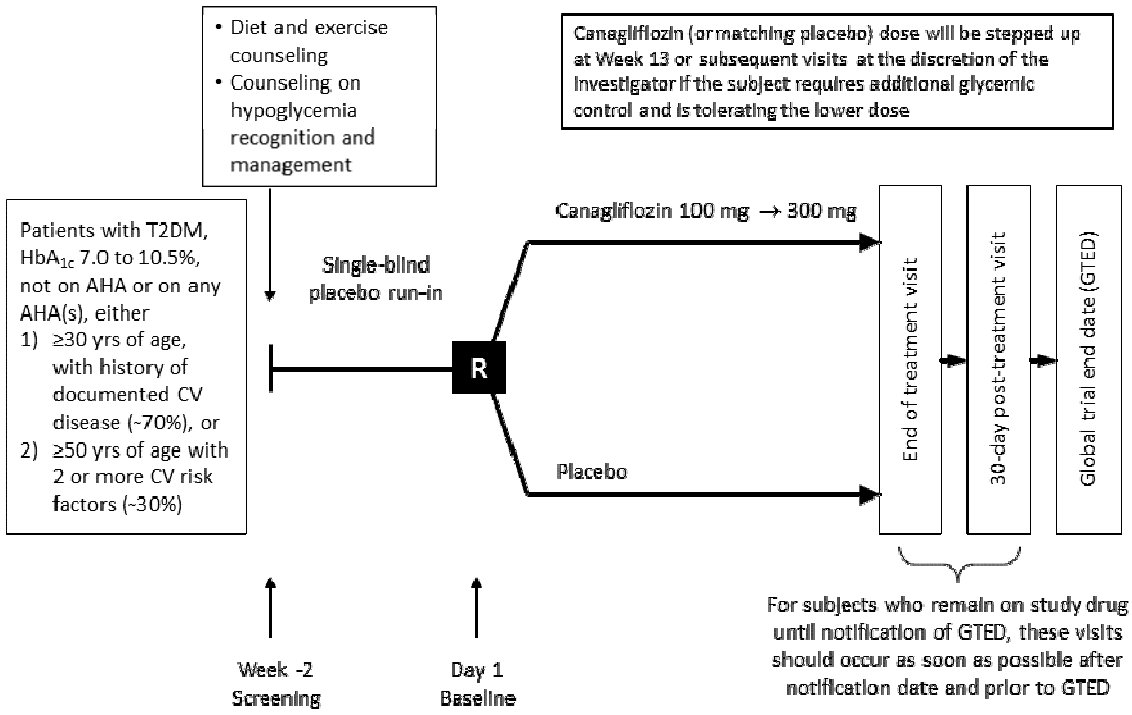
Screening Period

Subjects will undergo a screening visit for a preliminary determination of eligibility. Men or women with T2DM who are known to have inadequate glycemic control (HbA_{1c} ≥7.0 and ≤10.5%), not on an AHA, or on an AHA (oral or injectable [eg, insulin or GLP-1 analogue] in monotherapy or combination therapy, and who have known CV events or who have 2 or more risk factors for CV events are eligible (refer to Section 4.2, Inclusion Criteria).

At this visit, potentially-eligible subjects will enter a 2-week single-blind placebo run-in period. All subjects should receive diet/exercise counseling at the screening visit, be counseled on hypoglycemia recognition and management, and be dispensed single-blind placebo capsules. During this period, the investigator should also adjust/optimize the subject's medications to reduce CV risk (eg, anti-hyperglycemic, lipid-altering or blood pressure-lowering medications) as necessary. If in the investigator's opinion additional time is required for adjustment/optimization of these medications, the 2-week period between screening and randomization may be extended by having the subject continue single-blind placebo up to 2 additional weeks. Subjects should be counseled to perform fasting self-monitored blood glucose (SMBG) determinations, according to standard guidelines. This counseling, as well as the counseling regarding diet/exercise and hypoglycemia recognition/management, should begin with a focus during the screening phase and be reinforced as needed throughout the study.

An overview of the study design is illustrated in Figure 4.

Figure 4: Study Design Outline



AHA=antihyperglycemic agent; CV=cardiovascular; R = randomization; SU=sulfonylurea; T2DM= type 2 diabetes mellitus

Double-Blind Treatment Phase

Subjects meeting all inclusion and none of the exclusion criteria, and successfully completing the 2-week run-in period, will be randomly allocated to initial treatment with canagliflozin 100 mg or matching placebo administered once daily (in a 1:1 ratio). A total of 5,700 subjects will be randomized. After 13 weeks, the dose of canagliflozin (or matching placebo) may be increased from 100 mg to 300 mg if the subject requires additional glycemic control, provided the 100 mg dose is well tolerated. The dose should be increased if the subject requires additional glycemic control (eg, ≥50% of the subject's glucose determinations from the fasting SMBG [finger stick] readings [a minimum of 3 readings recommended] are >110 mg/dL [6 mmol/L] during the 2 weeks preceding the clinic visit or telephone contact) and the subject had no events of hypoglycemia or volume depletion in the preceding 2-week interval that in the opinion of the investigator would preclude dose titration. After increasing the dose to 300 mg, the dose should remain at 300 mg; however, if necessary, in the investigator's judgment, the dose may be decreased to 100 mg at any time point (eg, due to an adverse event of reduced intravascular volume). In addition, if there is need for additional glycemic control, the investigator should adjust the subject's AHA regimen as, per standard diabetes care guidelines, individualized as considered appropriate by the investigator. Adjustments in the AHA regimen should be carefully implemented throughout the study to minimize the risk of hypoglycemia. The investigator should optimize agents to reduce CV risk (eg, antihyperglycemic, lipid-altering and blood pressure-lowering medications) as required during the course of the trial to assure appropriate control consistent with standard care guidelines.

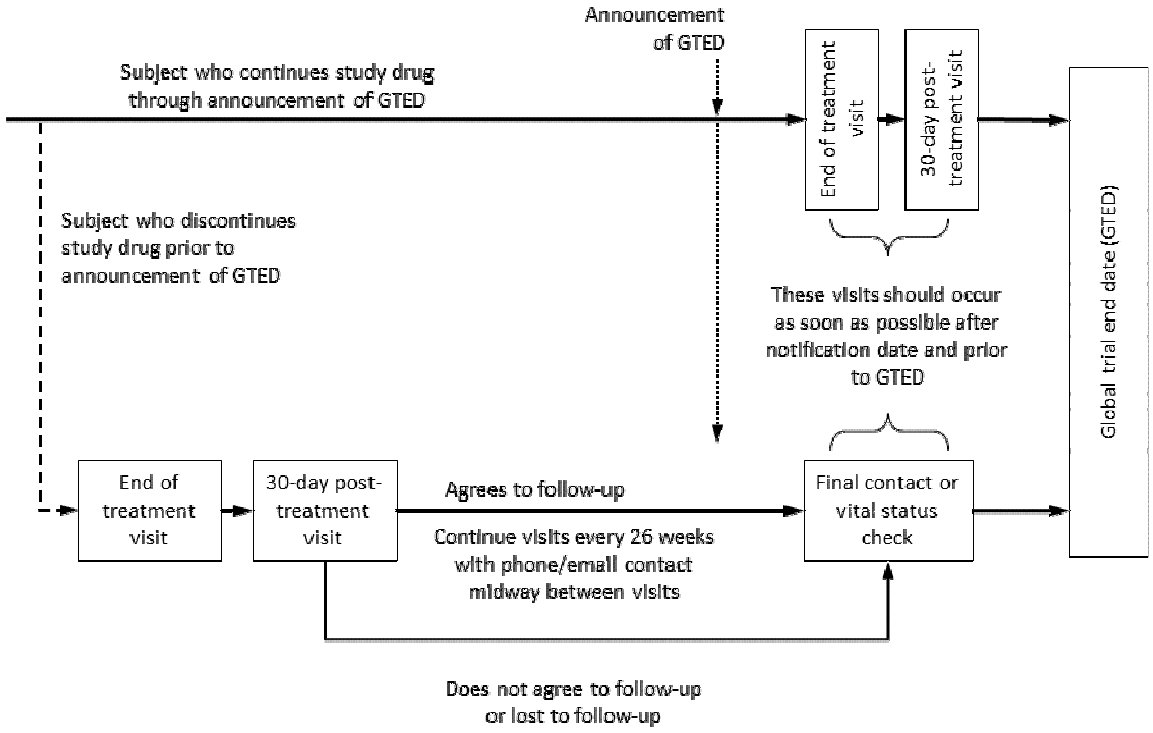
Study Duration

Subjects are expected to be followed for a maximum of about 3.5 years with the last visit for the last subject targeted to occur when all subjects have approximately 78 weeks of follow-up or when 688 MACE events are accumulated between the CANVAS and CANVAS-R (DIA4003) studies. All sites will be notified of the projected global trial end date (GTED) (projected to occur between January 2017 and April 2017). Immediately after the projected GTED notification is sent, for subjects who remain on double-blind study drug, sites will be required to schedule the last on treatment visits and the 30-day off drug follow-up visits as per the Time and Events schedule; for subjects who prematurely discontinue study drug, sites will be required to make a final contact (eg, schedule the last follow-up visit) or vital status check as soon as possible after announcement of GTED.

All visits (including the 30-day off drug follow-up visit) will need to be completed prior to the GTED.

Figure 5 shows the intended follow-up of randomized subjects with respect to the GTED.

Figure 5: Follow-up of Randomized Subjects with Respect to the GTED



Collection of data about Cardiovascular Safety Outcomes

Investigators will be required to report any cardiovascular (CV) event that they consider could possibly be a nonfatal MI or nonfatal stroke (refer to Section 9.2, Reporting/Adjudication of Events in the CV Composite Endpoint and Other Events for Adjudication), as well as all deaths. Additional information and documentation will be requested from investigators for all such

events to support a detailed assessment of these outcomes by an Endpoint Adjudication Committee.

Collection of Information After Early Discontinuation of Randomized Treatment

It is the intent that subjects who discontinue treatment with the study drug will continue in the study according to the visit schedule described in the Post-treatment Time & Events Schedule. After early discontinuation of randomized treatment, subjects will continue to be followed up for specific data collection, including any MACE events, vital signs, serious adverse events, and adverse events of interest.

Participants who prematurely discontinue study drug will require an immediate follow-up assessment (either on the day of study drug discontinuation or as soon as possible following study drug discontinuation) as well as a follow-up assessment approximately 30 days (±12 days) after last dose after which they should then continue to be followed for the full originally scheduled follow-up period through to study completion. If for some reason the subject is unable to be seen shortly after discontinuing study drug, the end of treatment visit may be omitted, but the 30-day off-drug follow-up visit should be performed. The follow-up regimen for these individuals will require 26-week visits interspersed with phone/email contact exactly as for those individuals that continue with randomized therapy (refer to Section 9.1.4, End-of-Treatment/Early Withdrawal, and Section 9.1.5, Posttreatment Phase [Follow-Up] for collection of information on CV events and other assessments).Safety Evaluations and Adverse Events of Interest

Safety evaluations will include the monitoring of serious adverse events, adverse events resulting in discontinuation, adverse events of interest, clinical laboratory tests, vital sign measurements, and measurement of body weight. For adverse events of interest, investigators will be asked to provide additional information, on separate electronic case report forms (eCRFs), so as to support more detailed analyses. Adverse events of interest include: all malignancies, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (eg, angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, male genital infections (balanitis, phimosis, events leading to circumcision), and pregnancy. Information on these events will be recorded on the supplemental eCRFs or other designated forms for any event that is serious or that leads to study drug discontinuation. The only exceptions are for malignancies, photosensitivity reactions, fractures, amputations, and venous thromboembolic events for which information on non-serious adverse events will also be recorded on the supplemental CRF pages or other designated forms (in addition to the information collected on serious AEs and AEs leading to study drug discontinuation). Diabetic ketoacidosis has been designated an adverse event of special interest and therefore adverse events related to diabetic ketoacidosis, ketoacidosis, metabolic acidosis or acidosis need to be reported to Janssen within 24 hours of becoming aware of the event, which is the same timeframe for reporting of serious adverse events. These adverse events must be reported using a supplemental DKA Reporting form, to complement standard information collected on the eCRF AE/SAE page. Amputations have also been designated as adverse events of special interest and

therefore amputations need to be reported to the sponsor within 24 hours of becoming aware of the event. If adverse events of interest are identified in the future, guidance concerning the reporting of those events may be provided to investigators via appropriately-documented study communications. Investigators may also be asked to provide additional information on other adverse events, based upon review by the Medical Safety Review Committee (MSRC) or the study Independent Data Monitoring Committee (IDMC) (Section 9.3.3, Medical Safety Review Committee, and Section 9.3.4, Independent Data Monitoring Committee). Refer to Section 3.2, Study Design Rationale, for review of rationale for collection of additional information on these selected adverse events.

Section 9.3, Study Management: Committees, provides details regarding the committees commissioned to provide oversight for the management of this study.

3.2. Study Design Rationale

Overall Design, Blinding, Control, Study Phases/Periods, Treatment Groups

This study was based upon the design of CANVAS and developed both to address the primary renal hypothesis and to meet the post-marketing requirements for canagliflozin defined by the US FDA. Broadly, the pretreatment phase allows sufficient time for study-related procedures to be performed, for subject eligibility to be determined and for optimization of background therapy by the investigators. Randomization, placebo control, and blinding will be used to minimize bias in the assignment of subjects to treatment groups and throughout data collection, and to maximize the likelihood that the study precisely and reliably addresses the questions it is designed to answer.

Study Population

The study population includes a broad spectrum of subjects on a variety of different AHAs with a range of different levels of baseline glycemic control and background risks of vascular and renal disease. The ratio of subjects with a history of CV events versus a high risk of CV events will be approximately 70% to 30%, respectively. Conducting the trial in this population will ensure broad generalizability of the trial results upon study completion.

Dosage Selection, Route of Administration, Dose Interval, Treatment Period

Both the 100 mg and 300 mg doses of canagliflozin are being used in this study. These are the doses that have been filed with health agencies for approval based on the results of the clinical program, and have been approved for marketing in some countries.

Choice of Renal Efficacy Measures

The development and progression of renal disease in people with diabetes follows a clearly defined pathway starting with microalbuminuria, progressing to macroalbuminuria, then to reduced renal function (lower glomerular filtration rate), and finally to renal failure with the need for dialysis or transplantation. To assess the effects of canagliflozin on the progression of diabetic nephropathy, the proportion of subjects with categorical progression of albuminuria based upon the urinary albumin/creatinine ratio in the first morning void is the primary endpoint

and will be assessed according to the categorizations defined in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Guideline #1 (KDOQI 2007): the definition of microalbuminuria is urinary albumin/creatinine ratio of 30 to 300 mg/g, and the definition of macroalbuminuria is urinary albumin/creatinine ratio greater than 300 mg/g.

In diabetes, the onset of urinary albumin excretion is a strong signal for progression of diabetic nephropathy (ADA 2004), and is associated with an increase in CV events (de Zeeuw 2004). In the present study, duplicate first morning void urine collections on consecutive days, made by subjects at home (collection of the first urine void after the individual awakes from sleep), are being used. These collections have been shown to be more accurate than spot urine collections (Witte 2009) because they are less influenced by urinary albumin changes associated with physical activity. In addition to the progression and regression of albuminuria, changes in eGFR will be analyzed in this study, since it is the basic measurement of renal function and is used to assess progression of renal disease (ADA 2004).

4. STUDY POPULATION

4.1. General Considerations

The study will include subjects with a diagnosis of T2DM and a history or high risk of CV events; the ratio of subjects with a history of versus high risk of CV events will be approximately 70% to 30%, respectively. The inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling the subject in the study.

4.2. Inclusion Criteria

Potential subjects must satisfy all of the following criteria to be enrolled in the study:

Inclusion Criteria at Screening Visit

- Man or woman with a diagnosis of T2DM with HbA_{1c} level ≥7.0% to ≤10.5% at screening and be either (1) not currently on AHA therapy or (2) on AHA monotherapy or combination therapy with any approved agent: eg, sulfonylurea, metformin, pioglitazone, alpha-glucosidase inhibitor, GLP-1 analogue, DPP-4 inhibitor, or insulin.
- History or high risk of CV events defined on the basis of either:
  - Age ≥30 years with documented symptomatic atherosclerotic CV events: including stroke; MI; hospital admission for unstable angina; coronary artery bypass graft; percutaneous coronary intervention (with or without stenting); peripheral revascularization (angioplasty or surgery); symptomatic with documented hemodynamically-significant carotid or peripheral vascular disease; or amputation secondary to vascular disease.
  - Age ≥50 years with 2 or more of the following risk factors determined at the screening visit: duration of T2DM of 10 years or more, systolic blood pressure >140 mmHg (average of 3 readings) recorded at the Screening Visit, while the subject is on at least one blood pressure-lowering treatment, current daily cigarette smoker, documented

micro- or macroalbuminuria (see Section 3.2, Study Design Rationale, for definition) within one year of screening, or documented HDL-C of <1 mmol/L (<39 mg/dL) within one year of screening.

Note: An overall target ratio of approximately 70%:30% for CV history (first category):risk factors (second category) will be implemented (with a maximum of approximately 40% in the second category). This target is intended to be a global ratio and may vary by region. The proportion of subjects in these categories will be monitored centrally.

Note: the term "documented" in the above paragraphs refers to the required information being clearly noted in hospital/clinical records or in physician-referral documents, copies of which should be retained in the subject's study files.

- Women must be:
  - postmenopausal, defined as
    - >45 years of age with amenorrhea for at least 18 months, or
    - >45 years of age with amenorrhea for at least 6 months and less than 18 months and a known serum follicle stimulating hormone (FSH) level >40 IU/L, or
  - surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal occlusion), or otherwise be incapable of pregnancy, or
  - heterosexually active *and* practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (eg, condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), or male partner sterilization, consistent with local regulations regarding use of birth control methods for subjects participating in clinical trials, for the duration of their participation in the study, or
  - not heterosexually active.

    Note: subjects who are not heterosexually active at screening must agree to utilize a highly effective method of birth control if they become heterosexually active during their participation in the study.
- Women of childbearing potential (ie, those subjects who do not meet the postmenopausal definition above, regardless of age) must have a negative urine pregnancy test at baseline (Day 1) and at screening if required by local regulations (Note: a serum pregnancy test is acceptable in lieu of a urine pregnancy test if required by local regulations).
- Willing and able to adhere to the prohibitions and restrictions specified in this protocol
- Subjects must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study

Inclusion Criterion for Randomization

- Subjects must have taken ≥80% of their single-blind placebo doses during the 2-weeks prior to randomization on Day 1 to be eligible for randomization.

4.3. Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

Diabetes-Related/Metabolic

- History of diabetic ketoacidosis, T1DM, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy
- History of one or more severe hypoglycemic episodes within 6 months before screening

  Note: a severe hypoglycemic episode is defined as an event that requires the help of another person.
- History of hereditary glucose-galactose malabsorption or primary renal glucosuria
- Ongoing, inadequately controlled thyroid disorder

  Note: subjects on thyroid hormone replacement therapy must be on a stable dose for at least 6 weeks before Day 1.

Renal/Cardiovascular

- Renal disease that required treatment with immunosuppressive therapy or a history of chronic dialysis or renal transplant. Note: subjects with a history of treated childhood renal disease, without sequelae, may participate.
- Myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident within 3 months before screening, or a planned revascularization procedure, or history of New York Heart Association (NYHA) Class IV cardiac disease (The Criteria Committee of the New York Heart Association).
- Known ECG findings within 3 months before screening that would require urgent diagnostic evaluation or intervention (eg, new clinically important arrhythmia or conduction disturbance)

Gastrointestinal

- Known history of hepatitis B surface antigen or hepatitis C antibody positive (unless known to be associated with documented persistently stable/normal range aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels), or other clinically active liver disease
- Any history of or planned bariatric surgery

Laboratory

- eGFR <30 mL/min/1.73m^2 at screening visit
- ALT levels >2.0 times the upper limit of normal (ULN) or total bilirubin >1.5 times the ULN, unless in the opinion of the investigator and as agreed upon by the sponsor's medical officer, the findings are consistent with Gilbert's disease

Other conditions

- History of malignancy within 5 years before screening (exceptions: squamous and basal cell carcinomas of the skin and carcinoma of the cervix in situ, or a malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence)
- History of human immunodeficiency virus (HIV) antibody positive
- Subject has a current clinically important hematological disorder (eg, symptomatic anemia, proliferative bone marrow disorder, thrombocytopenia)
- Investigator's assessment that the subject's life expectancy is less than 1 year, or any condition that in the opinion of the investigator would make participation not in the best interest of the subject, or could prevent, limit, or confound the protocol-specified safety or efficacy assessments
- Major surgery (ie, requiring general anesthesia) within 3 months of the screening visit or any surgery planned during the subject's expected participation in the study (except minor surgery, ie, outpatient surgery under local anesthesia)
- Any condition that, in the opinion of the investigator, would compromise the well-being of the subject or prevent the subject from meeting or performing study requirements

Medications/Therapies

- Current or prior use of an SGLT2 inhibitor.
- Prior or current participation in another canagliflozin study.
- Known allergies, hypersensitivity, or intolerance to canagliflozin or its excipients (refer to Section 14.1, Physical Description of Study Drug[s])
- Current use of a corticosteroid medication or immunosuppressive agent, or likely to require treatment with a corticosteroid medication (for longer than 2 weeks in duration) or an immunosuppressive agent. **Note**: subjects using inhaled, intranasal, intra-articular, or topical corticosteroids, or corticosteroids in therapeutic replacement doses may participate
- Received an active investigational drug (including vaccines) or used an investigational medical device within 3 months before Day 1/baseline

General

- History of drug or alcohol abuse within 3 years before screening
- Pregnant or breast-feeding or planning to become pregnant or breast-feed during the study
- Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator

  Note: Investigators should assure that all study enrollment criteria have been met and determine that the subject has not had any interval change in clinical status since screening. Before randomization, subjects whose status changes after screening, such that they now meet an exclusion criterion, should be excluded from participation.

4.4. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

- Prohibited medications include other SGLT2 inhibitors (including commercially available canagliflozin); subjects must not take any other investigational agents during the study (if a subject prematurely discontinues from the study medication but continues in the posttreatment follow-up phase, entering another investigational trial is discouraged but is not prohibited; however, entering another canagliflozin trial is prohibited)
- Strenuous exercise may affect urine protein excretion and other safety laboratory results; for this reason, strenuous exercise should be avoided within 72 hours before planned study visits
- Subjects should not collect first morning void urine specimens during acute illness with fever. The collection and respective visit should be postponed until the subject is recovered from the acute illness.

4.5. Rescreening

Subjects who do not meet all inclusion criteria or who meet an exclusion criterion may, at the discretion of the investigator, be rescreened if appropriate clinical management leads to study eligibility (eg, HbA_{1c} >10.5% that prompts adjustment of the subject's AHA regimen). Generally, a subject may only be rescreened once, but an additional rescreening may be allowed with concurrence of the sponsor's Medical Monitor.

Typically, rescreening will require that all screening parameters be repeated. However, with the concurrence of the sponsor's Medical Monitor, a non-qualifying laboratory test may be repeated one time, without completely rescreening the subject, in situations where there is a clinical reason to do so.

5. TREATMENT ALLOCATION

To ensure sufficient experience in subjects with a documented history of CV events – the highest risk group – approximately 70% of subjects (globally) are targeted to be in this group. The proportion of subjects in these categories will be monitored centrally.

Randomization and Blinding Procedures

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared under the supervision of the sponsor before the study. The randomization will be balanced by using randomly permuted blocks. Based on this randomization schedule, the study drug will be packaged and labeled. Medication numbers will be preprinted on the study drug labels and assigned as subjects qualify for the study and are assigned to double-blind treatment.

At baseline (Day 1), the randomization number and medication numbers, the treatment code, which is linked to the randomization schedule, will be assigned after logging on to the interactive web response system (IWRS) designated by the sponsor. The requestor must use his/her own

user identification (ID) and personal identification number (PIN) when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject. Based on this information, the IWRS will assign a unique treatment code, which will dictate the treatment assignment and study drug kit for the subject. As subjects are randomly assigned to treatment, the IWRS will assign a study drug kit to be dispensed at that visit. New medication numbers will be assigned each time the IWRS is contacted for dispensing additional study drug. The randomization (or initial subject allocation) number at baseline will be the identifying number linking all subsequent kits to the individual subject.

The study drugs, whether canagliflozin or placebo, will be identical in appearance and will be packaged accordingly to maintain the blind. The randomization code that links the randomization number assigned to the subject with a treatment group assignment will be maintained within the IWRS. This randomization code will not be provided to the investigator unless required, as described below, for unblinding in emergency situations.

The treatment blind should be broken to provide unblinded information to the site only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment through IWRS. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. The reason for unblinding is not captured through IWRS. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the appropriate section of the electronic case report form (eCRF) and in the source documents. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner (eg, in a sealed envelope) so as not to unblind the treatment assignment to the study site or sponsor personnel. The investigator is also advised not to reveal the study treatment assignment to the study site or sponsor personnel.

All randomization codes will be released after completion of the study. The translation of randomization codes into treatment and control groups will be disclosed only to those authorized.

Urine glucose measurements will not be performed on first morning void urine specimens, as an additional step to ensure the maintenance of the treatment blind. If a urinalysis must be performed locally for appropriate subject management (eg, to evaluate a potential infection), investigators should request microscopic rather than dipstick urinalysis (if microscopic evaluation is considered clinically sufficient).

6. DOSAGE AND ADMINISTRATION

6.1. Study Drugs

Two-week Single-Blind Placebo period following Screening

Upon completion of initial screening, all potentially eligible individuals will receive single-blind placebo capsules (one capsule to be administered once-daily) for 2-weeks to assess compliance.

Double-Blind Study Medication

On Day 1, subjects will be randomly assigned in a 1:1 ratio to 1 of 2 treatment groups: canagliflozin or matching placebo. Initially, canagliflozin will be provided at a dose of 100 mg daily, but at Week 13 (or any time thereafter) the dose of canagliflozin (or matching placebo) may be increased from 100 mg to 300 mg if the subject requires additional glycemic control, provided the 100 mg dose is well tolerated. The dose of study drug should be increased if the subject requires additional glycemic control (for example, ≥50% of the subject's glucose determinations from the fasting SMBG [finger stick] readings [a minimum of 3 readings recommended] are >110 mg/dL [6 mmol/L] during the 2 weeks preceding the clinic visit or telephone contact) and the subject had no events of hypoglycemia or volume depletion in the preceding 2-week interval that in the opinion of the investigator would preclude dose titration. After increasing the dose to 300 mg, the dose should remain at 300 mg; however, if necessary, in the investigator's judgment, the dose may be decreased to 100 mg at any time point (eg, due to an adverse event of reduced intravascular volume).

Subjects will be counseled to take their dose of canagliflozin or matching placebo, one capsule once daily, before the first meal of the day for the duration of the study or until early discontinuation. Subjects should take the first dose of study drug at the study center on Day 1.

The study drug must be swallowed whole with liquid and not chewed, divided, dissolved, or crushed. If the subject does not take the study drug within 12 hours after the first meal of the day, the dose of study drug should be skipped for that day and the subject should be instructed to take the study drug on the following day before the first meal of the day.

Study drug may be interrupted (eg, for safety and/or tolerability reasons such as hospitalizations for major surgical procedure or serious medical illness). Study drug interruptions, occurring for any reason and lasting 7 days or longer, will be documented on the eCRF. Study drug should be reinstituted once the subject has recovered and the safety and/or tolerability concern is no longer present.

For subjects who develop conditions that are associated with or leading to amputation such as a lower extremity infection, skin ulcer, osteomyelitis, gangrene or critical limb ischemia, study drug should be interrupted until the condition has resolved in the opinion of the investigator. In the event of an amputation, restarting of dosing with canagliflozin should only be done after careful consideration of the individual risk:benefit and following discussion with the sponsor.

6.2. Concomitant Antihyperglycemic and Other Therapies

6.2.1. Management of Glycemic Control and CV Risk Factors

Screening Management

Subjects will receive diet/exercise counseling at entry into the screening period. During this visit, subjects should also be counseled to perform fasting self-monitored blood glucose (SMBG) determinations, according to standard guidelines.

Double-blind Treatment Phase Glycemic Management

The background AHA regimen may be adjusted at any time during the study to achieve glycemic goals, using standard guidelines, and as considered appropriate by the investigator for the individual subject. Adjustment to the AHA regimen should be carefully implemented so as to avoid events of hypoglycemia.

Adjustment of AHA therapy after randomization will be performed by the investigator. The preferred initial option for enhancing glucose control is to increase the dose of canagliflozin/placebo, so if possible, after Week 13 the investigator should increase the dose of canagliflozin/placebo from 100 mg to 300 mg (see Section 6.1). If increasing the dose of canagliflozin/placebo is not effective, there is no specific AHA treatment algorithm required for this study and the responsible clinician is free to adjust therapy as appropriate. Treatment may include reinforcement of lifestyle counseling, addition of or up-titration to maximum labeled doses of oral and/or injectable AHAs as locally applicable, **except the use of any other approved SGLT2 inhibitor**. Investigators should make all reasonable efforts to achieve and maintain the subject's individualized target glycemic control, and may add unscheduled visits, if clinically appropriate, to monitor glycemic control, and adjust the subject's regimen. Adjustments to the AHA regimen should be documented in the appropriate eCRF.

During the double-blind treatment period, investigators should counsel subjects to perform fasting SMBG determinations according to standard guidelines.

Therapeutic Management of CV Risk Factors

Before randomization and throughout the study, investigators will be expected to manage the subject's diet/exercise and other medication regimens so as to achieve goals for CV risk factors (eg, HbA_{1c}, lipid levels, blood pressure) based upon standard guidelines for the care of subjects with T2DM.

The 2-week period between screening and randomization provides investigators with the opportunity to adjust the subject's regimen as needed to optimize the subject's CV risk factors. If in the investigator's opinion additional time is required for adjustment/optimization of agents to reduce CV risk (eg, anti-hyperglycemia, lipid-altering or blood pressure-lowering medications) prior to randomization, the 2-week period pre-randomization may be extended by having the subject continue single-blind placebo up to 2 additional weeks. Additional amendments can also be made to background therapy at any time during the course of follow-up.

7. TREATMENT COMPLIANCE

The investigator or designated study research staff will maintain a log of all drug dispensed and returned (including a count of capsules dispensed and returned). Drug supplies for each subject will be inventoried and accounted for throughout the study. Subjects who are poorly compliant with the study drug (based on capsule counts) should receive counseling on the importance of dosing compliance and should continue in the study.

Subjects will receive clear instructions on compliance with study procedures at the screening visit. During the course of the study, the investigator or designated study research staff will be

responsible for providing additional instructions to reeducate any subject who is not compliant with taking the study drug or with making required clinic visits.

Study drug interruptions, occurring for any reason and lasting 7 days or longer, will be documented on the eCRF.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy therapy is defined as any therapy used before the first dose of double-blind study medication. Concomitant therapy is defined as any therapy used after the first dose of double-blind study drug.

Selected classes of prestudy therapies administered up to 30 days before screening and up to the time of the first dose of double-blind study drug will be documented. Likewise, selected classes of concomitant therapies taken after the first dose of double-blind study drug will be documented. Examples of the classes of interest may include AHAs such as sulfonylureas, metformin, pioglitazone, alpha-glucosidase inhibitors, GLP-1 analogs, DPP-4 inhibitors, all forms of insulin, as well as non-AHAs such as renin angiotensin aldosterone system (RAAS) inhibitors, diuretics, beta-blockers, calcium channel blockers, statins, and anti-thrombotics. Checkboxes may be used on eCRFs to capture the required information on prestudy and concomitant agents. Details will be provided in the eCRF completion guidelines regarding the specific types of medications that fall in the categories of interest and what information will be collected.

Concomitant therapies will not be provided or reimbursed by the sponsor.

Disallowed Therapies

Other SGLT2 inhibitors (including canagliflozin) may <u>not</u> be used concurrently, and subjects should not take any other investigational agents during the study. If the use of another SGLT2 inhibitor or investigational agent is reported during the study, the subject's physician should be contacted, the other agent discontinued, and the subject should continue in the study.

The sponsor must be notified as soon as possible of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule that follows the Synopsis summarizes the frequency and timing of efficacy, safety, and other measurements applicable to this study.

Visit Schedules and Visit Windows

Single-blind pre-randomization period - The recommended visit window for the initial single-blind placebo phase of the study is 2 weeks ±4 days. If in the investigator's opinion

additional screening time is required for adjustment/optimization of agents to reduce CV risk (eg, anti-hyperglycemia, lipid-altering, blood pressure-lowering or other medications), the screening period may be extended by having the subject continue single-blind placebo therapy for up to 2 additional weeks.

Post-randomization period - Subsequent scheduled in-clinic study visits during the first year of the study should occur at Day 1 (baseline, the day of randomization) and Weeks 13, 26, and 52. After the first year, scheduled in-clinic study visits should occur at 26-week intervals with telephone contacts approximately midway between visits. For the Week 13 and Week 26 visits, the recommended visit window is ±7 days. After Week 26, the recommended visit window is ±14 days. Phone/email contacts will occur at approximately 26-week intervals in between the scheduled in-clinic visits. Similar windows are proposed for the phone/email contacts made between visits.

In the event that it is impossible for a subject to make a scheduled clinic visit, telephone contacts may be conducted at the time of the missed visit, but a clinic visit should be scheduled as soon as possible thereafter. If a telephone contact or study visit is not possible, follow-up information may be collected via email or any other appropriate means. Details regarding discussions via telephone, email, or other such contacts must be properly documented in source records, including responses by the subject.

For study visits that are unable to be held within the protocol-recommended visit windows, the visit should be conducted as close as possible to the protocol-specified study visit timing. All subsequent visits should be scheduled based on the date of randomization, not the date of the rescheduled visit.

For subjects who complete double-blind study drug through the time of site notification of the projected GTED, it will be important for sites to schedule the last on-treatment visit as soon as possible after the notification date and the 30-day off drug visit prior to the GTED.

For subjects who prematurely discontinue study drug, sites will be required to make a final contact (eg, schedule the last follow-up visit) or vital status check as soon as possible after announcement of GTED.

Pregnancy Testing

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the study (refer to the Time and Events Schedule that follows the Synopsis for further details regarding urine pregnancy testing).

9.1.2. Pretreatment Phase

Screening Visit (Week -2)

Potential subjects will be seen at a screening visit, approximately 2 weeks before scheduled randomization, at which informed consent will be obtained and an initial assessment of eligibility will be performed.

At the screening visit, a focused medical history and initial screening assessment of inclusion/exclusion criteria will be performed and samples for required laboratory tests will be collected. Laboratory specimens will be obtained as described in the Time and Events Schedule. An operations manual will be provided to describe collection, processing, and shipping procedures for the duration of the study.

At this visit, subjects who appear to meet enrollment criteria may then be dispensed single-blind placebo capsules and enter the 2-week single-blind placebo run-in period. An assessment of the subjects' adherence to protocol procedures during this period will be made at the end of the period, before randomization, and will provide investigators with an opportunity to assess subjects' compliance with taking the single-blind study drug (by counting capsules).

Subjects who do not meet all inclusion criteria or meet a study exclusion criterion should be excluded from the study.

The screening visit and the 2-week run-in period provide investigators with the opportunity to evaluate and optimize management of CV risk factors prior to randomization as required (refer to Section 6.2.1, Management of Glycemic Control and CV Risk Factors) and to provide subjects with counseling regarding diet and exercise consistent with applicable local guidelines.

9.1.3. Double-Blind Treatment Phase

Day 1/Day of Randomization

Potential participants who return for the Day 1 (baseline) visit, who have taken ≥80% of the scheduled single-blind placebo capsules during the period between screening and randomization, and who meet the enrollment criteria will be randomly assigned to once-daily treatment with canagliflozin or matching placebo. Subjects will continue treatment until the study completes or the subject is prematurely withdrawn from double-blind study medication (refer to Section 10.2, Withdrawal From the Study, for reasons for withdrawal).

At the randomization visit, in some countries or regions (at the option of local sponsor representatives), subjects will be given a glucose meter and materials for SMBG measurements and instructed on the performance of SMBG.

Visits Following Randomization

Subjects will be seen in the clinic at visits as described in Section 9.1.1, Overview, and in the Time and Events Schedule. Procedures and clinical laboratory assessments for each visit or contact are outlined in the Time and Events Schedule.

Subjects who experience nonfatal CV events (ie, nonfatal MI, nonfatal stroke) during the double-blind treatment phase will continue in the study, continuing to receive double-blind study drug and complete all assessments at all scheduled visits, as appropriate.

On designated visits (see the Time and Events Schedule that follows the Synopsis), subjects will bring to the clinic duplicate first morning void urine specimens (collection of the first urine void after the individual awakes from sleep), one from the morning of the visit, and one from the morning of the day prior to the visit. If the urinary albumin/creatinine result reflects a stage change from an earlier measurement (eg, progression from normoalbuminuria to microalbuminuria, or regression from macroalbuminuria to microalbuminuria), the subject will be contacted to bring 2 additional consecutive-morning first morning void urine specimens to the clinic approximately 1 to 2 months later (or sooner under unusual circumstances, eg, subject is discontinuing study drug). If the subject is unable to return the specimens in person, the site may engage a courier service to deliver the specimen to the site. If the subject does not provide the morning void collections on the day of the visit, the subject may bring a first morning void specimen to the investigational site during the subsequent week. For subjects working a night shift, or who otherwise have atypical sleep patterns, the collection should be made at the end of the subject's usual sleep period. Collection containers and directions will be provided to subjects at prior visits. The site staff should call subjects a few days prior to visits to remind them to make the consecutive urine collections and bring them to the clinic.

9.1.4. Post-Treatment Follow-up for Participants who Withdraw from Randomized Treatment Early

Early withdrawal from randomized treatment will require the immediate collection of key data as soon as possible after stopping the study drug as well as an off-drug clinic visit approximately 30 days (+/-12 days) after discontinuation. The Time and Events Schedule that follows the Synopsis describes the evaluation required. It is important to note that subjects who discontinue randomized treatment early will be required, wherever possible, to continue with scheduled visits. While the data collection required for participants who discontinue randomized treatment early will be somewhat modified, comprehensive follow-up, as described in the Time and Events Schedule will be essential for every randomized subject.

For subjects who prematurely discontinue study drug, sites will be required to make a final contact (eg, schedule the last follow-up visit) or vital status check as soon as possible after announcement of GTED.

9.1.5. Post-Treatment Follow-up for Participants that Complete Randomized Treatment as Initially Scheduled

Subjects who complete double-blind study drug through the time of notification of the projected GTED will have a final on-treatment visit as soon as possible followed by a 30-day off-drug visit to occur no later than the GTED. At this visit, a blood specimen for laboratory measurement will be collected as well as assessments of any serious adverse event, CV event, or adverse events of interest.

9.1.6. Post-Randomization Follow-up for Participants Unable to Attend Scheduled Visits

Subjects who are no longer able to continue to attend clinic visits for scheduled follow-up must have an alternate follow-up plan put in place. The options for this follow-up include:

- Less frequent clinic visits (eg, annual or to coincide with other care)
- Telephone, e-mail, letter, social media, fax, or other contact with the subject
- Telephone, e-mail, letter, social media, fax, or other contact with relatives of the subject
- Telephone, e-mail, letter, social media, fax, or other contact the subject's physicians (family or specialist)
- Review of any available medical records

These alternate follow-up methods should be planned to coincide with the visit times outlined in Time and Events schedule. Wherever possible follow-up should be made at least once each year and in very rare cases where this cannot be achieved arrangements must be made to follow-up with the participant at the scheduled completion of the study. Details regarding discussions via telephone, email, or other such contacts must be properly documented in source records, including responses by the subject.

If all means of follow-up fail, at a minimum, the site must attempt to collect vital status data, as noted in Section 10.5, Circumstances for Reduced Follow-up, by consulting family members, the subject's physicians and medical records, or public records, including the use of locator agencies as permitted by local law.

In the rare instance that a site closes for operational, financial or other reasons and subjects are unable to be contacted regarding site closure, data from that site will be transferred to another site for a check of public records and/or vital status (at a minimum).

9.2. Reporting/Adjudication of MACE and Other Events for Adjudication

Investigators will be counseled to report any event that they assess as potentially being a MACE (CV death, nonfatal MI, nonfatal stroke). In addition, all deaths (to determine cause of death), as well as events of hospitalized heart failure, will be submitted for adjudication.

Investigators must provide a specific package of information to be submitted for adjudication evaluation that will be provided in a procedural manual. An independent Endpoint Adjudication Committee will assess these events according to the committee's charter. The Endpoint Adjudication Committee will classify the events while blinded to treatment assignment.

Note that events assessed by the investigator as nonfatal MI or nonfatal stroke (ie, nonfatal MACE) are not immediately subject to expedited serious adverse experiences reporting requirements (refer to Section 12, Adverse Event Reporting). If the event is adjudicated by the Endpoint Adjudication Committee as not meeting the nonfatal MACE definition, then the event will then be subject to expedited serious adverse experiences reporting requirements, (with

reporting timelines starting at the time of notification of this by the Endpoint Adjudication Committee).

9.3. Study Management: Committees

9.3.1. Academic Research Organization

An Academic Research Organization (ARO) will provide scientific and academic oversight of the study. The ARO will also have a role in site management and monitoring for a portion of the sites.

9.3.2. Steering Committee

The Steering Committee responsible for monitoring the CANVAS study will also be responsible for monitoring the current study, CANVAS-R. This Steering Committee, made up of external scientific experts, will provide scientific advice regarding the study design, conduct, and data collection. The Steering Committee is responsible for providing input on study design, academic leadership to study sites, reviewing study progress, and reviewing study results before publication. Details of the composition, roles, and responsibilities of the Steering Committee are documented in its charter.

9.3.3. Medical Safety Review Committee

An MSRC will be established to ensure that the safety of subjects participating in the study is not compromised. The MSRC will include, but will not be limited to, at least one medical expert and at least one statistician. The MSRC will include members from the sponsor organization and may also involve ARO representatives. The MSRC will monitor the progress of the study by reviewing blinded data on a regular basis and will refer safety concerns to the IDMC.

Details of the composition, roles, and responsibilities will be documented in its charter.

9.3.4. Independent Data Monitoring Committee

The IDMC responsible for monitoring the CANVAS study to periodically review accumulating unblinded safety information during the study will also be responsible for monitoring the current study, CANVAS-R. Details of the composition, roles, and responsibilities are documented in its charter.

The IDMC will have responsibility for review of serious adverse events, events resulting in study drug discontinuation, CV events, and adverse events of interest for this study as well as across the broader canagliflozin clinical trials program.

9.3.5. Endpoint Adjudication Committee

The independent Endpoint Adjudication Committee (EAC) responsible for adjudicating CV events in the CANVAS study will also be responsible for adjudicating CV events in the current study, CANVAS-R. The EAC is composed of external specialists, blinded to treatment assignment. The operations, processes, and endpoint definitions to be employed by the committee are defined in its charter.

9.4. Safety Evaluations

Safety and tolerability will be evaluated on the basis of the overall incidence of serious adverse events, adverse events that lead to study drug discontinuation, adverse events of interest, the incidence of MACE events (overall and within the first 30 days of study drug treatment), vital signs (pulse, blood pressure), and body weight. Adverse events that do not meet the definitions above will not be collected.

The safety data from this study will be combined with the data from the other large-scale study of the effects of canagliflozin compared to placebo (CANVAS) in a pre-specified meta-analysis of cardiovascular safety outcomes to meet regulatory requirements set at the time marketing authorization for canagliflozin was granted. The CV meta-analysis will be described in a separate document with a specific statistical analysis plan.

Serious Adverse Events and Adverse Events Leading to Discontinuation

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally-acceptable representative) for the duration of the study, beginning from when informed consent is provided. Information about all adverse events (serious or not) should be recorded in source documents (eg, progress notes) according to good clinical practice, and retained at the investigative sites. Only serious adverse events, nonserious adverse events that result in study drug discontinuation, and adverse events of interest will be recorded on eCRFs.

For purposes of reporting serious adverse events for this study, nonfatal MI and nonfatal stroke events (ie, nonfatal MACE) will not immediately be subject to expedited serious adverse event reporting requirements. Refer to Section 12, Adverse Event Reporting, for details regarding the handling of MACE.

Collection of Additional Information for Adverse Events of Interest

Adverse events of interest include: all malignancies, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (eg, angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, male genital infections (balanitis, phimosis, events leading to circumcision), and pregnancy. Information on these events will be recorded on the supplemental eCRFs or other designated forms for any event that is serious or that leads to study drug discontinuation. In addition, non-serious adverse events of malignancies, photosensitivity reactions, fractures, amputations, and venous thromboembolic events will also be recorded on the supplemental CRF pages or other designated forms (in addition to the information collected on serious AEs and AEs leading to study drug discontinuation). Diabetic ketoacidosis has been designated an adverse event of special interest and therefore adverse events related to diabetic ketoacidosis, ketoacidosis, metabolic acidosis or acidosis need to be reported to Janssen within 24 hours of becoming aware of the event, which is the same timeframe for reporting of serious adverse events. These adverse events must be reported using a supplemental DKA Reporting form, to complement standard information collected on the eCRF AE/SAE page. Amputations have also been designated as adverse events of special interest and therefore amputations need to be reported to the sponsor within 24 hours

of becoming aware of the event. If adverse events of interest are identified in the future, guidance concerning the reporting of those events may be provided to investigators via appropriately-documented study communications.

Investigators will be asked to provide additional information so as to support more detailed analyses. Investigators may also be asked to provide additional information on other adverse events, based upon review by the MSRC or the IDMC (refer to Section 9.3.3, Medical Safety Review Committee, and Section 9.3.4, Independent Data Monitoring Committee).

Events with characteristics of DKA will be adjudicated by an ad hoc adjudication committee, to verify whether or not the event meets a specified definition of DKA. Other categories of events (eg, renal) may undergo adjudication as necessary based on regulatory agency requests or to supplement data analyses.

Follow-Up Collection of Safety Information

Any clinically significant abnormalities persisting at the time treatment is discontinued (either prematurely or at completion of the study) will be followed by the investigator until resolution or until a clinically stable outcome is reached, or until further follow-up is no longer considered by the investigator to provide clinically meaningful information. (see Sections 9.1.4, 9.1.5, and 12.2.2 for additional details regarding follow-up).

Clinical Safety Laboratory Tests

Subjects will be monitored with safety laboratory measurements as described in Attachment 1.

The investigator must review the laboratory reports, document this review, and record any serious adverse changes occurring during the study in the adverse event section of the eCRF.

Vital Signs (pulse, blood pressure)

Vital signs will consist of pulse and blood pressure measurements and will be obtained after the subject has been in the sitting position for 5 minutes and before blood sample collection for laboratory tests. Pulse rate will be measured once at each clinic visit. Blood pressure will be assessed manually with a mercury sphygmomanometer, or an automated blood pressure monitor; if neither of these is available, a high-quality aneroid sphygmomanometer will be acceptable. Calibration of the blood pressure measuring device is not required for this trial, but if the institution has a calibration policy, compliance with this policy is expected. Three consecutive blood pressure readings will be taken and recorded, at intervals of at least 1 minute apart, as specified in the Time and Events Schedule; the average of the 3 readings will be recorded in the eCRFs.

For each subject, a consistent arm should be used for blood pressure measurements across the course of the study. If possible, if blood pressure is measured manually, it should be measured by the same individual, using the same equipment, at each clinic visit to reduce variability.

Body Weight

Body weight will be measured using a consistent scale at each visit. Scale calibration is not required for this trial, but if the institution has a scale calibration policy, compliance with this policy is expected. As far as possible, subjects should be weighed at approximately the same time of day on the same scale, wearing underwear and a gown and without shoes (note: if disrobing for weighing is logistically impossible, the subject should be dressed as lightly as possible, with consistency from visit to visit); subjects will be asked to urinate before being weighed.

Urine Pregnancy Testing

Urine pregnancy testing will be performed on all women unless they are surgically sterile or unless there is a documented history of their postmenopausal status. A urine pregnancy test will be performed at the baseline visit unless a serum pregnancy test is preferred at the discretion of the investigator or if required by local regulations (if a serum pregnancy test is required, it will be performed at the screening visit). Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the study (refer to Section 12.2.3, Pregnancy, for instructions in cases of a positive pregnancy test).

9.5. Measures of Efficacy/Efficacy Endpoints

The categorical efficacy endpoint of the proportion of subjects with progression of albuminuria (defined as ≥1 step increase in category of albuminuria [ie, none to micro- or macro, or micro- to macroalbuminuria]) will be assessed from urine collections according to the categorizations defined in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Guideline #1 (KDOQI 2007). The definition of microalbuminuria is urinary albumin/creatinine ratio of 30 to 300 mg/g and the definition of macroalbuminuria is urinary albumin/creatinine ratio greater than 300 mg/g.

On designated visits, subjects will bring to the clinic duplicate first morning void urine specimens (collection of the first urine void after the individual awakes from sleep), one from the morning of the visit, and one from the morning of the day prior to the visit. If the urinary albumin/creatinine result reflects progression or regression of albuminuria from the baseline (eg, progression from normoalbuminuria to microalbuminuria or macroalbuminuria accompanied by a urinary ACR value increase of ≥30% from baseline; or regression from macroalbuminuria to microalbuminuria or normoalbuminuria accompanied by a urinary ACR value decrease of ≥30% from baseline), the subject will be contacted to bring 2 additional consecutive-morning first morning void urine specimens to the clinic approximately 1 to 2 months later (or sooner under unusual circumstances, eg, subject is discontinuing study drug). If the subject is unable to return the specimens in person, the site may engage a courier service to deliver the specimen to the site. If the subject does not provide the morning void collections on the day of the visit, the subject may bring a first morning void specimen to the investigational site during the subsequent week. For subjects working a night shift, or who otherwise have atypical sleep patterns, the collection should be made at the end of the subject's usual sleep period. Collection containers and directions will be provided to subjects at prior visits. The site staff should call subjects a few

days prior to visits to remind them to make the consecutive urine collections and bring them to the clinic.

10. SUBJECT COMPLETION, PREMATURE DISCONTINUATION OF TREATMENT, LOSS TO FOLLOW-UP AND WITHDRAWAL OF CONSENT

10.1. Subject Completion

A subject will be considered as having completed the study, regardless of whether the subject is on or off study drug, if the subject is followed until a time point between the notification of the GTED and the GTED (eg, subjects who complete the treatment need to have a final posttreatment follow-up visit; subjects who withdraw early from the treatment need to have a final contact after the notification of the GTED), or at the time of death for subjects who die prior to the GTED. The occurrence of a nonfatal MI, nonfatal stroke or any other safety of efficacy outcome does not comprise study completion and is not a criterion for withdrawal from the study or study drug.

10.2. Premature Discontinuation of Study Medication

A subject will discontinue study medication for any of the following reasons:

- The investigator believes that for safety or tolerability reasons it is essential for the subject to stop treatment
- The investigator formally unblinds the subject's treatment allocation
- The subject becomes pregnant (study therapy should be immediately discontinued based upon a positive urinary hCG, and permanently discontinued if confirmed by a serum β-hCG test)
- The subject's eGFR is <15 mL/min/1.73m^2 (as reported by the central laboratory).

  Note: the central laboratory will alert the investigator for eGFR falls to <15 mL/min/1.73m^2. A repeat determination should be performed within 2 weeks, and study treatment discontinued if the repeat eGFR is <15 mL/min/1.73m^2 (unless a reversible cause is identified [eg, short-term illness or transient volume depletion] in which case an additional repeat determination can be performed after resolution of the short-term illness).
- Subject requires dialysis or renal transplantation
- Subject requires disallowed therapy (refer to Section 8, Prestudy and Concomitant Therapy)
- The subject experiences a serious adverse event of biochemically-confirmed (eg, pH, serum ketones, anion gap) DKA.

Premature discontinuation of study treatment does not comprise study completion and is not a criterion for withdrawal from the study. All subjects who prematurely discontinue study treatment should continue study follow-up, although the nature of follow-up may be modified (see Section 9.1.4 and the Time and Events Schedule). Treatment should be recommenced wherever possible and routinely considered at every visit following discontinuation.

Subjects who decide to withdraw from double-blind study drug must be interviewed by the investigator so as to determine if a specific reason for withdrawal can be identified. Withdrawing

subjects should be explicitly asked about the contribution of possible adverse events to their decision to withdraw consent, and any adverse event information elicited should be documented. If the subject elects to withdraw due to an adverse event, the event should be recorded as the reason for withdrawal, even if the investigator's assessment is that the adverse event would not require study drug withdrawal. The reason for withdrawal is to be documented in the eCRF and in the source documentation. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

10.3. Reinstitution of Treatment for Subjects Who Have Prematurely Discontinued Double-Blind Study Drug to Active Status

Subjects for whom study drug is interrupted as a result of an adverse event, a life event (eg, temporary relocation to care for an ill family member), or other unforeseen circumstance should be encouraged to recommence study drug unless there is a clear contraindication at the discretion of the investigator, with concurrence from the sponsor's medical monitor.

Study drug interruptions, occurring for any reason and lasting 7 days or longer, will be documented on the eCRF.

10.4. Lost to Follow-up

If a subject is lost to follow-up, all possible efforts must be made by the study site personnel to contact the subject and to achieve as complete follow-up as possible until after the site notification of the GTED. The measures taken to achieve follow-up are discussed in Section 10.5, Circumstances for Reduced Follow-up, and must be documented. The informed consent form will stipulate that even if double-blind study drug is discontinued, he/she will agree to continue follow-up.

10.5. Circumstances for Reduced Follow-up

There may be circumstances in which a reduced follow-up schedule is required and the options for this are described in Section 9.1.6, Post-Randomization Follow-up for Participants Unable to Attend Scheduled Visits. If one of these regimens is not possible, it will be necessary for the site investigator to contact the Sponsor representative to indicate the reasons why no further follow-up is necessary. It is important to note that a subject declining further follow-up does not constitute withdrawal of consent and the alternate follow-up mechanisms that the participant agreed to when signing the consent form will still apply (eg, searches of databases, use of locator agencies at study completion) as permitted by local regulations.

In this regard, the subject will be asked as a condition of entry into the study to agree to grant permission for the investigator to consult family members, the subject's physicians and medical records, or public records, including the use of locator agencies as permitted by local law, to determine the subject's status with respect to the CV safety composite endpoint, in the event the subject is not reachable by conventional means (eg, office visit, telephone, e-mail, or certified mail). The subject is also to be advised that if the site of the study doctor closes, and the study doctor cannot reach the subject to inform him/her, the contact information will be transferred to another site where a new study doctor will consult with family members, the subject's physicians

and medical records, or public records, including the use of locator agencies as permitted by local law, to determine the subject's endpoint status.

10.6. Withdrawal of Consent

Withdrawal of consent should be a very unusual occurrence in a clinical trial. The investigator should make every effort to maintain a good relationship with subjects to avoid this occurrence. In many instances where withdrawal of consent could potentially be recorded, the subject could be expected to be followed-up through one of the alternative follow-up mechanisms discussed in Section 10.5, Circumstances for Reduced Follow-up.

Withdrawal of consent in this trial may only be logged in the eCRF after a discussion between the investigator and the appropriate sponsor representative.

For subjects truly requesting withdrawal of consent, it is recommended that the subject withdraw consent in writing; if the subject or the subject's representative refuses or is physically unavailable, the site should document and sign the reason for the subject's failure to withdraw consent in writing.

If a subject had previously withdrawn consent but decides to retract that withdrawal, the subject will be reconsented. The investigator will be responsible for making all required notifications to the IRB or Ethical Committee.

11. STATISTICAL METHODS

11.1. Analysis Sets

The intent-to-treat (ITT) analysis set includes all subjects who are randomized via the Interactive Web Response System (IWRS). The assessment of the primary and most of the secondary objectives will be based upon this analysis set.

The modified intent-to-treat (mITT) or On-Treatment analysis set includes all subjects who are randomly assigned to a treatment group and receive at least one dose of double-blind study. It will be used in the analyses assessing on-treatment effects, e.g. time slope of on-treatment eGFR.

Efficacy data will be analyzed according to the initial randomization assignment regardless of actual treatment received.

11.2. Sample Size Determination

Based on the interim data from the CANVAS study, where ACR was measured periodically at scheduled visits, it is projected that the annual progression rate for the CANVAS-R study will be approximately 7.4%. Assuming a 22% relative risk reduction for albuminuria progression, an annual progression rate in the placebo arm of 7.4%, an 18-month accrual period, a maximum treatment period of 36 months, and an annual discontinuation (from treatment) rate of 10%, it is estimated that 693 events will be reported. With 5,700 subjects enrolled, the power to demonstrate the superiority of canagliflozin over placebo for albuminuria progression is 90.5%, with type I error rate of 0.05 (two-sided).

11.3. Efficacy Analyses

11.3.1. Primary Efficacy Analysis

In this study, duplicate urine specimens will be collected for all ACR measurements. At each visit, the geometric mean of the duplicate measurements will be computed and used for all subsequent analysis unless otherwise specified.

Subjects will be classified as having normoalbuminuria (urinary ACR of <3.5 mg/mmol [<30 mg/g]), microalbuminuria (ACR ≥3.5 mg/mmol [≥30 mg/g] and ≤35 mg/mmol [≤300 mg/g]), or macroalbuminuria (ACR of >35 mg/mmol [>300 mg/g]).

The primary efficacy analysis seeks to demonstrate the superiority of canagliflozin in the reduction of albuminuria progression relative to placebo.

The time from first study drug administration to first visit date observing progression (ie, not using the visit date of the repeat sample collection) of albuminuria will be analyzed using a Cox proportional hazards regression model. The model will include treatment and baseline albuminuria status as covariates. The hazard ratio between canagliflozin and placebo will be provided, including its 95% confidence interval. The observation period for this time-to-event analysis will include all available measurements from first study drug administration to the visit date of the last ACR measurement. Subjects with no progression will be censored at the visit date of the last albuminuria measurement.

As a sensitivity analysis, the actual onset time of progression of albuminuria can be determined to lie within an interval from a sequence of examination times (ie, data are interval censored). As a supportive analysis, the accelerated failure time (AFT) model with log normal error structure will be implemented considering interval censoring. The dependent variable in AFT model is logarithm of time to progression of albuminuria. The model will include treatment group and baseline albuminuria status as covariates. We can use speed of progression to interpret AFT model. For any time (t), the probability of a subject on placebo progression-free beyond time t is the probability of a subject on canagliflozin progression-free beyond t/α, where α is the acceleration factor which can be estimated from the model. Additional sensitivity analyses will be specified in the study SAP.

The cumulative progression rate derived from Kaplan-Meier estimate will be displayed graphically to evaluate the timing of progression and the consistency of the treatment effect over time.

11.3.2. Secondary Efficacy Analyses

The secondary efficacy analysis seeks to demonstrate the superiority of canagliflozin in the reduction of the following CV events relative to placebo.

- Composite of CV death or hospitalization for heart failure
- CV death

The analysis of these CV endpoints will be based on the time to first occurrence of the events using the ITT analysis set. The hazard ratio of all canagliflozin compared to placebo and its 95% CI will be estimated using a stratified Cox proportional hazards regression model with treatment (all canagliflozin and placebo) as the explanatory variable and prior CV disease subgroup (secondary prevention and primary prevention) as the stratification factor.

11.3.3. Exploratory Efficacy Analyses

Regression of albuminuria will be analyzed in a similar fashion as the analysis for progression of albuminuria.

For change in eGFR from baseline to the off-treatment measurement, an analysis of covariance (ANCOVA) model will be used with treatment as a fixed effect and adjusting for the baseline eGFR value. The treatment difference in the least-squares means and their 2-sided 95% CI will be estimated.

Since the distribution of ACR is highly skewed, the log-transformed ACR values for all the post-baseline and scheduled visits will be modeled using a linear mixed-effect model. The model will include treatment group and logarithm of baseline ACR value, visit, and treatment-by-visit interaction as fixed effects. The percentage treatment difference can be calculated by taking the anti-logarithm of the estimated coefficient for the treatment group and subtracting 1.

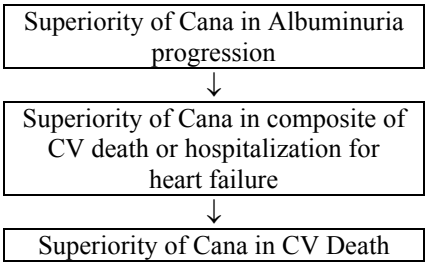
For on-treatment eGFR measurements, a linear mixed effects model will be fitted to eGFR as a dependent variable, including treatment, baseline eGFR value, time (as a continuous variable), and treatment time interaction as fixed effects and including subject effect as a random intercept and time as a random slope. The parameter of interest is the coefficient for treatment and time interaction term, which measures the slope difference between canagliflozin and placebo.

The effect of canagliflozin relative to placebo on changes in HbA_{1c} over time will evaluated using a linear mixed effects model. The use of AHA therapy over time will also be summarized by treatment group.

11.3.4. Multiplicity Adjustment

A testing sequence for the CV program consisting of the integrated database of CANVAS and CANVAS-R is specified. The testing of the endpoints in CANVAS-R is specified as part of the sequence. To control the type I error in the CV program, testing of the hypotheses in CANVAS-R will not proceed until the hypothesis tests related to the integrated database are significant. When the hypotheses in the integrated analysis succeed in rejecting the null hypotheses, all of the alpha for testing (ie, 5%) will pass to CANVAS-R. The primary and the key secondary endpoints will be tested as follows.

Hypothesis



For other efficacy endpoints assessed in CANVAS-R, nominal p-values will be reported.

There are no interim analyses planned.

11.4. Safety Analyses

The safety analysis will be based on all randomized subjects who receive at least one dose of double-blind study medication (ie, the same as the mITT analysis set). There will be no imputation for missing values for clinical laboratory test results and vital sign measurements.

The study objective regarding safety and tolerability will be assessed based upon a review of the incidence of overall and specific adverse events, discontinuations due to adverse events, laboratory results, and other safety and tolerability measurements.

Major Adverse Cardiac Event (MACE)

Time to the MACE composite of non-fatal myocardial infarction, non-fatal stroke, or CV death occurring post-randomization will be analyzed via a stratified Cox proportional hazards model treatment (all canagliflozin and placebo) as the explanatory variable and prior CV disease subgroup (secondary prevention and primary prevention) as the stratification factor. The hazard ratio estimate and the 95% CI will be derived from the model.

For supplementary purpose, the CV risk ratio will be assessed at the early treatment phase. The MACE events occurring within the first 30 days and 90 days post-randomization will be analyzed in a similar fashion.

Adverse Events

The original terms used in the eCRFs by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the treatment phase (ie, treatment-emergent adverse events) will be included in the analysis. For each adverse event, the percentage of subjects who experienced at least one occurrence of the given event will be summarized by treatment group. An adverse event will be considered to be a treatment-emergent event if it occurs within 30 days of the last date of blinded study medication. The percentage of subjects with specific treatment-emergent adverse events will be summarized by severity and relationship to study drug, as classified by the investigators, for each treatment group.

Further analyses, described in the SAP for this study, will be conducted on the prespecified adverse events for which additional information is collected from the investigators (refer to Section 9.4, Safety Evaluations).

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Normal reference ranges will be provided. Criteria for markedly abnormal laboratory values will be prespecified in the SAP. The percentage of subjects with markedly abnormal results will be summarized for each laboratory analyte. Descriptive statistics will be reported for each laboratory analyte at baseline and at each scheduled time point and for change from baseline.

Vital Signs, Weight

Descriptive statistics for pulse and sitting blood pressure (systolic and diastolic), weight values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures (SOPs) in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

All deaths and events that are assessed by the investigator as being one of the components of the CV safety composite endpoints (ie, CV deaths, nonfatal MI, nonfatal stroke) should be handled as follows:

Investigator Responsibilities:

All SAEs must be reported to the sponsor within 24 hours of knowledge of the event. This reporting timeline is also applicable to CV events. The investigator will record the event on the AE eCRF and will submit an SAE report to the Sponsor. For CV events, an adjudication package will also be submitted; details on assembly and submission of adjudication packages will be provided in an Adjudication Manual.

Sponsor Responsibilities:

Nonfatal MACE Events (ie, nonfatal stroke, nonfatal myocardial infarction):

- The sponsor will submit non-fatal MACE events for adjudication to the Endpoint Adjudication Committee.
- Nonfatal events that are adjudicated to be components of the primary endpoint will not be unblinded or reported to either Health Authorities (HAs) or investigators as safety reports. These events will be included in the final analysis which will be unblinded and submitted to HAs.

- Non-fatal events that are adjudicated NOT to be components of the primary endpoint, and are considered possibly, probably or definitely related by the investigator will be unblinded and subject to reporting requirements to both HAs and investigators. The reporting timeline starts when the Adjudication Committee notifies the sponsor of the decision.

Fatal Events:

- The sponsor will submit all deaths for adjudication to the Endpoint Adjudication Committee.
- Fatal events will be submitted to HAs but to protect the integrity of the trial, the event will not be unblinded prior to review of the death by the EAC. The US FDA has agreed to receive these fatal cases blinded. These will also be submitted blinded to other HAs worldwide, if allowed by local regulation (eg, where local regulations do not allow for submission of blinded safety reports, those regulations should be followed).
- Fatal events that are adjudicated to be a component of the primary endpoint (ie, CV death) will remain blinded and will not be reported to either HAs or investigators as safety reports. These events will be included in the final analysis which will be unblinded and submitted to HAs.
- Fatal events that are adjudicated NOT to be a component of the primary endpoint (ie, non-CV death) and considered possibly, probably or definitely related will be unblinded and subject to reporting requirements to both HAs and investigators. The reporting timeline starts when the Adjudication Committee notifies the sponsor of the adjudication decision.

For specific adverse events of interest, investigators will be asked to provide additional information so as to support more detailed analyses.

Adverse events of interest include: all malignancies, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (eg, angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, male genital infections (balanitis, phimosis, events leading to circumcision), and pregnancy. Information on these events will be recorded on the supplemental eCRFs or other designated forms for any event that is serious or that leads to study drug discontinuation. In addition, non-serious adverse events of malignancies, photosensitivity reactions, fractures, amputations, and venous thromboembolic events will also be recorded on the supplemental CRF pages or other designated forms (in addition to the information collected on serious AEs and AEs leading to study drug discontinuation). Diabetic ketoacidosis has been designated an adverse event of special interest and therefore adverse events related to diabetic ketoacidosis, ketoacidosis, metabolic acidosis or acidosis need to be reported to Janssen within 24 hours of becoming aware of the event, which is the same timeframe for reporting of serious adverse events. These adverse events must be reported using a supplemental DKA Reporting form, to complement standard information collected on the eCRF AE/SAE page. Amputations have also been designated as adverse events of special interest and therefore amputations need to be reported to the sponsor within 24 hours of becoming aware of the event. If adverse events of interest are identified in the future, guidance

concerning the reporting of those events may be provided to investigators via appropriately-documented study communications.

Additional information and documentation will be requested from investigators to support a detailed assessment and all deaths. Investigators may also be asked to provide additional information on other adverse events, based upon review by the MSRC or the IDMC (refer to Sections 9.3.3, Medical Safety Review Committee, and 9.3.4, Independent Data Monitoring Committee). Refer to Section 3.2, Study Design Rationale, for review of rationale for collection of additional information on these selected adverse events.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonization [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the informed consent form (refer to Section 12.2.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

See above for handling of components of the composite CV endpoint other than CV deaths.

A serious adverse event as defined by ICH is any untoward medical occurrence that at any dose meets any of the following conditions:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An unlisted adverse event is one for which the nature or severity of which is not consistent with the applicable product reference safety information. For an investigational product, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Not related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

Mild: Awareness of symptoms that are easily tolerated causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the intensity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Procedures

12.2.1. All Adverse Events

For this study, all serious adverse events, nonserious adverse events that result in study drug discontinuation and other selected adverse events as specified later in this section are to be reported from the time a signed and dated informed consent form is obtained until completion of the study (including subjects who withdraw prematurely). For specific adverse events of interest, a supplemental eCRF page or other designated form will be used to collect additional information. Adverse events of interest include: all malignancies, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (eg, angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, male genital infections (balanitis, phimosis, events leading to circumcision), and pregnancy. Information on these events will be recorded on the supplemental eCRFs or other designated forms for any event that is serious or that leads to study drug discontinuation. In addition, non-serious adverse events of malignancies, photosensitivity reactions, fractures, amputations, and venous thromboembolic events will also be recorded on the supplemental CRF pages or other designated forms (in addition to the information collected on serious AEs and AEs leading to study drug discontinuation). Diabetic ketoacidosis has been designated an adverse event of special interest and therefore adverse events related to diabetic ketoacidosis, ketoacidosis, metabolic acidosis or acidosis need to be reported to Janssen within 24 hours of becoming aware of the event, which is the same timeframe for reporting of serious adverse events. These adverse events must be reported using a supplemental DKA Reporting form, to complement standard information collected on the eCRF AE/SAE page. Amputations have also been designated as adverse events of special interest and therefore amputations need to be reported to the sponsor within 24 hours of becoming aware of the event. If adverse events of interest are identified in the future, guidance concerning the reporting of those events may be provided to investigators via appropriately-documented study communications.

Data will be collected in source documents and on the eCRF for these adverse events.

Serious adverse events, including those spontaneously reported to the investigator must be reported using a Serious Adverse Event Form, which must be completed and signed by a member of the investigational staff, and transmitted to the sponsor within 24 hours. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Adverse events, regardless of severity or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

Study research staff should make study subjects aware of potential signs and symptoms of diabetic ketoacidosis such as difficulty breathing, nausea, vomiting, abdominal pain, feeling confused, fruity-smelling breath, and unusual fatigue or sleepiness. Study subjects should be instructed to contact the site if they experience such symptoms. If the investigator suspects these symptoms may be related to diabetic ketoacidosis (even if the subject's blood glucose levels are less than 250 mg/dL [13.9 mmol/L]), testing for urine or blood ketones should be considered.

Consistent with standard diabetes treatment guidelines, all study participants should be provided with routine preventative foot care and early intervention for foot problems. Specifically:

- Provide or ensure that all subjects have had general foot self-care education.
- Perform a comprehensive foot evaluation at each visit to identify risk factors for ulcers and amputations. The examination should include inspection of the skin, assessment of foot deformities, neurological assessment including pinprick or vibration testing or assessment of ankle reflexes, and vascular assessment including pulses in the legs and feet.
- Subjects who have a history of prior lower extremity complications, loss of protective sensation, structural abnormalities, or peripheral arterial disease should be referred to foot care specialists for ongoing preventive care.

For all study participants, there should be a clinical evaluation at every visit to assess the presence of any sign or symptom suggestive of volume depletion (eg, hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), which if present should be adequately treated either by decreasing dose or eliminating use of diuretics or other antihypertensive medications or interrupting study drug until the condition resolves.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator all serious adverse events that are unlisted (unexpected) and associated with the use of the drug, according to standard operating procedures and the requirements outlined in this protocol. These events will be reported blinded to the investigator when and where possible. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

Subjects (or their designees, if appropriate) will be provided with a "study card" indicating the name of the investigational study drug, the study number, the investigator's name, a 24-hour emergency contact number, and, if applicable, excluded concomitant medications.

12.2.2. Serious Adverse Events

All serious adverse events occurring during clinical studies must be reported to the appropriate sponsor contact person by investigational staff within 24 hours of their knowledge of the event.

Nonfatal MI and nonfatal stroke events will be reported on the AE eCRF pages; the entry must be completed within 24 hours of the investigator staff's knowledge of the event. Events that are adjudicated as not meeting with charter-specified event definitions by the Endpoint Adjudication Committee will be subject to standard reporting requirements, but the reporting time limit will start when the sponsor learns that the event is not a CV safety event as per the Endpoint Adjudication Committee.

All serious adverse events that have not resolved by the end of the study, or that have not resolved after a reasonable time following the discontinuation of study drug, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The cause of death of a subject in a clinical study, whether or not the event is expected or associated with the investigational agent, is considered a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical study must be reported as a serious adverse event, except hospitalizations for the following:

- Social reasons in absence of an adverse event
- Surgery or procedure planned before entry into the study or a procedure to treat or explore a non-worsened pre-existing condition (eg, elective knee replacement, routine coronary angiogram without intervention, elective bariatric surgery); the non-worsening of the pre-existing condition must be documented in the source documents and the eCRF.

12.2.3. Pregnancy

All initial reports of pregnancy must be reported to the sponsor by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must immediately discontinue further study treatment. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.3. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability of a product, including its labeling or package integrity. PQCs may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the investigational staff as soon as possible after being made aware of the event.

If the defect is combined with a serious adverse event, the investigational staff must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.2.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

Canagliflozin will be supplied for this study as over encapsulated 100- or 300-mg tablets in a gray-colored, hard, gelatin capsule. The over encapsulated tablet will be backfilled with microcrystalline cellulose to prevent the tablet from rattling in the capsule shell.

Matching placebo capsules will consist of microcrystalline cellulose within a gray-colored, hard, gelatin capsule.

14.2. Packaging

The study drug will be packaged as individual bottles. The study drug will be packaged according to good manufacturing practices and local regulations. The study supplies will be

packaged according to the randomization code and each unit will be labeled with a medication ID number.

All study drug will be dispensed in child-resistant packaging.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

All study drug must be stored at controlled temperatures ranging from 15°C to 30°C (59°F to 86°F) and kept out of reach of children.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject, must be documented on the drug accountability form. Subjects, or their legally-acceptable representative where applicable, must be instructed to return all original containers, whether empty or containing study drug. All study drug will be stored and disposed of according to the sponsor's instructions. Site staff must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label and must be stored in a limited access area or in a locked cabinet under appropriate environmental conditions. Unused study drug and partially used study drug returned by the subject (if applicable), must be available for verification by the sponsor's or sponsor-delegated site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or partially used study drug returned for destruction, will be documented on the drug return form. When the site is an authorized destruction unit and study drug supplies are destroyed on site, this must also be documented on the drug return form.

Study drug should be dispensed under the supervision of the investigator, a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Recruitment and retention tools
- IWRS manual and worksheets

- eCRF completion guidelines
- Study binder with all other necessary documentation (eg, protocol, IB, clinical trial agreement)
- Manual of instructions regarding CV events, documentation required, and adjudication-related procedures
- Home blood glucose monitoring system, glucose strips, lancets, and calibration solution (optional by country/region)
- Materials to promote healthy dietary and exercise habits
- Laboratory operations manual, requisition forms, sampling supplies, and equipment, if necessary
- Computer, if the study site is assessed to require a laptop computer to enter eCRF data for the study

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

This study is being conducted under U.S. FDA IND regulations as part of a post-approval commitment. The protocol was submitted to and reviewed by the FDA prior to implementation.

The primary ethical concern of this study is that, though the safety profile of canagliflozin has been demonstrated in a clinical program involving more than 10,000 subjects, long-term safety data under conditions of extensive market use have not yet been established. Thus, subjects may be placing themselves at an increased risk of unexpected adverse events by participating in this study, and that subjects with T2DM who have not achieved optimal glycemic control at study entry could fail to achieve optimal glycemic control for a prolonged period. The investigator is asked to appropriately manage glycemic control and CV risk according to standard guidelines across the study. The potential risks in the present study include exposure to study drug, with the potential for side effects (Section 1.1.2, “Safety”) and the inherent risks associated with venipuncture and multiple blood sample collections. The study has been designed to mitigate these inherent risk factors. As per Section 9.3.4, an IDMC is commissioned for this study to review unblinded safety information on a periodic basis during the study.

Based on data from clinical studies with canagliflozin and the theoretical possibilities associated with SGLT2 and intestinal SGLT1 inhibition, potential human adverse effects may occur (Section 1.1.2, “Safety”). The following adverse of interest have been identified for follow-up in post-marketing studies by the US FDA: all malignancies, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (eg, angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, male genital infections (balanitis, phimosis, events leading to circumcision), and pregnancy. Information on these events will be recorded on the supplemental eCRFs or other designated forms for any event that is serious or that leads to study drug discontinuation. In addition, non-serious adverse events of malignancies, photosensitivity reactions, fractures, amputations, and

venous thromboembolic events. for which information on non-serious adverse events will also be recorded on the supplemental CRF pages or other designated forms (in addition to the information collected on serious AEs and AEs leading to study drug discontinuation). Diabetic ketoacidosis has been designated an adverse event of special interest and therefore adverse events related to diabetic ketoacidosis, ketoacidosis, metabolic acidosis or acidosis need to be reported to Janssen within 24 hours of becoming aware of the event, which is the same timeframe for reporting of serious adverse events. These adverse events must be reported using a supplemental DKA Reporting form, to complement standard information collected on the eCRF AE/SAE page. These events will be recorded and analyzed in this study, as will all serious adverse events, adverse events that result in study drug discontinuation, all deaths, nonfatal MI and nonfatal stroke. Amputations have also been designated as adverse events of special interest and therefore amputations need to be reported to the sponsor within 24 hours of becoming aware of the event. If adverse events of interest are identified in the future, guidance concerning the reporting of those events may be provided to investigators via appropriately-documented study communications.

Clinical and laboratory evaluations will be performed throughout the study (according to the Time and Events Schedule that follows the Synopsis) to monitor the safety of subjects. HbA_{1c} will be measured approximately every 6 months.

Subjects will be followed after prematurely discontinuing study drug until scheduled study completion in line with the Time and Event Schedule to obtain comprehensive information about their health and well-being. The investigator will be provided with detailed information about the study to ensure that the study research staff is fully informed. Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

Subjects will sign an informed consent form before any study-related procedure is performed.

The maximum blood volume that would be collected if a subject were to continue in the study for about 3.5 years would be approximately 300 mL. The maximum amount that would be collected at a single visit would be approximately 30 mL. These volumes are considered to be well within the normal range for this subject population over this time frame according to blood donation standards (American Red Cross).

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board (IEC/IRB)

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents:

- Final protocol and, if applicable, amendments
- Sponsor-approved informed consent form (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the informed consent form, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to informed consent form and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's Brochure amendments or new edition(s)

- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted, and associated with the investigational drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or trial conduct), the amendment and applicable informed consent form revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this clinical study. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data or trial conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the sponsor and by the reviewing IEC/IRB. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the investigational staff must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor staff without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By

signing the informed consent form the subject is authorizing such access, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, or to obtain information about his or her survival status.

The subject will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's personally dated signature. After having obtained the consent, a copy of the informed consent form must be given to the subject.

If the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the informed consent form after the oral consent of the subject is obtained.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational study drug(s) used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator to allow direct access to his or her original medical records for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

16.2.5. Country Selection

Unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations, this study will only be conducted in those countries where the intent is to help ensure access to the developed product.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor or its designee. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (refer to Contact Information pages provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the investigational site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed written IEC/IRB approval of the protocol, amendments, informed consent form, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee.
- Name and address of the IEC/IRB including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the investigational staff is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.

- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all clinical sub-investigators
- Documentation of sub-investigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject-screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: subject identification, eligibility, and study identification; study discussion and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events; and follow-up of adverse events; concomitant medications of interest; drug receipt/dispensing/return records; study drug administration information; and date of study completion, and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

It is recommended that the author of an entry in the source documents be identifiable.

At a minimum, the type and level of detail of source data available for a study subject should be consistent with that commonly recorded at the site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study personnel from the source documents onto an eCRF, and transmitted in a secure manner to the sponsor within 3 working days of the subject's visit or in the time frame specified in the clinical trial agreement. The electronic file will be considered to be the eCRF. Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subjects' source documentation. All data relating to the study must be recorded in eCRFs prepared by the sponsor. Data must be entered into eCRFs in English. Designated site personnel must complete eCRFs as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or an authorized member of the investigational staff must adjust the eCRF (if applicable) and complete the query. A query is generally to be answered within 5 days of generation of the query or in the time frame specified in the clinical trial agreement.

If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- Site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool)
- Site manager (SM) can generate a query (field data correction form [DCF]) for resolution by the investigational staff
- Clinical data manager (CDM) can generate a query for resolution by the investigational staff

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits by the sponsor, and transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, preparation, and shipment of blood, plasma, and urine samples.

Guidelines for eCRF completion will be provided and reviewed with study personnel before the start of the study.

The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the clinical study database they will be verified for accuracy.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator must permit access to such reports.

17.8. Monitoring

The sponsor and ARO designated by the sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study center visit log that will be kept at the site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and investigational staff and are accessible for verification by the sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents will be discussed with the investigational staff. The sponsor expects that, during monitoring visits, the relevant investigational staff will be

available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed with the last visit/contact of the last subject participating in the study. The final data from the investigational site will be sent to the sponsor (or designee) after completion of the final subject visit/contact at that site, 3 days after the subject's visit/contact (query generation and resolution excluded), or in the time frame specified in the clinical trial agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the investigational site or terminate the study at any time for any reason at the sole discretion of the sponsor. Investigational sites will be closed upon study completion. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigational site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further drug development.

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the eCRFs. Subject privacy must, however, be respected. The investigator and staff are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding canagliflozin or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the clinical study will be used by the sponsor in connection with the continued development of canagliflozin, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain eCRF data from all investigational sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of pharmacogenomic analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of pharmacogenomic results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

The sponsor shall have the right to publish such data and information without approval from the investigator. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, results may need to be published in a given sequence (eg, substudies) should not generally be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not publishing data derived from the individual site until the combined results from the completed study have been published in full, within 12 months after conclusion, abandonment, or termination of the study at all sites, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted

to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

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Attachment 1: Clinical Laboratory Tests

Blood samples for serum chemistry and hematology, and a baseline random urine sample for urinalysis will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF and take appropriate action (eg, repeating abnormal laboratory result or further evaluation as considered clinically appropriate). The following tests will be performed by the central laboratory.

- Hematology Panel

  -hemoglobin
  -hematocrit
  -white blood cell (WBC) count with differential
  -platelet count
  -red blood cell (RBC) count

- Serum Chemistry Panel

  -sodium
  -potassium
  -chloride
  -bicarbonate
  -blood urea nitrogen (BUN)
  -creatinine
  -aspartate aminotransferase (AST)
  -alanine aminotransferase (ALT)
  -gamma-glutamyltransferase (GGT)
  -total bilirubin
  -alkaline phosphatase
  -creatine phosphokinase (CPK)
  -lactic acid dehydrogenase (LDH)
  -uric acid
  -calcium
  -phosphate
  -albumin
  -total protein
  -magnesium

- Fasting serum lipid profile (triglycerides, LDL-C, HDL-C, total cholesterol).
- HbA_{1c}
- Urinalysis (dipstick analysis; from spot urine collection in the clinic on Day 1; performed at central laboratory; microscopic analysis is not required)*

  - specific gravity
  - pH
  - protein
  - blood
  - ketones
  - bilirubin/urobilinogen
  - nitrite
  - leukocyte esterase

  *Urine glucose will not be measured by the central laboratory

Central laboratory will report the eGFR according to the Modification of Diet in Renal Disease Study (MDRD) equation (Levey 2006) at study visits when serum creatinine is measured. The 4-variable MDRD eGFR includes serum creatinine, age, race, and sex according to the equation below:

For creatinine in mg/dL:

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203}$$
$$\times (0.742 \text{ if female}) \times (1.21 \text{ if black})$$

For creatinine in µmol/L:

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{serum creatinine} \times 0.0113)^{-1.154} \times (\text{age})^{-0.203}$$
$$\times (0.742 \text{ if female}) \times (1.21 \text{ if black})$$

INVESTIGATOR AGREEMENT

JNJ-28431754: Canagliflozin

Clinical Protocol 28431754DIA4003 – Amendment INT-5

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Ngozi Erondu, MD, PhD

Institution: [redacted] Janssen Research & Development

Signature: _____ Date: 1-Sept-2016

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Approved, Date: 01 September 2016

Janssen Research & Development

Statistical Analysis Plan

A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects with Type 2 Diabetes Mellitus

The CANVAS Trial (CANagliflozin cardioVascular Assessment Study)

Protocol 28431754DIA3008; Phase 3

JNJ-28431754 (canagliflozin)

Status: Approved

Date: 20 September 2016

Prepared by: Janssen Research & Development, LLC

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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ABBREVIATIONS

ACR	albumin creatinine ratio
AE	adverse event
AHA	antihyperglycemic agent
ANCOVA	analysis of covariance
BL	baseline
BMI	body mass index
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CV	cardiovascular
DBP	diastolic blood pressure
DKA	diabetic ketoacidosis
EAC	Endpoint Adjudication Committee
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GTED	Global Trial End Date
HbA_{1c}	hemoglobin A_{1c}
HDL-C	high-density lipoprotein cholesterol
HR	hazard ratio
IDMC	independent data monitoring committee
ITT	intent-to-treat
IWRS	interactive web response system
LDL-C	low-density lipoprotein cholesterol
LLN	lower limit of normal
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
PDLC	pre-defined limit of change
PT	preferred term
QTcF	QTc using the Fridericia
RAAS	renin angiotensin aldosterone system
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	steering committee
SCr	serum creatinine
SD	standard deviation
SGLT2	sodium-glucose co-transporter 2
SI	standard international
SOC	System Organ Class
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent AE
ULN	upper limit of normal
UTI	urinary tract infection
VTE	venous thromboembolic events

1. INTRODUCTION

Canagliflozin (JNJ-28431754) is an inhibitor of the sodium-glucose co-transporter 2 (SGLT2) that has been developed as an oral anti-hyperglycemic agent (AHA) for the treatment of patients with type 2 diabetes mellitus (T2DM). To meet the FDA guidance on assessing cardiovascular (CV) safety of AHAs, the sponsor initiated the CV outcomes study 28431754DIA3008 (CANVAS) in December, 2009 intended to supply data to support the CV safety of canagliflozin and to also evaluate whether canagliflozin reduces CV risk.

As part of the marketing authorization application, the sponsor performed an integrated analysis of CV events from the Phase 2 and Phase 3 canagliflozin program using data from 9,632 subjects, which included interim data harvested on 31 January 2012 from the ongoing CANVAS study of 4,330 subjects at high risk for CV disease. Subsequently, in response to a request arising during review of the canagliflozin Marketing Authorization Application by the Committee for Medicinal Products for Human Use (CHMP), the sponsor conducted a second integrated CV analysis of the Phase 2 and Phase 3 studies, which included interim data from CANVAS harvested on 19 November 2012. Data on major adverse cardiovascular events (MACE) and mortality outcomes beyond 19 November 2012 have remained blinded to the sponsor.

The primary endpoint of CANVAS was to evaluate whether there was a risk reduction in MACE associated with canagliflozin treatment. Due to unblinding of the interim summary results of CANVAS at the time of marketing approval, the planned expansion of enrollment in CANVAS was eliminated. Accordingly, the study itself is underpowered for the primary hypothesis of the reduction in CV risk as measured by the hazard ratio (HR) for MACE.

As a result of the discussions with FDA, the sponsor proposed to conduct a second CANVAS-like study (referenced as CANVAS-R) with approximately 5,700 randomized subjects. As such, the CANVAS and CANVAS-R trials are purposefully similar in design and in subject characteristics. Data from these studies are to be harvested for an integrated analysis to meet the FDA post approval CV safety requirement and if safety is demonstrated, to assess whether canagliflozin reduces all-cause mortality no later than June 2017 with study reports submitted to FDA by September 2017.

This statistical analysis plan (SAP) stipulates definitions of analysis sets, key derived variables and statistical methods for analysis of efficacy and safety specific for CANVAS based on the latest amendment INT-8 (5 May 2016) of the protocol. Additional CV and renal outcome endpoints are added in this SAP for exploratory analysis. Since the Clinical Study Reports of the 18-week substudies were submitted in the NDA of canagliflozin and the 52-week interim results were published, the analyses in these sub studies will not be addressed in this plan.

1.1. Trial Design

The CANVAS study enrolled the first subject in December 2009. The original design called for the study to be conducted in 2 cohorts (an initial cohort of 4,500 subjects enrolled prior to regulatory submissions followed by a subsequent cohort of 14,000 subjects to be enrolled post approval).

However, due to unblinding of the interim summary results of CANVAS at the time of marketing approval, the planned expansion of enrollment in CANVAS was eliminated.

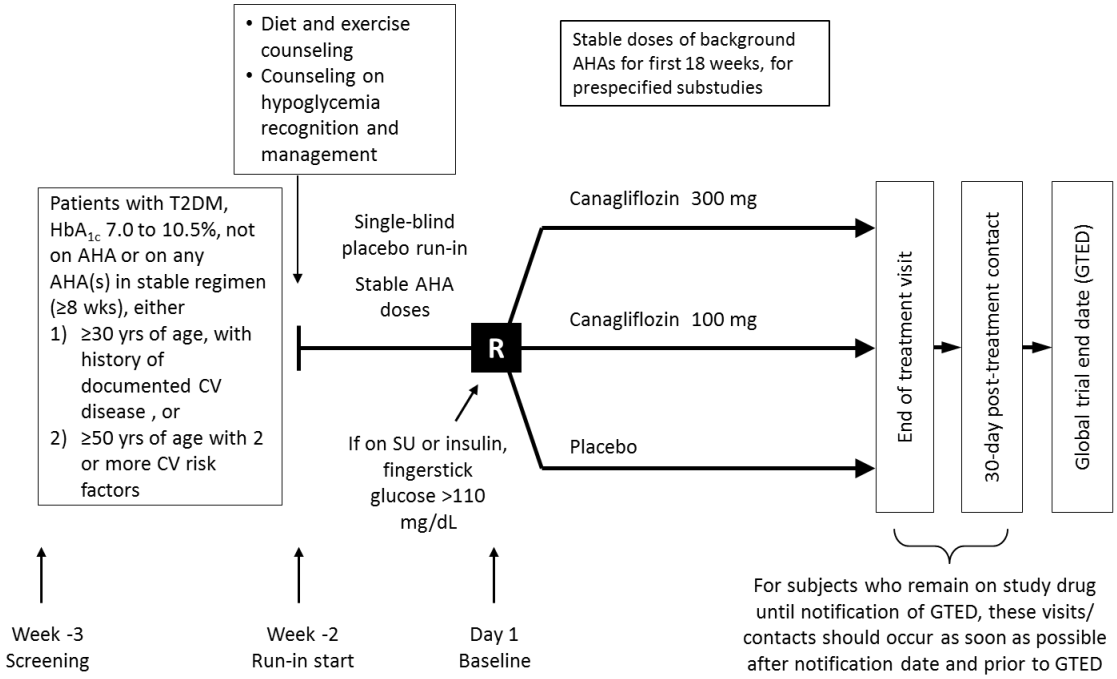
The study enrolled 4,330 subjects who met all inclusion criteria and none of the exclusion criteria. Subjects were randomly assigned to treatment with 1 of 2 doses of canagliflozin (100 or 300 mg) or placebo, in a 1:1:1 ratio. The CANVAS and CANVAS-R studies will complete when the last subject randomized has approximately 78 weeks of follow-up or when 688 MACE events are accumulated between both studies (estimated to occur between January 2017 and April 2017). The announcement of the Global Trial End Date (GTED) will mark the anticipated date on which one of these requirements for ending the study will occur.

Following announcement of the projected GTED and for subjects remaining on double-blind study drug, sites will schedule the End of Treatment (EOT) and the 30-day off-drug follow-up contact as per the Time and Events schedule in the protocol; for subjects that have prematurely discontinued study drug prior to the announcement of the projected GTED, sites will be required to make a final contact or vital status check as soon as possible after the announcement of the GTED.

A single Steering Committee (SC) and an Independent Data Monitoring Committee (IDMC) are commissioned for this and the CANVAS-R study. The SC oversees the study conduct, and the IDMC regularly (and on an ad hoc basis) reviews safety data.

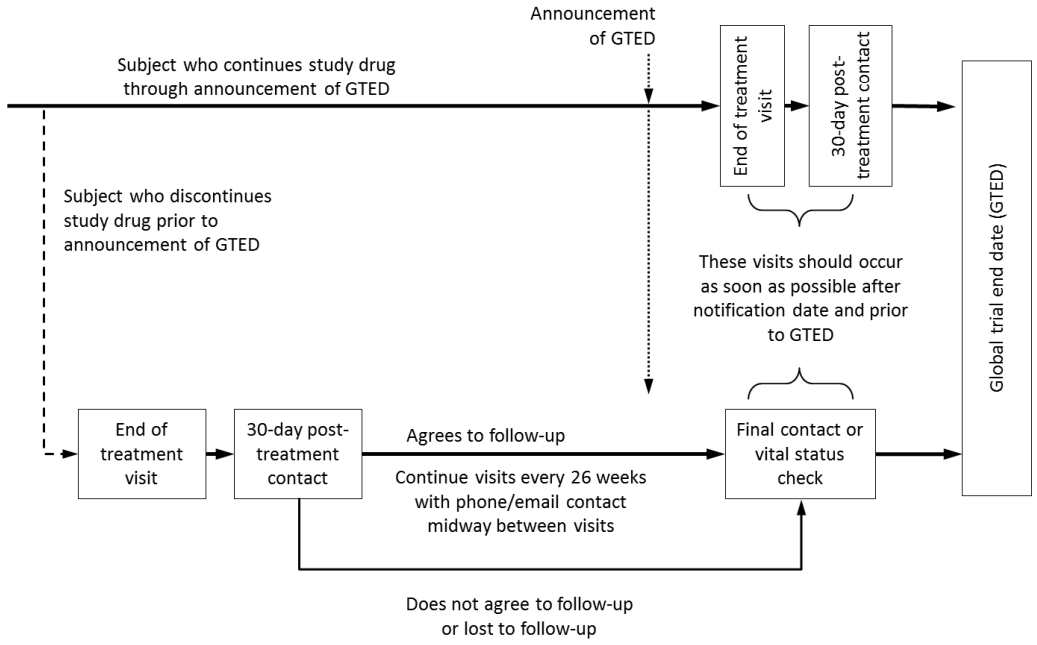
Figure 1 shows an overview of the study design and Figure 2 shows the scheduled follow-up of randomized subjects prior to the GTED.

Figure 1: Diagram of Study Design



AHA=antihyperglycemic agent; CV=cardiovascular; HbA_{1c}=hemoglobin A_{1c}; GTED=global trial end date; R=randomization; SU=sulfonylurea; T2DM=type 2 diabetes mellitus

Figure 2: Follow-up of Randomized Subjects with Respect to the GTED



Note: Following the announcement of the GTED, investigators are not expected to continue collecting data for purposes of the clinical trial after the 30-day post-treatment contact.

1.2. Randomization

Subjects were stratified into one of 6 predefined strata based on AHA use at the run-in visit through to the randomization visit. The investigators were instructed to hold AHA use constant through Week 18 and to adjust the subject's AHA regimen after Week 18 so as to achieve target glycemic control throughout the remainder of the study.

Central randomization was implemented in this study. Subjects were randomly assigned to 1 of 3 treatment groups based on a computer-generated randomization schedule prepared by the sponsor before the study. The randomization was balanced by using randomly permuted blocks and was stratified based on the use of specific concomitant AHA medications at baseline.

1.3. Trial Objectives

1.3.1. Primary Objectives

In subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease:

- To assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care on CV risk as measured by the HR for a composite endpoint (MACE including CV death, nonfatal MI, or nonfatal stroke);
- To assess the safety and tolerability of canagliflozin plus standard of care relative to placebo plus standard of care.

1.3.2. Secondary Objectives

In subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease, to assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care at the end of the treatment period on:

- Fasting measures of beta-cell function (HOMA-B and the proinsulin/insulin ratio) (note: this assessment will be conducted in a subset of subjects at sites that elected to participate, including only subjects who did not receive insulin at randomization);
- The proportion of subjects with progression of albuminuria (progression defined as the development of microalbuminuria or macroalbuminuria in a subject with baseline normoalbuminuria or the development of macroalbuminuria in a subject with baseline microalbuminuria);
- Urinary albumin/creatinine ratio (ACR);
- Change from baseline in estimated glomerular filtration rate (eGFR);
- Change from baseline in HbA_{1c} and fasting plasma glucose (FPG);
- Change in body weight;
- Change in blood pressure (systolic and diastolic);
- Change in fasting plasma lipids (triglycerides, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], total cholesterol, and the ratio of LDL-C to HDL-C).

1.3.3. Exploratory Objectives

In subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease, to assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care on:

- Hospitalization for heart failure;
- The composite of hospitalization for heart failure or CV death;
- The composite of 40% decrease in eGFR, renal death or requirement for renal replacement therapy;
- The composite of doubling of serum creatinine (SCr), renal death or requirement for renal replacement therapy;
- The composite of 40% decrease in eGFR, renal death, requirement for renal replacement therapy or CV death;
- The composite of doubling of SCr, renal death, requirement for renal replacement therapy or CV death;
- The composite of 40% decrease in eGFR, conversion to macroalbuminuria, renal death or requirement for renal replacement therapy;
- The composite of doubling of SCr, conversion to macroalbuminuria, renal death or requirement for renal replacement therapy;

- Progression of albuminuria (defined as the development of microalbuminuria or macroalbuminuria in a subject with baseline normoalbuminuria or the development of macroalbuminuria in a subject with baseline microalbuminuria), accompanied by an ACR value increase of greater than or equal to 30% from baseline;
- Regression of albuminuria (regression defined as the development of normoalbuminuria in a subject with baseline microalbuminuria or macroalbuminuria or the development of microalbuminuria in a subject with baseline macroalbuminuria), accompanied by an ACR value decrease of greater than or equal to 30% from baseline;
- Change in eGFR from baseline to the last off-drug value;
- Change in eGFR determined from a between-group comparison of the eGFR slopes using all on-drug measurements (ie, off-drug values will not be included) of eGFR made from the first on-drug measurement to the final on-drug measurement.

1.4. Statistical Hypotheses

The following hypotheses are specified in the study protocol, however they are considered to be exploratory in the canagliflozin CV outcome consisting of CANVAS and CANVAS-R. The hypotheses in this trial are not included as part of the testing sequence of the program. Accordingly, any p-value reported will be considered as nominal and 95% confidence intervals (CIs) for the treatment effect will be presented for descriptive purposes.

In subjects with T2DM with inadequate glycemic control, who have a history of or a high risk of CV disease, relative to placebo plus standard of care, canagliflozin plus standard of care:

- Reduces CV risk (as measured by the HR for MACE including CV death, nonfatal MI, and nonfatal stroke);
- Improves beta-cell function (change from baseline in HOMA-B) at the end of the treatment period;
- Reduces progression of albuminuria (ie, proportion of subjects with a ≥1-step progression of albuminuria measured by the urine ACR) at the end of the treatment period.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Analysis Populations

- Randomized subjects—subjects who are randomized via the Interactive Web Response System (IWRS);
- Treated subjects—randomized subjects who received at least one dose of double-blind study medication.

For efficacy analyses and baseline summaries, subjects will be analyzed according to their randomization assignment. For safety analyses (eg, adverse events [AEs]) and the summary of exposure, subjects will be analyzed according to the predominant treatment received (defined as the treatment to which the subject was exposed for the greatest duration), in the event that subjects receive a treatment other than the one to which they were randomized.

2.2. Analysis Sets

Analysis sets consist of 2 components: 1) analysis population (Section 2.1), which specifies the subjects included in an analysis; 2) data period, defining the time window during which data will be included in the analysis.

Safety data collection in CANVAS was streamlined after protocol amendment INT-6 (effective starting on 07 January 2014) such that AEs were only collected if they were serious or leading to study drug discontinuation, with the exception of selected AEs of interest. For the purpose of summarizing safety data *prior* to amendment INT-6, the On-Treatment Pre-INT6 analysis set was created as described below.

Table 1: Summary of Analysis Sets

Analysis Set	Analysis Population	Data Period
ITT	Randomized subjects	Day 1 to the last trial contact date (refer to Section 2.3.2) up to the GTED
On-Treatment	Treated subjects	Day 1 to the last dose date (refer to Section 2.3.2) plus X[a] days or the last trial contact date, whichever is earlier
On-Treatment Pre-INT6	Treated subjects	Day 1 to the last dose date plus X[a] days or the last trial contact date, whichever is earlier, up to 07 January 2014

[a] X is 2 days for safety laboratory and vital sign measurements, and 30 days for CV, mortality, and renal endpoints, adverse events (AEs), and laboratory values specific for efficacy.

2.3. Data Handling

2.3.1. Censoring Rules

For each analysis set, events that occur any time during the data period of the corresponding analysis set (refer to Table 1) will be considered as eligible events; otherwise subjects not experiencing an event will be censored at the earlier of the last trial contact date or end of the respective data period, if not otherwise specified.

2.3.2. Handling of Key Milestone Dates

- Trial reference start date (Day 1): the first double-blind dose date for each subject (First dose date). If missing or incomplete, the first dose date will be imputed as the randomization date.
- Last dose date: the date on which the last dose of double-blind study drug was taken by the subject. If only the day is missing, impute the last day of the month. If the month or the year is missing, impute the date as the date of the scheduled visit subsequent to the last visit when the study drug was dispensed. The imputed last dose date should be no later than the end of treatment visit date or the last trial contact date. In addition, the imputed last dose date should be no earlier than the first dose date. The last dose date is the date of permanent study drug discontinuation regardless of any temporary drug interruption.
- Last trial contact date: the date when the last trial-related procedure is conducted. It is defined as the latest of:
  - The date of last visit (scheduled or unscheduled visit; office or phone visit), or

- The latest known date of an adverse event (AE) or the study endpoint event status, concomitant medication, vital sign measurements or laboratory results as reported on their respective electronic case report form (eCRF), or
- The date of alternate contact made (eg, family members, relatives, friends, health care providers, public search) confirming the subject's survival status at the time of the GTED.
- For subjects who die during the study, the last trial contact date will be defined as the date of death.

2.3.3. Visit Windows

The Time and Events schedule of the protocol indicates the visit timing and procedures (eg, laboratory, vital signs, and other key safety variables) for each visit; however, the timing of a subject's actual visit may not be exactly as per the protocol indicated target day / visit window. Consequently, for by-visit or over-time summaries, depending on the time period(s) involved in the summaries, the conventions outlined below will be used to allocate the data collected at each actual visit to a planned protocol visit by defining visit windows.

Baseline will be defined as the pre-dose measurement closest to or including Day 1 (prior to dose administration). If the pre-dose measurement on Day 1 is missing, the missing value will be imputed by the latest available measurement prior to Day 1.

If a subject has 2 or more actual visits in one analysis visit window, the visit closest to the target day will be used as the study visit for that analysis visit window. However, results from all visits will be included in the safety analyses (eg, pre-defined limits of change analysis) to assure that all results are included. If 2 study visits are the same number of days from the target day within the same visit window, the later visit will be considered the study visit for that target day. Even though all visits will be allocated an analysis visit window, only planned protocol visits for each variable will be included in the by-visit summaries or repeated measure analyses.

Note that the algorithms for calculating visit windows are the same for all the data periods (refer to Table 1). Table 2 summarizes the analysis visit windows for laboratory, vital signs, and other key safety variables.

Table 2: Time Intervals for Analysis (in clinic) Visit Windows

Scheduled Visit Time (label on output)	Time Interval (Day)[a]	Target Time Point (Day)
Baseline	≤1[b]	1
Week 6	1[c] – 64	43
Week 12	65 – 99	85
Week 18	100 – 155	127
Week 26	156 – 197	183
Week 39	198 – 288	274
Week 52	289 – 456	365
Week 78	457–638	547
Week 104	639–820	729
Week 130	821–1002	911
Week 156	1003–1184	1093
Week 182	1185–1366	1275
Week 208	1367–1548	1457
Week 234	1549 – 1730	1639
Week 260	1731 – 1912	1821
Week 286	1913 – 2094	2003
Week 312	2095 – 2276	2185
Week 338	2277 – 2458	2367
Week 364	2459 – 2640	2549
Week 390	2641 – 2822	2731

[a] Relative to the day of the first dose of double-blind study drug.
[b] Up to the first dose of double-blind study drug.
[c] Immediately following the first dose of double-blind study drug. For variables with no time or reference collected at baseline, the first window after baseline starts on Day 2 according to the protocol.

3. SUBJECT INFORMATION

3.1. Baseline Anthropometric and Demographic Characteristics

Baseline anthropometric and demographic characteristics will be summarized by treatment group (each canagliflozin dose and all canagliflozin group, as well as placebo). Descriptive statistics (N, mean, standard deviation, median, and range) will be provided by treatment group for baseline age and baseline body weight.

Additionally, the number and percentage of subjects in the categories of the following variables at baseline will also be summarized by treatment group:

- Age group: <65, ≥ 65 years old;
- Sex: Male, Female;
- Race: White, Black or African American, Asian, Others;
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Unknown, Not reported;
- Region: North America, Central/South America, Europe, Rest of the World.

3.2. Baseline Disease Characteristics

Descriptive statistics (N, mean, SD, median, and range) will be provided by treatment group and overall for the following baseline continuous variables: duration of diabetes (in years), eGFR, ACR, systolic blood pressure (SBP), weight, body mass index (BMI), HbA_{1c}, LDL-C, HDL-C, triglycerides, total cholesterol, and LDL-C/HDL-C.

Additionally, the number and percentage of subjects will be summarized by treatment group and overall for the following:

- Baseline BMI categories (<30, ≥30 kg/m^2);
- Currently daily cigarette smoker: Yes/No;
- Baseline HbA_{1c} ≥ 8%: Yes/No;
- Duration of T2DM ≥ 10 years: Yes/No;
- Baseline blood pressure categories (≤140, >140mmHg);
- Baseline LDL-C categories (≤70, >70mg/dL);
- Baseline HDL-C categories (<39, ≥39 mg/dL);
- Baseline eGFR categories (<30, 30 to <60, 60 to <90, ≥90 mL/min/1.73m^2);
- Baseline albuminuria categories:
  - Normoalbuminuria (0 ≤ ACR <30 mg/g); Microalbuminuria (ACR ≥30 mg/g and ≤300 mg/g); Macroalbuminuria (ACR > 300 mg/g: ACR >300 mg/g and ≤3000 mg/g, ACR > 3000 mg/g).
- History of hypertension: Yes/No;
- History of CV disease: Yes/No;
- History of coronary artery disease: Yes/No;
- History of cerebrovascular disease: Yes/No;
- History of peripheral vascular disease: Yes/No;
- History of heart failure: Yes/No;
- Microvascular diabetes complications (Any, 1, 2 or 3 of retinopathy, neuropathy [diabetic or autonomic neuropathy] and nephropathy);
- History of fracture: Yes/No;

The number and percentage of subjects with a history of medical conditions by system organ class and preferred term (based upon the general medical history eCRF) will be summarized by treatment group and overall.

3.3. Disposition Information

Disposition will be summarized for all randomized subjects by treatment group using the categories listed below:

- Screen failure;
- Subjects who are randomized (ITT);
- Subjects who are treated;
- Subjects who complete the study (ie, defined as having been followed until a time point between the notification of the GTED and the GTED, or if the subject has died prior to the GTED);
- Subjects who prematurely discontinued study medication;
- Subjects without final vital status.

The reasons for non-randomization, withdrawal from study (eg lost to follow-up, consent withdrawal), and discontinuation from study medication will be summarized. The distribution of time to premature discontinuation of study medication will be displayed using a Kaplan-Meier plot, where one minus the survival function will be shown.

Listings will be provided for subjects whose predominant treatment differs from their randomized treatment.

3.4. Extent of Exposure and Follow-Up

Total exposure time for each subject is defined as the number of days from Day 1 to the last dose date (inclusive), regardless of any temporary drug interruption(s). Follow-up time is defined as the number of days from Day 1 to the last contact day (inclusive) for each subject. Descriptive statistics (N, mean, SD, median, and range) for total exposure or follow-up time will be presented by treatment group.

The number of subjects with duration in each of the following categories (<3 week, 3 to <13 week, 13 to <26 weeks, 26 to <52 weeks, 52 to <78 weeks, 78 to <104 weeks, 104 to <130 weeks, 130 to <156 weeks, 156 to <182 weeks, 182 to <208 weeks, 208 to <234 weeks, 234 to <260 weeks, 260 to <286 weeks, 286 to <312 weeks, 312 to <338 weeks, and ≥338 weeks) will also be presented by treatment group as well as overall.

3.5. Prior and Concomitant Medications

Concomitant medication usage is collected on the eCRF at baseline, and during the on-drug period. The number of subjects receiving medication in pre-specified categories will be presented by treatment group at baseline and on-drug period. In addition, SGLT2 inhibitor use during the off-drug follow-up period will also be summarized by treatment group.

All study medications are coded using World Health Organization Drug Utilization Research Group (WHODRUG) and Anatomical Therapeutic Chemical (ATC) codes.

Additionally, the number and percentage of subjects taking the following concomitant medications at baseline will be summarized by treatment group and overall:

- Baseline insulin use: Yes/No;
- Baseline sulphonylurea use: Yes/No;
- Baseline metformin use: Yes/No;
- Baseline statin use: Yes/No;
- Baseline anti-thrombotic use: Yes/No;
- Baseline diuretic use: Yes/No;
  - Baseline loop diuretic use: Yes/No;
  - Baseline non-loop diuretic use: Yes/No;
- Baseline renin angiotensin aldosterone system (RAAS) inhibitor use: Yes/No.

4. EFFICACY

The primary analysis will be performed based on the ITT analysis set and secondary efficacy endpoints will be based on the On-treatment analysis set, if not otherwise specified.

As noted in Section 1, there will be no formal statistical hypothesis testing and therefore all statistical tests will be considered nominal and reported using a 2-sided 95% confidence level.

Unless otherwise stated, all efficacy analyses and summaries will be performed using the treatment groups assigned by IWRS.

A tabulation of all the key analyses planned for the CV endpoints and the mortality endpoint is presented in Appendix 1.1.

4.1. Primary Efficacy Endpoint

4.1.1. Definition

The primary efficacy endpoint is the time to MACE (ie, composite of non-fatal MI[a], non-fatal stroke, and CV death), which is calculated as the time from Day 1 to the first occurrence of MACE. Adjudication of these outcomes by the Endpoint Adjudication Committee (EAC) will be done in a blinded fashion.

4.1.2. Analysis Methods

The primary analysis will be based on the ITT analysis set for adjudicated MACE. The HR of canagliflozin (all canagliflozin group as well as each canagliflozin dose) compared to placebo and its 95% CI will be estimated using a stratified Cox proportional hazards model with a term for

[a] Silent MIs are excluded from the analysis.

treatment as the explanatory variable and history of CV disease (secondary and primary prevention) as a stratification factor.

The percentage of subjects who experience a MACE and the corresponding incidence rate per 1,000 patient-years will be reported. The cumulative event rate over time will be presented using a Kaplan-Meier plot by treatment (all canagliflozin group and placebo as well as each canagliflozin dose and placebo).

4.1.3. Subgroup Analyses

The homogeneity of treatment effect on the occurrence of the primary endpoint across subgroups will be examined (at a 2-sided significance level of 0.05) via a test for the treatment by subgroup interaction by adding this term and the subgroup as covariates (treated as class variables) to the primary efficacy analysis (Section 4.1.2) model. Subgroup analysis will be conducted when the total number of events is greater than 10 for two treatment groups (all canagliflozin group and placebo) and at least 1 event in both groups. Factors exhibiting interactions at a significance level of $p \leq 0.05$ will be identified as suggesting treatment effect heterogeneity, recognizing the multiplicity in testing multiple subgroups such that one or more p-values ≤ 0.05 may be expected to be observed by chance alone.

If a significant interaction is observed, the Gail-Simon test will be used to further examine the nature of the interaction (qualitative or quantitative).

The HR of canagliflozin (all canagliflozin group) compared to placebo and its 95% CI will be estimated for each of the following subgroups:

- Age group: <65, ≥ 65 years old;
- Sex: Male, Female;
- Race: White, Black or African American, Asian, Other;
- Region: Central/South America, Europe, North America, Rest of the World;
- Baseline eGFR categories (30 to <60, 60 to <90, ≥90 mL/min/1.73m^2);
- Baseline HbA_{1c} ≥ 8%: Yes/No;
- Duration of diabetes ≥ 10 years: Yes/No;
- History of CV disease: Yes/No;
- History of peripheral vascular disease: Yes/No;
- History of amputation: Yes/No.

4.1.4. Supportive Analyses

If not otherwise specified, the supportive analyses will use the same analysis set as in the primary efficacy analysis.

4.1.4.1. On-Treatment Analysis

The primary analysis (as described in Section 4.1.2) will be repeated using the On-Treatment analysis set, in which data from Day 1 to 30 days after the last dose of the study drug are used.

4.1.4.2. Additional Supportive Analyses

4.1.4.3. Hazard Ratio Estimation for Individual MACE Components

A separate analysis will be performed for each individual MACE component (CV death, nonfatal MI, or nonfatal stroke) in both the ITT analysis set and the On-Treatment analysis set. Additionally, analyses of fatal/non-fatal MI as well as fatal/non-fatal stroke will be performed. For subjects who experience more than one MACE component, all events will be counted in the analysis for the relevant component (eg, if a subject has both non-fatal MI and non-fatal stroke, the subject will be counted as having each event). The percentage of subjects who experience each MACE component and the corresponding incidence rate per 1,000 patient-years will be summarized by treatment. The HR of canagliflozin (all canagliflozin group as well as each canagliflozin dose) compared to placebo and its 95% CI will be estimated using a stratified Cox proportional hazards model with a term for treatment as the explanatory variable and history of CV disease (secondary and primary prevention) as a stratification factor.

4.1.4.4. Assessment of Missing Data

The impact of missing data in the interpretation of the primary efficacy analysis will be explored. For subjects who are lost to follow-up or withdrew consent before the development of a MACE in the ITT analysis set, data collected between the last trial contact date and the GTED will be considered missing.

The proportion of data missing, defined as the ratio of the duration of missing follow-up (eg, days between last contact date + 1 day and the GTED) and the duration of intended follow-up (eg, days between randomization date and the GTED) will be summarized.

Multiple Imputation

The potential impact of missing data will be evaluated by multiple imputation. The methodology which accounts for informative censoring[1] is described as follows:

- Different parametric time to event models, eg, Exponential, Weibull, will be fit on observed data with the adjustment for treatment and other covariates such as baseline characteristics. The model will be fit separately for subjects with different disposition status, eg, completion of study, discontinuation from study early due to consent withdrawal or other reasons.
- Simulated time will be generated by random sampling using parameters from the above model for each disposition status. The simulated time will be used to impute the duration of missing follow-up after early discontinuation from the study.
- Imputation will be done for subjects who are lost to follow-up or withdrew consent without an event prior to the GTED.

- If the simulated time is less than the elapsed time between the last contact date and the GTED, an event is imputed for the corresponding subject with the time to event set to be last contact date plus the simulated time. Otherwise, the subjects will be censored at GTED.
- The imputed events and times will be added to the observed data and the primary efficacy model will be reanalyzed.
- The simulation process will be repeated and the results from the multiple imputed datasets combined to yield an overall inference, ie, HR and 95% CI, incorporating the within and between imputation variation using Rubin's rule.

4.2. Secondary Efficacy Endpoints

4.2.1. Definition

The secondary efficacy endpoints are:

- Change from baseline to the end of treatment in HOMA-B;
- The proportion of subjects with progression of albuminuria at the end of treatment (ie, the development of microalbuminuria or macroalbuminuria in a subject with baseline normoalbuminuria or the development of macroalbuminuria in a subject with baseline microalbuminuria);
- Change in proinsulin/insulin ratio;
- Change in urinary ACR;
- Change in eGFR;
- Change in HbA_{1c};
- Change in FPG;
- Percent change in body weight;
- Change in blood pressure (systolic and diastolic);
- Percent change in fasting plasma lipids (triglycerides, HDL-C, LDL-C, total cholesterol, and the ratio of LDL-C to HDL-C).

4.2.2. Analysis Methods

Unless otherwise specified, the analyses for the secondary efficacy endpoints will be using the On-Treatment analysis set. Only subjects with a baseline and at least 1 post-baseline measurement will be included in the analysis.

4.2.2.1. HOMA-B

The analyses for beta-cell function will be conducted in a subset of subjects at sites that elected to participate, including only subjects who are not receiving insulin at randomization. For subjects who initiated insulin during the study, all HOMA-B data after the initiation of insulin will be censored.

Changes in HOMA-B from baseline will be analyzed using an analysis of covariance (ANCOVA) model with treatment as the explanatory variable and baseline HOMA-B value as a covariate. The treatment difference in the least-squares means and the 2-sided 95% CI will be estimated based on this model.

Descriptive statistics will be calculated for the change from baseline over time based on observed data.

4.2.2.2. Progression of Albuminuria

The proportion of subjects with progression of albuminuria at the end of treatment will be analyzed using the logistic model with treatment as the explanatory variable and baseline albuminuria status as a covariate. Subjects without baseline and/or post-baseline ACR measurements will be excluded from the analysis. Furthermore, subjects with macroalbuminuria at baseline (ACR >300 mg/g) will also be excluded from the analysis. Baseline ACR value is derived as the geometric mean of all predose ACR measurements. For ACR values below the lower quantifiable limit, the lower quantifiable limit itself will be used for analysis. The odds ratios and the 2-sided 95% CIs for the treatment comparisons will be derived from the model. Albuminuria will be assessed according to the categorizations defined in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Guideline #1:[2] microalbuminuria is defined as ACR of 30 to 300 mg/g and macroalbuminuria is defined as an ACR greater than 300 mg/g.

Data obtained up to last dose plus 30 days will be included this analysis.

4.2.2.3. Additional Secondary Endpoints

The analyses for the additional secondary efficacy endpoints will be based on the On-Treatment analysis set. Only subjects with baseline and at least one post-baseline measurement will be included in the analysis.

Changes at the end of treatment from baseline in proinsulin/insulin ratio, eGFR, HbA_{1c}, FPG, blood pressure, percent change in body weight and fasting lipids (HDL-C, LDL-C, triglycerides, total cholesterol, and LDL-C/HDL-C) will be analyzed using an analysis of covariance (ANCOVA) model with treatment and the corresponding baseline value as covariates. The treatment difference in the least-squares means and the 2-sided 95% CI will be estimated based on this model.

Given the skewed nature of the ACR, the analysis will be performed similarly as described above on the log scale. The percentage of treatment difference, ie, treatment difference in mean ACR relative to placebo, can be calculated by taking the anti-logarithm of the estimated coefficient for the treatment group and subtracting 1. The ratio of mean ACR in treatment compared to placebo and its 95% CI will be presented.

Only subjects with baseline and at least one post-baseline measurement will be included in the analysis. The analysis for proinsulin/insulin ratio will be conducted on subjects who are not receiving insulin at randomization. For subjects who are started on insulin during the study, all proinsulin/insulin data after initiation of insulin will be censored.

Given the skewed nature of the distribution of the percent change in triglycerides, this additional secondary endpoint will be analyzed using nonparametric methods as outlined below. A Wilcoxon rank sum test will be performed. The Hodges-Lehman estimator for the difference in the medians and the distribution-free 95% CIs based on the Wilcoxon rank sum test[3] will also be presented.

4.3. Multiplicity Adjustment

Per the SAP for the integrated summary, only one alpha is proposed for the testing of the multiple hypotheses based on the integrated data and the data from CANVAS-R alone. The Type I error for these tests will be strictly controlled via a gatekeeping procedure. No alpha is preserved for evaluating hypotheses in CANVAS and all tests will be considered nominal with 2-sided 95% CIs provided for descriptive purposes.

4.4. Exploratory Efficacy Endpoints

4.4.1. Definition

The following exploratory endpoints will be analyzed:

- Time to the first occurrence of hospitalization for heart failure;
- Time to the first occurrence of the composite endpoint of hospitalization for heart failure or CV death;
- Time to all-cause mortality;
- Time to the first occurrence of composite endpoint of 40% decrease in eGFR, renal death or requirement for renal replacement therapy;
- Time to the first occurrence of composite endpoint of doubling of SCr, renal death or requirement for renal replacement therapy;
- Time to the first occurrence of composite endpoint of 40% decrease in eGFR, renal death, requirement for renal replacement therapy or CV death;
- Time to the first occurrence of composite endpoint of doubling of SCr, renal death, requirement for renal replacement therapy or CV death;
- Time to the first occurrence of composite endpoint of 40% decrease in eGFR, conversion to macroalbuminuria, renal death or requirement for renal replacement therapy;
- Time to the first occurrence of composite endpoint of doubling of SCr, conversion to macroalbuminuria, renal death or requirement for renal replacement therapy;
- Time to first progression of albuminuria, accompanied by an ACR value increase of greater than or equal to 30% from baseline;
- Time to first regression of albuminuria, accompanied by an ACR value decrease of greater than or equal to 30% from baseline;
- Change in eGFR from baseline to the last off-drug measurement;
- Change in eGFR determined from a between-group comparison of the eGFR slopes using all on-drug measurements of eGFR made from the first on-drug measurement to the final on-drug measurement.

4.4.2. Analysis Methods

4.4.2.1. CV Endpoints

The analyses of hospitalization for heart failure and the composite of hospitalization for heart failure or CV death will be based on both the ITT analysis set and the On-Treatment analysis set. The HR of canagliflozin (all canagliflozin group as well as each canagliflozin dose) compared to placebo and its 95% CI will be estimated using a stratified Cox proportional hazards regression model with treatment as the explanatory variable and the history of CV disease (secondary and primary prevention) as the stratification factor.

4.4.2.2. All-Cause Mortality

All-cause mortality will be analyzed in both the ITT analysis set and the On-Treatment analysis set using a stratified Cox proportional hazards model with treatment as the explanatory variable and history of CV disease (secondary and primary prevention) as a stratification factor. The HR of canagliflozin (all canagliflozin group as well as each canagliflozin dose) compared to placebo and its 95% CI will be estimated from the model.

4.4.2.3. Renal Endpoints

4.4.2.3.1. Composite Endpoints

The components of the renal composite endpoints, such as requirement for renal replacement therapy and doubling of serum creatinine, identified by the investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent EAC.

The time to the first occurrence of each of the renal composite endpoints (refer to Section 4.4.1) will be analyzed in the ITT analysis set using a Cox proportional hazards model with treatment and baseline eGFR (< 60, ≥ 60 mL/min/1.73m^2) as explanatory variables. The HR of canagliflozin (all canagliflozin as well as each canagliflozin dose) compared to placebo and its 95% CI will be estimated from the model.

4.4.2.3.2. Progression of Albuminuria

For the purpose of an exploratory analysis, progression of albuminuria will be assessed as in Section 4.2.2.2 with the additional condition that it must be accompanied by an increase in ACR value greater than or equal to 30% from baseline. The time to the first occurrence of the event will be analyzed in the ITT analysis set using a Cox proportional hazards regression model with treatment and baseline albuminuria status as the explanatory variables, excluding subjects with baseline macroalbuminuria. The HR of canagliflozin (all canagliflozin as well as each canagliflozin dose) compared to placebo and its 95% CI will be estimated from the model.

4.4.2.3.3. Regression of Albuminuria

Regression of albuminuria is defined as at least a one stage improvement of albuminuria, accompanied by an ACR value decrease of greater than or equal to 30% from baseline. The time to the first occurrence of the event will be analyzed in the ITT analysis set, using a Cox proportional hazards regression model with treatment and baseline albuminuria status as the explanatory

variables, excluding subjects with baseline normal albuminuria. The HR of canagliflozin (all canagliflozin as well as each canagliflozin dose) compared to placebo and its 95% CI will be estimated from the model.

4.4.2.3.4. Change in eGFR

The change in eGFR from baseline to the last off-drug measurement will be analyzed in the ITT analysis set using an analysis of covariance (ANCOVA) model with treatment and the baseline eGFR value as covariates. The treatment difference of canagliflozin (all canagliflozin as well as each canagliflozin dose) compared to placebo in the least-squares means and associated 95% CI will be estimated from the model. Subjects without baseline and/or only off-drug (ie, post-treatment) measurements will be excluded.

4.4.2.3.5. eGFR Slope

The time slope of eGFR will be analyzed in the On-Treatment analysis set using a linear mixed effects model with eGFR as a dependent variable, and treatment, baseline eGFR value, time (as a continuous variable), treatment by time interaction as fixed effects, and intercept and time as random effects. The parameter of interest is the coefficient for the treatment-by-time interaction term, which measures the slope difference between canagliflozin and placebo over time. Data will be censored at the date of last study medication and subjects without baseline and/or on-drug measurements will be excluded from the analysis.

5. SAFETY

Unless otherwise specified, 2 sets of summaries of AEs will be provided. The first set will be based on the data collected up to 07 January 2014 when INT-6 was first approved. The second set of summaries will focus on the serious AEs and AEs leading to study drug discontinuation throughout the entire study periods.

All other safety analyses and summaries (laboratory tests and vital signs) will be based on data collected throughout the entire study period using either the On-Treatment analysis set or the On-Treatment Pre-INT-6 analysis set, unless otherwise specified.

There will be no imputation of missing values for clinical laboratory test results, vital sign measurements in the safety analyses and there will be no hypothesis testing for results from safety analyses.

The treatment groups will be canagliflozin 100 mg, canagliflozin 300 mg, all canagliflozin, and placebo.

5.1. Adjudicated MACE Events

Please refer to Section 4.1 for the primary efficacy analysis of adjudicated MACE events.

5.2. Adverse Events

Adverse events (AEs) will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock.

A treatment-emergent adverse event (TEAE) is defined as an AE with an onset after the initiation of double-blind study medication and before the last study medication date plus 30 days. AEs with a start date prior to initiation of double-blind study medication which are reported to have an increase in intensity, or AEs reported to have an attribution in relationship to study medication (ie, attribution to possible, probably, very likely) after the initiation of double-blind study medication will also be considered as TEAEs. Most of the AE analyses will pertain to the TEAEs.

5.2.1. Adverse Event Collection

As one of the initial studies in the Phase 3 program, CANVAS was designed to collect detailed information on AEs. Upon the approval of canagliflozin in the United States, the safety profile of canagliflozin had been well established. The AE collection was then streamlined following the approval of INT-6 to include only:

- Serious adverse events (SAEs);
- Adverse events that resulted in study drug discontinuation;
- All AEs (serious and non-serious) for AEs of interest (refer to Table 3 below).

For selected AEs of interest, additional data will be collected on supplementary CRF pages primarily for the purposes of narrative description of certain events. Table 3 lists the AEs of interest that will be summarized.

Table 3: Adverse Events of Interest

Section A. All AEs (serious and non-serious) listed below were collected in CANVAS through INT-6. After INT-6, only the AEs that were serious or that led to study drug discontinuation were collected: Osmotic diuresis Volume depletion Hypoglycemia Urinary tract infection (UTI) Female mycotic genital infection Severe hypersensitivity /cutaneous reactions Pancreatitis Hepatic injury Renal related AEs (including Nephrotoxicity/ acute kidney injury)
Section B. The AEs listed below were collected regardless of whether they were serious and/or led to study drug discontinuation for the entire study: Male mycotic genital infection (balanitis, phimosis, events leading to circumcision) Malignancy Renal cell cancer Bladder cancer Pheochromocytoma Leydig cell tumors Breast cancer Photosensitivity Venous thromboembolic events (VTE) Amputation Fracture Diabetic ketoacidosis (DKA)

The AEs listed above will be identified using a MedDRA preferred term list (Appendix 1.4).

5.2.2. Analysis Methods

The study duration of CANVAS is long relative to the rest of the canagliflozin Phase 3 program. Accordingly, the incidences of AEs (ie, proportion of subjects reporting an AE) reported from this study are not comparable to the incidences generated in the Phase 3 program. Therefore, the exposure-adjusted incidence rate will also be reported in addition to the incidence. The exposure-adjusted incidence rate is calculated as the total number of subjects with the AE divided by the on-treatment exposure in subject-years. For some particular AEs such as malignancy where the off-drug follow up is included, the follow-up-adjusted incidence rate will be estimated. The rate is calculated as the total number of subjects with the related AE divided by the follow-up time in subject-years.

For general AEs and selected AEs of interest that are not routinely collected (refer to Section A of Table 3) after implementation of INT-6, the focus of the summary will be the serious AEs and the AEs leading to discontinuation of study medication.

5.2.2.1. General Adverse Events

Prior to the Approval of INT-6

On-Treatment Pre-INT6 analysis set will be used for the summary of general AEs prior to the approval of INT-6 unless otherwise specified.

The overall incidence and the exposure-adjusted incidence rate of AEs, AEs leading to discontinuation, drug-related AEs, drug-related AEs leading to discontinuation, SAEs, SAEs leading to discontinuation, serious drug-related AEs, serious drug-related AEs leading to discontinuation, and deaths will be summarized by treatment group.

AEs by System Organ Class (SOC) will be summarized by treatment group.

For each AE, the percentage of subjects who experienced at least one occurrence of the given event will be provided by preferred term, grouped by SOC, and presented by treatment group. In addition, the incidence of severe AEs and drug-related AEs (possibly related, probably related and very likely related, as reported by the investigator) will be summarized by preferred term, grouped by SOC, and presented by treatment group). The incidence of AEs (by preferred term, grouped by SOC, and presented by treatment group) will also be summarized by the action taken regarding the study medication, as well as by the outcome.

For reference, as a screening tool, the 95% CIs for incidence difference between treatment groups will be calculated for the AEs which are reported in at least 4 subjects in any treatment group. Four (rule-of-4) was chosen based on the recommendation from the Safety, Planning, Evaluation, and Reporting Team (SPERT).[4] The exclusion of "0" from the 95% CI for the between-group difference in incidence for a particular AE does not necessarily imply that the difference is due to the drug. The intent of providing the 95% CIs is as a filter to identify AEs that require additional

assessment. AEs identified by the above screening procedure will be presented and subject to further evaluation.

Through the Entire Study

Serious AEs and the AEs leading to discontinuation collected throughout the entire study will be analyzed based on On-Treatment analysis set unless otherwise specified.

An overview summary table with the incidence and the exposure-adjusted incidence will be generated for:

- Serious AEs;
- Deaths;
- AEs leading to discontinuation of study medication;
- Serious AEs leading to discontinuation of study medication;
- Serious AEs considered drug-related;
- AEs considered drug-related leading to discontinuation of study medication.

SAEs by SOC and preferred term will be summarized by treatment group using the On-Treatment analysis set. The same summary will be provided for AEs leading to discontinuation of study medication using the On-Treatment analysis set.

The incidence of all SAEs (by preferred term, grouped by SOC, and presented by treatment group) will also be summarized by the relationship to study drug, by the action taken regarding the study drug, as well as by the outcome. The relationship to study drug will be presented by 2 categories: related (which includes possibly related, probably related and very likely related, as reported by the investigator) and not related (which includes not related and doubtfully related, as reported by the investigator).

For reference, as a screening tool, the 95% CIs for incidence difference between treatment groups will be calculated for the AEs (regardless of seriousness) which are reported in at least 4 or more subjects in any treatment group. Only the AEs identified by the above screening procedure will be presented and subject to further evaluation.

Listings will also be provided for deaths, SAEs, and AEs leading to study drug discontinuation.

For AEs of special interest in Section A of Table 3 (with the exception of hypoglycemia, see Section 5.2.2.3), a summary similar to the analysis of general AEs will be provided. The AEs will be identified using the MedDRA preferred terms listed in Appendix 1.4.

5.2.2.2. Male Mycotic Genital Infections

Balanitis and phimosis AEs will be identified using the MedDRA preferred terms listed in Appendix 1.4 and the analyses will be based on On-Treatment analysis set only.

Using the On-Treatment analysis set, an overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- All AEs;
- Serious AEs;
- AEs considered drug-related AEs leading to discontinuation of study medication;
- Serious AEs leading to discontinuation of study medication;
- Serious AEs considered drug-related;
- AEs considered drug-related leading to discontinuation of study medication.

AEs by preferred term will be summarized by treatment group. A Kaplan-Meier plot for the time to first occurrence of balanitis will be provided by treatment group.

In addition, circumcision events will be identified based on blinded medical review of the clinical database prior to the database lock and summarized by treatment group.

Based on the additional information collected on the designated supplemental eCRF page in CANVAS, the following additional study-specific analyses will be performed:

- The incidence of male subjects with any genital mycotic infections will be summarized by treatment group and by circumcision status.
- Descriptive statistics (N, mean, SD, median, and range) will be calculated by treatment group for the duration (days) and severity (grouped as mild or moderate vs. severe) of all infections. If a subject experienced multiple events, all durations will be included in the summary.
- Descriptive statistics (N, mean, SD, median, and range) will be calculated by treatment group for the number of days from start of the AE treatment to the resolution of the symptoms.

5.2.2.3. Hypoglycemia

Hypoglycemia episodes were collected by a specific, dedicated eCRF for all hypoglycemia up to INT-6. Hypoglycemia episodes reported on the supplemental eCRF up to 07 January 2014 will be analyzed based on On-Treatment Pre-INT6 analysis set. For hypoglycemia reported on the general AE page throughout the study period, focus will be the serious events or the events leading to study drug discontinuation.

Prior to the Approval of INT-6

A subject will be counted as having a documented hypoglycemia episode when there is either a biochemically documented hypoglycemic episode (ie, concurrent fingerstick glucose or plasma glucose ≤ 70 mg/dL [3.9 mmol/L]), and/or a severe hypoglycemic episode as reported on the hypoglycemia eCRF, as follows:

- Biochemically documented hypoglycemia episode: a hypoglycemia episode with a concurrent reported glucose value of ≤ 70 mg/dL (3.9 mmol/L), regardless of whether the episode is associated with symptoms (symptomatic hypoglycemia) or not (asymptomatic hypoglycemia).

- Severe hypoglycemia episode: a hypoglycemia episode that has the answer "Yes" recorded for any of the following 3 questions on the hypoglycemia eCRF: "Did the subject require the assistance of others to treat?", "Did the subject lose consciousness during the episode?", or "Did the subject have a seizure during the episode?"

Only treatment emergent hypoglycemia episodes, reported on the eCRF for hypoglycemia, will be summarized. Treatment emergent is defined the same way as TEAEs (defined in Section 5.2).

The percentages of subjects with documented hypoglycemia episodes (ie, biochemically documented and/or severe) and subjects with biochemically documented, and with severe hypoglycemia episodes separately, will be summarized by treatment group. For subjects with biochemically documented hypoglycemia episodes, the percentage of subjects will be summarized for each of the following glucose levels (≤70 mg/dL [3.9 mmol/L], <56 mg/dL [3.1 mmol/L], and <36 mg/dL [2.0 mmol/L], "Low" results will be included in all 3 categories) by treatment group. For subjects with severe hypoglycemia episodes, the percentage of subjects by each answer of the 3 questions for severe hypoglycemia on the eCRF will be summarized by treatment group. The event rate by person-year (total number of episodes/total exposure) will be calculated by treatment group separately for documented and for severe hypoglycemia.

Subjects who had 0, 1, 2, or ≥3 documented episodes and subjects who had 0, 1, 2, or ≥3 severe hypoglycemic episodes will be summarized by treatment group.

In addition, the incidence of all episodes of hypoglycemia reported on the eCRF for hypoglycemia will be summarized (this includes events without concurrent fingerstick glucose reported and events with fingerstick glucose > 70 mg/dL [3.9 mmol/L]) by treatment group.

Through the Entire Study

Using the On-Treatment analysis set, an overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- Serious AEs;
- AEs leading to discontinuation of study medication;
- Serious AEs leading to discontinuation of study medication;
- Serious AEs considered drug-related;
- AEs considered drug-related leading to discontinuation of study medication;

SAEs by preferred term will be summarized by treatment group.

5.2.2.4. Selected Malignancies

The selected malignancies of interest are renal cell cancer, bladder cancer, testicular cancer (Leydig cell tumors), pheochromocytomas, and breast cancer. Selected malignancy AEs will be identified using the MedDRA preferred terms listed in Appendix 1.4 and the analyses will be based on the ITT analysis set.

For each selected malignancy of interest, an overview summary table with the incidence and the follow-up-adjusted incidence will be provided for:

- All AEs;
- Serious AEs;
- AEs considered drug-related (investigator assessment of possible, probable or very likely);
- AEs leading to discontinuation of study medication;
- Serious AEs leading to discontinuation of study medication;
- Serious AEs considered drug-related;
- AEs considered drug-related leading to discontinuation of study medication.

The preferred terms associated with each selected malignancy type will be summarized by treatment.

5.2.2.5. Photosensitivity

Photosensitivity AE will be identified using the MedDRA preferred terms listed in Appendix 1.4 and the analyses will use the On-Treatment analysis set.

An overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- All AEs;
- Serious AEs;
- AEs considered drug-related (investigator assessment of possible, probable or very likely);
- AEs leading to discontinuation of study medication;
- Serious AEs leading to discontinuation of study medication;
- Serious AEs considered drug-related;
- AEs considered drug-related leading to discontinuation of study medication.

AEs by preferred term will be summarized by treatment group.

5.2.2.6. Venous Thromboembolic Events

Venous thromboembolic (VTE) events will be identified using the list of MedDRA terms in Appendix 1.4. Adverse events identified by the investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent EAC for confirmation. The analyses will use the On-Treatment analysis set of adjudicated VTEs. Additionally, a similar analysis of investigator reported VTE events will also be provided.

An overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- All AEs;

- Serious AEs;
- AEs considered drug-related (investigator assessment of possible, probable or very likely);
- AEs leading to discontinuation of study medication;
- Serious AEs leading to discontinuation of study medication;
- Serious AEs considered drug-related;
- AEs considered drug-related leading to discontinuation of study medication.

AEs by preferred term will be summarized by treatment group.

The incidence of VTEs identified by the MedDRA preferred terms listed in Appendix 1.4 will also be summarized by preferred term. A summary table of all VTEs (regardless of adjudication) will also be provided by preferred term.

5.2.2.7. Fracture

Fracture events identified by the investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent Fracture Adjudication Committee to confirm that events were fractures, to determine fracture location (anatomic region) and type (low trauma or not). The main analysis will be based on the adjudicated low trauma fractures in the ITT analysis set.

An overview summary table with the incidence and the follow-up-adjusted incidence will be provided for:

- Adjudicated fractures;
- Adjudicated fractures considered serious (investigator assessment);
- Adjudicated fractures considered drug-related (investigator assessment of possible, probable or very likely);
- Adjudicated fractures leading to discontinuation of study medication;
- Adjudicated fractures considered serious and drug-related (investigator assessment);
- Adjudicated fractures considered drug-related (investigator assessment) and leading to discontinuation of study medication.

A summary of adjudicated fracture stratified by sex (male and female), and anatomical region by treatment will be provided. The incidence as well as the incidence rate will be presented.

A Kaplan-Meier plot for the time to the first occurrence of adjudicated fracture event will be provided by treatment group. The HR and the 95% CI will be derived from a Cox proportion hazards model with a term for treatment as an explanatory variable. The HR will be estimated in subgroups based on sex, baseline age (<65 and ≥65 years), duration of T2DM (<10 and ≥10 years), baseline eGFR (<60 and ≥60 mL/min/1.73 m^2), and prior fracture history (yes or no).

A summary of all adjudicated fractures by anatomic location will be provided. The HR and its 95% CI as well as a Kaplan-Meier plot for the first occurrence of all adjudicated fractures will be provided using the same analysis as low trauma fracture.

5.2.2.8. Amputation

The main analysis of lower extremity amputations as documented in the dedicated eCRF will be based on the ITT analysis set. An overview summary table with the incidence and the follow-up-adjusted incidence will be provided for:

- All lower limb amputations;
- Traumatic lower limb amputation;
- Atraumatic lower limb amputation.

Summary of anatomical region (toe, ankle, foot, below knee, above knee, other) of lower extremity atraumatic amputations will be reported by treatment group.

For atraumatic lower limb amputation, a Kaplan-Meier plot for the time to the first occurrence of event will be provided by treatment group. The association of amputation with treatment and the baseline risk factors listed in Table 4 will be assessed via logistic regression modeling. The relationship between amputation and some post-treatment factors such as volume depletion will also be explored.

For the post-treatment AEs that may be associated with amputation, groupings of selected MedDRA preferred terms used to identify events to be included in each of the following SOC categories are presented in Appendix 1.5:

- Infections and Infestations;
- Vascular disorders;
- Nervous System disorders;
- Skin and subcutaneous tissue disorders;
- Osteomyelitis.

The selected preferred terms in infections and infestation are further split into “Reversible Infection” and “Irreversible Infections”. In addition, the preferred terms grouped under the MedDRA high level term of “skin and subcutaneous tissue ulcerations” are also of interest.

For each AE group listed above, the incidence of the respective preferred terms will be summarized by treatment. Stratified by treatment, the odds ratio of amputation and each AE group listed above will be estimated.

Table 4: Baseline Factors Included in the Logistic Regression Analysis

Baseline Categorical Factors	
• Gender	• Smoking
• Cardiovascular disease history	• Use of insulin
• Peripheral vascular disease history [a]	• Baseline Systolic Blood Pressure
• Amputation history	○ > 120 vs ≤120 mmHg
• Neuropathy history	○ > 140 vs ≤140 mmHg
• Retinopathy history	• Baseline eGFR (ml/min/1.73m^2)
• Nephropathy history	○ < 60 vs ≥60
• Any diuretic use	○ < 45 vs ≥45
• Loop diuretic use	• Diabetes duration (< 10 vs ≥10 yrs.)
• Non-loop diuretic use	• Baseline HbA_{1c} (> 8 vs ≤8%)
Baseline Continuous Factors	
• Age (yrs.)	• eGFR (mL/min/1.73m^2)
• Diabetes duration (yrs.)	• HbA_{1c} (%)
• Systolic blood pressure (mmHg)	• Hemoglobin (g/L)

[a] Excludes amputation history

5.2.2.9. Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) and related AEs will be identified using the list of MedDRA terms in Appendix 1.4. Adverse events identified by the investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent EAC. The main analysis of the DKA events will be based on adjudicated events of DKA in the ITT analysis set. Events occurring at any time post-randomization, regardless of the timing of the last dose of study medication, will be included.

For the adjudicated DKA events, a table will summarize the incidence and the follow-up-adjusted incidence rate.

A listing of all DKA events identified by the sponsor's medical monitoring team and the subset of the events that went for adjudication will be provided.

5.3. Clinical Laboratory Tests

A list of clinical laboratory assessments made during the study is provided in Appendix 1.2. The percentage of subjects with specific treatment-emergent laboratory values meeting pre-defined limit of change (PDLC) criteria listed in Appendix 1.3 will be summarized. The 95% CI for the percentage difference between canagliflozin compared to the placebo group will be provided for each PDLC criterion which has at least 4 or more subjects in any treatment group. A corresponding listing will also be provided. As described above, PDLC values will be presented

based on measurements on study drug, and up to a maximum of 2 days after the last dose of study drug, as well as all measurements regardless of the time of the last dose of double-blind study drug. Summaries based on both standard units (SI) and conventional units will be provided.

5.4. Vital Signs

A treatment-emergent vital sign abnormality is defined as a change from baseline and subsequent post-baseline value that satisfies the PDLC criteria listed in Appendix 1.3. For each vital sign parameter, the proportion of subjects with a treatment-emergent abnormality will be tabulated by treatment group. PDLC values will be presented based on measurements up to a maximum of 2 days after the last dose of study drug.

The blood pressure measurements will be based on the average of the consecutive sitting blood pressure readings that were to be collected at each visit.

5.5. Electrocardiogram

The decision was made to stop collecting ECG measurements after Week 52 since INT-6. The analyses will use all the ECG data available up to Week 52. The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and QTc using the Fridericia (QTcF) correction methods. The QTcF corrected interval values are based on the following formula:[5]

- *Fridericia*: QTcF (msec) = QT(msec) * (HR(bpm)/60)1/3.

The PDLC criteria for defining an ECG abnormality for PR interval, QRS interval, QTcF values, and changes from baseline within each category are listed in Appendix 1.3. The number and the percentage of subjects in each category will be summarized by treatment group up to 2 days after the last dose of study drug.

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Janssen Research & Development

Statistical Analysis Plan

A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects with Type 2 Diabetes Mellitus

The CANVAS Trial (CANagliflozin cardioVascular Assessment Study)

Protocol 28431754DIA3008; Phase 3

JNJ-28431754 (canagliflozin)

Status:	Approved
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Prepared by:	Janssen Research & Development, LLC
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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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SUMMARY OF AMENDMENT

Relative to the statistical analysis plan (SAP) dated 20 September 2016, the major amendments made in this version are summarized as follows.

Applicable Section(s)	Description of Change(s)
1.3.3 4.4	Removed 'Change in eGFR from baseline to the last off-drug value' from objectives and exploratory efficacy endpoints.
2.2	The On-Study analysis set was added for MACE and replaced the ITT analysis set for several adverse events of interest. The upper bound of the data period for the On-Treatment analysis set was clarified as last dose plus 2 days for laboratory parameters except ACR.
4.1	Consistent with the analytic approach described in the Cardiovascular Endpoint adjudication charter, it is clarified that undetermined death is considered as CV death.
4.1.3	Additional subgroups were added for the analysis of MACE.
4.1.4.3.1	Added an analysis of MACE in the first 30, 60 and 90 days.
4.1.4.3.3	Updated the multiple imputation analysis section
4.2	Added analysis based on MMRM for continuous secondary efficacy endpoints.
4.4	Clarified that any adjudicated non-CV death event where the adjudication committee assigned a renal proximate cause is considered a renal death.
5.2.2.10	Added a section on the analysis of adjudicated pancreatitis.
Appendix 1.3	Additional lab analytes were included in the Pre-defined Limit of Change (PDLC) criteria.

ABBREVIATIONS

ACR	albumin creatinine ratio
AE	adverse event
AHA	antihyperglycemic agent
ANCOVA	analysis of covariance
BL	baseline
BMI	body mass index
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CV	cardiovascular
DBP	diastolic blood pressure
DKA	diabetic ketoacidosis
EAC	Endpoint Adjudication Committee
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GTED	Global Trial End Date
HbA_{1c}	hemoglobin A_{1c}
HDL-C	high-density lipoprotein cholesterol
HR	hazard ratio
IDMC	independent data monitoring committee
ITT	intent-to-treat
IWRS	interactive web response system
LDL-C	low-density lipoprotein cholesterol
LLN	lower limit of normal
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
PDLC	pre-defined limit of change
PT	preferred term
QTcF	QTc using the Fridericia
RAAS	renin angiotensin aldosterone system
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	steering committee
SCr	serum creatinine
SD	standard deviation
SGLT2	sodium-glucose co-transporter 2
SI	standard international
SOC	System Organ Class
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent AE
ULN	upper limit of normal
UTI	urinary tract infection
VTE	venous thromboembolic events

1. INTRODUCTION

Canagliflozin (JNJ-28431754) is an inhibitor of the sodium-glucose co-transporter 2 (SGLT2) that has been developed as an oral anti-hyperglycemic agent (AHA) for the treatment of patients with type 2 diabetes mellitus (T2DM). To meet the FDA guidance on assessing cardiovascular (CV) safety of AHAs, the sponsor initiated the CV outcomes study 28431754DIA3008 (CANVAS) in December, 2009 intended to supply data to support the CV safety of canagliflozin and to also evaluate whether canagliflozin reduces CV risk.

As part of the marketing authorization application, the sponsor performed an integrated analysis of CV events from the Phase 2 and Phase 3 canagliflozin program using data from 9,632 subjects, which included interim data harvested on 31 January 2012 from the ongoing CANVAS study of 4,330 subjects at high risk for CV disease. Subsequently, in response to a request arising during review of the canagliflozin Marketing Authorization Application by the Committee for Medicinal Products for Human Use (CHMP), the sponsor conducted a second integrated CV analysis of the Phase 2 and Phase 3 studies, which included interim data from CANVAS harvested on 19 November 2012. Data on major adverse cardiovascular events (MACE) and mortality outcomes beyond 19 November 2012 have remained blinded to the sponsor.

The primary endpoint of CANVAS was to evaluate whether there was a risk reduction in MACE associated with canagliflozin treatment. Due to unblinding of the interim summary results of CANVAS at the time of marketing approval, the planned expansion of enrollment in CANVAS was eliminated. Accordingly, the study itself is underpowered for the primary hypothesis of the reduction in CV risk as measured by the hazard ratio (HR) for MACE.

As a result of the discussions with FDA, the sponsor proposed to conduct a second CANVAS-like study (referenced as CANVAS-R) with approximately 5,700 randomized subjects. As such, the CANVAS and CANVAS-R trials are purposefully similar in design and in subject characteristics. Data from these studies are to be harvested for an integrated analysis to meet the FDA post-approval CV safety requirement and if safety is demonstrated, to assess whether canagliflozin reduces all-cause mortality no later than June 2017 with study reports submitted to FDA by September 2017.

This statistical analysis plan (SAP) stipulates definitions of analysis sets, key derived variables and statistical methods for analysis of efficacy and safety specific for CANVAS based on the latest amendment INT-8 (5 May 2016) of the protocol. Additional CV and renal outcome endpoints are added in this SAP for exploratory analysis. Since the Clinical Study Reports of the 18-week substudies were submitted in the NDA of canagliflozin and the 52-week interim results were published, the analyses in these sub studies will not be addressed in this plan.

1.1. Trial Design

The CANVAS study enrolled the first subject in December 2009. The original design called for the study to be conducted in 2 cohorts (an initial cohort of 4,500 subjects enrolled prior to regulatory submissions followed by a subsequent cohort of 14,000 subjects to be enrolled post approval).

However, due to unblinding of the interim summary results of CANVAS at the time of marketing approval, the planned expansion of enrollment in CANVAS was eliminated.

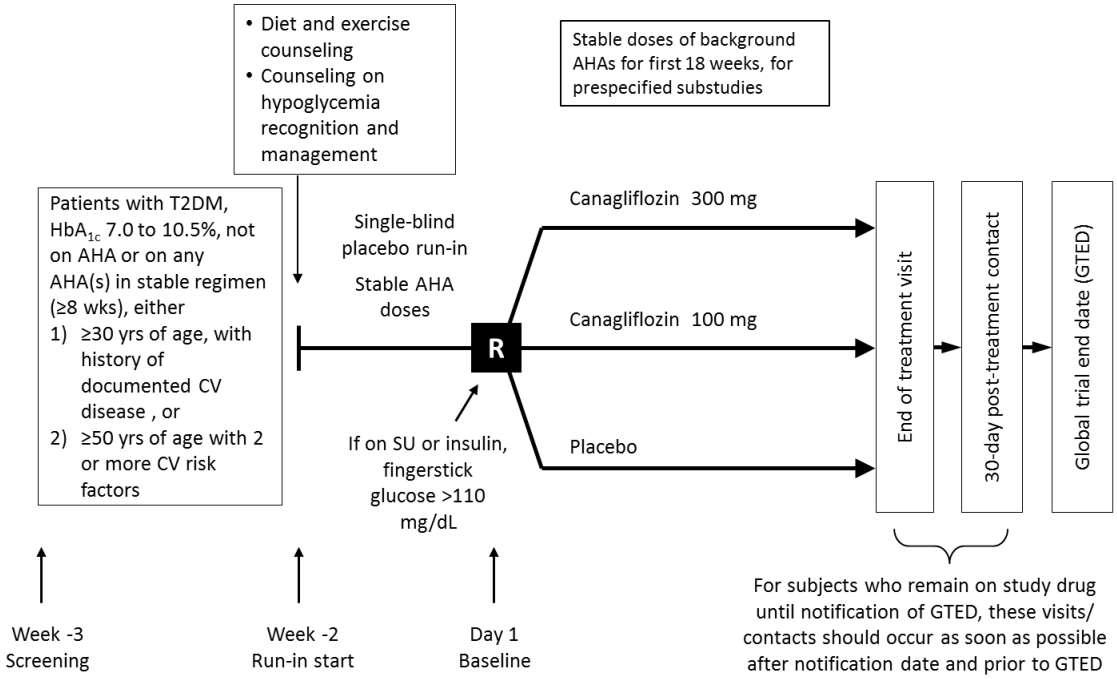
The study enrolled 4,330 subjects who met all inclusion criteria and none of the exclusion criteria. Subjects were randomly assigned to treatment with 1 of 2 doses of canagliflozin (100 or 300 mg) or placebo, in a 1:1:1 ratio. The CANVAS and CANVAS-R studies will complete when the last subject randomized has approximately 78 weeks of follow-up or when 688 MACE events are accumulated between both studies (estimated to occur between January 2017 and April 2017). The announcement of the Global Trial End Date (GTED) will mark the anticipated date on which one of these requirements for ending the study will occur.

Following announcement of the projected GTED and for subjects remaining on double-blind study drug, sites will schedule the End of Treatment (EOT) and the 30-day off-drug follow-up contact as per the Time and Events schedule in the protocol; for subjects that have prematurely discontinued study drug prior to the announcement of the projected GTED, sites will be required to make a final contact or vital status check as soon as possible after the announcement of the GTED.

A single Steering Committee (SC) and an Independent Data Monitoring Committee (IDMC) are commissioned for this and the CANVAS-R study. The SC oversees the study conduct, and the IDMC regularly (and on an ad hoc basis) reviews safety data.

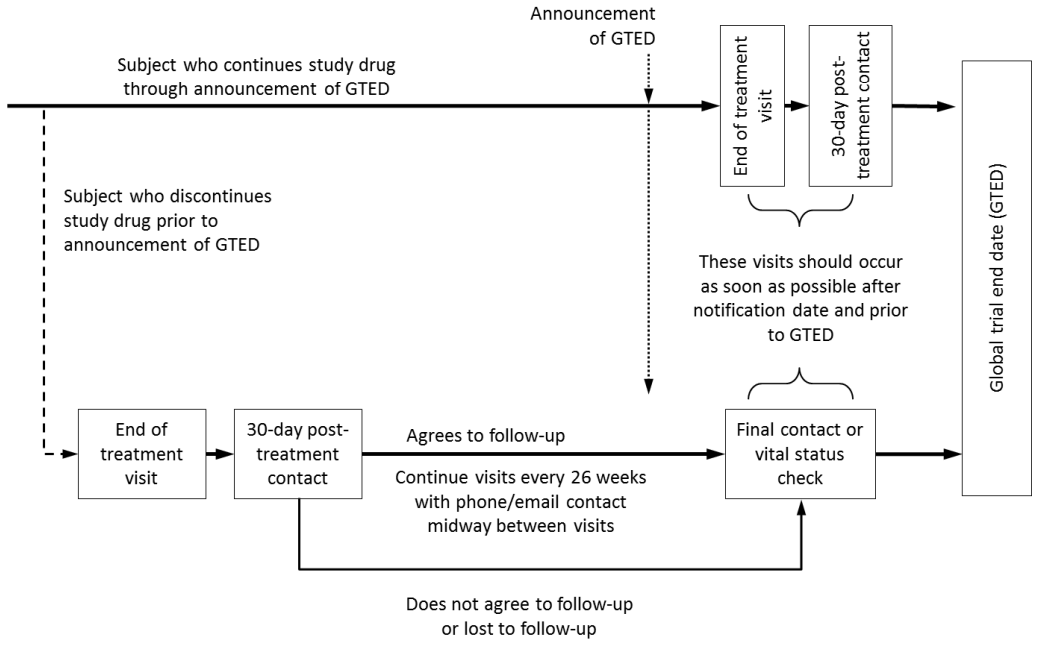
Figure 1 shows an overview of the study design and Figure 2 shows the scheduled follow-up of randomized subjects prior to the GTED.

Figure 1: Diagram of Study Design



AHA=antihyperglycemic agent; CV=cardiovascular; HbA_{1c}=hemoglobin A_{1c}; GTED=global trial end date; R=randomization; SU=sulfonylurea; T2DM=type 2 diabetes mellitus

Figure 2: Follow-up of Randomized Subjects with Respect to the GTED



Note: Following the announcement of the GTED, investigators are not expected to continue collecting data for purposes of the clinical trial after the 30-day post-treatment contact.

1.2. Randomization

Subjects were stratified into one of 6 predefined strata based on AHA use at the run-in visit through to the randomization visit. The investigators were instructed to hold AHA use constant through Week 18 and to adjust the subject's AHA regimen after Week 18 so as to achieve target glycemic control throughout the remainder of the study.

Central randomization was implemented in this study. Subjects were randomly assigned to 1 of 3 treatment groups based on a computer-generated randomization schedule prepared by the sponsor before the study. The randomization was balanced by using randomly permuted blocks and was stratified based on the use of specific concomitant AHA medications at baseline.

1.3. Trial Objectives

1.3.1. Primary Objectives

In subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease:

- To assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care on CV risk as measured by the HR for a composite endpoint (MACE including CV death, nonfatal MI, or nonfatal stroke);
- To assess the safety and tolerability of canagliflozin plus standard of care relative to placebo plus standard of care.

1.3.2. Secondary Objectives

In subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease, to assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care at the end of the treatment period on:

- Fasting measures of beta-cell function (HOMA-B and the proinsulin/insulin ratio) (note: this assessment will be conducted in a subset of subjects at sites that elected to participate, including only subjects who did not receive insulin at randomization);
- The proportion of subjects with progression of albuminuria (progression defined as the development of microalbuminuria or macroalbuminuria in a subject with baseline normoalbuminuria or the development of macroalbuminuria in a subject with baseline microalbuminuria);
- Urinary albumin/creatinine ratio (ACR);
- Change from baseline in estimated glomerular filtration rate (eGFR);
- Change from baseline in HbA_{1c} and fasting plasma glucose (FPG);
- Change in body weight;
- Change in blood pressure (systolic and diastolic);
- Change in fasting plasma lipids (triglycerides, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], total cholesterol, and the ratio of LDL-C to HDL-C).

1.3.3. Exploratory Objectives

In subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease, to assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care on:

- Hospitalization for heart failure;
- The composite of hospitalization for heart failure or CV death;
- The composite of 40% decrease in eGFR, renal death or requirement for renal replacement therapy;
- The composite of doubling of serum creatinine (SCr), renal death or requirement for renal replacement therapy;
- The composite of 40% decrease in eGFR, renal death, requirement for renal replacement therapy or CV death;
- The composite of doubling of SCr, renal death, requirement for renal replacement therapy or CV death;
- The composite of 40% decrease in eGFR, conversion to macroalbuminuria, renal death or requirement for renal replacement therapy;
- The composite of doubling of SCr, conversion to macroalbuminuria, renal death or requirement for renal replacement therapy;

- Progression of albuminuria (defined as the development of microalbuminuria or macroalbuminuria in a subject with baseline normoalbuminuria or the development of macroalbuminuria in a subject with baseline microalbuminuria), accompanied by an ACR value increase of greater than or equal to 30% from baseline;
- Regression of albuminuria (regression defined as the development of normoalbuminuria in a subject with baseline microalbuminuria or macroalbuminuria or the development of microalbuminuria in a subject with baseline macroalbuminuria), accompanied by an ACR value decrease of greater than or equal to 30% from baseline;
- Change in eGFR determined from a between-group comparison of the eGFR slopes using all on-drug measurements (ie, off-drug values will not be included) of eGFR made from the first on-drug measurement to the final on-drug measurement.

1.4. Statistical Hypotheses

The following hypotheses are specified in the study protocol, however they are considered to be exploratory in the canagliflozin CV outcome consisting of CANVAS and CANVAS-R. The hypotheses in this trial are not included as part of the testing sequence of the program. Accordingly, any p-value reported will be considered as nominal and 95% confidence intervals (CIs) for the treatment effect will be presented for descriptive purposes.

In subjects with T2DM with inadequate glycemic control, who have a history of or a high risk of CV disease, relative to placebo plus standard of care, canagliflozin plus standard of care:

- Reduces CV risk (as measured by the HR for MACE including CV death, nonfatal MI, and nonfatal stroke);
- Improves beta-cell function (change from baseline in HOMA-B) at the end of the treatment period;
- Reduces progression of albuminuria (ie, proportion of subjects with a ≥1-step progression of albuminuria measured by the urine ACR) at the end of the treatment period.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Analysis Populations

- Randomized subjects—subjects who are randomized via the Interactive Web Response System (IWRS);
- Treated subjects—randomized subjects who received at least one dose of double-blind study medication.

For efficacy analyses and baseline summaries, subjects will be analyzed according to their randomization assignment. For safety analyses (eg, adverse events [AEs]) and the summary of exposure, subjects will be analyzed according to the predominant treatment received (defined as the treatment to which the subject was exposed for the greatest duration), in the event that subjects receive a treatment other than the one to which they were randomized.

2.2. Analysis Sets

Analysis sets consist of 2 components: 1) analysis population (Section 2.1), which specifies the subjects included in an analysis; 2) data period, defining the time window during which data will be included in the analysis.

Safety data collection in CANVAS was streamlined after protocol amendment INT-6 (effective starting on 07 January 2014) such that AEs were only collected if they were serious or leading to study drug discontinuation, with the exception of selected AEs of interest. For the purpose of summarizing safety data *prior* to amendment INT-6, the On-Treatment Pre-INT6 analysis set was created as described below.

Table 1: Summary of Analysis Sets

Analysis Set	Analysis Population	Data Period
ITT	Randomized subjects	Day 1 to the last trial contact date (refer to Section 2.3.2) up to the GTED
On-Study	Treated subjects	Day 1 to the last trial contact date (see Section 2.3.1) up to GTED
On-Treatment	Treated subjects	Day 1 to the last dose date (refer to Section 2.3.2) plus X[a] days or the last trial contact date, whichever is earlier
On-Treatment Pre-INT6	Treated subjects	Day 1 to the last dose date plus X[a] days or the last trial contact date, whichever is earlier, up to 07 January 2014

[a] X is 2 days for laboratory (except ACR) and vital sign measurements, and 30 days for CV and mortality endpoints, and adverse events.

2.3. Data Handling

2.3.1. Censoring Rules

For each analysis set, events that occur any time during the data period of the corresponding analysis set (refer to Table 1) will be considered as eligible events; otherwise subjects not experiencing an event will be censored at the earlier of the last trial contact date or end of the respective data period, if not otherwise specified.

2.3.2. Handling of Key Milestone Dates

- Trial reference start date (Day 1): the first double-blind dose date for each subject (First dose date). If missing or incomplete, the first dose date will be imputed as the randomization date.
- Last dose date: the date on which the last dose of double-blind study drug was taken by the subject. If only the day is missing, impute the last day of the month. If the month or the year is missing, impute the date as the date of the scheduled visit subsequent to the last visit when the study drug was dispensed. The imputed last dose date should be no later than the end of treatment visit date or the last trial contact date. In addition, the imputed last dose date should be no earlier than the first dose date. The last dose date is the date of permanent study drug discontinuation regardless of any temporary drug interruption.

- Last trial contact date: the date when the last trial-related procedure is conducted. It is defined as the latest of:
  - The date of last visit (scheduled or unscheduled visit; office or phone visit), or
  - The latest known date of an AE or the study endpoint event status, concomitant medication, vital sign measurements or laboratory results as reported on their respective electronic case report form (eCRF), or
  - The date of alternate contact made (eg, family members, relatives, friends, health care providers, public search) confirming the subject's survival status at the time of the GTED.
  - For subjects who die during the study, the last trial contact date will be defined as the date of death.

2.3.3. Visit Windows

The Time and Events schedule of the protocol indicates the visit timing and procedures (eg, laboratory, vital signs, and other key safety variables) for each visit; however, the timing of a subject's actual visit may not be exactly as per the protocol indicated target day / visit window. Consequently, for by-visit or over-time summaries, depending on the time period(s) involved in the summaries, the conventions outlined below will be used to allocate the data collected at each actual visit to a planned protocol visit by defining visit windows.

Baseline will be defined as the pre-dose measurement closest to or including Day 1 (prior to dose administration). If the pre-dose measurement on Day 1 is missing, the missing value will be imputed by the latest available measurement prior to Day 1.

If a subject has 2 or more actual visits in one analysis visit window, the visit closest to the target day will be used as the study visit for that analysis visit window. However, results from all visits will be included in the safety analyses (eg, pre-defined limits of change analysis) to assure that all results are included. If 2 study visits are the same number of days from the target day within the same visit window, the later visit will be considered the study visit for that target day. Even though all visits will be allocated an analysis visit window, only planned protocol visits for each variable will be included in the by-visit summaries or repeated measure analyses.

Note that the algorithms for calculating visit windows are the same for all the data periods (refer to Table 1). Table 2 summarizes the analysis visit windows for laboratory, vital signs, and other key safety variables.

Table 2: Time Intervals for Analysis (in clinic) Visit Windows

Scheduled Visit Time (label on output)	Time Interval (Day)[a]	Target Time Point (Day)
Baseline	≤1[b]	1
Week 6	1[c] – 64	43
Week 12	65 – 99	85
Week 18	100 – 155	127
Week 26	156 – 197	183
Week 39	198 – 288	274
Week 52	289 – 456	365
Week 78	457–638	547
Week 104	639–820	729
Week 130	821–1002	911
Week 156	1003–1184	1093
Week 182	1185–1366	1275
Week 208	1367–1548	1457
Week 234	1549 – 1730	1639
Week 260	1731 – 1912	1821
Week 286	1913 – 2094	2003
Week 312	2095 – 2276	2185
Week 338	2277 – 2458	2367
Week 364	2459 – 2640	2549
Week 390	2641 – 2822	2731

[a] Relative to the day of the first dose of double-blind study drug.
[b] Up to the first dose of double-blind study drug.
[c] Immediately following the first dose of double-blind study drug. For variables with no time or reference collected at baseline, the first window after baseline starts on Day 2 according to the protocol.

3. SUBJECT INFORMATION

3.1. Baseline Anthropometric and Demographic Characteristics

Baseline anthropometric and demographic characteristics will be summarized by treatment group (each canagliflozin dose and all canagliflozin group, as well as placebo). Descriptive statistics (N, mean, standard deviation, median, and range) will be provided by treatment group for baseline age and baseline body weight.

Additionally, the number and percentage of subjects in the categories of the following variables at baseline will also be summarized by treatment group:

- Age group: <65, ≥ 65 years old;
- Sex: Male, Female;
- Race: White, Black or African American, Asian, Others;
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Unknown, Not reported;
- Region: North America, Central/South America, Europe, Rest of the World.

3.2. Baseline Disease Characteristics

Descriptive statistics (N, mean, SD, median, and range) will be provided by treatment group and overall for the following baseline continuous variables: duration of diabetes (in years), eGFR, ACR, systolic blood pressure (SBP), weight, body mass index (BMI), HbA_{1c}, LDL-C, HDL-C, triglycerides, total cholesterol, and LDL-C/HDL-C.

Additionally, the number and percentage of subjects will be summarized by treatment group and overall for the following:

- Baseline BMI categories (<30, ≥30 kg/m^2);
- Currently daily cigarette smoker: Yes/No;
- Baseline HbA_{1c} ≥ 8%: Yes/No;
- Duration of T2DM ≥ 10 years: Yes/No;
- Baseline systolic blood pressure categories (≤140, >140 mmHg);
- Baseline LDL-C categories (≤70, >70 mg/dL);
- Baseline HDL-C categories (<39, ≥39 mg/dL);
- Baseline eGFR categories (<30, 30 to <60, 60 to <90, ≥90 mL/min/1.73m^2);
- Baseline albuminuria categories:
  - Normoalbuminuria (0 ≤ ACR <30 mg/g); Microalbuminuria (ACR ≥30 mg/g and ≤300 mg/g); Macroalbuminuria (ACR > 300 mg/g: ACR >300 mg/g and ≤3000 mg/g, ACR > 3000 mg/g).
- History of hypertension: Yes/No;
- History of CV disease: Yes/No;
- History of coronary artery disease: Yes/No;
- History of cerebrovascular disease: Yes/No;
- History of peripheral vascular disease: Yes/No;
- History of heart failure: Yes/No;
- Microvascular diabetes complications (Any, 1, 2 or 3 of retinopathy, neuropathy [diabetic or autonomic neuropathy] and nephropathy);
- History of fracture: Yes/No;

The number and percentage of subjects with a history of medical conditions by system organ class and preferred term (based upon the general medical history eCRF) will be summarized by treatment group and overall.

3.3. Disposition Information

Disposition will be summarized for all randomized subjects by treatment group using the categories listed below:

- Screen failure;
- Subjects who are randomized (ITT);
- Subjects who are treated;
- Subjects who complete the study (ie, defined as having been followed until a time point between the notification of the GTED and the GTED, or if the subject has died prior to the GTED);
- Subjects who prematurely discontinued study medication;
- Subjects without final vital status.

The reasons for non-randomization, withdrawal from study (eg, lost to follow-up, consent withdrawal), and discontinuation from study medication will be summarized. The distribution of time to premature discontinuation of study medication will be displayed using a Kaplan-Meier plot, where one minus the survival function will be shown.

Listings will be provided for subjects whose predominant treatment differs from their randomized treatment.

3.4. Extent of Exposure and Follow-Up

Total exposure time for each subject is defined as the number of days from Day 1 to the last dose date (inclusive), regardless of any temporary drug interruption(s). Follow-up time is defined as the number of days from Day 1 to the last contact day (inclusive) for each subject. Descriptive statistics (N, mean, SD, median, and range) for total exposure or follow-up time will be presented by treatment group.

The number of subjects with duration in each of the following categories (<3 week, 3 to <13 week, 13 to <26 weeks, 26 to <52 weeks, 52 to <78 weeks, 78 to <104 weeks, 104 to <130 weeks, 130 to <156 weeks, 156 to <182 weeks, 182 to <208 weeks, 208 to <234 weeks, 234 to <260 weeks, 260 to <286 weeks, 286 to <312 weeks, 312 to <338 weeks, and ≥338 weeks) will also be presented by treatment group as well as overall.

3.5. Prior and Concomitant Medications

Concomitant medication usage is collected on the eCRF at baseline, and during the on-drug period. The number of subjects receiving medication in pre-specified categories will be presented by treatment group at baseline and on-drug period. In addition, SGLT2 inhibitor use during the off-drug follow-up period will also be summarized by treatment group.

All study medications are coded using World Health Organization Drug Utilization Research Group (WHODRUG) and Anatomical Therapeutic Chemical (ATC) codes.

Additionally, the number and percentage of subjects taking the following concomitant medications at baseline will be summarized by treatment group and overall:

- Baseline insulin use: Yes/No;
- Baseline sulphonylurea use: Yes/No;
- Baseline metformin use: Yes/No;
- Baseline statin use: Yes/No;
- Baseline anti-thrombotic use: Yes/No;
- Baseline diuretic use: Yes/No;
  - Baseline loop diuretic use: Yes/No;
  - Baseline non-loop diuretic use: Yes/No;
- Baseline renin angiotensin aldosterone system (RAAS) inhibitor use: Yes/No.

4. EFFICACY

The primary analysis will be performed based on the ITT analysis set and secondary efficacy endpoints will be based on the On-treatment analysis set, if not otherwise specified.

As noted in Section 1, there will be no formal statistical hypothesis testing and therefore all statistical tests will be considered nominal and reported using a 2-sided 95% confidence level.

Unless otherwise stated, all efficacy analyses and summaries will be performed using the treatment groups assigned by IWRS.

A tabulation of all the key analyses planned for the CV endpoints and the mortality endpoint is presented in Appendix 1.1.

4.1. Primary Efficacy Endpoint

4.1.1. Definition

The primary efficacy endpoint is the time to MACE (ie, composite of CV death[a], non-fatal MI[b], and non-fatal stroke), which is calculated as the time from Day 1 to the first occurrence of MACE. Adjudication of these outcomes by the Endpoint Adjudication Committee (EAC) will be done in a blinded fashion.

4.1.2. Analysis Methods

The primary analysis will be based on the ITT analysis set for adjudicated MACE. The HR of canagliflozin (all canagliflozin group as well as each canagliflozin dose) compared to placebo and

[a] Undetermined death is considered CV death.

[b] Silent MIs are excluded from the analysis.

its 95% CI will be estimated using a stratified Cox proportional hazards model with a term for treatment as the explanatory variable and history of CV disease (secondary and primary prevention) as a stratification factor.

The percentage of subjects who experience a MACE and the corresponding incidence rate per 1,000 patient-years will be reported. The cumulative event rate over time will be presented using a Kaplan-Meier plot by treatment (all canagliflozin group and placebo as well as each canagliflozin dose and placebo).

4.1.3. Subgroup Analyses

The homogeneity of treatment effect on the occurrence of the primary endpoint across subgroups will be examined (at a 2-sided significance level of 0.05) via a test for the treatment by subgroup interaction by adding this term and the subgroup as covariates (treated as class variables) to the primary efficacy analysis (Section 4.1.2) model. Subgroup analysis will be conducted when the total number of events is greater than 10 for two treatment groups (all canagliflozin group and placebo) and at least 1 event in both groups. Factors exhibiting interactions at a significance level of $p \leq 0.05$ will be identified as suggesting treatment effect heterogeneity, recognizing the multiplicity in testing multiple subgroups such that one or more p-values ≤ 0.05 may be expected to be observed by chance alone.

If a significant interaction is observed, the Gail-Simon test will be used to further examine the nature of the interaction (qualitative or quantitative).

The HR of canagliflozin (all canagliflozin group) compared to placebo and its 95% CI will be estimated for each of the following subgroups:

- Age group: <65, ≥ 65 years old;
- Sex: Male, Female;
- Race: White, Black or African American, Asian, Other;
- Region: Central/South America, Europe, North America, Rest of the World;
- Baseline BMI categories (<30, ≥30 kg/m^2);
- Baseline composite blood pressure categories ([SBP<140or DBP<90 mmHg] vs. [SBP ≥140 and DBP ≥90 mmHg]);
- Baseline eGFR categories (30 to <60, 60 to <90, ≥90 mL/min/1.73m^2);
- Baseline HbA_{1c} ≥ 8%: Yes/No;
- Duration of diabetes ≥ 10 years: Yes/No;
- History of CV disease: Yes/No;
- History of peripheral vascular disease: Yes/No;
- History of amputation: Yes/No;
- Baseline use of statin;

- Baseline use of anti-thrombotics;
- Baseline use of RAAS inhibitor;
- Baseline use of Beta blocker;
- Baseline use of insulin;
- Baseline use of diuretics.

4.1.4. Supportive Analyses

If not otherwise specified, the supportive analyses will use the same analysis set as in the primary efficacy analysis.

4.1.4.1. On-Study Analysis

The stratified Cox proportional hazards model (as described in Section 4.1.2) will be repeated using the On-Study analysis set, in which data of treated subjects from Day 1 to the last trial contact date up to the GTED are used.

The percentage of treated subjects who experience a MACE and the corresponding incidence rate per 1,000 patient-years will be reported.

4.1.4.2. On-Treatment Analysis

The primary analysis (as described in Section 4.1.2) will be repeated using the On-Treatment analysis set, in which data from Day 1 to 30 days after the last dose of the study drug are used.

4.1.4.3. Additional Supportive Analyses

4.1.4.3.1. MACE in the First 30, 60 and 90 Days

In addition to the Kaplan-Meier plot described in Section 4.1.2, frequency counts (n and %) of subjects experiencing the first occurrence of MACE within the first 30 days, 60 days and 90 days will be provided in the ITT analysis set.

4.1.4.3.2. Hazard Ratio Estimation for Individual MACE Components

A separate analysis will be performed for each individual MACE component (CV death, nonfatal MI, or nonfatal stroke) in both the ITT analysis set and the On-Treatment analysis set. Additionally, analyses of fatal/non-fatal MI as well as fatal/non-fatal stroke will be performed. For subjects who experience more than one MACE component, all events will be counted in the analysis for the relevant component (eg, if a subject has both non-fatal MI and non-fatal stroke, the subject will be counted as having each event). The percentage of subjects who experience each MACE component and the corresponding incidence rate per 1,000 patient-years will be summarized by treatment. The HR of canagliflozin (all canagliflozin group as well as each canagliflozin dose) compared to placebo and its 95% CI will be estimated using a stratified Cox proportional hazards model with a term for treatment as the explanatory variable and history of CV disease (secondary and primary prevention) as a stratification factor.

4.1.4.3.3. Assessment of Missing Data

The impact of missing data in the interpretation of the primary efficacy analysis will be explored. For subjects who are lost to follow-up or withdrew consent before the development of a MACE in the ITT analysis set, data collected between the last trial contact date and the GTED will be considered missing.

The proportion of data missing, defined as the ratio of the duration of missing follow-up (eg, days between last contact date + 1 day and the GTED) and the duration of intended follow-up (eg, days between randomization date and the GTED) will be summarized.

Multiple Imputation

The estimate of interest is the hazard ratio to develop MACE among all randomized subjects regardless of adherence to study medication over the period between randomization and the global trial end date (GTED). For subjects who are lost to follow up or withdrew consent before the development of a MACE, data between the last trial contact date and the GTED will be considered missing.

The subjects who discontinued from study medication prematurely prior to the announcement of the GTED can have a different hazard from those who stay on treatment throughout the trial, and their corresponding drop-out could be considered informative. This subpopulation is defined to be the subjects who

- discontinued from study medication prior to the announcement of the GTED, and
- for whom death is not the reason for the discontinuation of study medication.

The data used to model imputed outcomes for subjects with missing data will be those of the subpopulation including the retrieved drop-out data. The definition of the retrieved drop-out data is the follow up data between treatment discontinuation and the GTED. Subjects who developed MACE prior to the treatment discontinuation are included in the subpopulation and their time to MACE data will be used for the imputation modeling. With these subjects included, the model estimate of hazard should fully reflect the potential hazard of the subjects with missing outcome.

A Weibull parametric time to event model (the imputation model) will be fit using the observed time to MACE data from the subpopulation described above. The model will be stratified by study and prior cardiovascular disease (Yes/No), and adjust for treatment and the following covariates potentially correlated with missing mechanism and risk of MACE so that bias due to informative censoring in the estimation of hazard could be minimized and the precision could be optimized.

- Completion of follow up to GTED: Yes/No
- Age group: <65, ≥65 years old;
- Sex: Male, Female;
- Baseline use of Metformin: Yes/No;

- History of heart failure: Yes/No;
- Baseline SBP >140 mmHg: Yes/No;
- Baseline $HbA_{1c} \geq 8\%$: Yes/No;

In case the model does not converge, covariates will be removed from the model in the descending order as listed.

For subjects with missing data, follow up time post drop-out will be imputed with random values derived from the conditional distribution of the missing data, given the observed data and the parameters estimated from the imputation model with the pre-specified covariates. If the sum of the observed time and the simulated time is less than the expected follow-up time, ie, from randomization to the GTED, an event is imputed for the corresponding subject. Otherwise, the subjects will be censored at GTED.

The imputed events and follow-up times will be integrated with the observed data. The primary efficacy model will be reanalyzed with the imputed dataset. This process will be repeated 1,000 times. The multiple analysis results will be combined into a single inferential summary (ie, HR and 95% CI) using Rubin's rules.[1]

4.2. Secondary Efficacy Endpoints

4.2.1. Definition

The secondary efficacy endpoints are:

- Change from baseline to the end of treatment in HOMA-B;
- The proportion of subjects with progression of albuminuria at the end of treatment (ie, the development of microalbuminuria or macroalbuminuria in a subject with baseline normoalbuminuria or the development of macroalbuminuria in a subject with baseline microalbuminuria);
- Change in proinsulin/insulin ratio;
- Change in urinary ACR;
- Change in eGFR;
- Change in HbA_{1c};
- Change in FPG;
- Percent change in body weight;
- Change in blood pressure (systolic and diastolic);
- Percent change in fasting plasma lipids (triglycerides, HDL-C, LDL-C, total cholesterol, and the ratio of LDL-C to HDL-C).

4.2.2. Analysis Methods

Unless otherwise specified, the analyses for the secondary efficacy endpoints will be using the On-Treatment analysis set. Only subjects with a baseline and at least 1 post-baseline measurement will be included in the analysis.

4.2.2.1. HOMA-B

The analyses for beta-cell function will be conducted in a subset of subjects at sites that elected to participate, including only subjects who are not receiving insulin at randomization. For subjects who initiated insulin during the study, all HOMA-B data after the initiation of insulin will be censored.

Changes in HOMA-B from baseline will be analyzed using an analysis of covariance (ANCOVA) model with treatment as the explanatory variable and baseline HOMA-B value as a covariate. The treatment difference in the least-squares means and the 2-sided 95% CI will be estimated based on this model.

Change from baseline in HOMA-B over time will be analyzed using a mixed model for repeated measures (MMRM) based on restricted maximum likelihood (REML). The analysis will be based on observed data and will include the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. An unstructured covariance will be used to model the within-patient errors. The treatment comparison will be based on the least squares means and the 2-sided 95% CI will be estimated.

Descriptive statistics will be calculated for the change from baseline over time based on observed data.

4.2.2.2. Progression of Albuminuria

The proportion of subjects with progression of albuminuria at the end of treatment will be analyzed using the logistic model with treatment as the explanatory variable and baseline albuminuria status as a covariate. Subjects without baseline and/or post-baseline ACR measurements will be excluded from the analysis. Furthermore, subjects with macroalbuminuria at baseline (ACR >300 mg/g) will also be excluded from the analysis. Baseline ACR value is derived as the geometric mean of all predose ACR measurements. For ACR values below the lower quantifiable limit, the lower quantifiable limit itself will be used for analysis. The odds ratios and the 2-sided 95% CIs for the treatment comparisons will be derived from the model. Albuminuria will be assessed according to the categorizations defined in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Guideline #1:[2] microalbuminuria is defined as ACR of 30 to 300 mg/g and macroalbuminuria is defined as an ACR greater than 300 mg/g.

Data obtained up to last dose plus 30 days will be included this analysis.

4.2.2.3. Additional Secondary Endpoints

The analyses for the additional secondary efficacy endpoints will be based on the On-Treatment analysis set. Only subjects with baseline and at least one post-baseline measurement will be included in the analysis.

Changes at the end of treatment from baseline in proinsulin/insulin ratio, eGFR, HbA_{1c}, FPG, blood pressure, percent change in body weight and fasting lipids (HDL-C, LDL-C, triglycerides, total cholesterol, and LDL-C/HDL-C) will be analyzed using an analysis of covariance (ANCOVA) model with treatment and the corresponding baseline value as covariates. The treatment difference in the least-squares means and the 2-sided 95% CI will be estimated based on this model.

Given the skewed nature of the ACR, the analysis will be performed similarly as described above on the log scale. The percentage of treatment difference, ie, treatment difference in mean ACR relative to placebo, can be calculated by taking the anti-logarithm of the estimated coefficient for the treatment group and subtracting 1. The ratio of mean ACR in treatment compared to placebo and its 95% CI will be presented.

Only subjects with baseline and at least one post-baseline measurement will be included in the analysis. The analysis for proinsulin/insulin ratio will be conducted on subjects who are not receiving insulin at randomization. For subjects who are started on insulin during the study, all proinsulin/insulin data after initiation of insulin will be censored.

Given the skewed nature of the distribution of the percent change in triglycerides, this additional secondary endpoint will be analyzed using nonparametric methods as outlined below. A Wilcoxon rank sum test will be performed. The Hodges-Lehman estimator for the difference in the medians and the distribution-free 95% CIs based on the Wilcoxon rank sum test[3] will also be presented.

The change in these additional secondary endpoints from baseline over time will be explored using an MMRM model similar to the one used to analyze the change in HOMA-B (Section 4.2.2.1).

4.3. Multiplicity Adjustment

Per the SAP for the integrated summary, only one alpha is proposed for the testing of the multiple hypotheses based on the integrated data and the data from CANVAS-R alone. The Type I error for these tests will be strictly controlled via a gatekeeping procedure. No alpha is preserved for evaluating hypotheses in CANVAS and all tests will be considered nominal with 2-sided 95% CIs provided for descriptive purposes.

4.4. Exploratory Efficacy Endpoints

4.4.1. Definition

The following exploratory endpoints will be analyzed:

- Time to the first occurrence of hospitalization for heart failure;

- Time to the first occurrence of the composite endpoint of hospitalization for heart failure or CV death;
- Time to all-cause mortality;
- Time to the first occurrence of composite endpoint of 40% decrease in eGFR, renal death[a] or requirement for renal replacement therapy;
- Time to the first occurrence of composite endpoint of doubling of SCr, renal death or requirement for renal replacement therapy;
- Time to the first occurrence of composite endpoint of 40% decrease in eGFR, renal death, requirement for renal replacement therapy or CV death;
- Time to the first occurrence of composite endpoint of doubling of SCr, renal death, requirement for renal replacement therapy or CV death;
- Time to the first occurrence of composite endpoint of 40% decrease in eGFR, conversion to macroalbuminuria, renal death or requirement for renal replacement therapy;
- Time to the first occurrence of composite endpoint of doubling of SCr, conversion to macroalbuminuria, renal death or requirement for renal replacement therapy;
- Time to first progression of albuminuria, accompanied by an ACR value increase of greater than or equal to 30% from baseline;
- Time to first regression of albuminuria, accompanied by an ACR value decrease of greater than or equal to 30% from baseline;
- Change in eGFR from baseline to the last off-drug measurement;
- Change in eGFR determined from a between-group comparison of the eGFR slopes using all on-drug measurements of eGFR made from the first on-drug measurement to the final on-drug measurement.

4.4.2. Analysis Methods

4.4.2.1. CV Endpoints

The analyses of hospitalization for heart failure and the composite of hospitalization for heart failure or CV death will be based on both the ITT analysis set and the On-Treatment analysis set. The HR of canagliflozin (all canagliflozin group as well as each canagliflozin dose) compared to placebo and its 95% CI will be estimated using a stratified Cox proportional hazards regression model with treatment as the explanatory variable and the history of CV disease (secondary and primary prevention) as the stratification factor.

4.4.2.2. All-Cause Mortality

All-cause mortality will be analyzed in both the ITT analysis set and the On-Treatment analysis set using a stratified Cox proportional hazards model with treatment as the explanatory variable and

[a] Adjudicated non-CV death with a renal proximate cause is considered as renal death

history of CV disease (secondary and primary prevention) as a stratification factor. The HR of canagliflozin (all canagliflozin group as well as each canagliflozin dose) compared to placebo and its 95% CI will be estimated from the model.

4.4.2.3. Renal Endpoints

4.4.2.3.1. Composite Endpoints

The components of the renal composite endpoints, such as requirement for renal replacement therapy and doubling of serum creatinine, identified by the investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent EAC.

The time to the first occurrence of each of the renal composite endpoints (refer to Section 4.4.1) will be analyzed in the ITT analysis set using a Cox proportional hazards model with treatment and baseline eGFR ($< 60, \geq 60$ mL/min/1.73m^2) as explanatory variables. The HR of canagliflozin (all canagliflozin as well as each canagliflozin dose) compared to placebo and its 95% CI will be estimated from the model.

4.4.2.3.2. Progression of Albuminuria

For the purpose of an exploratory analysis, progression of albuminuria will be assessed as in Section 4.2.2.2 with the additional condition that it must be accompanied by an increase in ACR value greater than or equal to 30% from baseline. The time to the first occurrence of the event will be analyzed in the ITT analysis set using a Cox proportional hazards regression model with treatment and baseline albuminuria status as the explanatory variables, excluding subjects with baseline macroalbuminuria. The HR of canagliflozin (all canagliflozin as well as each canagliflozin dose) compared to placebo and its 95% CI will be estimated from the model.

4.4.2.3.3. Regression of Albuminuria

Regression of albuminuria is defined as at least a one stage improvement of albuminuria, accompanied by an ACR value decrease of greater than or equal to 30% from baseline. The time to the first occurrence of the event will be analyzed in the ITT analysis set, using a Cox proportional hazards regression model with treatment and baseline albuminuria status as the explanatory variables, excluding subjects with baseline normal albuminuria. The HR of canagliflozin (all canagliflozin as well as each canagliflozin dose) compared to placebo and its 95% CI will be estimated from the model.

4.4.2.3.4. eGFR Slope

The time slope of eGFR will be analyzed in the On-Treatment analysis set using a linear mixed effects model with eGFR as a dependent variable, and treatment, baseline eGFR value, time (as a continuous variable), treatment by time interaction as fixed effects, and intercept and time as random effects. The parameter of interest is the coefficient for the treatment-by-time interaction term, which measures the slope difference between canagliflozin and placebo over time. Data will be censored at the date of last study medication plus 2 days.

5. SAFETY

Unless otherwise specified, 2 sets of summaries of AEs will be provided. The first set will be based on the data collected up to 07 January 2014 when INT-6 was first approved. The second set of summaries will focus on the serious AEs and AEs leading to study drug discontinuation throughout the entire study periods.

All other safety analyses and summaries (laboratory tests and vital signs) will be based on data collected throughout the entire study period using either the On-Treatment analysis set or the On-Treatment Pre-INT-6 analysis set, unless otherwise specified.

There will be no imputation of missing values for clinical laboratory test results, vital sign measurements in the safety analyses and there will be no hypothesis testing for results from safety analyses.

The treatment groups will be canagliflozin 100 mg, canagliflozin 300 mg, all canagliflozin, and placebo.

5.1. Adjudicated MACE Events

Please refer to Section 4.1 for the primary efficacy analysis of adjudicated MACE events.

5.2. Adverse Events

Adverse events (AEs) will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock.

A treatment-emergent adverse event (TEAE) is defined as an AE with an onset after the initiation of double-blind study medication and before the last study medication date plus 30 days. AEs with a start date prior to initiation of double-blind study medication which are reported to have an increase in intensity, or AEs reported to have an attribution in relationship to study medication (ie, attribution to possible, probably, very likely) after the initiation of double-blind study medication will also be considered as TEAEs. Most of the AE analyses will pertain to the TEAEs.

5.2.1. Adverse Event Collection

As one of the initial studies in the Phase 3 program, CANVAS was designed to collect detailed information on AEs. Upon the approval of canagliflozin in the United States, the safety profile of canagliflozin had been well established. The AE collection was then streamlined following the approval of INT-6 to include only:

- Serious adverse events (SAEs);
- Adverse events that resulted in study drug discontinuation;
- All AEs (serious and non-serious) for AEs of interest (refer to Table 3 below).

For selected AEs of interest, additional data will be collected on supplementary CRF pages primarily for the purposes of narrative description of certain events. Table 3 lists the AEs of interest that will be summarized.

Table 3: Adverse Events of Interest

Section A. All AEs (serious and non-serious) listed below were collected in CANVAS through INT-6. After INT-6, only the AEs that were serious or that led to study drug discontinuation were collected: Osmotic diuresis Volume depletion Hypoglycemia Urinary tract infection (UTI) Female mycotic genital infection Severe hypersensitivity /cutaneous reactions Pancreatitis Hepatic injury Renal related AEs (including Nephrotoxicity/ acute kidney injury)
Section B. The AEs listed below were collected regardless of whether they were serious and/or led to study drug discontinuation for the entire study: Male mycotic genital infection (balanitis, phimosis, events leading to circumcision) Malignancy Renal cell cancer Bladder cancer Pheochromocytoma Leydig cell tumors Breast cancer Photosensitivity Venous thromboembolic events (VTE) Amputation Fracture Diabetic ketoacidosis (DKA)

The AEs listed above will be identified using a MedDRA preferred term list (Appendix 1.4).

5.2.2. Analysis Methods

The study duration of CANVAS is long relative to the rest of the canagliflozin Phase 3 program. Accordingly, the incidences of AEs (ie, proportion of subjects reporting an AE) reported from this study are not comparable to the incidences generated in the Phase 3 program. Therefore, the exposure-adjusted incidence rate will also be reported in addition to the incidence. The exposure-adjusted incidence rate is calculated as the total number of subjects with the AE divided by the on-treatment exposure in subject-years. For some particular AEs such as malignancy where the off-drug follow up is included, the follow-up-adjusted incidence rate will be estimated. The rate is calculated as the total number of subjects with the related AE divided by the follow-up time in subject-years.

For general AEs and selected AEs of interest that are not routinely collected (refer to Section A of Table 3) after implementation of INT-6, the focus of the summary will be the serious AEs and the AEs leading to discontinuation of study medication.

5.2.2.1. General Adverse Events

Prior to the Approval of INT-6

On-Treatment Pre-INT6 analysis set will be used for the summary of general AEs prior to the approval of INT-6 unless otherwise specified.

The overall incidence and the exposure-adjusted incidence rate of AEs, AEs leading to discontinuation, drug-related AEs, drug-related AEs leading to discontinuation, SAEs, SAEs leading to discontinuation, serious drug-related AEs, serious drug-related AEs leading to discontinuation, and deaths will be summarized by treatment group.

AEs by System Organ Class (SOC) will be summarized by treatment group.

For each AE, the percentage of subjects who experienced at least one occurrence of the given event will be provided by preferred term, grouped by SOC, and presented by treatment group. In addition, the incidence of severe AEs and drug-related AEs (possibly related, probably related and very likely related, as reported by the investigator) will be summarized by preferred term, grouped by SOC, and presented by treatment group). The incidence of AEs (by preferred term, grouped by SOC, and presented by treatment group) will also be summarized by the action taken regarding the study medication, as well as by the outcome.

For reference, as a screening tool, the 95% CIs for incidence difference between treatment groups will be calculated for the AEs which are reported in at least 4 subjects in any treatment group. Four (rule-of-4) was chosen based on the recommendation from the Safety, Planning, Evaluation, and Reporting Team (SPERT).[4] The exclusion of "0" from the 95% CI for the between-group difference in incidence for a particular AE does not necessarily imply that the difference is due to the drug. The intent of providing the 95% CIs is as a filter to identify AEs that require additional assessment. AEs identified by the above screening procedure will be presented and subject to further evaluation.

Through the Entire Study

Serious AEs and the AEs leading to discontinuation collected throughout the entire study will be analyzed based on On-Treatment analysis set unless otherwise specified.

An overview summary table with the incidence and the exposure-adjusted incidence will be generated for:

- Serious AEs;
- Deaths;
- AEs leading to discontinuation of study medication;
- Serious AEs leading to discontinuation of study medication;
- Serious AEs considered drug-related;
- AEs considered drug-related leading to discontinuation of study medication.

SAEs by SOC and preferred term will be summarized by treatment group using the On-Treatment analysis set. The same summary will be provided for AEs leading to discontinuation of study medication using the On-Treatment analysis set.

The incidence of all SAEs (by preferred term, grouped by SOC, and presented by treatment group) will also be summarized by the relationship to study drug, by the action taken regarding the study drug, as well as by the outcome. The relationship to study drug will be presented by 2 categories: related (which includes possibly related, probably related and very likely related, as reported by the investigator) and not related (which includes not related and doubtfully related, as reported by the investigator).

For reference, as a screening tool, the 95% CIs for incidence difference between treatment groups will be calculated for the AEs (regardless of seriousness) which are reported in at least 4 or more subjects in any treatment group. Only the AEs identified by the above screening procedure will be presented and subject to further evaluation.

Listings will also be provided for deaths, SAEs, and AEs leading to study drug discontinuation.

For AEs of interest in Section A of Table 3 (with the exception of hypoglycemia, see Section 5.2.2.3), a summary similar to the analysis of general AEs will be provided. The AEs will be identified using the MedDRA preferred terms listed in Appendix 1.4.

5.2.2.2. Male Mycotic Genital Infections

Balanitis and phimosis AEs will be identified using the MedDRA preferred terms listed in Appendix 1.4 and the analyses will be based on On-Treatment analysis set only.

Using the On-Treatment analysis set, an overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- All AEs;
- Serious AEs;
- AEs considered drug-related AEs leading to discontinuation of study medication;
- Serious AEs leading to discontinuation of study medication;
- Serious AEs considered drug-related;
- AEs considered drug-related leading to discontinuation of study medication.

AEs by preferred term will be summarized by treatment group. A Kaplan-Meier plot for the time to first occurrence of balanitis will be provided by treatment group.

In addition, circumcision events will be identified based on blinded medical review of the clinical database prior to the database lock and summarized by treatment group.

Based on the additional information collected on the designated supplemental eCRF page in CANVAS, the following additional study-specific analyses will be performed:

- The incidence of male subjects with any genital mycotic infections will be summarized by treatment group and by circumcision status.
- Descriptive statistics (N, mean, SD, median, and range) will be calculated by treatment group for the duration (days) and severity (grouped as mild or moderate vs. severe) of all infections. If a subject experienced multiple events, all durations will be included in the summary.
- Descriptive statistics (N, mean, SD, median, and range) will be calculated by treatment group for the number of days from start of the AE treatment to the resolution of the symptoms.

5.2.2.3. Hypoglycemia

Hypoglycemia episodes were collected by a specific, dedicated eCRF for all hypoglycemia up to INT-6. Hypoglycemia episodes reported on the supplemental eCRF up to 07 January 2014 will be analyzed based on On-Treatment Pre-INT6 analysis set. For hypoglycemia reported on the general AE page throughout the study period, focus will be the serious events or the events leading to study drug discontinuation.

Prior to the Approval of INT-6

A subject will be counted as having a documented hypoglycemia episode when there is either a biochemically documented hypoglycemic episode (ie, concurrent fingerstick glucose or plasma glucose ≤ 70 mg/dL [3.9 mmol/L]), and/or a severe hypoglycemic episode as reported on the hypoglycemia eCRF, as follows:

- Biochemically documented hypoglycemia episode: a hypoglycemia episode with a concurrent reported glucose value of ≤ 70 mg/dL (3.9 mmol/L), regardless of whether the episode is associated with symptoms (symptomatic hypoglycemia) or not (asymptomatic hypoglycemia).
- Severe hypoglycemia episode: a hypoglycemia episode that has the answer "Yes" recorded for any of the following 3 questions on the hypoglycemia eCRF: "Did the subject require the assistance of others to treat?", "Did the subject lose consciousness during the episode?", or "Did the subject have a seizure during the episode?"

Only treatment emergent hypoglycemia episodes, reported on the eCRF for hypoglycemia, will be summarized. Treatment emergent is defined the same way as TEAEs (defined in Section 5.2).

The percentages of subjects with documented hypoglycemia episodes (ie, biochemically documented and/or severe) and subjects with biochemically documented, and with severe hypoglycemia episodes separately, will be summarized by treatment group. For subjects with biochemically documented hypoglycemia episodes, the percentage of subjects will be summarized for each of the following glucose levels (≤70 mg/dL [3.9 mmol/L], <56 mg/dL [3.1 mmol/L], and <36 mg/dL [2.0 mmol/L], "Low" results will be included in all 3 categories) by treatment group. For subjects with severe hypoglycemia episodes, the percentage of subjects by each answer of the 3 questions for severe hypoglycemia on the eCRF will be summarized by treatment group. The

event rate by person-year (total number of episodes/total exposure) will be calculated by treatment group separately for documented and for severe hypoglycemia.

Subjects who had 0, 1, 2, or ≥3 documented episodes and subjects who had 0, 1, 2, or ≥3 severe hypoglycemic episodes will be summarized by treatment group.

In addition, the incidence of all episodes of hypoglycemia reported on the eCRF for hypoglycemia will be summarized (this includes events without concurrent fingerstick glucose reported and events with fingerstick glucose > 70 mg/dL [3.9 mmol/L]) by treatment group.

Through the Entire Study

Using the On-Treatment analysis set, an overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- Serious AEs;
- AEs leading to discontinuation of study medication;
- Serious AEs leading to discontinuation of study medication;
- Serious AEs considered drug-related;
- AEs considered drug-related leading to discontinuation of study medication;

SAEs by preferred term will be summarized by treatment group.

5.2.2.4. Selected Malignancies

The selected malignancies of interest are renal cell cancer, bladder cancer, testicular cancer (Leydig cell tumors), pheochromocytomas, and breast cancer. Selected malignancy AEs will be identified using the MedDRA preferred terms listed in Appendix 1.4 and the analyses will be based on the On-Study analysis set.

For each selected malignancy of interest, an overview summary table with the incidence and the follow-up-adjusted incidence will be provided for:

- All AEs;
- Serious AEs;
- AEs considered drug-related (investigator assessment of possible, probable or very likely);
- AEs leading to discontinuation of study medication;
- Serious AEs leading to discontinuation of study medication;
- Serious AEs considered drug-related;
- AEs considered drug-related leading to discontinuation of study medication.

The preferred terms associated with each selected malignancy type will be summarized by treatment.

5.2.2.5. Photosensitivity

Photosensitivity AE will be identified using the MedDRA preferred terms listed in Appendix 1.4 and the analyses will use the On-Treatment analysis set.

An overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- All AEs;
- Serious AEs;
- AEs considered drug-related (investigator assessment of possible, probable or very likely);
- AEs leading to discontinuation of study medication;
- Serious AEs leading to discontinuation of study medication;
- Serious AEs considered drug-related;
- AEs considered drug-related leading to discontinuation of study medication.

AEs by preferred term will be summarized by treatment group.

5.2.2.6. Venous Thromboembolic Events

Venous thromboembolic (VTE) events will be identified using the list of MedDRA terms in Appendix 1.4. Adverse events identified by the investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent EAC for confirmation. The analyses will use the On-Treatment analysis set of adjudicated VTEs. Additionally, a similar analysis of investigator reported VTE events will also be provided.

An overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- All AEs;
- Serious AEs;
- AEs considered drug-related (investigator assessment of possible, probable or very likely);
- AEs leading to discontinuation of study medication;
- Serious AEs leading to discontinuation of study medication;
- Serious AEs considered drug-related;
- AEs considered drug-related leading to discontinuation of study medication.

AEs by preferred term will be summarized by treatment group.

The incidence of VTEs identified by the MedDRA preferred terms listed in Appendix 1.4 will also be summarized by preferred term. A summary table of all VTEs (regardless of adjudication) will also be provided by preferred term.

5.2.2.7. Fracture

Fracture events identified by the investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent Fracture Adjudication Committee to confirm that events were fractures, to determine fracture location (anatomic region) and type (low trauma or not). The main analysis will be based on the adjudicated low trauma fractures in the On-Study analysis set.

An overview summary table with the incidence and the follow-up-adjusted incidence will be provided for:

- Adjudicated fractures;
- Adjudicated fractures considered serious (investigator assessment);
- Adjudicated fractures considered drug-related (investigator assessment of possible, probable or very likely);
- Adjudicated fractures leading to discontinuation of study medication;
- Adjudicated fractures considered serious and drug-related (investigator assessment);
- Adjudicated fractures considered drug-related (investigator assessment) and leading to discontinuation of study medication.

A summary of adjudicated fracture stratified by anatomical region by treatment will be provided. The incidence as well as the incidence rate will be presented.

A Kaplan-Meier plot for the time to the first occurrence of adjudicated fracture event will be provided by treatment group. The HR and the 95% CI will be derived from a Cox proportion hazards model with a term for treatment as an explanatory variable. The HR will be estimated in subgroups based on sex, baseline age (<65 and ≥65 years), duration of T2DM (<10 and ≥10 years), baseline eGFR (<60 and ≥60 mL/min/1.73 m^2), and prior fracture history (yes or no).

A summary of all adjudicated fractures by anatomic location will be provided. The HR and its 95% CI as well as a Kaplan-Meier plot for the first occurrence of all adjudicated fractures will be provided using the same analysis as low trauma fracture.

5.2.2.8. Amputation

The main analysis of lower extremity amputations as documented in the dedicated eCRF will be based on the On-Study analysis set. An overview summary table with the incidence and the follow-up-adjusted incidence will be provided for:

- All lower limb amputations;
- Traumatic lower limb amputation;
- Atraumatic lower limb amputation.

Summary of anatomical region (toe, ankle, trans-metatarsal, below knee, above knee) of lower extremity atraumatic amputations will be reported by treatment group.

For atraumatic lower limb amputation, a Kaplan-Meier plot for the time to the first occurrence of event will be provided by treatment group. The association of amputation with treatment and the baseline risk factors listed in Table 4 will be assessed via logistic regression modeling. The relationship between amputation and some post-treatment factors such as volume depletion will also be explored.

For the post-treatment AEs that may be associated with amputation, groupings of selected MedDRA preferred terms used to identify events to be included in each of the following SOC categories are presented in Appendix 1.5:

- Infections and Infestations;
- Vascular disorders;
- Nervous System disorders;
- Skin and subcutaneous tissue disorders;
- Osteomyelitis.

The selected preferred terms in infections and infestation are further split into "Reversible Infection" and "Irreversible Infections". In addition, the preferred terms grouped under the MedDRA high level term of "skin and subcutaneous tissue ulcerations" are also of interest.

For each AE group listed above, the incidence of the respective preferred terms will be summarized by treatment. Stratified by treatment, the odds ratio of amputation and each AE group listed above will be estimated.

Table 4: Baseline Factors Included in the Logistic Regression Analysis

Baseline Categorical Factors	

• Gender
• Cardiovascular disease history
• Peripheral vascular disease history [a]
• Amputation history
• Neuropathy history
• Retinopathy history
• Nephropathy history
• Any diuretic use
• Loop diuretic use
• Non-loop diuretic use
	• Smoking
	• Use of insulin
	• Baseline Systolic Blood Pressure
	  ○ > 120 vs ≤120 mmHg
	  ○ > 140 vs ≤140 mmHg
	• Baseline eGFR (ml/min/1.73m^2)
	  ○ < 60 vs ≥60
	  ○ < 45 vs ≥45
	• Diabetes duration (< 10 vs ≥10 yrs.)
	• Baseline HbA_{1c} (> 8 vs ≤8%)

Baseline Continuous Factors	
• Age (yrs.) • Diabetes duration (yrs.) • Systolic blood pressure (mmHg)	• eGFR (mL/min/1.73m^2) • HbA_{1c} (%) • Hemoglobin (g/L)

[a] Excludes amputation history

5.2.2.9. Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) and related AEs will be identified using the list of MedDRA terms in Appendix 1.4. Adverse events identified by the investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent DKA Adjudication Committee. The main analysis of the DKA events will be based on adjudicated events of DKA in the On-Study analysis set. Events occurring at any time post-randomization, regardless of the timing of the last dose of study medication, will be included.

For the adjudicated DKA events, a table will summarize the incidence and the follow-up-adjusted incidence rate.

A listing of all DKA events identified by the sponsor's medical monitoring team and the subset of the events that went for adjudication will be provided.

5.2.2.10. Pancreatitis

Pancreatitis and related AEs identified by the sponsor using the list of MedDRA terms pre-specified in the charter will be sent to the independent Pancreatitis Adjudication Committee. The main analysis of events will be based on adjudicated, confirmed events in the On-Treatment analysis set. Analysis based on events occurring at any time post-randomization, regardless of the timing of the last dose of study medication, will be performed. The incidence rate and proportion of adjudicated pancreatitis events by severity will be summarized. The total number of subjects with an event not confirmed by the Pancreatitis Adjudication Committee will also be summarized.

5.3. Clinical Laboratory Tests

A list of clinical laboratory assessments made during the study is provided in Appendix 1.2. The percentage of subjects with specific treatment-emergent laboratory values meeting pre-defined limit of change (PDLC) criteria listed in Appendix 1.3 will be summarized. The 95% CI for the percentage difference between canagliflozin compared to the placebo group will be provided for each PDLC criterion which has at least 4 or more subjects in any treatment group. A corresponding listing will also be provided. As described above, PDLC values will be presented based on measurements on study drug, and up to a maximum of 2 days after the last dose of study drug, as well as all measurements regardless of the time of the last dose of double-blind study drug. Summaries based on both standard units (SI) and conventional units will be provided.

5.4. Vital Signs

A treatment-emergent vital sign abnormality is defined as a change from baseline and subsequent post-baseline value that satisfies the PDLC criteria listed in Appendix 1.3. For each vital sign parameter, the proportion of subjects with a treatment-emergent abnormality will be tabulated by treatment group. PDLC values will be presented based on measurements up to a maximum of 2 days after the last dose of study drug.

The blood pressure measurements will be based on the average of the consecutive sitting blood pressure readings that were to be collected at each visit.

5.5. Electrocardiogram

The decision was made to stop collecting ECG measurements after Week 52 since INT-6. The analyses will use all the ECG data available up to the approval of INT-6. The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and QTc using the Fridericia (QTcF) correction methods. The QTcF corrected interval values are based on the following formula:[5]

- *Fridericia*: QTcF (msec) = QT(msec) * (HR(bpm)/60)1/3.

The PDLC criteria for defining an ECG abnormality for PR interval, QRS interval, QTcF values, and changes from baseline within each category are listed in Appendix 1.3. The number and the percentage of subjects in each category will be summarized by treatment group up to 2 days after the last dose of study drug.

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APPENDIX

Appendix 1.1: List of Key Analyses of CV and Mortality Endpoints

Analysis Set	Endpoint	Section
Primary Efficacy Assessment of MACE		
ITT	MACE	4.1.2
On-Study	MACE	4.1.4.1
On-Treatment	MACE	4.1.4.2
ITT	MACE components	4.1
On-Treatment	MACE components	4.1
ITT	Subgroup analysis of MACE	4.1.3
Exploratory Assessment of Additional CV Endpoints		
ITT	Hospitalization for heart failure	4.4.2.1
On-Treatment	Hospitalization for heart failure	4.4.2.1
ITT	Composite of hospitalization for heart failure or CV Death	4.4.2.1
On-Treatment	Composite of hospitalization for heart failure or CV Death	4.4.2.1
ITT	All-cause Mortality	4.4.2.2
On-Treatment	All-cause Mortality	4.4.2.2

Appendix 1.2: Clinical Laboratory Tests

The clinical laboratory tests include following panels and assessments:

- Hematology panel
    - hemoglobin
    - platelet count
    - hematocrit
    - red blood cell (RBC) count
    - white blood cell (WBC) count with differential
- Serum chemistry panel
    - Sodium
    - potassium
    - chloride
    - bicarbonate
    - BUN
    - creatinine
    - aspartate aminotransferase (AST)
    - alanine aminotransferase (ALT)
    - gamma-glutamyltransferase (GGT)
    - total bilirubin
    - alkaline phosphatase
    - creatine phosphokinase (CPK)
    - lactic acid dehydrogenase (LDH)
    - uric acid
    - calcium
    - phosphate
    - albumin
    - total protein
    - magnesium
- Fasting serum lipid profile (triglycerides, LDL-C, HDL-C, total cholesterol).
- HbA_{1c}
- Urinalysis (dipstick analysis; from spot urine collection in the clinic on Day 1; performed at central laboratory; microscopic analysis is not required). Urine glucose will not be measured by the central laboratory.
    - specific gravity - ketones
    - pH - bilirubin/urobilinogen
    - protein - nitrite
    - blood - leukocyte esterase
- Central laboratory will report the estimated glomerular filtration rate (eGFR) according to the Modification of Diet in Renal Disease Study (MDRD) equation (Levey 2006) at study visits when serum creatinine is measured. The 4-variable MDRD eGFR includes serum creatinine, age, race, and sex according to the equation below:

For creatinine in mg/dL:

$$eGFR\ (mL/min/1.73\ m^2) = 175 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$$

For creatinine in µmol/L:

$$eGFR\ (mL/min/1.73m^2) = 175 \times (\text{serum creatinine} \times 0.0113)^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$$

Appendix 1.3: Pre-defined Limit of Change (PDLC) Criteria

Laboratory Test	Parameter for ANY value and LAST value
CHEMISTRY	
Albumin	Composite: <LLN and >25% decrease from BL
ALT	Absolute Value: >3X ULN
	Absolute Value: >5X ULN
	Absolute Value: >8X ULN
AST	Absolute Value: >3X ULN
	Absolute Value: >5X ULN
	Absolute Value: >8X ULN
ALT >3X ULN and Tbili >2X ULN	Composite: ALT >3X ULN and Tbili >2X ULN [with the Tbili elevation >2 X ULN within 30 days of the ALT elevation >3x ULN]
AST >3X ULN and Tbili >2X ULN	Composite: AST >3X ULN and Tbili >2X ULN [with the Tbili elevation >2 X ULN within 30 days of the AST elevation >3x ULN]
Bilirubin	Composite: >ULN and > 25% increase from BL
	Absolute Value: >2XULN
Bicarbonate	Absolute Value: <16 mEq/L
Calcium	Composite: >ULN and > 10 % increase from BL
Creatinine Kinase	Absolute Value: >1000U/L
eGFR	Composite: < 80 and decrease>30% from BL
	Change: decrease>50% from BL
Magnesium	Composite: <LLN and >25% decrease from BL
	Composite: >ULN and >25% increase from BL
Phosphorus	Composite: >ULN and >25% increase from BL
Potassium	Composite: <LLN and >15% decrease from BL
	Composite: >ULN and >15% increase from BL
	Absolute Value: ≥ 6.5 mEq/L
Sodium	Composite: <LLN and decrease >5 mEq/L or more from BL
	Composite: >ULN and increase>5 mEq/L or more from BL
Uric Acid	Composite: <LLN and >25% decrease from BL
HEMATOLOGY	
Hemoglobin	Change: ≥ 2 g/dl decrease from BL
	Change: ≥ 2 g/dL increase from BL
Platelets	Composite: >ULN and increase >25% from BL
White Blood Count	Composite: < LLN and >25% decrease from BL
	Composite: > ULN and >50 % increase from BL
VITAL SIGNS	
Pulse	Absolute Value: ≤50 beats per minute
	Absolute Value: ≥100 beats per minute
Systolic Blood Pressure	Composite: ≥ 20 mm Hg decrease from BL and ≤90 mm Hg
	Composite: ≥ 20 mm Hg increase from BL and ≥ 160 mm Hg
Diastolic Blood Pressure	Composite: ≥ 15 mm Hg decrease from BL and ≤ 50 mm Hg
	Composite: ≥ 15 mm Hg increase from BL and ≥ 100 mm Hg
ECG PARAMETERS	
QTcF	
	Change: >30-60 ms
	Change: >60 ms
	Absolute Value: > 450-480 ms
	Absolute Value: > 480-500 ms
	Absolute Value: >500 ms
PR Interval	Absolute Value: ≥ 200 ms
QRS Interval	Absolute Value: ≤ 50 ms
	Absolute Value: ≥ 120 ms

Appendix 1.4: List of Preferred Terms for Selected AEs of Interest

Diabetic ketoacidosis	Female Mycotic Genital Infections	Fracture
Acidosis	Genital candidiasis	Acetabulum fracture
Acidosis aggravated	Genital infection	Ankle fracture
Acidosis diabetic	Genital infection female	Atypical femur fracture
Acidosis metabolic	Genital infection fungal	Atypical fracture
Acidosis NOS	Urogenital infection fungal	Avulsion fracture
Acute acidosis	Vaginal infection	Bone fragmentation
Anion gap acidosis	Vaginal inflammation	Cervical vertebral fracture
Blood ketone body	Vulvitis	Chance fracture
Blood ketone body increased	Vulvovaginal candidiasis	Clavicle fracture
Blood ketone body present	Vulvovaginal mycotic infection	Closed fracture manipulation
Diabetes mellitus with ketoacidosis	Vulvovaginitis	Comminuted fracture
Diabetes with hyperosmolarity		Complicated fracture
Diabetes with ketoacidosis		Compression fracture
Diabetic acidosis		Craniofacial fracture
Diabetic hyperglycemic coma		Elevation skull fracture
Diabetic hyperosmolar coma		Epiphyseal fracture
Diabetic ketoacidosis		External fixation of fracture
Diabetic ketoacidotic hyperglycemic coma		Facial bones fracture
Diabetic metabolic decompensation		Femoral neck fracture
High anion gap metabolic acidosis		Femur fracture
Hyperglycemic seizure		Fibula fracture
Hyperosmolar hyperglycemic state		Foot fracture
Hyperosmolar state		Forearm fracture
Ketoacidosis		Fracture
Ketonuria		Fracture debridement
Ketosis		Fracture delayed union
Metabolic acidosis		Fracture displacement
Metabolic acidosis exacerbated		Fracture malunion
Metabolic acidosis NOS exacerbated		Fracture nonunion
Metabolic acidosis not otherwise specified (NOS)		Fracture pain
Metabolic acidosis worsened		Fracture reduction
Type I diabetes mellitus with ketoacidosis		Fracture treatment
Type II diabetes mellitus with ketoacidosis		Fractured coccyx
		Fractured ischium
		Fractured maxilla elevation
		Fractured sacrum
		Fractured skull depressed
		Fractured zygomatic arch elevation
		Greenstick fracture
		Hand fracture
		Hip fracture
		Humerus fracture
		Ilium fracture
		Impacted fracture
		Internal fixation of fracture
		Jaw fracture
		Limb crushing injury
		Limb fracture

Diabetic ketoacidosis	Female Mycotic Genital Infections	Fracture
		Loss of anatomical alignment after fracture reduction
		Lower limb fracture
		Lumbar vertebral fracture
		Multiple fractures
		Open fracture
		Open reduction of fracture
		Open reduction of spinal fracture
		Osteochondral fracture
		Osteoporotic fracture
		Patella fracture
		Pathological fracture
		Pelvic fracture
		Periprosthetic fracture
		Pubis fracture
		Radius fracture
		Rib fracture
		Sacroiliac fracture
		Scapula fracture
		Skull fracture
		Skull fractured base
		Spinal compression fracture
		Spinal fracture
		Spinal fusion fracture
		Sternal fracture
		Stress fracture
		Thoracic vertebral fracture
		Tibia fracture
		Torus fracture
		Traumatic fracture
		Ulna fracture
		Upper limb fracture
		Wrist fracture

Hepatic Injury	Hypoglycaemia	Male Mycotic Genital Infections
Acute graft versus host disease in liver	Hypoglycaemia	Balanitis
Acute hepatic failure	Hypoglycaemic coma	Balanitis candida
Acute yellow liver atrophy	Hypoglycaemic seizure	Balanoposthitis
Allergic hepatitis		Balanoposthitis infective
Ammonia increased		Erosive balanitis
Ascites		Gangrenous balanitis
Asterixis		Genital candidiasis
Autoimmune hepatitis		Genital infection
Bacterascites		Genital infection fungal
Biliary ascites		Genital infection male
Biliary cirrhosis		Penile infection
Biliary cirrhosis primary		Posthitis
Biliary fibrosis		
Bilirubin excretion disorder		
Biopsy liver abnormal		
Child-Pugh-Turcotte score increased		
Cholaemia		
Cholestasis		
Cholestatic liver injury		
Cholestatic pruritus		

Hepatic Injury	Hypoglycaemia	Male Mycotic Genital Infections
Chronic graft versus host disease in liver		
Chronic hepatic failure		
Chronic hepatitis		
Coma hepatic		
Cryptogenic cirrhosis		
Diabetic hepatopathy		
Drug-induced liver injury		
Duodenal varices		
Focal nodular hyperplasia		
Gallbladder varices		
Gastric varices		
Gastric varices haemorrhage		
Graft versus host disease in liver		
Haemangioma of liver		
Haemorrhagic ascites		
Haemorrhagic hepatic cyst		
Hepatectomy		
Hepatic adenoma		
Hepatic atrophy		
Hepatic calcification		
Hepatic cirrhosis		
Hepatic cyst		
Hepatic cyst ruptured		
Hepatic encelalopathy		
Hepatic encephalopathy prophylaxis		
Hepatic failure		
Hepatic fibrosis		
Hepatic fibrosis marker abnormal		
Hepatic haemangioma rupture		
Hepatic hydrothorax		
Hepatic infiltration eosinophilic		
Hepatic lesion		
Hepatic necrosis		
Hepatic steatosis		
Hepatitis		
Hepatitis acute		
Hepatitis cholestatic		
Hepatitis chronic active		
Hepatitis chronic persistent		
Hepatitis fulminant		
Hepatitis toxic		
Hepatobiliary disease		
Hepatocellular foamy cell syndrome		
Hepatocellular injury		
Hepatopulmonary syndrome		
Hepatorenal failure		
Hepatorenal syndrome		
Hepatotoxicity		
Hyperbilirubinaemia		
Icterus index increased		
Intestinal varices		
Ischaemic hepatitis		
Jaundice		
Jaundice cholestatic		
Jaundice hepatocellular		
Liver and small intestine transplant		

Hepatic Injury	Hypoglycaemia	Male Mycotic Genital Infections
Liver disorder		
Liver injury		
Lupoid hepatic cirrhosis		
Lupus hepatitis		
Mixed liver injury		
Nodular regenerative hyperplasia		
Non-alcoholic steatohepatitis		
Non-cirrhotic portal hypertension		
Ocular icterus		
Oedema due to hepatic disease		
Oesophageal varices haemorrhage		
Parenteral nutrition associated liver disease		
Peripancreatic varices		
Periportal oedema		
Portal hypertension		
Portal hypertensive enteropathy		
Portal hypertensive gastropathy		
Portal triaditis		
Portal vein cavernous transformation		
Portal vein dilatation		
Portopulmonary hypertension		
Radiation hepatitis		
Renal and liver transplant		
Retrograde portal vein flow		
Reye's syndrome		
Reynold's syndrome		
Splenic varices		
Splenic varices haemorrhage		
Subacute hepatic failure		
Varices oesophageal		
Varicose veins of abdominal wall		

Malignancy Bladder Cancer	Malignancy Breast Cancer	Malignancy Phaeochromocytoma
Bladder adenocarcinoma recurrent	Apocrine breast carcinoma	Phaeochromocytoma
Bladder adenocarcinoma stage 0	Breast angiosarcoma	Phaeochromocytoma crisis
Bladder adenocarcinoma stage I	Breast angiosarcoma metastatic	Phaeochromocytoma excision
Bladder adenocarcinoma stage II	Breast cancer	Phaeochromocytoma malignant
Bladder adenocarcinoma stage III	Breast cancer female	
Bladder adenocarcinoma stage IV	Breast cancer in situ	
Bladder adenocarcinoma stage unspecified	Breast cancer male	
Bladder cancer	Breast cancer metastatic	
Bladder cancer recurrent	Breast cancer recurrent	
Bladder cancer stage 0, with cancer in situ	Breast cancer stage I	
Bladder cancer stage 0, without cancer in situ	Breast cancer stage II	
Bladder cancer stage I, with cancer in situ	Breast cancer stage III	
Bladder cancer stage I, without cancer in situ	Breast cancer stage IV	
Bladder cancer stage II	Breast neoplasm	
Bladder cancer stage III	Breast sarcoma	
Bladder cancer stage IV	Breast sarcoma metastatic	
Bladder squamous cell carcinoma recurrent	Breast sarcoma recurrent	
Bladder squamous cell carcinoma stage 0	Contralateral breast cancer	

Malignancy Bladder Cancer	Malignancy Breast Cancer	Malignancy Phaeochromocytoma
Bladder squamous cell carcinoma stage I	HER-2 positive breast cancer	
Bladder squamous cell carcinoma stage II	Hormone refractory breast cancer	
Bladder squamous cell carcinoma stage III	Inflammatory carcinoma of breast recurrent	
Bladder squamous cell carcinoma stage IV	Inflammatory carcinoma of breast stage III	
Bladder squamous cell carcinoma stage unspecified	Inflammatory carcinoma of breast stage IV	
Bladder transitional cell carcinoma	Inflammatory carcinoma of the breast	
Bladder transitional cell carcinoma metastatic	Intraductal papillary breast neoplasm	
Bladder transitional cell carcinoma recurrent	Intraductal proliferative breast lesion	
Bladder transitional cell carcinoma stage 0	Invasive breast carcinoma	
Bladder transitional cell carcinoma stage I	Invasive ductal breast carcinoma	
Bladder transitional cell carcinoma stage II	Invasive lobular breast carcinoma	
Bladder transitional cell carcinoma stage III	Invasive papillary breast carcinoma	
Bladder transitional cell carcinoma stage IV	Lobular breast carcinoma in situ	
Metastases to bladder	Malignant nipple neoplasm	
Metastatic carcinoma of the bladder	Malignant nipple neoplasm female	
Transitional cell carcinoma	Malignant nipple neoplasm male	
	Medullary carcinoma of breast	
	Metaplastic breast carcinoma	
	Metastases to breast	
	Mucinous breast carcinoma	
	Neuroendocrine breast tumour	
	Nipple neoplasm	
	Oestrogen receptor positive breast cancer	
	Paget's disease of nipple	
	Phyllodes tumour	
	Triple negative breast cancer	
	Tubular breast carcinoma	

Malignancy Renal Cell Cancer	Malignancy Testicular	Osmotic Diuresis
Clear cell renal cell carcinoma	Benign neoplasm of testis	Dry mouth
Clear cell sarcoma of the kidney	Leydig cell tumour of the testis	Dry throat
Denys-Drash syndrome	Sertoli cell testicular tumour	Micturition disorder
Hereditary leiomyomatosis renal cell carcinoma	Spermatocytic seminoma	Micturition urgency
Hereditary papillary renal carcinoma	Testicle adenoma	Nocturia
Metastatic renal cell carcinoma	Testicular cancer metastatic	Pollakiuria
Nephroblastoma	Testicular neoplasm	Polydipsia
Non-renal cell carcinoma of kidney	Testicular papilloma	Polyuria
Renal cancer	Testis cancer	Thirst
Renal cancer metastatic		Tongue dry
Renal cancer recurrent		Urine output increased
Renal cancer stage I		
Renal cancer stage II		
Renal cancer stage III		
Renal cancer stage IV		
Renal cell carcinoma		
Renal cell carcinoma recurrent		
Renal cell carcinoma stage I		
Renal cell carcinoma stage II		
Renal cell carcinoma stage III		
Renal cell carcinoma stage IV		
Rhabdoid tumour of the kidney		

Phimosis	Photosensitivity
Acquired phimosis	Actinic elastosis
Phimosis	Actinic prurigo
	Administration site photosensitivity reaction
	Application site photosensitivity reaction
	Chronic actinic dermatitis
	Hartnup disease
	Implant site photosensitivity
	Infusion site photosensitivity reaction
	Injection site photosensitivity reaction
	Juvenile spring eruption
	Medical device site photosensitivity
	Photodermatosis
	Photokeratitis
	Photoonycholysis
	Photosensitivity reaction
	Polymorphic light eruption
	Solar dermatitis
	Solar urticaria
	Sunburn
	Vaccination site photosensitivity

Renal Related	Severe Hypersensitivity/Cutaneous AEs	Upper UTI
Acute kidney injury	Acute generalised exanthematous pustulosis	Bacterial pyelonephritis
Acute phosphate nephropathy	Allergic oedema	Emphysematous pyelonephritis
Acute prerenal failure	Anaphylactic reaction	Kidney infection
Anuria	Anaphylactic shock	Perinephric abscess
Azotaemia	Anaphylactic transfusion reaction	Pyelocystitis
Blood creatinine increased	Anaphylactoid reaction	Pyelonephritis
Blood urea increased	Anaphylactoid shock	Pyelonephritis acute
Continuous haemodiafiltration	Angioedema	Pyelonephritis chronic
Dialysis	Circulatory collapse	Pyelonephritis fungal
Glomerular filtration rate decreased	Circumoral oedema	Pyelonephritis mycoplasmal
Haemodialysis	Conjunctival oedema	Pyelonephritis viral
Haemofiltration	Corneal exfoliation	Pyonephrosis
Hypercreatininaemia	Corneal oedema	Renal abscess
Neonatal anuria	Cutaneous vasculitis	Renal cyst infection
Nephritis	Dermatitis bullous	Urosepsis
Nephropathy toxic	Dermatitis exfoliative	
Oliguria	Dermatitis exfoliative generalised	
Peritoneal dialysis	Drug eruption	
Prerenal failure	Drug hypersensitivity	
Renal failure	Drug reaction with eosinophilia and systemic symptoms	
Renal failure acute	Epidermal necrosis	
Renal failure neonatal	Epiglottic oedema	
Renal impairment	Erythema multiforme	
Renal impairment neonatal	Exfoliative rash	
	Eye oedema	
	Eye swelling	
	Eyelid oedema	
	Face oedema	
	First use syndrome	
	Fixed drug eruption	
	Gingival oedema	
	Gingival swelling	
	Gleich's syndrome	
	Hereditary angioedema	
	Hypersensitivity vasculitis	
	Idiopathic angioedema	
	Idiopathic urticaria	
	Kounis syndrome	
	Laryngeal dyspnoea	
	Laryngeal oedema	
	Laryngospasm	
	Laryngotracheal oedema	
	Limbal swelling	
	Lip exfoliation	
	Lip oedema	
	Lip swelling	
	Mucocutaneous ulceration	
	Mucosa vesicle	
	Mucosal erosion	
	Mucosal exfoliation	
	Mucosal necrosis	
	Mucosal ulceration	
	Nikolsky's sign	
	Oculomucocutaneous syndrome	

Renal Related	Severe Hypersensitivity/Cutaneous AEs	Upper UTI
	Oculorespiratory syndrome	
	Oedema mouth	
	Oedema mucosal	
	Oral mucosal blistering	
	Oral mucosal exfoliation	
	Orbital oedema	
	Oropharyngeal blistering	
	Oropharyngeal swelling	
	Palatal oedema	
	Penile exfoliation	
	Periorbital oedema	
	Pharyngeal oedema	
	Scleral oedema	
	Shock	
	Shock symptom	
	Skin exfoliation	
	Skin necrosis	
	Small bowel angioedema	
	Stevens-Johnson syndrome	
	Stridor	
	Swelling face	
	Swollen tongue	
	Throat tightness	
	Tongue exfoliation	
	Tongue oedema	
	Toxic epidermal necrolysis	
	Type I hypersensitivity	
	Urticaria	
	Urticaria cholinergic	
	Urticaria chronic	
	Urticaria papular	
	Urticarial vasculitis	
	Vaginal exfoliation	

UTI	Venous Thromboembolic events	Volume Depletion
Bladder candidiasis	Deep vein thrombosis	Blood pressure decreased
Cystitis	Deep vein thrombosis postoperative	Blood pressure orthostatic decreased
Cystitis bacterial	Embolism venous	Dehydration
Cystitis escherichia	Iliac vein occlusion	Diastolic hypotension
Cystitis gonococcal	Inferior vena cava syndrome	Dizziness postural
Cystitis haemorrhagic	Inferior vena caval occlusion	Hypotension
Cystitis interstitial	Jugular vein occlusion	Hypovolaemia
Cystitis klebsiella	Mesenteric vein occlusion	Hypovolaemic shock
Cystitis pseudomonal	Obstructive shock	Orthostatic hypotension
Emphysematous cystitis	Portosplenomesenteric venous thrombosis	Orthostatic intolerance
Escherichia urinary tract infection	Post procedural pulmonary embolism	Postural orthostatic tachycardia syndrome
Fungal cystitis	Postpartum venous thrombosis	Presyncope
Funguria	Pulmonary embolism	Shock
Genitourinary tract infection	Pulmonary infarction	Shock symptom
Streptococcal urinary tract infection	Pulmonary microemboli	Syncope
Ureter abscess	Pulmonary oil microembolism	Urine output decreased
Ureteritis	Pulmonary thrombosis	
Urethritis	Renal vein embolism	

UTI	Venous Thromboembolic events	Volume Depletion
Urethral abscess	Renal vein occlusion	
Urethral carbuncle	Subclavian vein thrombosis	
Urethral stricture post infection	Vascular occlusion	
Urinary bladder abscess	Venous thrombosis	
Urinary tract abscess	Venous thrombosis in pregnancy	
Urinary tract infection	Venous thrombosis limb	
Urinary tract infection bacterial	Visceral venous thrombosis	
Urinary tract infection enterococcal		
Urinary tract infection fungal		
Urinary tract infection pseudomonal		
Urinary tract infection staphylococcal		

Appendix 1.5: Adverse Events with Potential Amputation Association

List of selected preferred terms included within the SOCs of infections and infestations, vascular disorders, nervous system disorders, and skin and subcutaneous tissue disorders

Infections and Infestations	Vascular Disorders	Nervous System Disorders	Skin and Subcutaneous Tissue Disorders	High Level Term (HLT) Skin and subcutaneous tissue ulcerations	
Infected skin ulcer	Arteriosclerosis	Paraesthesia	Diabetic ulcer	Penile ulceration	Medical device site erosion
Skin infection	Peripheral arterial occlusive disease	Hypoaesthesia	Neuropathic ulcer	Implant site ulcer	Ulcerated haemangioma
Staphylococcal skin infection	Peripheral vascular disorder	Diabetic neuropathy	Fungating wound	Cytomegalovirus mucocutaneous ulcer	Incision site erosion
Gangrene	Peripheral artery stenosis	Neuropathy peripheral	Diabetic foot	Skin ulcer	Incision site ulcer
Osteomyelitis	Peripheral ischaemia	Areflexia	Diabetic neuropathic ulcer	Eyelid erosion	Vaccination site ulcer
Diabetic gangrene	Arterial stenosis	Hyporeflexia	Skin erosion	Implant site erosion	Fungating wound
Localised infection	Diabetic vascular disorder	Polyneuropathy		Diabetic foot infection	Ecthyma
Wound abscess	Femoral artery occlusion	Autonomic neuropathy		Application site erosion	Perineal ulceration
Wound infection	Thrombosis	Neuropathy peripheral		Infusion site erosion	Tropical ulcer
Subcutaneous abscess	Poor peripheral circulation	Burning sensation		Mycobacterium ulcerans infection	Injection site erosion
Abscess limb	Microangiopathy	Diabetic autonomic neuropathy		Infusion site ulcer	Pyogenic sterile arthritis pyoderma gangrenosum and acne syndrome
Staphylococcal osteomyelitis	Peripheral coldness	Peripheral sensory neuropathy		Neuropathic ulcer	Scleroderma associated digital ulcer
Diabetic foot infection	Diabetic microangiopathy	Peripheral sensorimotor neuropathy		Skin ulcer haemorrhage	Vulval ulceration
Staphylococcal skin infection	Arterial occlusive disease	Sensory disturbance		Burn infection	Mucocutaneous ulceration
Soft tissue infection	Arterial thrombosis	Diabetic neuropathic ulcer		Diabetic foot	Injection site ulcer
Bone abscess	Peripheral artery thrombosis			Diabetic ulcer	Pyoderma gangrenosum
Osteitis	Arterial occlusive disease			Catheter site erosion	Scrotal ulcer
Cellulitis	Angiopathy			Pyostomatitis vegetans	Application site ulcer
Wound [a]	Intermittent claudication			Catheter site ulcer	Genital ulceration
Dry gangrene	Arterial disorder			Medical device site ulcer	Infected skin ulcer
Post-operative wound infection	Impaired healing [a]			Administration site ulcer	Diabetic neuropathic ulcer
Post-operative wound complication [a]				Instillation site erosion	Varicose ulceration
Wound dehiscence				Breast ulceration	Vaginal ulceration
Burn infection				Instillation site ulcer	Vulvovaginal ulceration
Extremity necrosis				Administration site erosion	Auditory meatus external erosion
				Vasculitic ulcer	Skin erosion
				Vaccination site erosion	

[a] Although these PTs belong in the SOC of Injury, Poisoning and Procedural Complications or in the SOC of General Disorders and Administration Site Conditions, these terms were retained for the search strategy because of their relevance

List of preferred terms classified as reversible infections, irreversible infections and osteomyelitis

Reversible Infections	Irreversible Infections	Osteomyelitis
Abscess limb	Diabetic gangrene	Bone abscess
Burn infection	Dry gangrene	Osteitis
Cellulitis	Extremity necrosis	Osteomyelitis
Diabetic foot infection	Gangrene	Staphylococcal osteomyelitis
Infected skin ulcer		
Localised infection		
Skin infection		
Soft tissue infection		
Staphylococcal skin infection		
Subcutaneous abscess		
Wound		
Wound abscess		
Wound dehiscence		
Wound infection		

Janssen Research & Development

Statistical Analysis Plan

A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects With Type 2 Diabetes Mellitus

The CANVAS-R Trial (CANagliflozin cardioVascular Assessment Study-Renal)

Protocol 28431754DIA4003; Phase 4**

JNJ-28431754 (canagliflozin)

****This is a Phase 4 postmarketing study required by the US Food & Drug Administration but may be considered a Phase 3 study in some countries in which canagliflozin has not been approved.

Status: Approved

Date: 20 September 2016

Prepared by: Janssen Research & Development, LLC

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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ABBREVIATIONS

ACR	albumin creatinine ratio
AE	adverse event
AFT	accelerated failure time model
AHA	antihyperglycemic agent
ANCOVA	analysis of covariance
BL	baseline
BMI	body mass index
CI	confidence interval
CSR	clinical study report
CV	cardiovascular
DBP	diastolic blood pressure
DKA	diabetic ketoacidosis
EAC	Endpoint Adjudication Committee
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
GTED	Global Trial End Date
HbA_{1c}	hemoglobin A_{1c}
HDL-C	high-density lipoprotein cholesterol
HR	hazard ratio
IDMC	Independent Data Monitoring Committee
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LDL-C	low-density lipoprotein cholesterol
LLN	lower limit of normal
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MH	medical history
MI	myocardial infarction
PDLC	Pre-defined Limit of Change
PT	preferred term
RAAS	renin angiotensin aldosterone system
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	steering committee
SCr	serum creatinine
SD	standard deviation
SGLT2	sodium- glucose cotransporter 2
SI	standard international
SOC	system organ class
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent AE
ULN	upper limit of normal
UTI	urinary tract infection

1. INTRODUCTION

Canagliflozin (JNJ-28431754) is an inhibitor of the sodium-glucose co-transporter 2 (SGLT2) that has been developed as an oral anti-hyperglycemic agent (AHA) for the treatment of patients with type 2 diabetes mellitus (T2DM). In March 2013, canagliflozin was approved for marketing by the United States (US) Food and Drug Administration (FDA).

Following market authorization, the sponsor is required to demonstrate that the upper bound of the 2-sided 95% confidence interval (CI) of the cardiovascular (CV) risk ratio of test drug to comparator be less than 1.3 in accord with FDA Guidance on assessing CV safety of AHAs.[1] As a result of the discussions with FDA, 28431754DIA4003 (CANVAS-R) was initiated in January 2014. The design and the subject characteristics of CANVAS-R are purposefully similar to 28431754DIA3008 (CANVAS), an ongoing CV outcome study initiated in December 2009.

This SAP stipulates definitions of analysis sets, key derived variables and statistical methods for analysis of efficacy and safety specific for CANVAS-R based on the latest amendment INT-5 (September 2016) of the protocol.

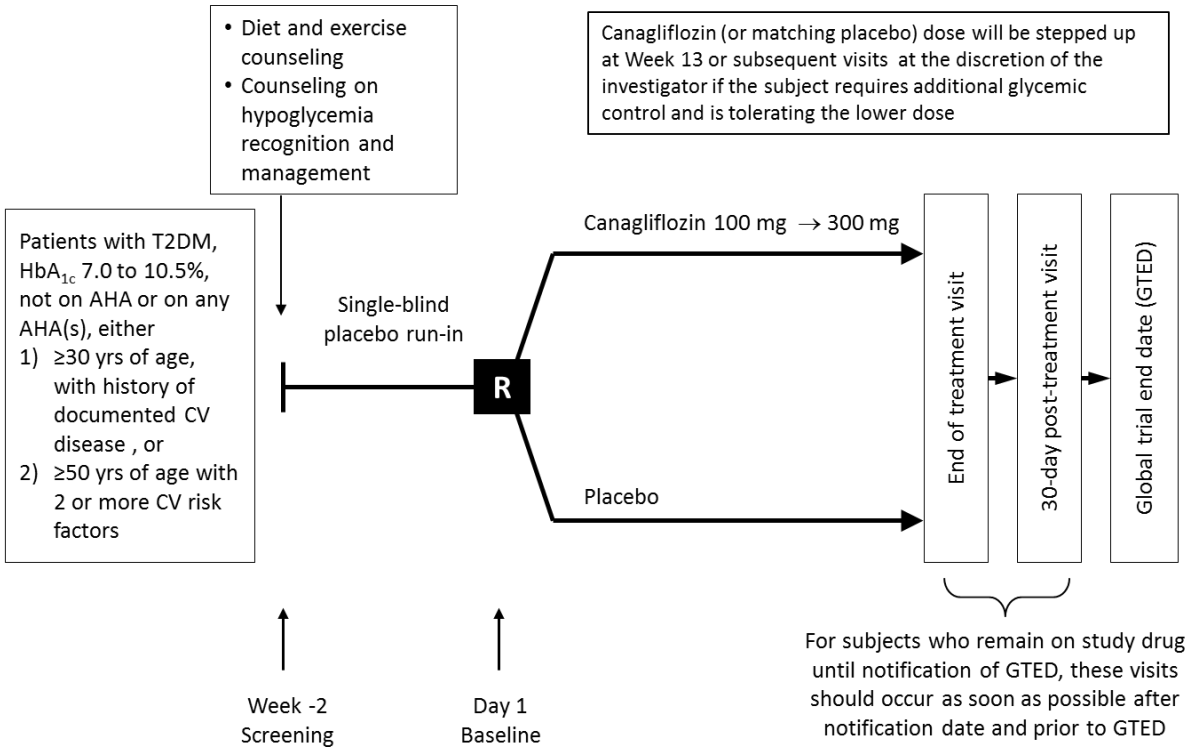
1.1. Trial Design

The CANVAS-R study enrolled the first subject in January 2014. The study recruited 5,812 subjects who met all inclusion criteria and none of the exclusion criteria. Subjects were randomly assigned to initial treatment with canagliflozin 100 mg or matching placebo administered once daily (in a 1:1 ratio). The randomization was balanced by using permutated blocks with no stratification factor. After 13 weeks, the dose of canagliflozin (or matching placebo) may be up titrated from 100 mg to 300 mg if the subject requires additional glycemic control, provided the 100 mg dose is well tolerated. The CANVAS and CANVAS-R studies will complete when the last subject randomized has approximately 78 weeks of follow-up or when 688 MACE are accumulated between both studies (estimated to occur between January 2017 and April 2017). The announcement of the GTED will mark the anticipated date on which one of these requirements for ending the study will occur.

Following announcement of the projected GTED, for subjects who remain on double-blind study drug, sites will be required to schedule the End of Treatment (EOT) and the 30-day off-drug follow-up visits as per the Time and Events schedule in the protocol; for subjects who prematurely discontinue study drug, sites will be required to make a final contact (ie, schedule the last follow-up visit) or vital status check as soon as possible after announcement of the GTED. All visits (including the 30-day off-drug follow-up visit) will need to be completed prior to the GTED. A single Steering Committee (SC) and an Independent Data Monitoring Committee (IDMC) have been commissioned for this and the CANVAS study. The SC oversees the study conduct, and the IDMC regularly (and on an ad hoc basis) reviews safety data.

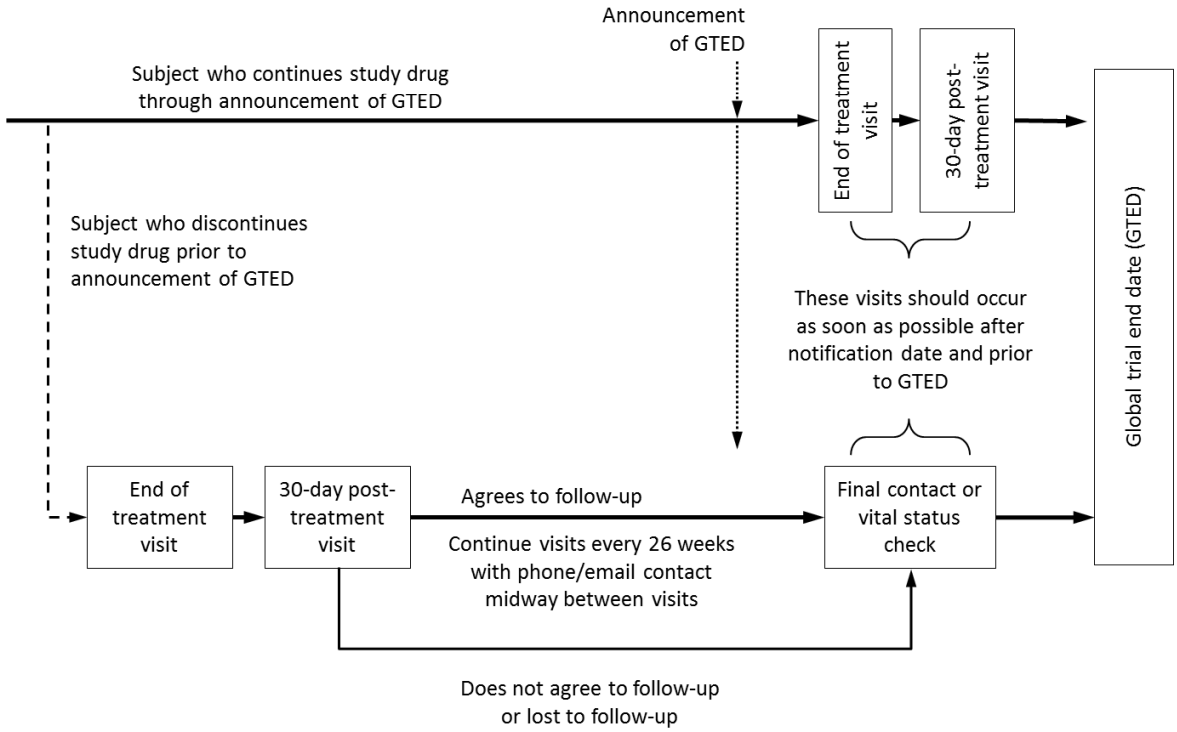
Figure 1 shows an overview of the study design and Figure 2 shows the scheduled follow-up of randomized subjects prior to the GTED.

Figure 1: Diagram of Study Design



AHA=antihyperglycemic agent; CV=cardiovascular; HbA_{1c}=hemoglobin A_{1c}; GTED=global trial end date; R=randomization; T2DM=type 2 diabetes mellitus

Figure 2: Follow-up of Randomized Subjects with Respect to the GTED



Note: Following the announcement of the GTED, investigators are not expected to continue collecting data for purposes of the clinical trial after the 30-day post-treatment contact.

In this study, duplicate urinary samples will be collected from 2 consecutive days (first morning void urine samples from the visit day and the day prior to the visit). The scheduled albumin creatinine ratio (ACR) measurements will be made on Day 1 (baseline), Week 26, Week 52, Week 78, Week 104, Week 156 and the last on-drug visit.

1.2. Randomization

Central randomization was implemented in this study. Subjects were randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared by an external vendor based on the specification tested by the sponsor before the study. The randomization was balanced by using randomly permuted blocks; the randomization did not incorporate any stratification factors.

1.3. Trial Objectives

1.3.1. Primary Objective

In subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk of CV events, to assess the effect of canagliflozin compared to placebo on progression of albuminuria.

1.3.2. Secondary Objectives

In subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk of CV events, to assess the effect of canagliflozin compared to placebo on:

- The composite endpoint of death from CV causes or hospitalization for heart failure;
- Death from CV causes.

1.3.3. Exploratory Objectives

In subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk of CV events, to assess the effect of canagliflozin compared to placebo on:

- Regression of albuminuria;
- Change in estimated glomerular filtration rate (eGFR) from baseline to the last off-drug value;
- Urinary albumin/creatinine ratio (ACR);
- The composite of 40% decrease in eGFR, renal death or requirement for renal replacement therapy;
- The composite of doubling of serum creatinine (SCr), renal death or requirement for renal replacement therapy;
- The composite of 40% decrease in eGFR, renal death, requirement for renal replacement therapy or CV death;

- The composite of doubling of SCr, renal death, requirement for renal replacement therapy or CV death;
- The composite of 40% decrease in eGFR, conversion to macroalbuminuria, renal death or requirement for renal replacement therapy;
- The composite of doubling of SCr, conversion to macroalbuminuria, renal death or requirement for renal replacement therapy;
- Change in eGFR determined from a between-group comparison of the eGFR slopes using all on-drug measurements (ie, off-drug values will not be included) of eGFR made from the first on-drug measurement to the final on-drug measurement;
- Changes in $HbA_{1c;}$
- Utilization of AHA therapy.

1.4. Statistical Hypotheses

The hypotheses in CANVAS-R are to support superiority claims of canagliflozin relative to placebo in reducing the following events:

- Progression of albuminuria;
- The composite endpoint of death from CV causes or hospitalization for heart failure;
- Death from CV causes.

For each endpoint, the following statistical hypothesis on the hazard ratio (HR) of canagliflozin over placebo will be tested:

H_0: The hazard ratio ≥ 1.0, versus H_1: The hazard ratio < 1.0

Canagliflozin will be claimed to be superior in the reduction of the target events as compared to placebo if the upper bound of 95% CIs of the hazard ratio is less than 1.0.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Analysis Populations

- Randomized subjects—subjects who are randomized via the Interactive Web Response System (IWRS);
- Treated subjects—randomized subjects who received at least one dose of double-blind study medication.

For efficacy analyses and baseline summaries, subjects will be analyzed according to their randomization assignment. For safety analysis (eg, adverse events [AEs]) and summary of exposure, subjects will be analyzed according to the predominant treatment received (defined as the treatment to which the subject was exposed for the greatest duration), in the event that subjects receive a treatment other than the one to which they were randomized. The treatment groups referred in this SAP will be all canagliflozin and placebo.

2.2. Analysis Sets

Analysis sets consist of 2 components: 1) analysis population (Section 2.1), which specifies the subjects included in an analysis; 2) data period, defining the time window during which data will be included in the analysis.

Table 1: Summary of Analysis Sets

Analysis Set	Analysis Population	Data Period
ITT	Randomized subjects	Day 1 to the last trial contact date (see Section 2.3.2) up to the GTED
On-Treatment	Treated subjects	Day 1 to the last dose date (see Section 2.3.2) plus X[a] days or the last trial contact date, whichever is earlier.

[a] X is 2 days for safety laboratory and vital sign measurements, and 30 days for CV, mortality, and renal endpoints, adverse events (AEs), and laboratory values specific for efficacy.

2.3. Data Handling

2.3.1. Censoring Rules

For each analysis set, events that occur any time during the data period of the corresponding analysis set (see Table 1) will be considered as eligible events; otherwise subjects not experiencing an event will be censored at the earlier of the last trial contact day or end of the respective data period, if not otherwise specified.

2.3.2. Handling of Key Milestone Dates

- Trial reference start date (Day 1): the first double-blind dose date for each subject (First dose date). If missing or incomplete, the first dose date will be imputed as the randomization date.
- Last dose date: the date on which the last dose of double-blind study drug was taken by the subject. If only the day is missing, impute the last day of the month. If the month or the year is missing, impute the date as the date of the scheduled visit subsequent to the last visit when the study drug was dispensed. The imputed last dose date should be no later than the end of treatment visit date or the last trial contact date. In addition, the imputed last dose date should be no earlier than the first dose date. The last dose date is the date of permanent study drug discontinuation regardless of any temporary drug interruption.
- Last trial contact date: the date when the last trial-related procedure is conducted. It is defined as the latest of:
  - The date of last visit (scheduled or unscheduled visit; office or phone visit), or
  - The latest known date of an adverse event (AE) or the study endpoint event status, concomitant medication, vital sign measurements or laboratory results as reported on their respective electronic case report form (eCRF), or
  - The date of alternate contact made (eg, family members, relatives, friends, health care providers, public search) confirming the subject's survival status at the time of the GTED.
  - For subjects who die during the study, the last trial contact date will be defined as the date of death.

2.3.3. Visit Windows

The Time and Events Schedule of the protocol indicates the visit timing and procedures (eg, laboratory, vital signs, and other key safety variables) for each visit; however, the timing of a subject's actual visit may not be exactly as per the protocol indicated target day / visit window. Consequently, for by-visit or over-time summaries, depending on the time period(s) involved in the summaries, the conventions outlined below will be used to allocate the data collected at each actual visit to a planned protocol visit by defining visit windows.

Baseline will be defined as the pre-dose measurement closest to or including Day 1 (prior to dose administration). If the pre-dose measurement on Day 1 is missing, the missing value will be imputed by the latest available measurement prior to Day 1. For serum creatinine, the average of the last 2 pre-dose measurement will be used as baseline.

If a subject has 2 or more actual visits in one analysis visit window, the visit closest to the target day will be used as the study visit for that analysis visit window. However, results from all visits will be included in the safety analyses (eg, pre-defined limits of change analysis) to assure that all results are included. If 2 study visits are the same number of days from the target day within the same visit window, the later visit will be considered the study visit for that target day. Even though all visits will be allocated an analysis visit window, only planned protocol visits for each variable will be included in the by-visit summaries or repeated measure analyses.

Note that the algorithms for calculating visit windows are the same for all the data periods (see Table 1). Table 2 summarizes the analysis visit windows for laboratory, vital signs, and other key safety variables.

Table 2: Time Intervals for Analysis (in clinic) Visit Windows

Scheduled Visit Time (label on output)	Time Interval (Day)[a]	Target Time Point (Day)
Baseline	≤1[b]	1
Week 13	1[c] –137	92
Week 26	138–229	183
Week 52	230–456	365
Week 78	457–638	547
Week 104	639–820	729
Week 130	821–1002	911
Week 156	1003–1184	1093
Week 182	1185–1366	1275
Week 208	1367–1548	1457

[a] Relative to the day of the first dose of double-blind study drug.
[b] Up to the first dose of double-blind study drug.
[c] Immediately following the first dose of double-blind study drug. For variables with no time or reference collected at baseline, the first window after baseline starts on Day 2 according to the protocol.

3. SUBJECT INFORMATION

3.1. Baseline Anthropometric and Demographic Characteristics

Baseline anthropometric and demographic characteristics will be summarized by treatment group. Descriptive statistics (N, mean, standard deviation [SD], median, and range) will be provided by treatment group for the baseline age and baseline body weight.

Additionally, the number and percentage of subjects in the categories of the following variables at baseline will also be summarized by treatment group:

- Age group: <65, ≥65 years old;
- Sex: Male, Female;
- Race: White, Black or African American, Asian, Others;
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Unknown, Not reported;
- Region: North America, Central/South America, Europe, Rest of the World.

3.2. Baseline Disease Characteristics

Descriptive statistics (N, mean, SD, median, and range) will be provided by treatment group and overall for the following baseline continuous variables: duration of diabetes (in years), baseline eGFR, baseline ACR, systolic blood pressure (SBP), weight, body mass index (BMI), HbA_{1c}, LDL-C, HDL-C, triglycerides, total cholesterol and LDL-C/HDL-C.

Additionally, the number and percentage of subjects will be summarized by treatment group and overall for the following:

- Baseline BMI categories (<30, ≥30 kg/m^2);
- Currently daily cigarette smoker: Yes/No;
- Baseline HbA_{1c} ≥ 8%: Yes/No;
- Duration of T2DM ≥ 10 years: Yes/No;
- Baseline blood pressure categories (≤140, >140 mmHg);
- Baseline LDL-C categories (≤70, >70mg/dL);
- Baseline HDL-C categories (<39, ≥39 mg/dL);
- Baseline eGFR categories (<30, 30 to <60, 60 to <90, ≥90 mL/min/1.73m^2);
- Baseline albuminuria category:
  - Normoalbuminuria (0 ≤ ACR <30 mg/g); Microalbuminuria (ACR ≥30 mg/g and ≤300 mg/g); Macroalbuminuria (ACR >300 mg/g: ACR >300 mg/g and ≤3000 mg/g, ACR > 3000 mg/g).
- History of hypertension: Yes/No ;
- History of CV disease: Yes/No;

- History of coronary artery disease: Yes/No;
- History of cerebrovascular disease: Yes/No;
- History of peripheral vascular disease: Yes/No;
- History of heart failure: Yes/No;
- Microvascular diabetes complications (Any, 1, 2 or 3 of retinopathy, neuropathy [diabetic or automatic neuropathy] and nephropathy)
- History of fracture: Yes/No;

The number and percentage of subjects with a history of medical conditions by system organ class and preferred term (based upon the general medical history eCRF) will be summarized by treatment group and overall.

3.3. Disposition Information

Disposition will be summarized for all randomized subjects by treatment group using the categories listed below:

- Screen failure;
- Subjects who are randomized (ITT);
- Subjects who are treated;
- Subjects who complete the study (ie, defined as having been followed until a time point between the notification of the GTED and the GTED, or if the subject has died prior to the GTED);
- Subjects who prematurely discontinued study medication;
- Subjects without final vital status.

The reasons for non-randomization, withdrawal from study (eg, lost to follow-up, consent withdrawal), and discontinuation from study medication will be summarized. The distribution of time to premature discontinuation of study medication will be displayed using a Kaplan-Meier plot, where one minus the survival function will be shown.

Listings will be provided for subjects whose predominant treatment differs from their randomized treatment.

3.4. Extent of Exposure and Follow-Up

Total exposure time for each subject is defined as the number of days from Day 1 to the last dose date (inclusive), regardless of any temporary drug interruption(s). Follow-up time is defined as the number of days from Day 1 to the last contact day (inclusive) for each subject. Descriptive statistics (N, mean, SD, median, and range) for total exposure or follow-up time will be presented by treatment group.

The number of subjects with duration in each of the following categories (<13 weeks, 13 to <26 weeks, 26 to <52 weeks, 52 to <104 weeks, 104 to <156 weeks, ≥156 weeks) will also be presented by treatment group as well as overall.

3.5. Prior and Concomitant Medications

Concomitant medications of special interest is collected on the eCRF at baseline and at each on-drug visit. The number of subjects receiving medication in pre-specified categories, such as insulin, sulphonylurea, metformin, statin, anti-thrombotic, diuretic (loop, and non-loop), renin angiotensin aldosterone system (RAAS) inhibitor, will be presented by treatment group at baseline and during on-drug period. In addition, SGLT2 inhibitor use during the off-drug follow-up period will be summarized by treatment group.

4. EFFICACY

The analysis will be performed based on the ITT analysis set, if not otherwise specified.

All statistical tests, except those for the primary and secondary efficacy endpoints, will be considered nominal and reported with a 2-sided 95% confidence level.

Unless otherwise stated, all efficacy analyses and summaries will be performed using the treatment groups assigned by IWRS.

4.1. Primary Efficacy Endpoint

Subjects without baseline and/or post-baseline ACR measurements will be excluded from the primary efficacy analysis. Furthermore, subjects with macroalbuminuria at baseline (ACR >300 mg/g) will also be excluded from the analysis.

4.1.1. Definition

The primary efficacy endpoint is the time to the first occurrence of progression of albuminuria.

Urinary albumin creatinine ratio (ACR) is used to assess albuminuria. Subjects will be classified as having normoalbuminuria (ACR <30 mg/g), microalbuminuria (ACR ≥ 30 mg/g and ≤300 mg/g), or macroalbuminuria (ACR of >300 mg/g]).[2]

Progression is the development of microalbuminuria or macroalbuminuria in a subject with baseline normoalbuminuria or the development of macroalbuminuria in a subject with baseline microalbuminuria, accompanied by an ACR value increase of greater than or equal to 30% from baseline.[3]

If the ACR at a visit meets the definition of progression as described, a confirmatory ACR collection approximately 1 to 2 months later (or sooner under unusual circumstances, eg, subject is stopping study drug) should be done. In cases where a confirmatory sample is not collected within 1 to 2 months, the next available set of ACR measurements can be used for confirmation.

The primary efficacy analysis will be based on results of ACR measurements from a single visit whether confirmed or unconfirmed. The date of the progression/regression event will be defined as the visit date of the first urine sample for the potential progression/regression findings. A sensitivity analysis (see Section 4.1.4.2) will be based on results of ACR measurements from a single visit that were confirmed at a subsequent visit.

4.1.2. Analysis Methods

At each visit, the geometric mean of the duplicate measurements will be computed and used for all subsequent analyses unless otherwise specified. For ACR values below the lower quantifiable limit, the lower quantifiable limit itself will be used in the geometric mean calculation.

As the primary analysis for the primary efficacy endpoint, the time from Day 1 to first visit date observing progression (ie, using the visit date of the original sample collection and not using the visit date of the confirmatory sample collection) of albuminuria will be analyzed using a Cox proportional hazards regression model. The response variable in the model is time to progression and the model will include treatment and baseline albuminuria status as the explanatory variables. The hazard ratio of canagliflozin compared to placebo and its 95% CI will be estimated. Canagliflozin will be considered superior to placebo in the reduction of progression if the p-value of the test of significance, ie, the Wald test from the Cox model specified above, is ≤ 0.05 in the context of multiplicity adjustment described in Section 4.3.

For ITT analysis, endpoint events that occur during the data period (see Table 1) will be considered as eligible events; otherwise subjects will be censored at the last ACR measurement up to GTED.

4.1.3. Subgroup Analyses

The homogeneity of treatment effect on the occurrence of the primary endpoint across subgroups will be examined (at a 2-sided significance level of 0.05) via a test for the treatment by subgroup interaction by adding this term and the subgroup as covariates (treated as class variables) to the primary efficacy analysis (Section 4.1.2) model. Subgroup analysis will be conducted when the total number of events is greater than 10 for two treatment groups (all canagliflozin group and placebo) and at least 1 event in both groups. Factors exhibiting interactions at a significance level of $p < 0.05$ will be identified as suggesting treatment effect heterogeneity, recognizing the multiplicity in testing multiple subgroups such that one or more p-values < 0.05 may be expected to be observed by chance alone.

If a significant interaction is observed, the Gail-Simon test will be used to further examine the nature of the interaction (qualitative or quantitative).

The hazard ratio of canagliflozin (all canagliflozin group) compared to placebo and its 95% confidence interval will be estimated for each of the following subgroups:

- Age group: <65, ≥65 years old;
- Sex: Male, Female;

- Race: White, Black or African American, Asian, Other;
- Region: Central/South America, Europe, North America, Rest of the World;
- Baseline eGFR categories (30 to <60, 60 to <90, ≥90 mL/min/1.73m^2);
- Baseline HbA_{1c} ≥8%: Yes/No;
- Baseline albuminuria: Normoalbuminuria, Microalbuminuria;
- Duration of diabetes ≥ 10 years: Yes/No;
- History of CV disease: Yes/No;
- Baseline use of Renin angiotensin aldosterone system (RAAS) inhibitor: Yes/No.

4.1.4. Supportive Analyses

If not otherwise specified, the supportive analyses will use the same analysis set as in the primary efficacy analysis.

4.1.4.1. On-Treatment Analysis

For On-Treatment analysis, endpoint events that occur within the data period (see Table 1) will be eligible events; otherwise subjects will be censored at the earliest of the last ACR measurement date, last study drug dose date + 30 days, or GTED.

The Cox model for primary analysis (as described in Section 4.1.2) will be repeated using the On-Treatment analysis set.

4.1.4.2. Additional Supportive Analyses

Several Cox models analogous to the primary efficacy analysis model will also be performed for exploratory purposes:

- The first Cox proportional hazards model involves the use of confirmed progression;
- Secondly, there will be an analysis that only excludes subjects with baseline nephrotic range macroalbuminuria (ie, ACR > 3000 mg/g). This analysis will evaluate time to first occurrence of ≥1 step progression in the following categories (ie, baseline normoalbuminuria, baseline microalbuminuria, baseline non-nephrotic range macroalbuminuria).

Additionally, the actual onset time of progression of albuminuria can be determined to occur within an interval from a sequence of examination times (ie, data are interval censored). The accelerated failure time (AFT) model with log normal error structure will be implemented considering interval censoring excluding subjects with baseline macroalbuminuria.[4] The dependent variable in the AFT model is the logarithm of time to progression of albuminuria, expressed as time intervals. The model will include treatment group and baseline albuminuria status as the explanatory variables.

The cumulative progression rate derived from Kaplan-Meier estimate will be displayed graphically to evaluate the timing of progression and the consistency of the treatment effect over time.

4.1.4.3. Assessment of Missing Data

The potential impact of missing data in the interpretation of the primary efficacy analysis will be explored. For subjects who are lost to follow up or withdrew consent before the development of any progression of albuminuria, data collected between the last ACR collection date and GTED will be considered missing.

For subjects with missing data, the unobserved ACR measurements at each scheduled visit up to GTED will be imputed based on a sample being randomly drawn from a Bayesian posterior distribution which was estimated from the observed data. The time to event data for those subjects will be re-defined based on the imputed dataset where subjects with imputed ACR meeting the progression criteria will be considered having events at the corresponding visit. Subjects remaining event-free will be censored at the last scheduled visit before GTED. The imputed data will be re-analyzed using the same Cox model for the primary analysis (see Section 4.1.2). The imputation process will be repeated multiple times and the multiple versions of analysis results will be combined into single inferential summary using Rubin's rule.

4.2. Secondary Efficacy Endpoints

4.2.1. Definition

There are 2 secondary efficacy endpoints specified in this study:

- The composite endpoint of death from CV causes or hospitalization for heart failure;
- Death from CV causes (CV Death).

Analyses will be using adjudicated events and adjudication of these outcomes by the Endpoint Adjudication Committee (EAC) will be done in a blinded fashion.

4.2.2. Analysis Methods

The analyses will be using the ITT analysis set.

4.2.2.1. The Composite of CV Death or Hospitalization for Heart Failure

The analysis will be based on time to the first occurrence of the composite event using ITT analysis set. The hazard ratio of canagliflozin compared to placebo and its 95% CI will be estimated using a stratified Cox proportional hazards regression model with treatment as the explanatory variable and history of CV disease (secondary and primary prevention) as the stratification factor. The p-value from the stratified log rank test for the treatment effect will also be reported.

The subgroup analysis will be conducted using the same approaches described in Section 4.1.3 and the following subgroups:

- Age group: <65, ≥65 years old;
- Sex: Male, Female;
- Race: White, Black or African American, Asian, Other;

- Region: Central/South America, Europe, North America, Rest of the World;
- Baseline eGFR categories (30 to <60, 60 to <90, ≥90 mL/min/1.73m^2);
- Baseline HbA_{1c} ≥ 8%: Yes/No;
- Duration of diabetes ≥ 10 years: Yes/No;
- History of CV disease: Yes/No;
- History of peripheral vascular disease: Yes/No;
- History of amputation: Yes/No.

4.2.2.2. CV Death

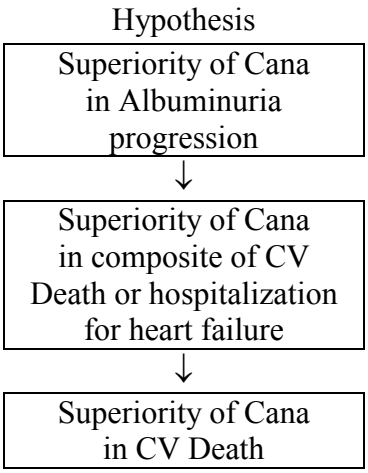
The analysis will be based on time to the first occurrence of CV death using ITT analysis set. The hazard ratio of canagliflozin compared to placebo and its 95% CI will be estimated using a stratified Cox proportional hazards regression model with treatment as the explanatory variable and history of CV disease (secondary and primary prevention) as the stratification factor. The p-value from the stratified log rank test for the treatment effect will also be reported.

Subgroup analyses will be performed using the same subgroups and the analysis methods described in Section 4.2.2.1.

4.3. Multiplicity Adjustment

Per the SAP of the integrated summary of CANVAS and CANVASR studies, only one alpha family is proposed for the testing of the multiple hypotheses based on the integrated data and the CANVAS-R data. The Type I error for these tests will be strictly controlled via a gatekeeping procedure. If the MACE and the mortality endpoints in the integrated analysis succeed in rejecting the null hypotheses, all of the alpha for testing (ie, 5%) will pass to the CANVAS-R for testing of the primary and the secondary hypotheses of the study. Tests for CANVAS-R hypotheses will proceed sequentially conditional on the statistical significance of the hypothesis tests in the integrated summary at the 5% significant level.

Figure 3: Hypothesis Testing Sequence



4.4. Exploratory Efficacy Endpoints

4.4.1. Definition

The following exploratory endpoints will be analyzed:

- Time to the first occurrence of composite endpoint of 40% decrease in eGFR, renal death or requirement for renal replacement therapy;
- Time to the first occurrence of composite endpoint of doubling of SCr, renal death or requirement for renal replacement therapy;
- Time to the first occurrence of composite endpoint of 40% decrease in eGFR, renal death, requirement for renal replacement therapy or CV death;
- Time to the first occurrence of composite endpoint of doubling of SCr, renal death, requirement for renal replacement therapy or CV death;
- Time to the first occurrence of composite endpoint of 40% decrease in eGFR, conversion to macroalbuminuria, renal death or requirement for renal replacement therapy;
- Time to the first occurrence of composite endpoint of doubling of SCr, conversion to macroalbuminuria, renal death or requirement for renal replacement therapy;
- Regression of albuminuria;

  Regression of albuminuria is the development of normoalbuminuria in a subject with baseline microalbuminuria or macroalbuminuria or the development of microalbuminuria in a subject with baseline macroalbuminuria, accompanied by a decrease in the ACR value of greater than or equal to 30% from baseline. If the ACR at a visit meets the definition of potential regression described above, a confirmatory ACR collection approximately 1 to 2 months later (or sooner under unusual circumstances, eg, subject is stopping study drug), should be done. In cases where a confirmatory sample is not collected within 1 to 2 months, the next available set of ACR measurements can be used for confirmation.

- Change in urinary ACR over time;
- Change in eGFR from baseline to the last off-drug measurement;
- Estimated eGFR slopes using all on-drug measurements;
- Changes in HbA_{1c}.
- AHA utilization

4.4.2. Analysis Methods

4.4.2.1. Renal Endpoints

4.4.2.1.1. Composite Endpoints

The components of the renal composite endpoints, such as requirement for renal replacement therapy and doubling of serum creatinine, identified by the investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent EAC.

The time to the first occurrence of each of the renal composite endpoints (see Section 4.4.1) will be analyzed in the ITT analysis set using a Cox proportional hazards model with treatment and baseline eGFR (< 60, ≥ 60 mL/min/1.73m^2) as the explanatory variables. The hazard ratio of canagliflozin compared to placebo and its 95% confidence interval will be estimated from the model.

4.4.2.1.2. Regression of Albuminuria

Regression of albuminuria will be analyzed in a similar fashion in modeling and censoring rule as the analysis for progression of albuminuria. The analysis will be using the ITT analysis set based on ACR measurements from a single visit whether confirmed or unconfirmed. Subjects with normal albuminuria at baseline will be excluded. The hazard ratio of canagliflozin compared to placebo and its 95% confidence interval will be estimated from the model. Additionally, analyses based on confirmed regression using ITT analysis set will be performed in a similar fashion.

4.4.2.1.3. Urinary ACR

Post-baseline ACR will be analyzed using mixed effect model repeat measurement (MMRM) and the ITT analysis set.

Since the distribution of ACR is highly skewed, the log transformed ACR values of all the post-baseline and scheduled visits will be modeled, using a linear mixed effects model. The linear mixed effects model will be fit to the logarithm of ACR as a dependent variable, including treatment, logarithm of baseline ACR value, visit, and treatment by visit interaction as fixed effects. The percentage of treatment difference, ie, treatment difference in mean ACR relative to placebo, can be calculated by taking the anti-logarithm of the estimated coefficient for the treatment group and subtracting 1. The ratio of mean ACR in treatment compared to placebo and its 95% CI will be presented. An unstructured covariance will be used to model the within subject errors.

4.4.2.1.4. Change in eGFR

For change in eGFR from baseline to the last off-drug measurement will be analyzed in the ITT analysis set using an analysis of covariance (ANCOVA) model with treatment and the baseline eGFR value as covariates. The treatment difference of canagliflozin compared to placebo in the least-squares means and associated 95% CI will be estimated from the model.

4.4.2.1.5. eGFR Slope

The time slope of eGFR will be analyzed in the On-Treatment analysis set using a linear mixed effects model with eGFR as a dependent variable and treatment, baseline eGFR value, time (as a continuous variable), and treatment by time interaction as fixed effects and intercept and time as random effects. The parameter of interest is the coefficient for treatment by time interaction term, which measures the slope difference between canagliflozin and placebo over time.

4.4.2.2. Changes in HbA_{1c}

Change in HbA_{1c} from baseline will be analyzed using MMRM and the ITT analysis set. The effect of canagliflozin relative to placebo on the changes in HbA_{1c} from baseline over time will be assessed using MMRM. The analysis will include the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. An unstructured covariance will be used to model the within subject errors.

4.4.2.3. AHA Utilization

Summary of AHA utilization is described under Section 3.5.

5. SAFETY

The safety analysis will be mainly based on the On-Treatment analysis set unless otherwise specified.

There will be no imputation of missing values for clinical laboratory test results, vital sign measurements in the safety analyses.

5.1. Adjudicated MACE Events

The MACE is the composite of CV outcomes including CV death, non-fatal MI[a], or non-fatal stroke. Adjudication of these outcomes by the EAC has been done in a blinded fashion.

5.1.1. Analysis Methods

The analysis will be based on the time to first occurrence of MACE using the ITT analysis set. The HR of all canagliflozin compared to placebo and its 95% CI will be estimated using a stratified Cox proportional hazards regression model with treatment (all canagliflozin and

[a] Silent MIs are excluded from the analysis.

placebo) as the explanatory variable, and prior CV disease subgroup (secondary prevention and primary prevention) as the stratification factors. P-value of stratified log rank test for treatment effect will also be reported for the primary analysis.

5.1.2. Supplementary Analysis

A prior post-hoc analysis performed by the FDA of the MACE-plus events occurring during the first 30 days post-randomization in CANVAS showed an imbalance in favor of placebo. In the PMR, FDA requested that the pattern of MACE events occurring in the first 30 days post randomization in CANVAS-R be explored.

An excess of volume depletion AEs in the canagliflozin groups could provide a possible biologic basis for an imbalance in MACE events between canagliflozin and control. In the CANVAS study, the Kaplan-Meier (KM) time-to-event analysis comparing canagliflozin and placebo showed that the greatest separation in the curves for volume depletion AEs occurred during the first 90 days post-randomization.

To assess the potential association between MACE events and volume depletion AEs and fulfill the PMR request, hazard ratio will be estimated using the same stratified Cox model as in the main analysis (see Section 5.1.1) for events occurring within the first 30 days, and within the first 90 days post-randomization. In addition, Kaplan-Meier plots including data within first 30 days and first 90 days will be presented.

Additionally, time to the first occurrence of each component of MACE as well as fatal/non-fatal MI and fatal/non-fatal stroke will be analyzied using the same Cox model described in Section 5.1.1.

5.2. Adverse Events

Adverse events (AEs) will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock.

A treatment-emergent AE (TEAE) is defined as an AE with an onset after the initiation of double-blind study drug and before the last study medication date plus 30 days. AEs with a start date prior to initiation of double-blind study drug which are subsequently reported to have either an increase in intensity or change in attribution in relationship to study drug (ie, attribution to possible, probably, very likely) after the initiation of double-blind study drug will also be considered as TEAEs.

5.2.1. Adverse Event Collection

The AE collection in CANVAS-R is streamlined to include serious adverse events (SAEs), AEs that lead to study drug discontinuation, and all AEs (serious and non-serious) for selected AEs of interest (Table 3, Section B).

For selected AEs of interest, additional data will be collected on supplementary CRF pages mainly for the purposes of narrative description of certain events. Table 3 lists the AEs of interest.

Table 3: Adverse Events of Interest

Section A:Only serious AEs or AEs that led to drug discontinuation are collected: Osmotic diuresis Volume depletion Hypoglycemia Urinary tract infection (UTI) Female mycotic genital infection Severe hypersensitivity /cutaneous reactions Pancreatitis Hepatic injury Renal related AEs (including Nephrotoxicity/ acute kidney injury)
Section B: The AEs listed below are collected regardless of whether they are serious and/or led to study drug discontinuation for the study: Male mycotic genital infection (balanitis, phimosis, events leading to circumcision) Malignancy Renal cell cancer Bladder cancer Pheochromocytoma Leydig cell tumors Breast cancer Photosensitivity Venous thromboembolic events (VTE) Amputation Fracture Diabetic Ketoacidosis

The AEs listed above will be identified using a MedDRA preferred term list (Appendix 1.3).

5.2.2. Analysis Methods

The study duration of CANVAS-R is long relative to the rest of the canagliflozin Phase 3 program. Accordingly, the incidences of AEs (ie, proportion of subjects reporting the AEs) derived from the study are not comparable to the incidences generated in the Phase 3 program. Therefore, the exposure-adjusted incidence rate will be reported in addition to the incidence. The rate is calculated as the total number of subjects with the AE divided by the On-treatment exposure in subject-years. For some particular AEs such as malignancy where the off-drug follow up is included, the follow-up-adjusted incidence rate will be estimated. The rate is calculated as the total number of subjects with the AEs divided by the total follow-up time in subject-years.

For general AEs and selected AEs of interest that are not routinely collected in CANVAS-R (refer to Section A of Table 3), the main interest will be the serious AEs and the AEs leading to discontinuation of study medication.

5.2.2.1. General Adverse Events

An overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- Serious AEs;
- Deaths;
- AEs leading to discontinuation of study medication;
- Serious AEs leading to discontinuation of study medication;
- Serious AEs considered drug-related;
- AEs considered drug-related leading to discontinuation of study medication.

SAEs by system organ class and preferred term will be summarized by treatment group using the On-Treatment analysis set. The same summary will be provided for AE leading to discontinuation of study medication using the On-Treatment analysis set.

The incidence of all SAEs (by preferred term, grouped by SOC, and presented by treatment group) will also be summarized by the relationship to study drug, by the action taken regarding the study drug, as well as by the outcome. The relationship to study drug will be presented by 2 categories: related (which includes possibly related, probably related and very likely related, as reported by the investigator) and not related (which includes not related and doubtfully related, as reported by the investigator).

For reference, as a screening tool, the 95% CIs for incidence difference between treatment groups will be calculated for the AEs which are reported in at least 4 or more subjects in any treatment group. Four (rule-of-4) was chosen based on the recommendation from the Safety, Planning, Evaluation, and Reporting Team (SPERT).[5] The exclusion of "0" from the 95% CI for the between-group difference in incidence for a particular AE does not necessarily imply that the difference is due to drug. The intent of providing the 95% CIs is as a filter to identify AEs that require additional assessment. AEs identified by the above screening procedure will be presented and may be subject to further evaluation.

Listings will also be provided for deaths, SAEs, and AEs leading to study drug discontinuation.

For AEs of special interest in Section A of Table 3, a summary similar to the analysis of general AEs will be provided. The AEs will be identified using the MedDRA preferred terms listed in Appendix 1.3.

5.2.2.2. Male Mycotic Genital Infections

Balanitis and phimosis AEs will be identified using the MedDRA preferred terms listed in Appendix 1.3, and the analyses will be based on the On-Treatment analysis set.

An overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- All AEs;
- Serious AEs;
- AEs considered drug-related (investigator assessment of possible, probable or very likely);
- AEs leading to discontinuation of study medication;
- Serious AEs leading to discontinuation of study medication;
- Serious AEs considered drug-related;
- AEs considered drug-related leading to discontinuation of study medication.

AEs by preferred term will be summarized by treatment group. A Kaplan-Meier plot for the time to first occurrence of balanitis will be provided by treatment group.

In addition, circumcision events will be identified using the sponsor's pharmacovigilance database and summarized by treatment group.

5.2.2.3. Selected Malignancies

The selected malignancies of interest are renal cell cancer, bladder cancer, testicular cancer (Leydig cell tumors), pheochromocytomas, and breast cancer. Selected malignancy AEs will be identified using the MedDRA Preferred terms listed in Appendix 1.3, and the analyses will be based on the ITT analysis set.

For each selected malignancy of interest, an overview summary table with the incidence and the follow-up-adjusted incidence will be provided for:

- All AEs;
- Serious AEs;
- AEs considered drug-related (investigator assessment of possible, probable or very likely);
- AEs leading to discontinuation of study medication;
- Serious AEs leading to discontinuation of study medication;
- Serious AEs considered drug-related;
- AEs considered drug-related leading to discontinuation of study medication.

The preferred terms associated with each selected malignancy type will be summarized by treatment.

A summary of all malignancy events as reported in the malignancy supplementary page will be reported by treatment and primary site. For breast, bladder, or renal cancers, the risk factors for each cancer type captured in the supplementary page will be summarized by treatment.

5.2.2.4. Photosensitivity

Photosensitivity AE will be identified using the MedDRA preferred terms listed in Appendix 1.3, and the analyses will be based on the On-Treatment analysis set.

An overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- All AEs;
- Serious AEs;
- AEs considered drug-related (investigator assessment of possible, probable or very likely);
- AEs leading to discontinuation of study medication;
- Serious AEs leading to discontinuation of study medication;
- Serious AEs considered drug-related;
- AEs considered drug-related leading to discontinuation of study medication.

AEs by preferred term will be summarized by treatment group.

5.2.2.5. Venous Thromboembolic Events

Venous thromboembolic (VTE) events will be identified using the MedDRA preferred terms listed in Appendix 1.3.

An overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- All AEs;
- Serious AEs;
- AEs considered drug-related (investigator assessment of possible, probable or very likely);
- AEs leading to discontinuation of study medication;
- Serious AEs leading to discontinuation of study medication;
- Serious AEs considered drug-related;
- AEs considered drug-related leading to discontinuation of study medication.

AEs by preferred term will be summarized by treatment group.

5.2.2.6. Fracture

Fracture events identified by the investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent Fracture Adjudication Committee to confirm that events were fractures and to determine fracture location (anatomic region) and type (low trauma or not). The main analyses of the adjudicated low trauma fracture AEs will be based on the ITT analysis set.

An overview summary table with the incidence and the follow-up-adjusted incidence will be provided for:

- Adjudicated fractures;
- Adjudicated fractures considered serious (investigator assessment);
- Adjudicated fractures considered drug-related (investigator assessment of possible, probable or very likely);
- Adjudicated fractures leading to discontinuation of study medication;
- Adjudicated fractures considered serious and drug-related (investigator assessment);
- Adjudicated fractures considered drug-related (investigator assessment) and leading to discontinuation of study medication.

A summary of adjudicated fracture stratified by sex (male and female) and anatomical region by treatment will be provided. The incidence as well as the incidence rate will be presented.

Adjudicated AEs associated with fall will be summarized by treatment group.

A Kaplan-Meier plot for the time to the first occurrence of adjudicated fracture event will be provided by treatment group. The hazard ratio between canagliflozin (all canagliflozin) compared to placebo and its 95% confidence interval will be estimated from a Cox proportion hazards model with treatment as the explanatory variable.

A summary of all adjudicated fractures by anatomic location will be provided. The hazard ratio and its 95% CI as well as a Kaplan-Meier plot for the first occurrence of all adjudicated fractures will be provided using the same analysis as the adjudicated low trauma fractures.

5.2.2.7. Amputation

The main analysis of lower extremity amputations as documented in the dedicated case report form page will be based on the ITT analysis set. An overview summary table with the incidence and the follow-up-adjusted incidence will be generated for:

- All lower limb amputations;
- Traumatic lower limb amputation;
- Atraumatic lower limb amputation.

Summary of anatomical region (toe, ankle, foot, below knee, above knee, other) of lower extremity atraumatic amputations will be reported by treatment group.

For atraumatic lower limb amputation, a Kaplan-Meier plot for the time to the first occurrence of event will be provided by treatment group.

For the post-treatment AEs that may be associated with amputation, groupings of selected MedDRA preferred terms used to identify events to be included in each of the following SOC categories are presented in Appendix 1.4:

- Infections and Infestations;
- Vascular disorders;
- Nervous System disorders;
- Skin and subcutaneous tissue disorders;
- Osteomyelitis.

The selected preferred terms in infections and infestation are further split into "Reversible Infection" and "Irreversible Infections". In addition, the preferred terms grouped under the MedDRA high level term of "skin and subcutaneous tissue ulcerations" are also of interest.

For each AE group listed above, the incidence of the respective preferred terms will be summarized by treatment group.

5.2.2.8. Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) and related AEs will be identified using the list of MedDRA terms in Appendix 1.3. Adverse events identified by the investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent EAC. The main analysis of the DKA events will be based on adjudicated events of DKA in the ITT analysis set. Events occurring at any time post-randomization, regardless of the timing of the last dose of study medication, will be included. For the adjudicated DKA events, a table will summarize the incidence and the follow-up-adjusted incidence rate.

A listing of all DKA and related events identified by the sponsor's medical monitoring team and the subset of these events that went for adjudication will be provided.

5.3. Clinical Laboratory Tests

A list of clinical laboratory assessments made during the study is provided in Appendix 1.1. The percentage of subjects with specific treatment-emergent laboratory values meeting pre-defined limit of change (PDLC) criteria listed in Appendix 1.2 will be summarized. The 95% CI for the percentage difference between canagliflozin compared to placebo group will be provided for each PDLC criterion which have at least 4 or more subjects in any treatment group. A corresponding listing will also be provided. As described above, PDLC values will be presented based on measurements on study drug and up to a maximum of 2 days after the last dose of study drug, as well as all measurements regardless of the time of the last dose of double-blind study drug. Summaries based on both standard units (SI) and conventional units will be provided.

5.4. Vital Signs

A treatment-emergent vital sign abnormality is defined as a change from baseline and subsequent post-baseline value that satisfies the PDLC criteria in Appendix 1.2. For each vital sign

parameter, the proportion of subjects with a treatment-emergent abnormality will be tabulated by treatment group. PDLC values will be presented based on measurements up to a maximum of 2 days after the last dose of study medication.

The blood pressure measurements will be based on the average of the consecutive sitting blood pressure readings that were to be collected at each visit.

5.5. Electrocardiogram

Electrocardiogram will not be collected in this study.

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Janssen Research & Development

Statistical Analysis Plan

A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects With Type 2 Diabetes Mellitus

The CANVAS-R Trial (CANagliflozin cardioVascular Assessment Study-Renal)

Protocol 28431754DIA4003; Phase 4**

JNJ-28431754 (canagliflozin)

**This is a Phase 4 postmarketing study required by the US Food & Drug Administration but may be considered a Phase 3 study in some countries in which canagliflozin has not been approved.

Status:	Approved
Date:	20 March 2017
Prepared by:	Janssen Research & Development, LLC
Document No.:	EDMS-ERI-130850882, 2.0

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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SUMMARY OF AMENDMENT

Relative to the statistical analysis plan (SAP) dated 20 September 2016, the major amendments made in this version are summarized as follows.

Applicable Section(s)	Description of Change(s)
2.2	The On-Study analysis set was added for MACE and replaced the ITT analysis set for several adverse events of interest. The upper bound of the data period for the On-Treatment analysis set was clarified as last dose plus 2 days for laboratory parameters except ACR.
4.1.3	Additional subgroups were added for the analysis of ACR progression.
4.1.4.2 (4.4.1.2)	To be consistent with the protocol, confirmed progression (regression) is now changed to confirmed progression (regression) plus the unconfirmed progression (regression) from the last ACR measures.
4.1.4.3	Updated the multiple analysis section
4.2.1	Consistent with the analytic approach described in the Cardiovascular Endpoint adjudication charter, it is clarified that undetermined death is considered as CV death.
4.2.2.1	Additional subgroups were added for the analysis of secondary efficacy endpoints.
4.4.1	Clarified that any adjudicated non-CV death event where the adjudication committee assigned a renal proximate cause is considered a renal death.
4.4.2.1.3	Mixed model of repeated measure (MMRM) will include baseline and visit interaction.
5.1.2	Added examination of MACE data in the first 60 and 90 days on the top of the first 30 days analysis.
5.2.2.9	Added a section on the analysis of adjudicated pancreatitis.
Appendix 8	Additional lab analytes were included in the Pre-defined Limit of Change (PDLC) criteria.

ABBREVIATIONS

ACR	albumin creatinine ratio
AE	adverse event
AFT	accelerated failure time model
AHA	antihyperglycemic agent
ANCOVA	analysis of covariance
BL	baseline
BMI	body mass index
CI	confidence interval
CSR	clinical study report
CV	cardiovascular
DBP	diastolic blood pressure
DKA	diabetic ketoacidosis
EAC	Endpoint Adjudication Committee
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
GTED	Global Trial End Date
HbA_{1c}	hemoglobin A_{1c}
HDL-C	high-density lipoprotein cholesterol
HR	hazard ratio
IDMC	Independent Data Monitoring Committee
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LDL-C	low-density lipoprotein cholesterol
LLN	lower limit of normal
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MH	medical history
MI	myocardial infarction
PDLC	Pre-defined Limit of Change
PT	preferred term
RAAS	renin angiotensin aldosterone system
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	steering committee
SCr	serum creatinine
SD	standard deviation
SGLT2	sodium- glucose cotransporter 2
SI	standard international
SOC	system organ class
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent AE
ULN	upper limit of normal
UTI	urinary tract infection

1. INTRODUCTION

Canagliflozin (JNJ-28431754) is an inhibitor of the sodium-glucose co-transporter 2 (SGLT2) that has been developed as an oral anti-hyperglycemic agent (AHA) for the treatment of patients with type 2 diabetes mellitus (T2DM). In March 2013, canagliflozin was approved for marketing by the United States (US) Food and Drug Administration (FDA).

Following market authorization, the sponsor is required to demonstrate that the upper bound of the 2-sided 95% confidence interval (CI) of the cardiovascular (CV) risk ratio of test drug to comparator be less than 1.3 in accord with FDA Guidance on assessing CV safety of AHAs.[1] As a result of the discussions with FDA, 28431754DIA4003 (CANVAS-R) was initiated in January 2014. The design and the subject characteristics of CANVAS-R are purposefully similar to 28431754DIA3008 (CANVAS), an ongoing CV outcome study initiated in December 2009.

This SAP stipulates definitions of analysis sets, key derived variables and statistical methods for analysis of efficacy and safety specific for CANVAS-R based on the latest amendment INT-5 (September 2016) of the protocol.

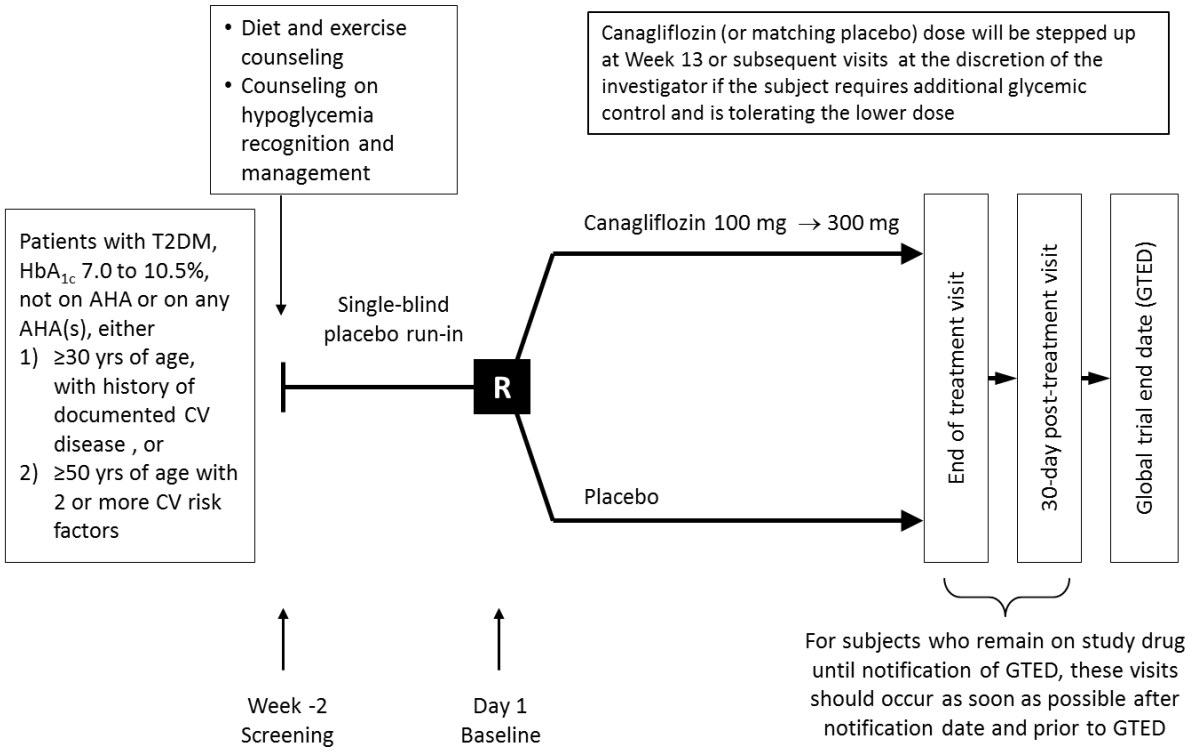
1.1. Trial Design

The CANVAS-R study enrolled the first subject in January 2014. The study recruited 5,812 subjects who met all inclusion criteria and none of the exclusion criteria. Subjects were randomly assigned to initial treatment with canagliflozin 100 mg or matching placebo administered once daily (in a 1:1 ratio). The randomization was balanced by using permutated blocks with no stratification factor. After 13 weeks, the dose of canagliflozin (or matching placebo) may be up titrated from 100 mg to 300 mg if the subject requires additional glycemic control, provided the 100 mg dose is well tolerated. The CANVAS and CANVAS-R studies will complete when the last subject randomized has approximately 78 weeks of follow-up or when 688 MACE are accumulated between both studies (estimated to occur between January 2017 and April 2017). The announcement of the GTED will mark the anticipated date on which one of these requirements for ending the study will occur.

Following announcement of the projected GTED, for subjects who remain on double-blind study drug, sites will be required to schedule the End of Treatment (EOT) and the 30-day off-drug follow-up visits as per the Time and Events schedule in the protocol; for subjects who prematurely discontinue study drug, sites will be required to make a final contact (ie, schedule the last follow-up visit) or vital status check as soon as possible after announcement of the GTED. All visits (including the 30-day off-drug follow-up visit) will need to be completed prior to the GTED. A single Steering Committee (SC) and an Independent Data Monitoring Committee (IDMC) have been commissioned for this and the CANVAS study. The SC oversees the study conduct, and the IDMC regularly (and on an ad hoc basis) reviews safety data.

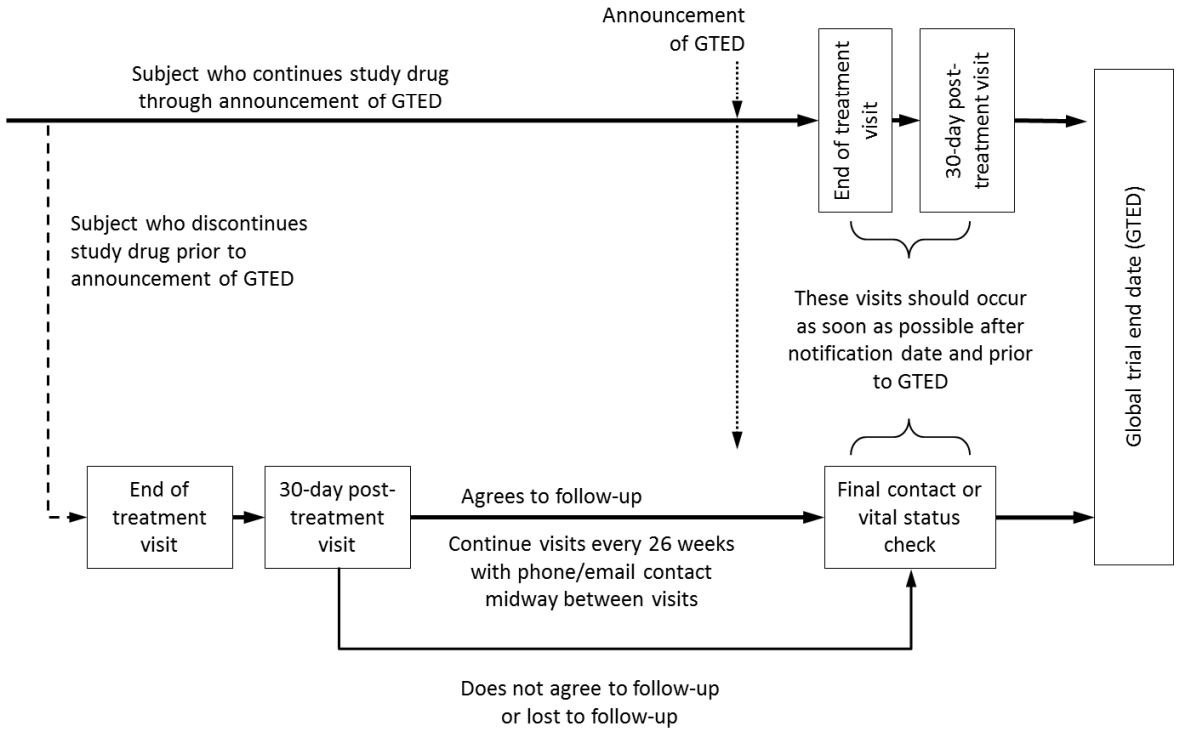
Figure 1 shows an overview of the study design and Figure 2 shows the scheduled follow-up of randomized subjects prior to the GTED.

Figure 1: Diagram of Study Design



AHA=antihyperglycemic agent; CV=cardiovascular; HbA_{1c}=hemoglobin A_{1c}; GTED=global trial end date; R=randomization; T2DM=type 2 diabetes mellitus

Figure 2: Follow-up of Randomized Subjects with Respect to the GTED



Note: Following the announcement of the GTED, investigators are not expected to continue collecting data for purposes of the clinical trial after the 30-day post-treatment contact.

In this study, duplicate urinary samples will be collected from 2 consecutive days (first morning void urine samples from the visit day and the day prior to the visit). The scheduled albumin creatinine ratio (ACR) measurements will be made on Day 1 (baseline), Week 26, Week 52, Week 78, Week 104, Week 156 and the last on-drug visit.

1.2. Randomization

Central randomization was implemented in this study. Subjects were randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared by an external vendor based on the specification tested by the sponsor before the study. The randomization was balanced by using randomly permuted blocks; the randomization did not incorporate any stratification factors.

1.3. Trial Objectives

1.3.1. Primary Objective

In subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk of CV events, to assess the effect of canagliflozin compared to placebo on progression of albuminuria.

1.3.2. Secondary Objectives

In subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk of CV events, to assess the effect of canagliflozin compared to placebo on:

- The composite endpoint of death from CV causes or hospitalization for heart failure;
- Death from CV causes.

1.3.3. Exploratory Objectives

In subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk of CV events, to assess the effect of canagliflozin compared to placebo on:

- Regression of albuminuria;
- Change in estimated glomerular filtration rate (eGFR) from baseline to the last off-drug value;
- Urinary albumin/creatinine ratio (ACR);
- The composite of 40% decrease in eGFR, renal death or requirement for renal replacement therapy;
- The composite of doubling of serum creatinine (SCr), renal death or requirement for renal replacement therapy;
- The composite of 40% decrease in eGFR, renal death, requirement for renal replacement therapy or CV death;

- The composite of doubling of SCr, renal death, requirement for renal replacement therapy or CV death;
- The composite of 40% decrease in eGFR, conversion to macroalbuminuria, renal death or requirement for renal replacement therapy;
- The composite of doubling of SCr, conversion to macroalbuminuria, renal death or requirement for renal replacement therapy;
- Change in eGFR determined from a between-group comparison of the eGFR slopes using all on-drug measurements (ie, off-drug values will not be included) of eGFR made from the first on-drug measurement to the final on-drug measurement;
- Changes in $HbA_{1c;}$
- Utilization of AHA therapy.

1.4. Statistical Hypotheses

The hypotheses in CANVAS-R are to support superiority claims of canagliflozin relative to placebo in reducing the following events:

- Progression of albuminuria;
- The composite endpoint of death from CV causes or hospitalization for heart failure;
- Death from CV causes.

For each endpoint, the following statistical hypothesis on the hazard ratio (HR) of canagliflozin over placebo will be tested:

H_0: The hazard ratio ≥ 1.0, versus H_1: The hazard ratio < 1.0

Canagliflozin will be claimed to be superior in the reduction of the target events as compared to placebo if the upper bound of 95% CIs of the hazard ratio is less than 1.0.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Analysis Populations

- Randomized subjects—subjects who are randomized via the Interactive Web Response System (IWRS);
- Treated subjects—randomized subjects who received at least one dose of double-blind study medication.

For efficacy analyses and baseline summaries, subjects will be analyzed according to their randomization assignment. For safety analysis (eg, adverse events [AEs]) and summary of exposure, subjects will be analyzed according to the predominant treatment received (defined as the treatment to which the subject was exposed for the greatest duration), in the event that subjects receive a treatment other than the one to which they were randomized. The treatment groups referred in this SAP will be all canagliflozin and placebo.

2.2. Analysis Sets

Analysis sets consist of 2 components: 1) analysis population (Section 2.1), which specifies the subjects included in an analysis; 2) data period, defining the time window during which data will be included in the analysis.

Table 1: Summary of Analysis Sets

Analysis Set	Analysis Population	Data Period
ITT	Randomized subjects	Day 1 to the last trial contact date (see Section 2.3.2) up to the GTED
On-Study	Treated subjects	Day 1 to the last trial contact date (see Section 2.3.2) up to GTED
On-Treatment	Treated subjects	Day 1 to the last dose date (see Section 2.3.2) plus X[a] days or the last trial contact date, whichever is earlier.

[a] X is 2 days for laboratory (except ACR) and vital sign measurements, and 30 days for CV and mortality endpoints, and adverse events (AEs).

2.3. Data Handling

2.3.1. Censoring Rules

For each analysis set, events that occur any time during the data period of the corresponding analysis set (see Table 1) will be considered as eligible events; otherwise subjects not experiencing an event will be censored at the earlier of the last trial contact day or end of the respective data period, if not otherwise specified.

2.3.2. Handling of Key Milestone Dates

- Trial reference start date (Day 1): the first double-blind dose date for each subject (First dose date). If missing or incomplete, the first dose date will be imputed as the randomization date.
- Last dose date: the date on which the last dose of double-blind study drug was taken by the subject. If only the day is missing, impute the last day of the month. If the month or the year is missing, impute the date as the date of the scheduled visit subsequent to the last visit when the study drug was dispensed. The imputed last dose date should be no later than the end of treatment visit date or the last trial contact date. In addition, the imputed last dose date should be no earlier than the first dose date. The last dose date is the date of permanent study drug discontinuation regardless of any temporary drug interruption.
- Last trial contact date: the date when the last trial-related procedure is conducted. It is defined as the latest of:
  - The date of last visit (scheduled or unscheduled visit; office or phone visit), or
  - The latest known date of an adverse event (AE) or the study endpoint event status, concomitant medication, vital sign measurements or laboratory results as reported on their respective electronic case report form (eCRF), or
  - The date of alternate contact made (eg, family members, relatives, friends, health care providers, public search) confirming the subject's survival status at the time of the GTED.

– For subjects who die during the study, the last trial contact date will be defined as the date of death.

2.3.3. Visit Windows

The Time and Events Schedule of the protocol indicates the visit timing and procedures (eg, laboratory, vital signs, and other key safety variables) for each visit; however, the timing of a subject's actual visit may not be exactly as per the protocol indicated target day / visit window. Consequently, for by-visit or over-time summaries, depending on the time period(s) involved in the summaries, the conventions outlined below will be used to allocate the data collected at each actual visit to a planned protocol visit by defining visit windows.

Baseline will be defined as the pre-dose measurement closest to or including Day 1 (prior to dose administration). If the pre-dose measurement on Day 1 is missing, the missing value will be imputed by the latest available measurement prior to Day 1. For serum creatinine, the average of the last 2 pre-dose measurement will be used as baseline.

If a subject has 2 or more actual visits in one analysis visit window, the visit closest to the target day will be used as the study visit for that analysis visit window. However, results from all visits will be included in the safety analyses (eg, pre-defined limits of change analysis) to assure that all results are included. If 2 study visits are the same number of days from the target day within the same visit window, the later visit will be considered the study visit for that target day. Even though all visits will be allocated an analysis visit window, only planned protocol visits for each variable will be included in the by-visit summaries or repeated measure analyses.

Note that the algorithms for calculating visit windows are the same for all the data periods (see Table 1). Table 2 summarizes the analysis visit windows for laboratory, vital signs, and other key safety variables.

Table 2: Time Intervals for Analysis (in clinic) Visit Windows

Scheduled Visit Time (label on output)	Time Interval (Day)[a]	Target Time Point (Day)
Baseline	≤1[b]	1
Week 13	1[c] –137	92
Week 26	138–229	183
Week 52	230–456	365
Week 78	457–638	547
Week 104	639–820	729
Week 130	821–1002	911
Week 156	1003–1184	1093
Week 182	1185–1366	1275
Week 208	1367–1548	1457

[a] Relative to the day of the first dose of double-blind study drug.
[b] Up to the first dose of double-blind study drug.
[c] Immediately following the first dose of double-blind study drug. For variables with no time or reference collected at baseline, the first window after baseline starts on Day 2 according to the protocol.

3. SUBJECT INFORMATION

3.1. Baseline Anthropometric and Demographic Characteristics

Baseline anthropometric and demographic characteristics will be summarized by treatment group. Descriptive statistics (N, mean, standard deviation [SD], median, and range) will be provided by treatment group for the baseline age and baseline body weight.

Additionally, the number and percentage of subjects in the categories of the following variables at baseline will also be summarized by treatment group:

- Age group: <65, ≥65 years old;
- Sex: Male, Female;
- Race: White, Black or African American, Asian, Others;
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Unknown, Not reported;
- Region: North America, Central/South America, Europe, Rest of the World.

3.2. Baseline Disease Characteristics

Descriptive statistics (N, mean, SD, median, and range) will be provided by treatment group and overall for the following baseline continuous variables: duration of diabetes (in years), baseline eGFR, baseline ACR, systolic blood pressure (SBP), weight, body mass index (BMI), HbA_{1c}, LDL-C, HDL-C, triglycerides, total cholesterol and LDL-C/HDL-C.

Additionally, the number and percentage of subjects will be summarized by treatment group and overall for the following:

- Baseline BMI categories (<30, ≥30 kg/m^2);
- Currently daily cigarette smoker: Yes/No;
- Baseline HbA_{1c} ≥ 8%: Yes/No;
- Duration of T2DM ≥ 10 years: Yes/No;
- Baseline systolic blood pressure categories (≤140, >140 mmHg);
- Baseline LDL-C categories (≤70, >70 mg/dL);
- Baseline HDL-C categories (<39, ≥39 mg/dL);
- Baseline eGFR categories (<30, 30 to <60, 60 to <90, ≥90 mL/min/1.73m^2);
- Baseline albuminuria category:
  - Normoalbuminuria (0 ≤ ACR <30 mg/g); Microalbuminuria (ACR ≥30 mg/g and ≤300 mg/g); Macroalbuminuria (ACR >300 mg/g: ACR >300 mg/g and ≤3000 mg/g, ACR > 3000 mg/g).
- History of hypertension: Yes/No ;
- History of CV disease: Yes/No;

- History of coronary artery disease: Yes/No;
- History of cerebrovascular disease: Yes/No;
- History of peripheral vascular disease: Yes/No;
- History of heart failure: Yes/No;
- Microvascular diabetes complications (Any, 1, 2 or 3 of retinopathy, neuropathy [diabetic or automatic neuropathy] and nephropathy)
- History of fracture: Yes/No;

The number and percentage of subjects with a history of medical conditions by system organ class and preferred term (based upon the general medical history eCRF) will be summarized by treatment group and overall.

3.3. Disposition Information

Disposition will be summarized for all randomized subjects by treatment group using the categories listed below:

- Screen failure;
- Subjects who are randomized (ITT);
- Subjects who are treated;
- Subjects who completed the study (ie, defined as having been followed until a time point between the notification of the GTED and the GTED, or if the subject had died prior to the GTED);
- Subjects who prematurely discontinued study medication;
- Subjects without final vital status.

The reasons for non-randomization, withdrawal from study (eg, lost to follow-up, consent withdrawal), and discontinuation from study medication will be summarized. The distribution of time to premature discontinuation of study medication will be displayed using a Kaplan-Meier plot, where one minus the survival function will be shown.

Listings will be provided for subjects whose predominant treatment differs from their randomized treatment.

3.4. Extent of Exposure and Follow-Up

Total exposure time for each subject is defined as the number of days from Day 1 to the last dose date (inclusive), regardless of any temporary drug interruption(s). Follow-up time is defined as the number of days from Day 1 to the last contact day (inclusive) for each subject. Descriptive statistics (N, mean, SD, median, and range) for total exposure or follow-up time will be presented by treatment group.

The number of subjects with duration in each of the following categories (<13 weeks, 13 to <26 weeks, 26 to <52 weeks, 52 to <104 weeks, 104 to <156 weeks, ≥156 weeks) will also be presented by treatment group as well as overall.

3.5. Prior and Concomitant Medications

Concomitant medications of interest is collected on the eCRF at baseline and at each on-drug visit. The number of subjects receiving medication in pre-specified categories, such as insulin, sulphonylurea, metformin, statin, anti-thrombotic, diuretic (loop, and non-loop), renin angiotensin aldosterone system (RAAS) inhibitor, will be presented by treatment group at baseline and during on-drug period. In addition, SGLT2 inhibitor use during the off-drug follow-up period will be summarized by treatment group.

4. EFFICACY

The analysis will be performed based on the ITT analysis set, if not otherwise specified.

All statistical tests, except those for the primary and secondary efficacy endpoints, will be considered nominal and reported with a 2-sided 95% confidence level.

Unless otherwise stated, all efficacy analyses and summaries will be performed using the treatment groups assigned by IWRS.

4.1. Primary Efficacy Endpoint

Subjects without baseline and/or post-baseline ACR measurements will be excluded from the primary efficacy analysis. Furthermore, subjects with macroalbuminuria at baseline (ACR >300 mg/g) will also be excluded from the analysis.

4.1.1. Definition

The primary efficacy endpoint is the time to the first occurrence of progression of albuminuria.

Urinary albumin creatinine ratio (ACR) is used to assess albuminuria. Subjects will be classified as having normoalbuminuria (ACR <30 mg/g), microalbuminuria (ACR ≥30 mg/g and ≤300 mg/g), or macroalbuminuria (ACR of >300 mg/g]).[2]

Progression is the development of microalbuminuria or macroalbuminuria in a subject with baseline normoalbuminuria or the development of macroalbuminuria in a subject with baseline microalbuminuria, accompanied by an ACR value increase of greater than or equal to 30% from baseline.[3]

If the ACR at a visit meets the definition of progression as described, a confirmatory ACR collection approximately 1 to 2 months later (or sooner under unusual circumstances, eg, subject is stopping study drug) should be done. In cases where a confirmatory sample is not collected within 1 to 2 months, the next available set of ACR measurements can be used for confirmation.

The primary efficacy analysis will be based on results of ACR measurements from a single visit whether confirmed or unconfirmed. The date of the progression/regression event will be defined as the visit date of the first urine sample for the potential progression/regression findings. A sensitivity analysis (see Section 4.1.4.2) will be based on results of ACR measurements from a single visit that were confirmed at a subsequent visit.

4.1.2. Analysis Methods

At each visit, the geometric mean of the duplicate measurements will be computed and used for all subsequent analyses unless otherwise specified. For ACR values below the lower quantifiable limit, the lower quantifiable limit itself will be used in the geometric mean calculation.

As the primary analysis for the primary efficacy endpoint, the time from Day 1 to first visit date observing progression (ie, using the visit date of the original sample collection and not using the visit date of the confirmatory sample collection) of albuminuria will be analyzed using a Cox proportional hazards regression model. The response variable in the model is time to progression and the model will include treatment and baseline albuminuria status as the explanatory variables. The hazard ratio of canagliflozin compared to placebo and its 95% CI will be estimated. Canagliflozin will be considered superior to placebo in the reduction of progression if the p-value of the test of significance, ie, the Wald test from the Cox model specified above, is ≤ 0.05 in the context of multiplicity adjustment described in Section 4.3.

For ITT analysis, endpoint events that occur during the data period (see Table 1) will be considered as eligible events; otherwise subjects will be censored at the last ACR measurement up to GTED.

4.1.3. Subgroup Analyses

The homogeneity of treatment effect on the occurrence of the primary endpoint across subgroups will be examined (at a 2-sided significance level of 0.05) via a test for the treatment by subgroup interaction by adding this term and the subgroup as covariates (treated as class variables) to the primary efficacy analysis (Section 4.1.2) model. Subgroup analysis will be conducted when the total number of events is greater than 10 for two treatment groups (all canagliflozin group and placebo) and at least 1 event in both groups. Factors exhibiting interactions at a significance level of $p < 0.05$ will be identified as suggesting treatment effect heterogeneity, recognizing the multiplicity in testing multiple subgroups such that one or more p-values < 0.05 may be expected to be observed by chance alone.

If a significant interaction is observed, the Gail-Simon test will be used to further examine the nature of the interaction (qualitative or quantitative).

The hazard ratio of canagliflozin (all canagliflozin group) compared to placebo and its 95% confidence interval will be estimated for each of the following subgroups:

- Age group: <65, ≥65 years old;
- Sex: Male, Female;

- Race: White, Black or African American, Asian, Other;
- Region: Central/South America, Europe, North America, Rest of the World;
- Baseline BMI categories (<30, ≥30 kg/m^2);
- Baseline composite blood pressure categories ([SBP<140or DBP<90 mmHg] vs. [SBP ≥ 140 and DBP ≥90 mmHg]);
- Baseline eGFR categories (30 to <60, 60 to <90, ≥90 mL/min/1.73m^2);
- Baseline HbA_{1c} ≥8%: Yes/No;
- Baseline albuminuria: Normoalbuminuria, Microalbuminuria;
- Duration of diabetes ≥ 10 years: Yes/No;
- History of CV disease: Yes/No;
- Baseline use of Renin angiotensin aldosterone system (RAAS) inhibitor: Yes/No.

4.1.4. Supportive Analyses

If not otherwise specified, the supportive analyses will use the same analysis set as in the primary efficacy analysis.

4.1.4.1. On-Treatment Analysis

For On-Treatment analysis, endpoint events that occur within the data period (see Table 1) will be eligible events; otherwise subjects will be censored at the earliest of the last ACR measurement date, last study drug dose date + 30 days, or GTED.

The Cox model for primary analysis (as described in Section 4.1.2) will be repeated using the On-Treatment analysis set.

4.1.4.2. Additional Supportive Analyses

Several Cox models analogous to the primary efficacy analysis model will also be performed for exploratory purposes:

- The first Cox proportional hazards model involves the use of confirmed progression, plus the unconfirmed progression from the last ACR values;
- Secondly, there will be an analysis that only excludes subjects with baseline nephrotic range macroalbuminuria (ie, ACR > 3000 mg/g). This analysis will evaluate time to first occurrence of ≥1 step progression in the following categories (ie, baseline normoalbuminuria, baseline microalbuminuria, baseline non-nephrotic range macroalbuminuria).

Additionally, the actual onset time of progression of albuminuria can be determined to occur within an interval from a sequence of examination times (ie, data are interval censored). The accelerated failure time (AFT) model with log normal error structure will be implemented considering interval censoring excluding subjects with baseline macroalbuminuria.[4] The dependent variable in the AFT model is the logarithm of time to progression of albuminuria,

expressed as time intervals. The model will include treatment group and baseline albuminuria status as the explanatory variables.

The cumulative progression rate derived from Kaplan-Meier estimate will be displayed graphically to evaluate the timing of progression and the consistency of the treatment effect over time.

4.1.4.3. Assessment of Missing Data

The potential impact of missing data in the interpretation of the primary efficacy analysis will be explored. The primary efficacy endpoint, progression of albuminuria was derived from urinary albumin/creatinine ratio (ACR) laboratory measurements which were generally collected biannually while subjects were on treatment (ie on treatment period) up to the global trial end date (GTED). For subjects who discontinue from treatment early before the development of progression of albuminuria, unobserved data of post-baseline ACR measurements at each scheduled visit up to the GTED will be considered missing and will be imputed. The multiple imputation procedure will apply to ACR data and the time to ACR progession data will then be generated based on the imputed data at the schedule visits.

Data for model development

Due to the staggered enrollment of the study, for those randomized at a later stage of the enrollment period, pseudo visits up to the max possible visit week prior to GTED, i.e. week 130, will be created according to the protocol schedule. In addition, multiple data points at each visit, e.g. confirmatory samples, will be aggregated using geometric mean according to the variability of ACR data. There is small proportion of subjects (less than 2.5%) with unscheduled visits which will be combined with the closest scheduled visit using the same approach.

Imputation model

Assuming that after treatment discontinuation, subjects discontinued from the canagliflozin arm will exhibit a response similar to subjects in the placebo arm, the imputation model will be fit using the non-missing data in the placebo group and adjusted for covariates that may be related to the missing data mechanism and the risk of progression based on clinical judgment. The potential covariates include:

- Baseline ACR (continuous);
- Baseline eGFR categories (30 to <60, 60 to <90, ≥90 mL/min/1.73m^2);
- Baseline blood pressure (SBP<140, DBP<90 mmHg): Yes/No;
- Baseline HbA_{1c} ≥8%: Yes/No;
- Age group: <65, ≥65 years old;
- Race: White, Other;
- Sex: Male, Female;

In case of convergence issues, the covariates will be removed from the model in the descending order of the list (ie, starting from the bottom of the list).

Due to the highly skewed data of ACR, both baseline and post baseline ACR in the imputation model will be log transformed.

Imputation Procedures

There are about 3% of subjects with intermittent missing in post-baseline ACR data. Those missing data will be imputed with data estimated from all observed data using the Markov Chain Monte Carlo procedure such that the missing data pattern is monotonic.

The post-treatment ACR data increased gradually over time from the end-of-treatment data. Therefore, a "copy control" strategy will be applied and the imputation model will be fit sequentially at each visit using non-missing data in the placebo arm and any preceding visits (O'Kelly and Ratitch 2014, Section 7.4.2)[5]. The estimates of the model parameters are then used to parameterize a Bayesian posterior distribution. At each imputation, missing data in both active and placebo arms will be replaced with predicted values randomly drawn from the distribution. The imputed data will also be applied to the models of subsequent visits. For example, the imputation model at week 26 will be fit using baseline and covariate data (see Section of Imputation Model) and week 26 data of the placebo arm. The ACR data that are missing at week 26 in both active and treatment arms will be imputed in the same way. Similarly, the imputation model for week 52 will utilize observed data of control arm at week 52 and all the preceding data points, whether imputed or observed.

For subjects with missing data, the imputed data up to the earlier of death date or GTED will be combined with observed data. For subjects completing the treatment or developing progression, only data imputed for intermittent missing will be added back to the observed data.

Re-construction of time to progression data

The time to progression will be re-defined based on the imputed dataset where subjects with imputed or observed ACR that met the progression criteria will be considered having events at the corresponding visit. Subjects remaining event-free will be censored at the last scheduled visit before death date or GTED, whichever is earlier.

Analysis summary

The imputed data will be re-analyzed using the same Cox model for the primary analysis (see Section 4.1.2). The imputation process will be repeated 1000 times and the multiple versions of analysis results will be combined into single inferential summary using Rubin's rule.

4.2. Secondary Efficacy Endpoints

4.2.1. Definition

There are 2 secondary efficacy endpoints specified in this study:

- The composite endpoint of death from CV causes[a] or hospitalization for heart failure;
- Death from CV causes (CV Death).

Analyses will be using adjudicated events and adjudication of these outcomes by the Endpoint Adjudication Committee (EAC) will be done in a blinded fashion.

4.2.2. Analysis Methods

The analyses will be using the ITT analysis set.

4.2.2.1. The Composite of CV Death or Hospitalization for Heart Failure

The analysis will be based on time to the first occurrence of the composite event using ITT analysis set. The hazard ratio of canagliflozin compared to placebo and its 95% CI will be estimated using a stratified Cox proportional hazards regression model with treatment as the explanatory variable and history of CV disease (secondary and primary prevention) as the stratification factor. The p-value from the stratified log rank test for the treatment effect will also be reported.

The subgroup analysis will be conducted using the same approaches described in Section 4.1.3 and the following subgroups:

- Age group: <65, ≥65 years old;
- Sex: Male, Female;
- Race: White, Black or African American, Asian, Other;
- Region: Central/South America, Europe, North America, Rest of the World;
- Baseline BMI categories (<30, ≥30 kg/m^2);
- Baseline composite blood pressure categories ([SBP <140 or DBP <90 mmHg] vs. [SBP ≥140 and DBP ≥90 mmHg]);
- Baseline eGFR categories (30 to <60, 60 to <90, ≥90 mL/min/1.73m^2);
- Baseline HbA_{1c} ≥ 8%: Yes/No;
- Duration of diabetes ≥ 10 years: Yes/No;
- History of CV disease: Yes/No;
- History of peripheral vascular disease: Yes/No;

[a] Undetermined death is considered CV death.

- History of amputation: Yes/No;
- Baseline use of statin;
- Baseline use of anti-thrombotics;
- Baseline use of RAAS inhibitor;
- Baseline use of Beta blocker;
- Baseline use of insulin;
- Baseline use of diuretics.

4.2.2.2. CV Death

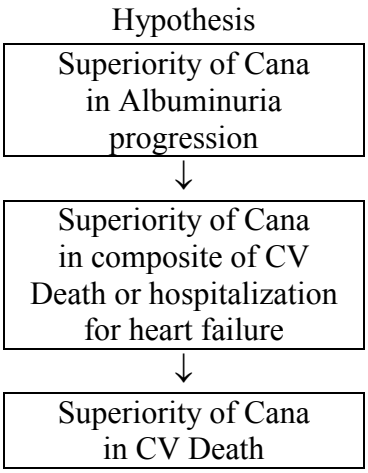
The analysis will be based on time to the first occurrence of CV death using ITT analysis set. The hazard ratio of canagliflozin compared to placebo and its 95% CI will be estimated using a stratified Cox proportional hazards regression model with treatment as the explanatory variable and history of CV disease (secondary and primary prevention) as the stratification factor. The p-value from the stratified log rank test for the treatment effect will also be reported.

Subgroup analyses will be performed using the same subgroups and the analysis methods described in Section 4.2.2.1.

4.3. Multiplicity Adjustment

Per the SAP of the integrated summary of CANVAS and CANVAS-R studies, only one alpha family is proposed for the testing of the multiple hypotheses based on the integrated data and the CANVAS-R data. The Type I error for these tests will be strictly controlled via a gatekeeping procedure. If the MACE and the mortality endpoints in the integrated analysis succeed in rejecting the null hypotheses, all of the alpha for testing (ie, 5%) will pass to the CANVAS-R for testing of the primary and the secondary hypotheses of the study. Tests for CANVAS-R hypotheses will proceed sequentially conditional on the statistical significance of the hypothesis tests in the integrated summary at the 5% significant level.

Figure 3: Hypothesis Testing Sequence



4.4. Exploratory Efficacy Endpoints

4.4.1. Definition

The following exploratory endpoints will be analyzed:

- Time to the first occurrence of composite endpoint of 40% decrease in eGFR, renal death[a] or requirement for renal replacement therapy;
- Time to the first occurrence of composite endpoint of doubling of SCr, renal death or requirement for renal replacement therapy;
- Time to the first occurrence of composite endpoint of 40% decrease in eGFR, renal death, requirement for renal replacement therapy or CV death;
- Time to the first occurrence of composite endpoint of doubling of SCr, renal death, requirement for renal replacement therapy or CV death;
- Time to the first occurrence of composite endpoint of 40% decrease in eGFR, conversion to macroalbuminuria, renal death or requirement for renal replacement therapy;
- Time to the first occurrence of composite endpoint of doubling of SCr, conversion to macroalbuminuria, renal death or requirement for renal replacement therapy;
- Regression of albuminuria;

  Regression of albuminuria is the development of normoalbuminuria in a subject with baseline microalbuminuria or macroalbuminuria or the development of microalbuminuria in a subject with baseline macroalbuminuria, accompanied by a decrease in the ACR value of greater than or equal to 30% from baseline. If the ACR at a visit meets the definition of potential regression described above, a confirmatory ACR collection approximately 1 to 2 months later

[a] Non-CV death with a renal proximate cause is considered as renal death.

(or sooner under unusual circumstances, eg, subject is stopping study drug), should be done. In cases where a confirmatory sample is not collected within 1 to 2 months, the next available set of ACR measurements can be used for confirmation.

- Change in urinary ACR over time;
- Change in eGFR from baseline to the last off-drug measurement;
- Estimated eGFR slopes using all on-drug measurements;
- Changes in HbA_{1c}.
- AHA utilization

4.4.2. Analysis Methods

4.4.2.1. Renal Endpoints

4.4.2.1.1. Composite Endpoints

The components of the renal composite endpoints, such as requirement for renal replacement therapy and doubling of serum creatinine, identified by the investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent EAC.

The time to the first occurrence of each of the renal composite endpoints (see Section 4.4.1) will be analyzed in the ITT analysis set using a Cox proportional hazards model with treatment and baseline eGFR (< 60, ≥ 60 mL/min/1.73m^2) as the explanatory variables. The hazard ratio of canagliflozin compared to placebo and its 95% confidence interval will be estimated from the model.

4.4.2.1.2. Regression of Albuminuria

Regression of albuminuria will be analyzed in a similar fashion in modeling and censoring rule as the analysis for progression of albuminuria. The analysis will be using the ITT analysis set based on ACR measurements from a single visit whether confirmed or unconfirmed. Subjects with normal albuminuria at baseline will be excluded. The hazard ratio of canagliflozin compared to placebo and its 95% confidence interval will be estimated from the model. Additionally, analyses based on confirmed regression plus unconfirmed regression from the last ACR values will be performed in a similar fashion using ITT analysis set.

4.4.2.1.3. Urinary ACR

Post-baseline ACR will be analyzed using mixed effect model repeat measurement (MMRM) and the ITT analysis set.

Since the distribution of ACR is highly skewed, the log transformed ACR values of all the post-baseline and scheduled visits will be modeled, using a linear mixed effects model. The linear mixed effects model will be fit to the logarithm of ACR as a dependent variable, including treatment, logarithm of baseline ACR value, visit, treatment by visit interaction, and logarithm of baseline ACR value by visit interaction as fixed effects. The percentage of treatment difference,

ie, treatment difference in mean ACR relative to placebo, can be calculated by taking the anti-logarithm of the estimated coefficient for the treatment group and subtracting 1. The ratio of mean ACR in treatment compared to placebo and its 95% CI will be presented. An unstructured covariance will be used to model the within subject errors.

4.4.2.1.4. Change in eGFR

For change in eGFR from baseline to the last off-drug measurement will be analyzed in the ITT analysis set using an analysis of covariance (ANCOVA) model with treatment and the baseline eGFR value as covariates. The treatment difference of canagliflozin compared to placebo in the least-squares means and associated 95% CI will be estimated from the model.

4.4.2.1.5. eGFR Slope

The time slope of eGFR will be analyzed in the On-Treatment analysis set using a linear mixed effects model with eGFR as a dependent variable and treatment, baseline eGFR value, time (as a continuous variable), and treatment by time interaction as fixed effects and intercept and time as random effects. The parameter of interest is the coefficient for treatment by time interaction term, which measures the slope difference between canagliflozin and placebo over time.

4.4.2.2. Changes in HbA_{1c}

Change in HbA_{1c} from baseline will be analyzed using MMRM and the ITT analysis set. The effect of canagliflozin relative to placebo on the changes in HbA_{1c} from baseline over time will be assessed using MMRM. The analysis will include the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. An unstructured covariance will be used to model the within subject errors.

4.4.2.3. AHA Utilization

Summary of AHA utilization is described under Section 3.5.

5. SAFETY

The safety analysis will be mainly based on the On-Treatment analysis set unless otherwise specified.

There will be no imputation of missing values for clinical laboratory test results, vital sign measurements in the safety analyses.

5.1. Adjudicated MACE Events

The MACE is the composite of CV outcomes including CV death, non-fatal MI[a], or non-fatal stroke. Adjudication of these outcomes by the EAC has been done in a blinded fashion.

[a] Silent MIs are excluded from the analysis.

5.1.1. Analysis Methods

The analysis will be based on the time to first occurrence of MACE using the ITT analysis set. The HR of all canagliflozin compared to placebo and its 95% CI will be estimated using a stratified Cox proportional hazards regression model with treatment (all canagliflozin and placebo) as the explanatory variable, and prior CV disease subgroup (secondary prevention and primary prevention) as the stratification factors. P-value of stratified log rank test for treatment effect will also be reported for the primary analysis.

5.1.2. Supplementary Analysis

A prior post-hoc analysis performed by the FDA of the MACE-plus events occurring during the first 30 days post-randomization in CANVAS showed an imbalance in favor of placebo. In the PMR, FDA requested that the pattern of MACE events occurring in the first 30 days post randomization in CANVAS-R be explored. Additional examination of the MACE events in the first 60 and 90 days using the ITT analysis set will be made.

An excess of volume depletion AEs in the canagliflozin groups could provide a possible biologic basis for an imbalance in MACE events between canagliflozin and control. In the CANVAS study, the Kaplan-Meier (KM) time-to-event analysis comparing canagliflozin and placebo showed that the greatest separation in the curves for volume depletion AEs occurred during the first 90 days post-randomization.

To assess the potential association between MACE events and volume depletion AEs and fulfill the PMR request, hazard ratio will be estimated using the same stratified Cox model as in the main analysis (see Section 5.1.1) for events occurring within the first 30 days, and within the first 90 days post-randomization. In addition, Kaplan-Meier plots including data within first 30 days and first 90 days will be presented.

Additionally, time to the first occurrence of each component of MACE as well as fatal/non-fatal MI and fatal/non-fatal stroke will be analyzied using the same Cox model described in Section 5.1.1.

5.2. Adverse Events

Adverse events (AEs) will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock.

A treatment-emergent AE (TEAE) is defined as an AE with an onset after the initiation of double-blind study drug and before the last study medication date plus 30 days. AEs with a start date prior to initiation of double-blind study drug which are subsequently reported to have either an increase in intensity or change in attribution in relationship to study drug (ie, attribution to possible, probably, very likely) after the initiation of double-blind study drug will also be considered as TEAEs.

5.2.1. Adverse Event Collection

The AE collection in CANVAS-R is streamlined to include serious adverse events (SAEs), AEs that lead to study drug discontinuation, and all AEs (serious and non-serious) for selected AEs of interest (Table 3, Section B).

For selected AEs of interest, additional data will be collected on supplementary CRF pages mainly for the purposes of narrative description of certain events. Table 3 lists the AEs of interest.

Table 3: Adverse Events of Interest

Section A: For the AEs listed below, only serious AEs or AEs that led to drug discontinuation were collected: Osmotic diuresis Volume depletion Hypoglycemia Urinary tract infection (UTI) Female mycotic genital infection Severe hypersensitivity /cutaneous reactions Pancreatitis Hepatic injury Renal related AEs (including Nephrotoxicity/ acute kidney injury)
Section B: The AEs listed below were collected regardless of whether they were serious and/or led to study drug discontinuation for the study: Male mycotic genital infection (balanitis, phimosis, events leading to circumcision) Malignancy Renal cell cancer Bladder cancer Pheochromocytoma Leydig cell tumors Breast cancer Photosensitivity Venous thromboembolic events (VTE) Amputation Fracture Diabetic Ketoacidosis

The AEs listed above will be identified using a MedDRA preferred term list (Appendix 1.3).

5.2.2. Analysis Methods

The study duration of CANVAS-R is long relative to the rest of the canagliflozin Phase 3 program. Accordingly, the incidences of AEs (ie, proportion of subjects reporting the AEs) derived from the study are not comparable to the incidences generated in the Phase 3 program. Therefore, the exposure-adjusted incidence rate will be reported in addition to the incidence. The rate is calculated as the total number of subjects with the AE divided by the On-treatment exposure in subject-years. For some particular AEs such as malignancy where the off-drug follow

up is included, the follow-up-adjusted incidence rate will be estimated. The rate is calculated as the total number of subjects with the AEs divided by the total follow-up time in subject-years.

For general AEs and selected AEs of interest that are not routinely collected in CANVAS-R (refer to Section A of Table 3), the main interest will be the serious AEs and the AEs leading to discontinuation of study medication.

5.2.2.1. General Adverse Events

An overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- Serious AEs;
- Deaths;
- AEs leading to discontinuation of study medication;
- Serious AEs leading to discontinuation of study medication;
- Serious AEs considered drug-related;
- AEs considered drug-related leading to discontinuation of study medication.

SAEs by system organ class and preferred term will be summarized by treatment group using the On-Treatment analysis set. The same summary will be provided for AE leading to discontinuation of study medication using the On-Treatment analysis set.

The incidence of all SAEs (by preferred term, grouped by SOC, and presented by treatment group) will also be summarized by the relationship to study drug, by the action taken regarding the study drug, as well as by the outcome. The relationship to study drug will be presented by 2 categories: related (which includes possibly related, probably related and very likely related, as reported by the investigator) and not related (which includes not related and doubtfully related, as reported by the investigator).

For reference, as a screening tool, the 95% CIs for incidence difference between treatment groups will be calculated for the AEs which are reported in at least 4 or more subjects in any treatment group. Four (rule-of-4) was chosen based on the recommendation from the Safety, Planning, Evaluation, and Reporting Team (SPERT).[6] The exclusion of "0" from the 95% CI for the between-group difference in incidence for a particular AE does not necessarily imply that the difference is due to drug. The intent of providing the 95% CIs is as a filter to identify AEs that require additional assessment. AEs identified by the above screening procedure will be presented and may be subject to further evaluation.

Listings will also be provided for deaths, SAEs, and AEs leading to study drug discontinuation.

For AEs of interest in Section A of Table 3, a summary similar to the analysis of general AEs will be provided. The AEs will be identified using the MedDRA preferred terms listed in Appendix 1.3.

5.2.2.2. Male Mycotic Genital Infections

Balanitis and phimosis AEs will be identified using the MedDRA preferred terms listed in Appendix 1.3, and the analyses will be based on the On-Treatment analysis set.

An overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- All AEs;
- Serious AEs;
- AEs considered drug-related (investigator assessment of possible, probable or very likely);
- AEs leading to discontinuation of study medication;
- Serious AEs leading to discontinuation of study medication;
- Serious AEs considered drug-related;
- AEs considered drug-related leading to discontinuation of study medication.

AEs by preferred term will be summarized by treatment group. A Kaplan-Meier plot for the time to first occurrence of balanitis will be provided by treatment group.

In addition, circumcision events will be identified using the sponsor's pharmacovigilance database and summarized by treatment group.

5.2.2.3. Selected Malignancies

The selected malignancies of interest are renal cell cancer, bladder cancer, testicular cancer (Leydig cell tumors), pheochromocytomas, and breast cancer. Selected malignancy AEs will be identified using the MedDRA Preferred terms listed in Appendix 1.3, and the analyses will be based on the On-Study analysis set.

For each selected malignancy of interest, an overview summary table with the incidence and the follow-up-adjusted incidence will be provided for:

- All AEs;
- Serious AEs;
- AEs considered drug-related (investigator assessment of possible, probable or very likely);
- AEs leading to discontinuation of study medication;
- Serious AEs leading to discontinuation of study medication;
- Serious AEs considered drug-related;
- AEs considered drug-related leading to discontinuation of study medication.

The preferred terms associated with each selected malignancy type will be summarized by treatment.

A summary of all malignancy events as reported in the malignancy supplementary page will be reported by treatment and primary site. For breast, bladder, or renal cancers, the risk factors for each cancer type captured in the supplementary page will be summarized by treatment.

5.2.2.4. Photosensitivity

Photosensitivity AE will be identified using the MedDRA preferred terms listed in Appendix 1.3, and the analyses will be based on the On-Treatment analysis set.

An overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- All AEs;
- Serious AEs;
- AEs considered drug-related (investigator assessment of possible, probable or very likely);
- AEs leading to discontinuation of study medication;
- Serious AEs leading to discontinuation of study medication;
- Serious AEs considered drug-related;
- AEs considered drug-related leading to discontinuation of study medication.

AEs by preferred term will be summarized by treatment group.

5.2.2.5. Venous Thromboembolic Events

Venous thromboembolic (VTE) events will be identified using the MedDRA preferred terms listed in Appendix 1.3.

An overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- All AEs;
- Serious AEs;
- AEs considered drug-related (investigator assessment of possible, probable or very likely);
- AEs leading to discontinuation of study medication;
- Serious AEs leading to discontinuation of study medication;
- Serious AEs considered drug-related;
- AEs considered drug-related leading to discontinuation of study medication.

AEs by preferred term will be summarized by treatment group.

5.2.2.6. Fracture

Fracture events identified by the investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent Fracture Adjudication Committee to confirm that

events were fractures and to determine fracture location (anatomic region) and type (low trauma or not). The main analyses of the adjudicated low trauma fracture AEs will be based on the On-Study analysis set.

An overview summary table with the incidence and the follow-up-adjusted incidence will be provided for:

- Adjudicated fractures;
- Adjudicated fractures considered serious (investigator assessment);
- Adjudicated fractures considered drug-related (investigator assessment of possible, probable or very likely);
- Adjudicated fractures leading to discontinuation of study medication;
- Adjudicated fractures considered serious and drug-related (investigator assessment);
- Adjudicated fractures considered drug-related (investigator assessment) and leading to discontinuation of study medication.

A summary of adjudicated fracture stratified by anatomical region by treatment will be provided. The incidence as well as the incidence rate will be presented.

Adjudicated AEs associated with fall will be summarized by treatment group.

A Kaplan-Meier plot for the time to the first occurrence of adjudicated fracture event will be provided by treatment group. The hazard ratio between canagliflozin (all canagliflozin) compared to placebo and its 95% confidence interval will be estimated from a Cox proportion hazards model with treatment as the explanatory variable.

A summary of all adjudicated fractures by anatomic location will be provided. The hazard ratio and its 95% CI as well as a Kaplan-Meier plot for the first occurrence of all adjudicated fractures will be provided using the same analysis as the adjudicated low trauma fractures.

5.2.2.7. Amputation

The main analysis of lower extremity amputations as documented in the dedicated case report form page will be based on the On-Study analysis set. An overview summary table with the incidence and the follow-up-adjusted incidence will be generated for:

- All lower limb amputations;
- Traumatic lower limb amputation;
- Atraumatic lower limb amputation.

Summary of anatomical region (toe, ankle, trans-metatarsal, below knee, above knee) of lower extremity atraumatic amputations will be reported by treatment group.

For atraumatic lower limb amputation, a Kaplan-Meier plot for the time to the first occurrence of event will be provided by treatment group.

For the post-treatment AEs that may be associated with amputation, groupings of selected MedDRA preferred terms used to identify events to be included in each of the following SOC categories are presented in Appendix 1.4:

- Infections and Infestations;
- Vascular disorders;
- Nervous System disorders;
- Skin and subcutaneous tissue disorders;
- Osteomyelitis.

The selected preferred terms in infections and infestation are further split into "Reversible Infection" and "Irreversible Infections". In addition, the preferred terms grouped under the MedDRA high level term of "skin and subcutaneous tissue ulcerations" are also of interest.

For each AE group listed above, the incidence of the respective preferred terms will be summarized by treatment group.

5.2.2.8. Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) and related AEs will be identified using the list of MedDRA terms in Appendix 1.3. Adverse events identified by the investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent DKA Adjudication Committee. The main analysis of the DKA events will be based on adjudicated events of DKA in the On-Study analysis set. Events occurring at any time post-randomization, regardless of the timing of the last dose of study medication, will be included. For the adjudicated DKA events, a table will summarize the incidence and the follow-up-adjusted incidence rate.

A listing of all DKA and related events identified by the sponsor's medical monitoring team and the subset of these events that went for adjudication will be provided.

5.2.2.9. Pancreatitis

Pancreatitis and related AEs identified by the sponsor using the list of MedDRA terms pre-specified in the charter will be sent to the independent Pancreatitis Adjudication Committee. The main analysis of events will be based on adjudicated, confirmed events in the On-Treatment analysis set. Analysis based on events occurring at any time post-randomization, regardless of the timing of the last dose of study medication, will be performed. The incidence rate and proportion of adjudicated pancreatitis events by severity will be summarized. The total number of subjects with an event not confirmed by the Pancreatitis Adjudication Committee will also be summarized.

5.3. Clinical Laboratory Tests

A list of clinical laboratory assessments made during the study is provided in Appendix 1.1. The percentage of subjects with specific treatment-emergent laboratory values meeting pre-defined limit of change (PDLC) criteria listed in Appendix 1.2 will be summarized. The 95% CI for the percentage difference between canagliflozin compared to placebo group will be provided for each

PDLC criterion which have at least 4 or more subjects in any treatment group. A corresponding listing will also be provided. As described above, PDLC values will be presented based on measurements on study drug and up to a maximum of 2 days after the last dose of study drug, as well as all measurements regardless of the time of the last dose of double-blind study drug. Summaries based on both standard units (SI) and conventional units will be provided.

5.4. Vital Signs

A treatment-emergent vital sign abnormality is defined as a change from baseline and subsequent post-baseline value that satisfies the PDLC criteria in Appendix 1.2. For each vital sign parameter, the proportion of subjects with a treatment-emergent abnormality will be tabulated by treatment group. PDLC values will be presented based on measurements up to a maximum of 2 days after the last dose of study medication.

The blood pressure measurements will be based on the average of the consecutive sitting blood pressure readings that were to be collected at each visit.

5.5. Electrocardiogram

Electrocardiogram was not be collected in this study.

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APPENDIX

Appendix 1.1: Clinical Laboratory Tests

The clinical laboratory tests include following panels and assessments:

- Hematology panel
  - hemoglobin
  - platelet count
  - hematocrit
  - red blood cell (RBC) count
  - white blood cell (WBC) count with differential
- Serum chemistry panel
  - sodium
  - potassium
  - chloride
  - bicarbonate
  - BUN
  - creatinine
  - aspartate aminotransferase (AST)
  - alanine aminotransferase (ALT)
  - gamma-glutamyltransferase (GGT)
  - total bilirubin
  - alkaline phosphatase
  - creatine phosphokinase (CPK)
  - lactic acid dehydrogenase (LDH)
  - uric acid
  - calcium
  - phosphate
  - albumin
  - total protein
  - magnesium
- Fasting serum lipid profile (triglycerides, LDL-C, HDL-C, total cholesterol).
- HbA_{1c}
- Urinalysis (dipstick analysis; from spot urine collection in the clinic on Day 1; performed at central laboratory; microscopic analysis is not required). Urine glucose will not be measured by the central laboratory
  - specific gravity - ketones
  - pH - bilirubin/urobilinogen
  - protein - nitrite
  - blood - leukocyte esterase
- Central laboratory will report the estimated glomerular filtration rate (eGFR) according to the Modification of Diet in Renal Disease Study (MDRD) equation (Levey 2006) at study visits when serum creatinine is measured. The 4-variable MDRD eGFR includes serum creatinine, age, race, and sex according to the equation below:

  For creatinine in mg/dL:

  $$\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$$

For creatinine in µmol/L:

eGFR (mL/min/1.73m^2) = 175 x (serum creatinine x 0.0113) $^{-1.154}$ x (age) $^{-0.203}$ x (0.742 if female) x (1.21 if black)

Appendix 1.2: Criteria for Pre-defined Limit of Change (PDLC) and Abnormal Values

Laboratory Test	Parameter for ANY value and LAST value
CHEMISTRY	
Albumin	Composite: <LLN and >25% decrease from BL
ALT	Absolute Value: >3X ULN
	Absolute Value: >5X ULN
	Absolute Value: >8X ULN
AST	Absolute Value: >3X ULN
	Absolute Value: >5X ULN
	Absolute Value: >8X ULN
ALT >3X ULN and Tbili >2X ULN	Composite: ALT >3X ULN and Tbili >2X ULN [with the Tbili elevation >2 X ULN within 30 days of the ALT elevation >3x ULN]
AST >3X ULN and Tbili >2X ULN	Composite: AST >3X ULN and Tbili >2X ULN [with the Tbili elevation >2 X ULN within 30 days of the AST elevation >3x ULN]
Bilirubin	Composite: >ULN and > 25% increase from BL
	Absolute Value: >2XULN
Bicarbonate	Absolute Value: <16 mEq/L
Calcium	Composite: >ULN and > 10 % increase from BL
Creatinine Kinase	Absolute Value: >1000U/L
eGFR	Composite: < 80 and decrease>30% from BL
	Change: decrease>50% from BL
Magnesium	Composite: <LLN and >25% decrease from BL
	Composite: >ULN and >25% increase from BL
Phosphorus	Composite: >ULN and >25% increase from BL
Potassium	Composite: <LLN and >15% decrease from BL
	Composite: >ULN and >15% increase from BL
	Absolute Value: ≥ 6.5 mEq/L
Sodium	Composite: <LLN and decrease >5 mEq/L or more from BL
	Composite: >ULN and increase>5 mEq/L or more from BL
Uric Acid	Composite: <LLN and >25% decrease from BL
HEMATOLOGY	
Hemoglobin	Change: ≥ 2 g/dl decrease from BL
	Change: ≥ 2 g/dL increase from BL
Platelets	Composite: <LLN and decrease >25% from BL
	Composite: >ULN and increase >25% from BL
White Blood Count	Composite: < LLN and >25% decrease from BL
	Composite: > ULN and >50 % increase from BL
VITAL SIGNS	
Pulse	Absolute Value: ≤50 beats per minute
	Absolute Value: ≥100 beats per minute
Systolic Blood Pressure	Composite: ≥ 20 mm Hg decrease from BL and ≤90 mm Hg
	Composite: ≥ 20 mm Hg increase from BL and ≥ 160 mm Hg
Diastolic Blood Pressure	Composite: ≥ 15 mm Hg decrease from BL and ≤ 50 mm Hg
	Composite: ≥ 15 mm Hg increase from BL and ≥ 100 mm Hg

Appendix 1.3: List of Preferred Terms for Selected AEs of Interest

Diabetic ketoacidosis	Female Mycotic Genital Infections	Fracture
Acidosis	Genital candidiasis	Acetabulum fracture
Acidosis aggravated	Genital infection	Ankle fracture
Acidosis diabetic	Genital infection female	Atypical femur fracture
Acidosis metabolic	Genital infection fungal	Atypical fracture
Acidosis NOS	Urogenital infection fungal	Avulsion fracture
Acute acidosis	Vaginal infection	Bone fragmentation
Anion gap acidosis	Vaginal inflammation	Cervical vertebral fracture
Blood ketone body	Vulvitis	Chance fracture
Blood ketone body increased	Vulvovaginal candidiasis	Clavicle fracture
Blood ketone body present	Vulvovaginal mycotic infection	Closed fracture manipulation
Diabetes mellitus with ketoacidosis	Vulvovaginitis	Comminuted fracture
Diabetes with hyperosmolarity		Complicated fracture
Diabetes with ketoacidosis		Compression fracture
Diabetic acidosis		Craniofacial fracture
Diabetic hyperglycemic coma		Elevation skull fracture
Diabetic hyperosmolar coma		Epiphyseal fracture
Diabetic ketoacidosis		External fixation of fracture
Diabetic ketoacidotic hyperglycemic coma		Facial bones fracture
Diabetic metabolic decompensation		Femoral neck fracture
High anion gap metabolic acidosis		Femur fracture
Hyperglycemic seizure		Fibula fracture
Hyperosmolar hyperglycemic state		Foot fracture
Hyperosmolar state		Forearm fracture
Ketoacidosis		Fracture
Ketonuria		Fracture debridement
Ketosis		Fracture delayed union
Metabolic acidosis		Fracture displacement
Metabolic acidosis exacerbated		Fracture malunion
Metabolic acidosis NOS exacerbated		Fracture nonunion
Metabolic acidosis not otherwise specified (NOS)		Fracture pain
Metabolic acidosis worsened		Fracture reduction
Type I diabetes mellitus with ketoacidosis		Fracture treatment
Type II diabetes mellitus with ketoacidosis		Fractured coccyx
		Fractured ischium
		Fractured maxilla elevation
		Fractured sacrum
		Fractured skull depressed
		Fractured zygomatic arch elevation
		Greenstick fracture
		Hand fracture
		Hip fracture
		Humerus fracture
		Ilium fracture
		Impacted fracture
		Internal fixation of fracture
		Jaw fracture
		Limb crushing injury
		Limb fracture

Diabetic ketoacidosis	Female Mycotic Genital Infections	Fracture
		Loss of anatomical alignment after fracture reduction
		Lower limb fracture
		Lumbar vertebral fracture
		Multiple fractures
		Open fracture
		Open reduction of fracture
		Open reduction of spinal fracture
		Osteochondral fracture
		Osteoporotic fracture
		Patella fracture
		Pathological fracture
		Pelvic fracture
		Periprosthetic fracture
		Pubis fracture
		Radius fracture
		Rib fracture
		Sacroiliac fracture
		Scapula fracture
		Skull fracture
		Skull fractured base
		Spinal compression fracture
		Spinal fracture
		Spinal fusion fracture
		Sternal fracture
		Stress fracture
		Thoracic vertebral fracture
		Tibia fracture
		Torus fracture
		Traumatic fracture
		Ulna fracture
		Upper limb fracture
		Wrist fracture

Hepatic Injury	Hypoglycaemia	Male Mycotic Genital Infections
Acute graft versus host disease in liver	Hypoglycaemia	Balanitis
Acute hepatic failure	Hypoglycaemic coma	Balanitis candida
Acute yellow liver atrophy	Hypoglycaemic seizure	Balanoposthitis
Allergic hepatitis		Balanoposthitis infective
Ammonia increased		Erosive balanitis
Ascites		Gangrenous balanitis
Asterixis		Genital candidiasis
Autoimmune hepatitis		Genital infection
Bacterascites		Genital infection fungal
Biliary ascites		Genital infection male
Biliary cirrhosis		Penile infection
Biliary cirrhosis primary		Posthitis
Biliary fibrosis		
Bilirubin excretion disorder		
Biopsy liver abnormal		
Child-Pugh-Turcotte score increased		
Cholaemia		
Cholestasis		
Cholestatic liver injury		

Hepatic Injury	Hypoglycaemia	Male Mycotic Genital Infections
Cholestatic pruritus		
Chronic graft versus host disease in liver		
Chronic hepatic failure		
Chronic hepatitis		
Coma hepatic		
Cryptogenic cirrhosis		
Diabetic hepatopathy		
Drug-induced liver injury		
Duodenal varices		
Focal nodular hyperplasia		
Gallbladder varices		
Gastric varices		
Gastric varices haemorrhage		
Graft versus host disease in liver		
Haemangioma of liver		
Haemorrhagic ascites		
Haemorrhagic hepatic cyst		
Hepatectomy		
Hepatic adenoma		
Hepatic atrophy		
Hepatic calcification		
Hepatic cirrhosis		
Hepatic cyst		
Hepatic cyst ruptured		
Hepatic encelalopathy		
Hepatic encephalopathy prophylaxis		
Hepatic failure		
Hepatic fibrosis		
Hepatic fibrosis marker abnormal		
Hepatic haemangioma rupture		
Hepatic hydrothorax		
Hepatic infiltration eosinophilic		
Hepatic lesion		
Hepatic necrosis		
Hepatic steatosis		
Hepatitis		
Hepatitis acute		
Hepatitis cholestatic		
Hepatitis chronic active		
Hepatitis chronic persistent		
Hepatitis fulminant		
Hepatitis toxic		
Hepatobiliary disease		
Hepatocellular foamy cell syndrome		
Hepatocellular injury		
Hepatopulmonary syndrome		
Hepatorenal failure		
Hepatorenal syndrome		
Hepatotoxicity		
Hyperbilirubinaemia		
Icterus index increased		
Intestinal varices		
Ischaemic hepatitis		
Jaundice		
Jaundice cholestatic		

Hepatic Injury	Hypoglycaemia	Male Mycotic Genital Infections
Jaundice hepatocellular		
Liver and small intestine transplant		
Liver disorder		
Liver injury		
Lupoid hepatic cirrhosis		
Lupus hepatitis		
Mixed liver injury		
Nodular regenerative hyperplasia		
Non-alcoholic steatohepatitis		
Non-cirrhotic portal hypertension		
Ocular icterus		
Oedema due to hepatic disease		
Oesophageal varices haemorrhage		
Parenteral nutrition associated liver disease		
Peripancreatic varices		
Periportal oedema		
Portal hypertension		
Portal hypertensive enteropathy		
Portal hypertensive gastropathy		
Portal triaditis		
Portal vein cavernous transformation		
Portal vein dilatation		
Portopulmonary hypertension		
Radiation hepatitis		
Renal and liver transplant		
Retrograde portal vein flow		
Reye's syndrome		
Reynold's syndrome		
Splenic varices		
Splenic varices haemorrhage		
Subacute hepatic failure		
Varices oesophageal		
Varicose veins of abdominal wall		

Malignancy Bladder Cancer	Malignancy Breast Cancer	Malignancy Phaeochromocytoma
Bladder adenocarcinoma recurrent	Apocrine breast carcinoma	Phaeochromocytoma
Bladder adenocarcinoma stage 0	Breast angiosarcoma	Phaeochromocytoma crisis
Bladder adenocarcinoma stage I	Breast angiosarcoma metastatic	Phaeochromocytoma excision
Bladder adenocarcinoma stage II	Breast cancer	Phaeochromocytoma malignant
Bladder adenocarcinoma stage III	Breast cancer female	
Bladder adenocarcinoma stage IV	Breast cancer in situ	
Bladder adenocarcinoma stage unspecified	Breast cancer male	
Bladder cancer	Breast cancer metastatic	
Bladder cancer recurrent	Breast cancer recurrent	
Bladder cancer stage 0, with cancer in situ	Breast cancer stage I	
Bladder cancer stage 0, without cancer in situ	Breast cancer stage II	
Bladder cancer stage I, with cancer in situ	Breast cancer stage III	
Bladder cancer stage I, without cancer in situ	Breast cancer stage IV	
Bladder cancer stage II	Breast neoplasm	
Bladder cancer stage III	Breast sarcoma	
Bladder cancer stage IV	Breast sarcoma metastatic	

Malignancy Bladder Cancer	Malignancy Breast Cancer	Malignancy Phaeochromocytoma
Bladder squamous cell carcinoma recurrent	Breast sarcoma recurrent	
Bladder squamous cell carcinoma stage 0	Contralateral breast cancer	
Bladder squamous cell carcinoma stage I	HER-2 positive breast cancer	
Bladder squamous cell carcinoma stage II	Hormone refractory breast cancer	
Bladder squamous cell carcinoma stage III	Inflammatory carcinoma of breast recurrent	
Bladder squamous cell carcinoma stage IV	Inflammatory carcinoma of breast stage III	
Bladder squamous cell carcinoma stage unspecified	Inflammatory carcinoma of breast stage IV	
Bladder transitional cell carcinoma	Inflammatory carcinoma of the breast	
Bladder transitional cell carcinoma metastatic	Intraductal papillary breast neoplasm	
Bladder transitional cell carcinoma recurrent	Intraductal proliferative breast lesion	
Bladder transitional cell carcinoma stage 0	Invasive breast carcinoma	
Bladder transitional cell carcinoma stage I	Invasive ductal breast carcinoma	
Bladder transitional cell carcinoma stage II	Invasive lobular breast carcinoma	
Bladder transitional cell carcinoma stage III	Invasive papillary breast carcinoma	
Bladder transitional cell carcinoma stage IV	Lobular breast carcinoma in situ	
Metastases to bladder	Malignant nipple neoplasm	
Metastatic carcinoma of the bladder	Malignant nipple neoplasm female	
Transitional cell carcinoma	Malignant nipple neoplasm male	
	Medullary carcinoma of breast	
	Metaplastic breast carcinoma	
	Metastases to breast	
	Mucinous breast carcinoma	
	Neuroendocrine breast tumour	
	Nipple neoplasm	
	Oestrogen receptor positive breast cancer	
	Paget's disease of nipple	
	Phyllodes tumour	
	Triple negative breast cancer	
	Tubular breast carcinoma	

Malignancy Renal Cell Cancer	Malignancy Testicular	Osmotic Diuresis
Clear cell renal cell carcinoma	Benign neoplasm of testis	Dry mouth
Clear cell sarcoma of the kidney	Leydig cell tumour of the testis	Dry throat
Denys-Drash syndrome	Sertoli cell testicular tumour	Micturition disorder
Hereditary leiomyomatosis renal cell carcinoma	Spermatocytic seminoma	Micturition urgency
Hereditary papillary renal carcinoma	Testicle adenoma	Nocturia
Metastatic renal cell carcinoma	Testicular cancer metastatic	Pollakiuria
Nephroblastoma	Testicular neoplasm	Polydipsia
Non-renal cell carcinoma of kidney	Testicular papilloma	Polyuria
Renal cancer	Testis cancer	Thirst
Renal cancer metastatic		Tongue dry
Renal cancer recurrent		Urine output increased
Renal cancer stage I		
Renal cancer stage II		
Renal cancer stage III		
Renal cancer stage IV		
Renal cell carcinoma		
Renal cell carcinoma recurrent		
Renal cell carcinoma stage I		
Renal cell carcinoma stage II		
Renal cell carcinoma stage III		
Renal cell carcinoma stage IV		
Rhabdoid tumour of the kidney		

Phimosis	Photosensitivity
Acquired phimosis	Actinic elastosis
Phimosis	Actinic prurigo
	Administration site photosensitivity reaction
	Application site photosensitivity reaction
	Chronic actinic dermatitis
	Hartnup disease
	Implant site photosensitivity
	Infusion site photosensitivity reaction
	Injection site photosensitivity reaction
	Juvenile spring eruption
	Medical device site photosensitivity
	Photodermatosis
	Photokeratitis
	Photoonycholysis
	Photosensitivity reaction
	Polymorphic light eruption
	Solar dermatitis
	Solar urticaria
	Sunburn
	Vaccination site photosensitivity

Renal Related	Severe Hypersensitivity/Cutaneous AEs	Upper UTI
Acute kidney injury	Acute generalised exanthematous pustulosis	Bacterial pyelonephritis
Acute phosphate nephropathy	Allergic oedema	Emphysematous pyelonephritis
Acute prerenal failure	Anaphylactic reaction	Kidney infection
Anuria	Anaphylactic shock	Perinephric abscess
Azotaemia	Anaphylactic transfusion reaction	Pyelocystitis
Blood creatinine increased	Anaphylactoid reaction	Pyelonephritis
Blood urea increased	Anaphylactoid shock	Pyelonephritis acute
Continuous haemodiafiltration	Angioedema	Pyelonephritis chronic
Dialysis	Circulatory collapse	Pyelonephritis fungal
Glomerular filtration rate decreased	Circumoral oedema	Pyelonephritis mycoplasmal
Haemodialysis	Conjunctival oedema	Pyelonephritis viral
Haemofiltration	Corneal exfoliation	Pyonephrosis
Hypercreatininaemia	Corneal oedema	Renal abscess
Neonatal anuria	Cutaneous vasculitis	Renal cyst infection
Nephritis	Dermatitis bullous	Urosepsis
Nephropathy toxic	Dermatitis exfoliative	
Oliguria	Dermatitis exfoliative generalised	
Peritoneal dialysis	Drug eruption	
Prerenal failure	Drug hypersensitivity	
Renal failure	Drug reaction with eosinophilia and systemic symptoms	
Renal failure acute	Epidermal necrosis	
Renal failure neonatal	Epiglottic oedema	
Renal impairment	Erythema multiforme	
Renal impairment neonatal	Exfoliative rash	
	Eye oedema	
	Eye swelling	
	Eyelid oedema	
	Face oedema	
	First use syndrome	
	Fixed drug eruption	
	Gingival oedema	
	Gingival swelling	
	Gleich's syndrome	
	Hereditary angioedema	
	Hypersensitivity vasculitis	
	Idiopathic angioedema	
	Idiopathic urticaria	
	Kounis syndrome	
	Laryngeal dyspnoea	
	Laryngeal oedema	
	Laryngospasm	
	Laryngotracheal oedema	
	Limbal swelling	
	Lip exfoliation	
	Lip oedema	
	Lip swelling	
	Mucocutaneous ulceration	
	Mucosa vesicle	
	Mucosal erosion	
	Mucosal exfoliation	
	Mucosal necrosis	
	Mucosal ulceration	
	Nikolsky's sign	

Renal Related	Severe Hypersensitivity/Cutaneous AEs	Upper UTI
	Oculomucocutaneous syndrome	
	Oculorespiratory syndrome	
	Oedema mouth	
	Oedema mucosal	
	Oral mucosal blistering	
	Oral mucosal exfoliation	
	Orbital oedema	
	Oropharyngeal blistering	
	Oropharyngeal swelling	
	Palatal oedema	
	Penile exfoliation	
	Periorbital oedema	
	Pharyngeal oedema	
	Scleral oedema	
	Shock	
	Shock symptom	
	Skin exfoliation	
	Skin necrosis	
	Small bowel angioedema	
	Stevens-Johnson syndrome	
	Stridor	
	Swelling face	
	Swollen tongue	
	Throat tightness	
	Tongue exfoliation	
	Tongue oedema	
	Toxic epidermal necrolysis	
	Type I hypersensitivity	
	Urticaria	
	Urticaria cholinergic	
	Urticaria chronic	
	Urticaria papular	
	Urticarial vasculitis	
	Vaginal exfoliation	

UTI	Venous Thromboembolic events	Volume Depletion
Bladder candidiasis	Deep vein thrombosis	Blood pressure decreased
Cystitis	Deep vein thrombosis postoperative	Blood pressure orthostatic decreased
Cystitis bacterial	Embolism venous	Dehydration
Cystitis escherichia	Iliac vein occlusion	Diastolic hypotension
Cystitis gonococcal	Inferior vena cava syndrome	Dizziness postural
Cystitis haemorrhagic	Inferior vena caval occlusion	Hypotension
Cystitis interstitial	Jugular vein occlusion	Hypovolaemia
Cystitis klebsiella	Mesenteric vein occlusion	Hypovolaemic shock
Cystitis pseudomonal	Obstructive shock	Orthostatic hypotension
Emphysematous cystitis	Portosplenomesenteric venous thrombosis	Orthostatic intolerance
Escherichia urinary tract infection	Post procedural pulmonary embolism	Postural orthostatic tachycardia syndrome
Fungal cystitis	Postpartum venous thrombosis	Presyncope
Funguria	Pulmonary embolism	Shock
Genitourinary tract infection	Pulmonary infarction	Shock symptom
Streptococcal urinary tract infection	Pulmonary microemboli	Syncope
Ureter abscess	Pulmonary oil microembolism	Urine output decreased

UTI	Venous Thromboembolic events	Volume Depletion
Ureteritis	Pulmonary thrombosis	
Urethritis	Renal vein embolism	
Urethral abscess	Renal vein occlusion	
Urethral carbuncle	Subclavian vein thrombosis	
Urethral stricture post infection	Vascular occlusion	
Urinary bladder abscess	Venous thrombosis	
Urinary tract abscess	Venous thrombosis in pregnancy	
Urinary tract infection	Venous thrombosis limb	
Urinary tract infection bacterial	Visceral venous thrombosis	
Urinary tract infection enterococcal		
Urinary tract infection fungal		
Urinary tract infection pseudomonal		
Urinary tract infection staphylococcal		

Appendix 1.4: Adverse Events with Potential Amputation Association

List of selected preferred terms included within the system organ classes of infections and infestations, vascular disorders, nervous system disorders, and skin and subcutaneous tissue disorders

Infections and Infestations	Vascular Disorders	Nervous System Disorders	Skin and Subcutaneous Tissue Disorders	High Level Term (HLT) Skin and subcutaneous tissue ulcerations	
Infected skin ulcer	Arteriosclerosis	Paraesthesia	Diabetic ulcer	Penile ulceration	Medical device site erosion
Skin infection	Peripheral arterial occlusive disease	Hypoaesthesia	Neuropathic ulcer	Implant site ulcer	Ulcerated haemangioma
Staphylococcal skin infection	Peripheral vascular disorder	Diabetic neuropathy	Fungating wound	Cytomegalovirus mucocutaneous ulcer	Incision site erosion
Gangrene	Peripheral artery stenosis	Neuropathy peripheral	Diabetic foot	Skin ulcer	Incision site ulcer
Osteomyelitis	Peripheral ischaemia	Areflexia	Diabetic neuropathic ulcer	Eyelid erosion	Vaccination site ulcer
Diabetic gangrene	Arterial stenosis	Hyporeflexia	Skin erosion	Implant site erosion	Fungating wound
Localised infection	Diabetic vascular disorder	Polyneuropathy		Diabetic foot infection	Ecthyma
Wound abscess	Femoral artery occlusion	Autonomic neuropathy		Application site erosion	Perineal ulceration
Wound infection	Thrombosis	Neuropathy peripheral		Infusion site erosion	Tropical ulcer
Subcutaneous abscess	Poor peripheral circulation	Burning sensation		Mycobacterium ulcerans infection	Injection site erosion
Abscess limb	Microangiopathy	Diabetic autonomic neuropathy		Infusion site ulcer	Pyogenic sterile arthritis pyoderma gangrenosum and acne syndrome
Staphylococcal osteomyelitis	Peripheral coldness	Peripheral sensory neuropathy		Neuropathic ulcer	Scleroderma associated digital ulcer
Diabetic foot infection	Diabetic microangiopathy	Peripheral sensorimotor neuropathy		Skin ulcer haemorrhage	Vulval ulceration
Staphylococcal skin infection	Arterial occlusive disease	Sensory disturbance		Burn infection	Mucocutaneous ulceration
Soft tissue infection	Arterial thrombosis	Diabetic neuropathic ulcer		Diabetic foot	Injection site ulcer
Bone abscess	Peripheral artery thrombosis			Diabetic ulcer	Pyoderma gangrenosum
Osteitis	Arterial occlusive disease			Catheter site erosion	Scrotal ulcer
Cellulitis	Angiopathy			Pyostomatitis vegetans	Application site ulcer
Wound [a]	Intermittent claudication			Catheter site ulcer	Genital ulceration
Dry gangrene	Arterial disorder			Medical device site ulcer	Infected skin ulcer
Post-operative wound infection	Impaired healing [a]			Administration site ulcer	Diabetic neuropathic ulcer
Post-operative wound complication [a]				Instillation site erosion	Varicose ulceration
Wound dehiscence				Breast ulceration	Vaginal ulceration
Burn infection				Instillation site ulcer	Vulvovaginal ulceration
Extremity necrosis				Administration site erosion	Auditory meatus external erosion
				Vasculitic ulcer	Skin erosion
				Vaccination site erosion	

[a] Although these PTs belong in the SOC of Injury, Poisoning and Procedural Complications or in the SOC of General Disorders and Administration Site Conditions, these terms were retained for the search strategy because of their relevance

List of preferred terms classified as reversible infections, irreversible infections and osteomyelitis

Reversible Infections	**Irreversible Infections**	**Osteomyelitis**
Abscess limb	Diabetic gangrene	Bone abscess
Burn infection	Dry gangrene	Osteitis
Cellulitis	Extremity necrosis	Osteomyelitis
Diabetic foot infection	Gangrene	Staphylococcal osteomyelitis
Infected skin ulcer	**Osteomyelitis**	
Localised infection	Bone abscess	
Skin infection	Osteitis	
Soft tissue infection	Osteomyelitis	
Staphylococcal skin infection	Staphylococcal osteomyelitis	
Subcutaneous abscess		
Wound		
Wound abscess		
Wound dehiscence		
Wound infection		

Janssen Research & Development

Statistical Analysis Plan

Cardiovascular Outcomes Clinical Program
Integrated Database of CANVAS and CANVAS-R

Protocol 28431754DIA3008
Protocol 28431754DIA4003

JNJ-28431754 (canagliflozin)

Status:	Approved
Date:	20 September 2016
Prepared by:	Janssen Research & Development, LLC

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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SUMMARY OF AMENDMENT

Relative to the integrated statistical analysis plan (SAP) submitted in 2013, the major amendments made in this version are summarized as follows.

Applicable Section(s)	Description of Change(s)
1.3	Addition of 2 secondary objectives to demonstrate the superiority of canagliflozin to placebo in reduction of all-cause mortality and cardiovascular death.
1.4, 2.2	Proposal to evaluate the secondary objectives based on pooled CANVAS data, using the Truncated analysis set (defined in Section 2.2), with CANVAS-R.
1.4.1	Pre-specify the multiplicity adjustment for the CV Outcomes Clinical Program including the proposal to transfer alpha for the tests in CANVAS-R.
4.1.2.2	Outline the multiple imputation method for sensitivity analyses to evaluate the robustness of the conclusion due to missing data.
4.2.1	Analysis methods for the secondary endpoints.
4.2.2	Supportive analyses for the secondary endpoints including the worst case scenario analysis for missing data.
4.3	Addition of all-cause hospitalization, hospitalization for heart failure (HHF) and the composite of HHF or CV death as additional exploratory endpoints.
5	Addition of the renal endpoints as exploratory endpoints and their analysis methods.
6	Addition of the integrated safety analysis plan.

ABBREVIATION

ACM	all-cause mortality
ACR	albumin creatinine ratio
AE	adverse event
AHA	anti-hyperglycemic agent
BMI	body mass index
BP	blood pressure
Cana	canagliflozin
CANVAS	**CAN**agliflozin cardio**V**ascular **A**ssessment **S**tudy
CANVAS-R	**CAN**agliflozin cardio**V**ascular **A**ssessment **S**tudy - **R**enal
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CM	concomitant medication
CV	cardiovascular
CVD	cardiovascular death
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FDA	US Food and Drug Administration
GTED	Global Trial End Date
HF	heart failure
HR	hazard ratio
HbA1c	hemoglobin A1c
HDL-C	high-density lipoprotein cholesterol
IDMC	Independent Data Monitoring Committee
IWRS	Interactive Web Response System
ITT	Intent-to-Treat
LB	laboratory
LDL-C	low-density lipoprotein cholesterol
MACE	major adverse cardiovascular event
MH	medical history
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NI	non-inferiority
PMR	Post Marketing Requirement
PT	preferred term
SAP	statistical analysis plan
SCr	serum creatinine
SD	standard deviation
SGLT2	sodium-glucose co-transporter 2
SOC	system organ class
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TEAE	treatment emergent adverse event
VS	vital signs

1. INTRODUCTION

The canagliflozin cardiovascular (CV) outcomes clinical program consists of 2 studies 28431754DIA3008 (CANVAS) and 28431754DIA4003 (CANVAS-R) initiated in December 2009 and January 2014, respectively. Canagliflozin (Cana, JNJ-28431754) was approved for marketing in the US on 29 March 2013. It is an orally active inhibitor of the sodium-glucose co-transporter 2 (SGLT2) that has been developed as an oral anti-hyperglycemic agent (AHA) for the treatment of patients with type 2 diabetes mellitus (T2DM).

To meet the FDA guidance on assessing CV safety of AHAs, the sponsor initiated the CANVAS CV Outcomes study to supply data to support the CV safety of canagliflozin and to also evaluate whether canagliflozin reduces CV risk. As part of the marketing authorization application, the sponsor performed an integrated analysis of CV events from the Phase 2 and Phase 3 canagliflozin program using data from 9,632 subjects, which included interim data harvested on 31 January 2012 from the ongoing CANVAS CV Outcomes study of 4,330 subjects at high risk for CV disease. The primary CV endpoint for the pre-approval safety analysis was the composite of CV death, non-fatal myocardial infarction (MI), non-fatal stroke or hospitalization for unstable angina. In response to a request arising during review of the canagliflozin Marketing Authorization Application by the Committee for Medicinal Products for Human Use (CHMP), the sponsor conducted a second integrated CV analysis of the Phase 2 and Phase 3 studies, which included interim data from CANVAS harvested on 19 November 2012. Data on major adverse cardiovascular events (MACE; CV death, non-fatal MI, or non-fatal stroke) and mortality outcomes beyond 19 November 2012 have remained blinded to the sponsor and investigators.

As per the FDA guidance and following market authorization, the sponsor is required to demonstrate that the upper bound of the 2-sided 95% confidence interval (CI) of the CV risk ratio of test drug to comparator be less than 1.3. In the 19 February 2013 and 05 March 2013 teleconferences between the Agency and the sponsor, the Agency indicated that the sponsor needed to rule out 1.3 upper bound using MACE. The Agency indicated these data could be derived from a new dedicated study or from a pooled analysis including the CANVAS study along with a new CANVAS-like study (so as to accumulate sufficient events within an appropriate time period post-approval).

As a result of these discussions, the sponsor proposed to conduct a second CANVAS-like study (identified at that time as CANVAS2, now referenced as CANVAS-R) with approximately 5,700 randomized subjects. As such, the CANVAS and CANVAS-R trials are purposefully similar in design and in subject characteristics (see next section). Data from these studies are to be harvested for an integrated analysis no later than June 2017 with study reports submitted to FDA by September 2017. The integrated analysis for CV safety will use all subjects enrolled in CANVAS and CANVAS-R in an intent-to-treat (ITT) analysis to show that a canagliflozin-associated increase in the CV risk ratio, if any, was significantly less than 1.3 using the 2-sided 95% CI of the risk ratio. A previous CANVAS/CANVAS-R integrated SAP for the CV risk assessment Post Marketing Requirement (PMR) was submitted to FDA in October 2013.

The analysis plan for the integrated dataset to satisfy the CV risk assessment PMR was oriented to the role of safety evaluation; ie, to rule out a canagliflozin-associated increase in the risk ratio for MACE of 1.3 in accord with FDA Guidance. There were plans for independent SAPs for CANVAS and CANVAS-R, with separate strong control of the Type I error rate within each study. The primary endpoint of CANVAS was to evaluate whether there was a risk reduction in MACE associated with canagliflozin treatment. Due to unblinding of the interim summary results of CANVAS at the time of marketing approval, the planned expansion of enrollment in CANVAS was eliminated, and CANVAS-R was initiated to provide sufficient CV outcome data to support the CV safety PMR. The primary endpoint of CANVAS, MACE, was not changed although it was recognized that with the smaller sample size the study was substantially under-powered for the objective.

In the March 2016 submission to FDA, the sponsor proposed to modify the analysis plans for CANVAS and CANVAS-R. The new CANVAS/CANVAS-R integrated SAP would maintain, as originally planned, the use of the integrated dataset for purposes of the MACE CV safety PMR. As originally planned, this dataset would contain information from all subjects enrolled under either the CANVAS or CANVAS-R protocols, including all subject study-time before and since the 20 November 2012 CANVAS interim analysis related to the reviews for marketing approval. After the CV safety PMR is addressed, the sponsor proposed to add the endpoints to evaluate mortality benefit in this SAP revision. Key adjustments in the integrated dataset will be made for the main analysis of these additional endpoints of mortality and will be described in this document.

The CANVAS/CANVAS-R integrated SAP in this submission, which replaces the October 2013 document, specifies updated definitions of analysis sets, key derived variables and statistical methods for analysis of efficacy and safety of the canagliflozin program to evaluate CV risk for PMR and the benefit in mortality reduction.

The SAP for the integrated dataset will be the primary SAP for data from both CANVAS and CANVAS-R for purposes of maintaining strong control of the Type I error rate. Although there are separate SAP documents for the CANVAS-only and CANVAS-R-only data, these SAPs are subordinate to this SAP for the integrated dataset with regard to controlling the Type I error rate, and the relationship is further detailed in this document.

1.1. Similarity of CANVAS and CANVAS-R

The CANVAS and CANVAS-R trials are ongoing in subjects with CV disease (secondary-prevention) and subjects with at least 2 risk factors for a CV event (primary-prevention). The key design elements of the 2 trials are similar (refer to Table 1).

The similarities in study design, eligibility criteria, study population, key endpoints, etc, were done as per the PMR and in agreement with the FDA so as to support an integrated analyses of these studies. The selection criteria were virtually identical in CANVAS and CANVAS-R. The only differences were the following requirements in the CANVAS study: stable AHA regimen prior to randomization as required to evaluate glycemic efficacy in the 18-week sub studies; findings on ECG obtained at screening instead of simply “known” findings within 3 months

before screening; additional estimated glomerular filtration rate (eGFR) criterion for subjects taking metformin, and the exclusion of rosiglitazone; see Appendix 1 for a summary of operational specifics and key inclusion/exclusion criteria. An expanded list of the eligibility criteria is provided in Appendix 2.

1.2. Completion of CANVAS and CANVAS-R

The CANVAS and CANVAS-R studies will complete when the last subject randomized has approximately 78 weeks of follow-up or when 688 MACEs are accumulated between both studies (estimated to occur between January 2017 and April 2017).

All sites in CANVAS and CANVAS-R will be notified of the projected Global Trial End Date (GTED). Following announcement of the projected GTED and for subjects remaining on double-blind study drug, sites will schedule the End of Treatment visit and the 30-day off-drug follow-up visit as per the Time and Events schedule in the protocols; for subjects that have prematurely discontinued study drug prior to the announcement of the projected GTED, sites will be required to make a final contact or vital status check as soon as possible after the announcement. It is estimated that there will be 6.1 and 2.3 years of median observation in CANVAS and CANVAS-R, respectively.

Table 1: CANVAS and CANVAS-R: Key Design Elements

	CANVAS	CANVAS-R
Patient population	Men or women with T2DM who have inadequate glycemic control (HbA_{1c} ≥7.0 and ≤10.5%) with either known CV disease or 2 or more risk factors for CV events	
Renal function for trial entry	eGFR ≥ 30 mL/min/1.73m^2	
Renal function for study drug discontinuation	Confirmed eGFR < 15 mL/min/1.73m^2	
AHA background therapy	Drug naïve, AHA monotherapy or combination therapy	
CV risk factor management	The effects of canagliflozin will be evaluated against a background of standard of care for the treatment of hyperglycemia and CV risk factors (ie, blood pressure and lipids) with study investigators counseled to assure appropriate management according to applicable national guidelines for the care of patients with T2DM with treatment individualized as clinically appropriate.	
Governance and supporting committee	Single Academic Steering Committee, Independent Data Monitoring Committee and Endpoint Adjudication Committee. (note: consistent endpoint definitions were applied across both the CANVAS/CANVAS-R studies).	
Study treatment regime	Three arms: placebo, Cana 100 mg QD and Cana 300 mg QD	Two arms: placebo, Cana (100 mg QD for the 1st 13 weeks, with up-titration to 300 mg QD thereafter at investigator discretion and based on tolerability and glycemic needs)
Number of subjects randomized	4,330	5,812
First subject randomized	December 2009	January 2014
Last subject Randomized	March 2011	May 2015

1.3. Key Objectives of Integrated Analysis

- To demonstrate that canagliflozin is not associated with an unacceptable increase in cardiovascular risk by showing that the upper bound of the 2-sided 95% CI for the risk ratio of canagliflozin to placebo is less than 1.3 where the risk ratio is measured by hazard ratio (HR).
- To demonstrate the superiority of canagliflozin in the reduction of the following mortality endpoints relative to placebo:
  - All-cause mortality (ACM): Death from any cause
  - CV Death (CVD): Death from cardiovascular cause

1.4. Statistical Hypotheses

All hypotheses in the CV program will be tested with a Type I error strongly controlled at 5%.

Primary Hypothesis

The following statistical hypothesis is addressed by use of the entire integrated dataset (without any data truncation [see below]) and performing a non-inferiority test for the HR (all canagliflozin versus placebo) for MACE at the margin of 1.3:

H_0: The HR $\geq$ 1.3, versus H_1: The HR < 1.3.

The CV safety of canagliflozin will be demonstrated if, as compared to placebo, the upper bound of 95% CI of the HR is less than 1.3.

If the null hypothesis H_0 is rejected and if the upper bound of the 2-sided 95% CI of the HR is less than 1.0, then it will be concluded that canagliflozin is superior to placebo in terms of MACE reduction.

Secondary Hypotheses

The secondary objectives are to demonstrate that canagliflozin is superior to placebo in reducing all-cause mortality and CV death. Because there was an unblinded interim analysis of the CANVAS study in 2012, information from this study will be left-truncated; that is only deaths accrued from the study time from after 19 November 2012 will be used in these superiority analyses, and deaths up to the date of the interim analysis will be excluded. For these mortality endpoints, the following statistical hypothesis on the HR of canagliflozin to placebo will be tested.

H_0: The HR $\geq$ 1.0, versus H_1: The HR < 1.0

Canagliflozin will be deemed to be superior as compared to placebo if the upper bound of 95% CI of the HR is less than 1.0.

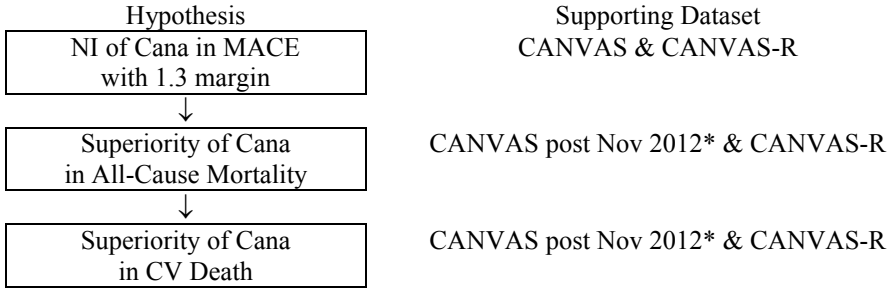
1.4.1. Control of the Type I Error Rate

The primary and the secondary hypotheses will be tested sequentially in order to strongly control the type I error at 5% (refer to Figure 1). For the primary non-inferiority MACE assessment,

canagliflozin will be tested against placebo to exclude the HR of 1.3. Testing of secondary hypotheses will proceed sequentially conditional on the statistical significance of the primary test at the 5% significance level and the testing of subsequent endpoints proceeds conditional on the statistical significance of the prior test.

If the MACE and the mortality endpoints in the integrated analysis succeed in rejecting the null hypotheses, all of the alpha for testing (ie, 5%) will pass to the CANVAS-R SAP for testing of the renal and the CV efficacy hypotheses in the CANVAS-R study. Therefore, no alpha is preserved for evaluating hypotheses in CANVAS and only nominal p-values will be reported for efficacy endpoints assessed in the CANVAS study.

Figure 1: Hypothesis Testing Sequence in Integrated Analysis



* Only subjects who were at risk for mortality after 19-Nov-2012 are included.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Analysis Populations

- Randomized subjects—subjects who are randomized via the Interactive Web Response System (IWRS);
- Treated subjects—randomized subjects who received at least one dose of double-blind study medication.

For efficacy analyses and baseline summaries, subjects will be analyzed according to their randomization assignment. For analysis of safety (eg, adverse events [AEs]) and summary of exposure, subjects will be analyzed according to the predominant treatment received (defined as the treatment to which the subject was exposed for the greatest duration), in the event that subjects receive a treatment other than the one to which they were randomized.

2.2. Analysis Sets

Analysis sets consist of 2 components: (1) analysis population (Section 2.1), which specifies the subjects included in an analysis; (2) data period, defining the time window during which data will be included in the analysis. Table 2 presents the 3 analysis sets defined for the integrated analysis with the component description. In the ITT and the On-Treatment analysis sets, Day 1 is the first double blind dose date for each subject. If missing or incomplete, the first dose date will be imputed as the randomization date (also see trial reference start date in Section 2.4.2).

All the integrated analyses are mainly based on either the ITT analysis set or the On-Treatment analysis set. The exception is in the testing of the treatment effects on all-cause and CV-specific mortality where the Truncated analysis set will be used.

As the results of the CV interim analysis of CANVAS (through November 2012) were known at the time of marketing approval, the inclusion of that information in analyses of the integrated dataset for the mortality endpoint tests of superiority of canagliflozin relative to placebo can raise concern of a biased analysis. Therefore, the dataset used in the analyses of secondary endpoints for the integrated dataset is adjusted to eliminate all mortality and censored cases that contributed to the 2012 CANVAS interim analysis. In the Truncated analysis set that will be used for these secondary endpoints, the CANVAS data will be left-truncated such that only the study time from after the 19 November 2012 interim analysis will be used. That is, study time from study initiation through 19 November 2012 will be excluded and Day 1 for CANVAS subjects in the Truncated analysis set will be 20 November 2012.

Table 2: Summary of Analysis set for Integrated Analysis

Analysis Set	Population	Data Period
ITT[a]	Randomized subjects	Day 1 to the last trial contact date (see Section 2.4.2) up to GTED
On-Treatment[a]	Treated subjects	Day 1 to the last dose date plus X[b] days or the last trial contact date, whichever is earlier.
Truncated	All randomized subjects in CANVAS-R and subjects in CANVAS who were at risk for mortality after 19-Nov-2012	For CANVAS, 20-NOV-2012 to the last trial contact date (see Section 2.4.2) up to GTED. For CANVAS-R, Day 1 to the last trial contact date (see Section 2.4.2) up to GTED

[a] The same definitions of the analysis set are applied in CANVAS and CANVAS-R.
[b] X is 2 days for safety labs and vital sign measurements, and 30 days for CV, mortality, and renal endpoints, AEs, and labs specific for efficacy.

2.3. Data Integration

In the integrated analysis, data from CANVAS and CANVAS-R will be combined. If not otherwise specified, subjects treated with canagliflozin will be pooled as the 'All canagliflozin' group. The table below presents the projected number of randomized subjects by treatment.

	Estimated Median Duration of Follow-Up	Number of Randomized Subjects			
		Cana 100 mg	Cana 300 mg	All Cana	Placebo
CANVAS	6.1 yrs.	1445	1443	2888	1442
CANVAS-R	2.3 yrs.			2906*	2905*

* Assumption that an equal number of subjects were randomized to Cana and Placebo

2.4. Data Handling

2.4.1. Censoring Rules

For each analysis set, events that occur any time during the data period of the corresponding analysis set (see Table 2) will be considered as eligible events; otherwise subjects not experiencing an event will be censored at the earlier of the last trial contact date or end of the respective data period, if not otherwise specified.

2.4.2. Handling of Key Milestone Dates

- Trial reference start date (Day 1): the first double-blind dose date for each subject (First dose date). If missing or incomplete, the first dose date will be imputed as the randomization date. In Truncated analysis set (Section 2.2), due to the data exclusion, Day 1 for eligible CANVAS subjects is defined to be 20-Nov-2012.
- Last dose date: the date on which the last dose of double-blind study drug was taken by the subject. If only the day is missing, impute the last day of the month. If the month or the year is missing, impute the date as the date of the scheduled visit subsequent to the last visit when the study drug was dispensed. The imputed last dose date should be no later than the end of treatment visit date or the last trial contact date. In addition, the imputed last dose date should be no earlier than the first dose date. The last dose date is the date of permanent study drug discontinuation regardless of any temporary drug interruption.
- Last trial contact date: the date when the last trial-related procedure is conducted. It is defined as the latest of:
  - The date of last visit/contact (scheduled or unscheduled visit; office or phone contact), or
  - The latest known date of an AE or the study endpoint event status, concomitant medication, vital sign measurements or laboratory results as reported on their respective eCRF, or
  - The date of alternate contact made (eg, family members, relatives, friends, health care providers, public search) confirming the patient's survival status at the time of the GTED.
  - For subjects who die during the study, the last trial contact date will be defined as the date of death.

3. SUBJECT INFORMATION

3.1. Baseline Anthropometric and Demographic Characteristics

Baseline anthropometric and demographic characteristics will be summarized by treatment group. Descriptive statistics (N, mean, standard deviation [SD], median, and range) will be provided by treatment group for continuous variables at baseline such as age and body weight.

Additionally, the number and percentage of subjects in the categories of the following variables at baseline will also be summarized by treatment group based on the ITT analysis set:

- Age group: <65, ≥65 years old;
- Sex: Male, Female;
- Race: White, Black or African American, Asian, Others;
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Unknown, Not reported;
- Region: North America, Central/South America, Europe, Rest of the World (refer to Appendix 3 for list of countries in each region).

A summary for the integrated database, CANVAS, and CANVAS-R presenting in a side-by-side format will be provided. Another summary based on the ITT analysis set and the Truncated analysis set will also be presented side-by-side.

3.2. Baseline Disease Characteristics

Descriptive statistics (N, mean, SD, median, and range) will be provided by treatment group and overall for continuous variables at baseline such as duration of diabetes (in years), baseline eGFR, baseline albumin creatinine ratio (ACR), systolic blood pressure (SBP), weight, body mass index (BMI), HbA1c, LDL-C, HDL-C , triglycerides (TG), total cholesterol (TC) and LDL-C/HDL-C.

Additionally, the number and percentage of subjects will be summarized by treatment group for the following:

- Baseline BMI categories (<30, ≥30 Kg/m^2);
- Currently daily cigarette smoker: Yes/No;
- Baseline HbA_{1c} ≥ 8%: Yes/No;
- Duration of T2DM ≥ 10 years: Yes/No;
- Baseline blood pressure categories (≤140, >140mmHg);
- Baseline LDL-C categories (≤70, >70mg/dL);
- Baseline HDL-C categories (<39, ≥39 mg/dL);
- Baseline eGFR categories (<30, 30 to <60, 60 to <90, ≥90 $mL/min/1.73m^2$);
- Baseline albuminuria categories: Normoalbuminuria (0 ≤ACR <30 mg/g); Microalbuminuria (ACR ≥30 mg/g and ≤300 mg/g); Macroalbuminuria (ACR > 300 mg/g: ACR >300 mg/g and ≤3000 mg/g, ACR > 3000 mg/g).
- History of hypertension: Yes/No ;
- History of prior CV disease: Yes/No;
- History of coronary artery disease: Yes/No;
- History of cerebrovascular disease: Yes/No;

- History of peripheral vascular disease: Yes/No;
- History of heart failure: Yes/No;
- Microvascular diabetes complications (Any, 1, 2 or 3 of retinopathy, neuropathy [diabetic or automatic neuropathy], and nephropathy)
- History of fracture: Yes/No;

A summary for the integrated database, CANVAS, and CANVAS-R presenting in a side-by-side format will be provided based on the ITT analysis set. Another summary based on the ITT analysis set and the Truncated analysis set will also be presented side-by-side.

3.3. Disposition Information

Disposition for all randomized subjects will be summarized by treatment group (all canagliflozin and placebo) using the categories listed below:

- Screen failure;
- Subjects who are randomized (ITT);
- Subjects who are treated;
- Subjects who are randomized and at risk of mortality on 20-Nov-2012 or afterward (Truncated);
- Subjects who complete the study (ie, defined as having been followed until a time point between the notification of the GTED and the GTED, or if the subject has died prior to the GTED);
- Subjects who prematurely discontinued study medication;
- Subjects without final vital status.

The reasons for non-randomization, withdrawal from study (lost to follow-up, consent withdrawal), and discontinuation from study medication will be summarized. Distribution of time to premature discontinuation of study medication will be displayed using a Kaplan-Meier plot, where one minus the survival function will be shown.

3.4. Extent of Exposure and Follow-Up

Total exposure time for each subject is defined as the number of days from Day 1 to the last dose date (inclusive), regardless of any temporary drug interruption(s). Follow-up time is defined as the number of days from Day 1 to the last contact day (inclusive) for each subject. Descriptive statistics (N, mean, standard deviation, median, and range) for total exposure or total follow-up will be presented by treatment and study.

3.5. Prior and Concomitant Medications

Medications of special interest are pre-specified and captured on the eCRF of CANVAS-R. In CANVAS, the medication usage was collected without any pre-specified categories. For the purpose of reporting, the medications in CANVAS, which are coded using World Health

Organization Drug Utilization Research Group (WHODRUG) and Anatomical Therapeutic Chemical (ATC) codes, will be aligned with the medication categories in CANVAS-R.

The number of subjects receiving medication in pre-specified categories, such as insulin, sulphonylurea, metformin, statin, anti-thrombotic, diuretic (loop and non-loop), renin angiotensin aldosterone system inhibitor, will be presented by treatment group at baseline and on-drug period. SGLT2 inhibitor use during the off-drug follow-up period will also be summarized by treatment group.

4. CARDIOVASCULAR AND MORTALITY ENDPOINTS

The primary objective to demonstrate CV safety will be assessed using data from all randomized subjects (ITT analysis set). The secondary objectives (ie, demonstration of superiority in reducing all-cause and CV mortality) will be assessed using the Truncated analysis set. Subjects treated with canagliflozin will be pooled (all canagliflozin group) for the comparison to placebo. A tabulation of the primary and the secondary analyses is presented in Appendix 4.

4.1. Primary Endpoint

The primary CV endpoint is MACE which is the composite of CV outcomes including CV death, non-fatal MI[a], or non-fatal stroke. Adjudication of these outcomes by the Endpoint Adjudication Committee (EAC) has been done in a blinded fashion.

4.1.1. Primary Analysis Methods

The objective of this analysis is to demonstrate that canagliflozin is not associated with an unacceptable increase in cardiovascular risk by showing that the upper bound of the 2-sided 95% CI of the HR of canagliflozin to placebo is less than 1.3.

The following statistical hypotheses on the HR (all canagliflozin versus placebo) will be tested:

H_0: The HR $\geq$ 1.3, versus H_1: The HR <1.3.

If the null hypothesis H_0 is rejected and if the upper bound of the 2-sided 95% CI of the HR is less than 1.0, then it will be concluded that canagliflozin is superior to placebo.

The primary analysis will be based on the time to first occurrence of MACE based on the ITT analysis set. The HR of all canagliflozin compared to placebo and its 95% CI will be estimated using a stratified Cox proportional hazards regression model with treatment (all canagliflozin and placebo) as the explanatory variable, and study (CANVAS and CANVAS-R) and prior CV disease subgroup (secondary prevention and primary prevention) as the stratification factors. P-value of stratified log rank test for treatment effect will also be reported for the primary analysis.

[a] Silent MIs are excluded from the analysis.

The percentage of subjects who experience a MACE and the corresponding incidence rate per 1,000 patient-years will be reported. The study-combined cumulative event rate over time will be presented using a Kaplan-Meier plot showing all canagliflozin and placebo.

4.1.2. Supportive Analyses

4.1.2.1. Proportional Hazard Assumptions

The plot of the log of cumulative hazard function by treatment over time will be made and the assumption of proportional hazards will be assessed. In addition, a treatment by logarithm-transformed time interaction term will be added into the primary Cox model and tested. A p-value greater than 0.05 for the interaction term will be interpreted as no statistical evidence against the proportional hazard assumption. If the p-value is 0.05 or less, the confidence interval for the CV risk ratio will be re-estimated based on the log rank method suggested by Peto et al. (1976)[1] (refer to Appendix 5 for details).

4.1.2.2. Assessment of Missing Data

For subjects who are lost to follow up or withdrew consent before the development of a MACE in ITT analysis set, data between the last trial contact date and the GTED, will be considered missing.

The proportion of data missing, defined as the ratio of the duration of missing follow up (ie, days between last contact date + 1 day and the GTED) and the duration of intended follow up (ie, days between randomization date and the GTED) will be summarized.

Distributions of baseline demographics and other characteristics will be compared between subjects with and without missing data, to evaluate the plausibility of the assumption of non-informative censoring used in the analysis. The information among those with missing data will also be summarized by treatment groups to further evaluate any imbalance of non-informative censoring if applicable.

Multiple Imputation

The potential impact of missing data will be evaluated by multiple imputation. The methodology which accounts for informative censoring[2] is described as follows:

- Different parametric time to event models, eg, Exponential, Weibull, will be fit on observed data with the adjustment for treatment and other covariates such as baseline characteristics. The model will be fit separately for subjects with different disposition status, eg, completion of study, discontinuation from study early due to consent withdrawal or other reasons.
- Simulated time will be generated by random sampling using parameters from the above model for each disposition status. The simulated time will be used to impute the duration of missing follow-up after early discontinuation from the study.
- Imputation will be done for subjects who are lost to follow-up or withdrew consent without an event prior to the GTED.

- If the simulated time is less than the elapsed time between the last contact date and the GTED, an event is imputed for the corresponding subject with the time to event set to be last contact date plus the simulated time. Otherwise, the subjects will be censored at GTED.
- The imputed events and times will be added to the observed data and the primary efficacy model will be reanalyzed.
- The simulation process will be repeated and the results from the multiple imputed datasets combined to yield an overall inference, ie, HR and 95% CI, incorporating the within and between imputation variation using Rubin's rules.

4.1.2.3. On-Treatment Analysis

The primary analysis will be repeated using the On-Treatment analysis set in which data from the first dose of study drug to 30 days after the last dose of the study drug are used.

For subjects without MACE who were lost to follow up or withdrew consent in the On-Treatment analysis set, data between the last trial contact date and last dose date plus 30 days will be considered missing. The fraction of data missing will be summarized using similar approach as described for the ITT analysis set.

4.1.2.4. Hazard Ratio Estimation for Individual MACE Components

A separate analysis will be performed on each component of MACE (CV death, non-fatal MI, or non-fatal stroke). Additionally, analyses of fatal/non-fatal MI as well as fatal/non-fatal stroke will be performed. In case of subjects with multiple types of events, all events will be counted towards analyses for relevant components (eg, if a subject has both non-fatal MI and non-fatal stroke, the subject will be counted as having event for both endpoints). Frequency count and percentage of subjects who have such events as well as the event rate will be summarized by treatment. The corresponding HR and its 2-sided 95% CI will also be estimated via the stratified Cox proportional hazards model in the primary analysis (refer to Section 4.1.1).

4.1.2.5. Test of Study Homogeneity

In the primary analysis, if the null hypothesis (ie, H_0: the HR $\geq$ 1.3) is rejected and if the upper bound of the 2-sided 95% CI of the is less than 1.0, an additional homogeneity assessment will be performed. A Cox proportional hazards model with treatment, study (ie, CANVAS and CANVAS-R), and treatment-by-study interaction as the explanatory variables will be fit. If the p-value for the interaction is greater than 0.05, the test result will be interpreted as a lack of statistical evidence for a difference in the treatment effect between CANVAS and CANVAS-R. The superiority of canagliflozin to placebo in MACE reduction will be claimed. Otherwise, a Gail-Simon test will be performed to assess if the interaction is quantitative or qualitative.

4.1.2.6. Subgroup Analyses

The homogeneity of treatment effects on the occurrence of the MACE across subgroups (if a total number of events is greater than 10 for two treatment groups and at least 1 event in both groups) will be examined (at a 2-sided significance level of 0.05) via a test for the treatment-by-subgroup interaction by adding this term and the subgroup as covariates (viewed as class

variables) to the primary efficacy analysis (Section 4.1.1) model. Factors exhibiting interactions with p <0.05 will be identified as exhibiting a possible treatment effect heterogeneity, recognizing that one or more p-values under 0.05 may be expected to be observed by chance when several subgroup factors are examined.

If a significant interaction is observed, Gail-Simon test will be used to further examine the nature of the interaction (qualitative or quantitative).

Estimates and 2-sided 95% confidence intervals for the HR (canagliflozin/placebo) will be provided for each subgroup. The analyses will be based on the primary analysis model separated for each of the following subgroups:

- Age group: <65, ≥65 years old;
- Sex: Male, Female;
- Race: White, Black or African American, Asian, Other;
- Region: Central/South America, Europe, North America, Rest of the World;
- Baseline eGFR categories (30 to <60, 60 to <90, ≥90 mL/min/1.73m^2);
- Baseline HbA_{1c} ≥ 8%: Yes/No;
- Duration of diabetes ≥ 10 years: Yes/No;
- History of prior CV disease: Yes/No;
- History of peripheral vascular disease: Yes/No;
- History of amputation: Yes/No.

4.2. Secondary Endpoints

The secondary endpoints are all-cause mortality and CV death. All mortality events are adjudicated in a blinded fashion by the EAC. The objectives of these analyses are to demonstrate that canagliflozin is superior to placebo in reducing all-cause mortality and CV death.

4.2.1. Main Analysis Method

The analysis will be based on the Truncated analysis set. For each endpoint, the following statistical hypothesis on the HR of canagliflozin over placebo will be tested.

H_0: The HR ≥ 1.0, versus H_1: The HR < 1.0 (*)

The HR of all canagliflozin compared to placebo will first be tested using a stratified Cox proportional hazards regression model with treatment (all canagliflozin and placebo) as the explanatory variables, and study (CANVAS and CANVAS-R) and prior CV disease subgroup (secondary and primary prevention) as the stratification factors. This base model can be expressed as follows.

$$\lambda(t) = \lambda_{0j}(t) \exp(\beta X)$$

where λ is the hazard function, λ_{0j} is the baseline hazard which is assumed to be heterogeneous for CANVAS (j=1) and CANVAS-R (j=2), and X is the indicator for the treatment of canagliflozin. With the linkage of HR = exp(β), the hypothesis in (*) can be translated in terms of the model parameter as below.

$$H_0: \beta \geq 0.0, \text{ versus } H_1: \beta < 0.0$$

The above hypothesis testing is considered final if there is no significant treatment-by-study qualitative interaction which will be evaluated by the Gail & Simon test as described below.

For each study, a proportional hazard model with term for treatment will be fit. Assuming the normality of the treatment estimate $\hat{\beta}_i \sim N(\log(\theta_i), V_i)$, i=1,2, (that is valid in large samples as in CANVAS and CANVAS-R studies), where $V_i = \{I(\hat{\beta}_i)\}^{-1}$ is the inverse of the observed Fisher's observed information, the null hypothesis of no treatment-by-study qualitative interaction can be rejected in the Gail & Simon test if

$$\min\{Q^+, Q^-\} > c$$

where

$$Q^+ = \frac{\hat{\beta}_1^2}{V_1} I\{\hat{\beta}_1 > 0\} + \frac{\hat{\beta}_0^2}{V_0} I\{\hat{\beta}_0 > 0\} \text{ and } Q^- = \frac{\hat{\beta}_1^2}{V_1} I\{\hat{\beta}_1 < 0\} + \frac{\hat{\beta}_0^2}{V_0} I\{\hat{\beta}_0 < 0\}$$

with c=2.71 for type I error rate of 0.05.

If there is no significant treatment-by-study interaction, the HR estimate and the CI will be derived from the base model.

For reference, p-value of stratified log rank test for treatment effect will also be provided.

An alternative overall treatment estimate using the estimates from each study will also be reported. The estimator is the minimum variance linear combination of estimators $\hat{\beta}_1$ and $\hat{\beta}_2$ as shown below:

$$\hat{\beta} = \frac{V_2}{V_1 + V_2}\hat{\beta}_1 + \frac{V_1}{V_1 + V_2}\hat{\beta}_2 .$$

4.2.2. Supportive Analyses

4.2.2.1. Full Analysis without Data Truncation

The analysis of the 2 secondary mortality endpoints (described in Section 4.2.1) will also be conducted using the ITT analysis set (ie, without data truncation) where all subjects at risk in CANVAS and CANVAS-R are included.

4.2.2.2. Proportional Hazard Assumption

The plot of the log of cumulative hazard function by treatment over time will be made and the assumption of proportional hazards will be assessed. In addition, a treatment by logarithm-transformed time interaction term will be added into the base model for the main analysis (refer to Section 4.2.1) and tested. A p-value greater than 0.05 for the interaction term will be interpreted as no statistical evidence against the proportional hazard assumption. If the p-value is 0.05 or less and the assumption is not justified, then the p-value of the stratified log rank test will be referred.

4.2.2.3. Single Imputation for Missing Data

Every effort will be made to ascertain vital status for subjects who discontinued from full scheduled follow-up prior to the announcement of the GTED. To assess the impacts of missing follow-up data, a worst case scenario analysis will be conducted. Among subjects with unknown vital status at the study completion, those on canagliflozin will be assumed to experience mortality on the date of censoring while the placebo subjects remain censored. The stratified Cox proportional hazards model (described in Section 4.2.1) will be applied to the Truncated analysis set with the single imputation pertaining only to the canagliflozin subjects with unknown vital status. The derived HRs and CIs will be compared with the estimates from the main analysis.

4.2.2.4. Subgroup Analysis

The subgroup analysis for MACE will also be conducted for the 2 mortality endpoints using the Truncated and the ITT analysis sets. The same subgroup factors as well as analysis method described in Section 4.1.2.6 will be followed.

4.2.2.5. Consistency Analysis

The following exploratory analyses will be conducted to examine if there are components of the data that appear inconsistent:

- Hazard ratio in each of the 3 treatment regimens (CANVAS: 100 mg QD, 300 mg QD; CANVAS-R: 100 mg QD with investigator option to increase to 300 mg QD);
- Hazard ratio in the 3 separate components of the data (CANVAS prior to 20 November, 2012, CANVAS post 20 November, 2012, and CANVAS-R);
- Hazard ratio in the truncated dataset after exclusion of all subjects who had a non-fatal MACE event prior to 20 November 2012.

Forest plots will be generated to present the HRs and the CIs in these analyses.

4.3. Multiplicity Adjustment

Please refer to Section 1.4.1 for multiplicity adjustment.

4.4. Additional Endpoints

Additional endpoints are the first occurrence of the following events:

- All-cause hospitalization;

- Adjudicated hospitalization for heart failure;
- Composite of adjudicated hospitalization for heart failure or CV death.

These analyses will be done on the ITT analysis set (without truncation). The time to these CV endpoints will be analyzed using a stratified Cox proportional hazards model with treatment as the explanatory variable, and study (CANVAS and CANVAS-R) and prior CV disease subgroup (secondary prevention and primary prevention) as the stratification factors. The HRs of canagliflozin to placebo and their 95% CIs will be estimated from the model.

5. RENAL ENDPOINTS

The integrated analysis of the renal endpoints are exploratory in nature. The analysis will be based on the ITT analysis set.

5.1. Endpoints Definition

The renal endpoints of interest are:

- Progression of albuminuria;
- Regression of albuminuria;
- Renal composites:
  - 40% decrease in eGFR, renal death, or requirement for renal replacement therapy;
  - 40% decrease in eGFR, renal death, requirement for renal replacement therapy or CV death;
  - 40% decrease in eGFR, conversion to macroalbuminuria, renal death, or requirement for renal replacement therapy;
  - doubling of serum creatinine (SCr), renal death, or requirement for renal replacement therapy;
  - doubling of SCr, renal death, requirement for renal replacement therapy or CV death;
  - doubling of SCr, conversion to macroalbuminuria, renal death, or requirement for renal replacement therapy.

Urinary ACR is used to assess albuminuria. Subjects will be classified as having normoalbuminuria (ACR <30 mg/g), microalbuminuria (ACR ≥30 mg/g and ≤300 mg/g), or macroalbuminuria (ACR of >300 mg/g).

Albuminuria progression is the development of microalbuminuria or macroalbuminuria in a subject with baseline normoalbuminuria or the development of macroalbuminuria in a subject with baseline microalbuminuria, accompanied by an ACR value increase of greater than or equal to 30% from baseline.

Albuminuria regression is the development of normoalbuminuria in a subject with baseline microalbuminuria or macroalbuminuria or the development of microalbuminuria in a subject with baseline macroalbuminuria, accompanied by a decrease in the urinary ACR value of greater than or equal to 30% from baseline.

The onset of events of albuminuria progression/regression are based on the ACR measurements quantified by a central laboratory. The date of the progression/regression event will be defined as the visit date of the first urine sample for the potential progression/regression findings.

The components of the renal composite endpoints, such as requirement for renal replacement therapy and doubling of SCr, identified by the investigators or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent EAC.

5.2. Analysis Methods

Progression of Albuminuria

The analysis will be based on the ITT analysis set. Only subjects with baseline and at least one post-baseline ACR measures will be included in the analysis. Subjects with macroalbuminuria at baseline (ACR >300 mg/g) will also be excluded from the analysis.

At each visit, the geometric mean of the duplicate measurements (when available) will be computed and used for all subsequent analysis unless otherwise specified. For ACR values below the lower quantifiable limit, the lower quantifiable limit itself will be used in the geometric mean calculation.

The HR estimate and the CI will be derived from a stratified Cox proportional hazards model with treatment and baseline albuminuria status as the explanatory variables and study as the stratification factor.

Regression of Albuminuria

Regression of albuminuria will be analyzed in a similar fashion as progression of albuminuria based on the ITT analysis set. Only subjects with baseline and at least one post-baseline ACR measures will be included in the analysis. Subjects with normal albuminuria at baseline will be excluded. The HR estimate and the CI will be derived from a stratified Cox proportional hazards model with treatment and baseline albuminuria status as the explanatory variables and study as the stratification factor.

Renal composite endpoints

The time to each of the renal composite endpoints will be analyzed using a stratified Cox proportional hazards model with treatment as the explanatory variable, and stage of baseline chronic kidney disease, measured by eGFR (< 60, ≥ 60 mL/min/1.73m^2) and study as the stratification factors. The HR of canagliflozin to placebo and its 95% confidence interval, will be derived from the model.

6. SAFETY

This section describes the integration of the safety data collected in CANVAS and CANVAS-R, and the analysis methods. The main summary will be based on the On-Treatment analysis set unless otherwise specified.

Treatment groups will be canagliflozin combined doses and placebo such that the canagliflozin 100 mg and 300 mg groups in CANVAS will be pooled with the canagliflozin group in CANVAS-R. The safety for the 100 mg and the 300 mg doses will be presented in the clinical study report of CANVAS separately.

6.1. Adjudicated MACE event

Please refer to Section 4.1 for the analysis of adjudicated MACE events.

6.2. Adverse Events

Adverse events (AEs) will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock.

A treatment-emergent adverse event (TEAE) is defined as an AE with an onset after the initiation of double-blind study medication and before the last study medication date plus 30 days. Adverse events with a start date prior to initiation of double-blind study medication which are reported to have an increase in intensity, or AEs reported to have an attribution in relationship to study medication (ie, attribution to possible, probably, very likely) after the initiation of double-blind study medication will also be considered as TEAEs. Most of the AE analysis will pertain to the TEAEs.

6.2.1. Collection of Adverse Events

CANVAS-R was started after the approval of canagliflozin. Since the safety profile of canagliflozin had been well established in the Phase 3 program, the AE collection in CANVAS-R was streamlined to include:

- serious AEs;
- AEs that resulted in study drug discontinuation;
- all AEs (serious and non-serious) for selected AEs of interest (refer Table 3 below).

After the approval of protocol amendment INT-6, the AE data collection in CANVAS was also streamlined in the same fashion as CANVAS-R.

For selected AEs of interest, additional data was collected on supplementary eCRF pages mainly for the purposes of narrative description of certain events. Table 3 lists the AEs of interest.

Table 3: Adverse Events of Interest

Section A. All AEs (serious and non-serious) listed below are collected in CANVAS through INT-6. After INT-6, only the AEs that were serious or that led to study drug discontinuation are collected. In CANVAS-R , only serious AEs or AEs that led to drug discontinuation are collected: Osmotic diuresis Volume depletion Hypoglycemia Urinary tract infection (UTI) Female mycotic genital infection Severe hypersensitivity /cutaneous reactions Pancreatitis Hepatic injury Renal related AEs (including Nephrotoxicity/ acute kidney injury)
Section B. The AEs listed below are collected regardless of whether they are serious and/or lead to study drug discontinuation: Male mycotic genital infection (balanitis, phimosis, events leading to circumcision) Malignancy Renal cell cancer Bladder cancer Pheochromocytoma Leydig cell tumors Breast cancer Photosensitivity Venous thromboembolic events (VTE) Amputation Fracture Diabetic ketoacidosis

The AEs listed above will be identified using a MedDRA preferred term list (see Appendix 6).

6.2.2. Analysis Methods

The study durations of CANVAS and CANVAS-R are long relative to the rest of the canagliflozin Phase 3 program. Accordingly, the incidences of AEs (ie, proportion of subjects reporting the AEs) derived from these 2 studies are not comparable to the incidences generated in the Phase 3 program. To adjust for duration of exposure, the exposure-adjusted incidence rate will be reported in addition to the incidence. The rate is calculated as the total number of subjects with the AE divided by the on-treatment exposure in subject-years. For some particular AEs such as malignancy where the off-drug follow up is included, the follow-up-adjusted incidence rate will be estimated. The rate is calculated as the total number of subjects with the AEs divided by the follow-up time in subject-years.

For the general AEs and selected AEs of interest that are not routinely collected in CANVAS-R and CANVAS post INT-6 (refer Section A of Table 3), the main interest in the integrated summary will be the serious AEs and the AEs leading to discontinuation of study medication.

Groupings of MedDRA preferred terms used to identify events to be included in each category of AEs of interest are presented in Appendix 6.

6.2.2.1. General Adverse Events

The analysis will be based on the TEAEs in the On-Treatment analysis set. An overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- Serious AEs
- Deaths
- AEs leading to discontinuation of study medication
- Serious AEs leading to discontinuation of study medication
- Serious AEs considered drug-related
- AEs considered drug-related leading to discontinuation of study medication

SAEs by system organ class and preferred term will be summarized by treatment group using the On-Treatment analysis set. The same summary will be provided for AEs leading to discontinuation of study medication using the On-Treatment analysis set.

The incidence of all SAEs (by preferred term, grouped by SOC, and presented by treatment group) will also be summarized by the relationship to study drug, by the action taken regarding the study drug, as well as by the outcome. The relationship to study drug will be presented by 2 categories: related (which includes possibly related, probably related and very likely related, as reported by the investigator) and not related (which includes not related and doubtfully related, as reported by the investigator).

For reference, as a screening tool, the 95% CIs for incidence difference between treatment groups will be provided for the AEs (regardless of seriousness) which are reported in at least 4 or more subjects in any treatment group. Four (rule-of-4) was chosen based on the recommendation from the Safety, Planning, Evaluation, and Reporting Team (SPERT). The exclusion of "0" from the 95% CI for the between-group the treatment difference in incidence for a particular AE does not necessarily imply that the higher incidence is due to the drug. The intent of providing the 95% CIs is as a filter to identify AEs that require additional assessment. AEs are identified by the above screening procedure will be subject to further evaluation.

For AEs of special interest in Section A of Table 3, a summary similar to the analysis of general AEs will be provided. The AEs will be identified using the MedDRA PTs listed in Appendix 6.

6.2.2.2. Male Mycotic Genital Infections

Balanitis and phimosis AEs will be identified using the MedDRA PTs listed in Appendix 6.

An overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- All AEs
- Serious AEs
- AEs considered drug-related (investigator assessment of possible, probable or very likely)

- AEs leading to discontinuation of study medication
- Serious AEs leading to discontinuation of study medication
- Serious AEs considered drug-related
- AEs considered drug-related leading to discontinuation of study medication

AEs by preferred term will be summarized by treatment group. A Kaplan-Meier plot for the time to first occurrence of balanitis will be provided by treatment group.

In addition, circumcision events will be identified by searching the AE, the Diagnostic or Therapeutic Procedure eCRF pages and the sponsor's pharmacovigilance database. A table will summarize the incidence and the exposure-adjusted incidence rate of TEAEs by treatment.

6.2.2.3. Selected Malignancies

The selected malignancies of interest are renal cell cancer, bladder cancer, testicular cancer (Leydig cell tumors), pheochromocytomas, and breast cancer. Selected malignancy AEs will be identified using the MedDRA PTs listed in Appendix 6, and the analyses will be based on the ITT analysis set. For each selected malignancy of interest, an overview summary table with the incidence and the follow-up-adjusted incidence will be provided for:

- All AEs
- Serious AEs
- AEs considered drug-related (investigator assessment of possible, probable or very likely)
- AEs leading to discontinuation of study medication
- Serious AEs leading to discontinuation of study medication
- Serious AEs considered drug-related
- AEs considered drug-related leading to discontinuation of study medication

The preferred terms associated with each selected malignancy type will be summarized by treatment.

6.2.2.4. Photosensitivity

Photosensitivity AEs will be identified using the MedDRA PTs listed in Appendix 6. The integrated summary will be based on the related AEs reported in the regular AE eCRF page.

An overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- All AEs
- Serious AEs
- AEs considered drug-related (investigator assessment of possible, probable or very likely)
- AEs leading to discontinuation of study medication

- Serious AEs leading to discontinuation of study medication
- Serious AEs considered drug-related
- AEs considered drug-related leading to discontinuation of study medication

AEs by preferred term will be summarized by treatment group.

6.2.2.5. Venous Thromboembolic Events

Venous thromboembolic events will be identified using the MedDRA PTs listed in Appendix 6. The integrated summary will be based on the related AEs reported in the regular AE eCRF page.

An overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- All AEs
- Serious AEs
- AEs considered drug-related (investigator assessment of possible, probable or very likely)
- AEs leading to discontinuation of study medication
- Serious AEs leading to discontinuation of study medication
- Serious AEs considered drug-related
- AEs considered drug-related leading to discontinuation of study medication

AEs by preferred term will be summarized by treatment group.

6.2.2.6. Fracture

Fracture events identified by the investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent Fracture Adjudication Committee to confirm that events were fractures, to determine fracture location (anatomic region) and type (low trauma or not). The main analysis will be based on the adjudicated low trauma fracture and the ITT analysis set.

An overview summary table with the incidence and the follow-up-adjusted incidence will be provided for:

- Adjudicated fractures;
- Adjudicated fractures considered serious (investigator assessment);
- Adjudicated fractures considered drug-related (investigator assessment of possible, probable or very likely);
- Adjudicated fractures leading to discontinuation of study medication;
- Adjudicated fractures considered serious and drug-related (investigator assessment);
- Adjudicated fractures considered drug-related (investigator assessment) and leading to discontinuation of study medication

A summary of adjudicated fracture stratified by sex (male and female), and anatomical region by treatment will be provided. The incidence as well as the incidence rate will be presented.

A Kaplan-Meier plot for the time to first occurrence of adjudicated fracture event will be provided by treatment group. The HR and the 95% confidence interval will be derived from a stratified Cox proportion hazards model with treatment as the explanatory variable and study as the stratification factor. The HR estimates will also be evaluated in subgroups based on sex, baseline age (<65 and ≥65 years), duration of T2DM (<10 and ≥10 years), baseline eGFR (<60 and ≥60 mL/min/1.73 m^2), and prior fracture history (yes or no).

A summary of all adjudicated fractures by anatomic location will be provided. The HR and its 95% CI as well as a Kaplan-Meier plot for the first occurrence of all adjudicated fracture will be provided using the same analysis as the low trauma fracture.

6.2.2.7. Amputation

To standardize data collection on lower extremity amputation procedures any such event identified on the AE, or Diagnostic or Therapeutic Procedure case report form pages or in the sponsor's pharmacovigilance database were to be entered on a dedicated amputation case report form page.

The main analysis of lower extremity amputations as documented in the dedicated case report form page will be based on the ITT analysis set. An overview summary table with the incidence and the follow-up-adjusted incidence will be provided for:

- All lower limb amputations;
- Traumatic lower limb amputation;
- Atraumatic lower limb amputation.

Summary of anatomical region (toe, ankle, foot, below knee, above knee, other) of lower extremity atraumatic amputations will be reported by treatment group.

For atraumatic lower limb amputation, a Kaplan-Meier plot for the time to first occurrence of event will be provided by treatment group. The association of amputation with treatment and the baseline risk factors listed in Table 4 will be assessed via logistic regression modeling. The relationship between amputation and some post-treatment factors such as volume depletion will also be explored.

For the post-treatment AEs that may be associated with amputation, groupings of selected MedDRA preferred terms used to identify events to be included in each of the following SOC categories are presented in Appendix 7:

- Infections and Infestations;
- Vascular disorders;
- Nervous System disorders;

- Skin and subcutaneous tissue disorders.

The selected PTs in infections and infestation are further split into "Reversible Infection" and "Irreversible Infections". In addition, the preferred terms grouped under the MedDRA high level term of "skin and subcutaneous tissue ulcerations" are also of interest.

For each AE group listed above, the incidence of the respective PTs will be summarized by treatment. Stratified by treatment, the odds ratio of amputation and each AE group listed above will be estimated.

Table 4: Baseline Factors Included in the Logistic Regression Analysis

Baseline Categorical Factors	
• Gender	• Smoking
• Cardiovascular disease history	• Use of insulin
• Peripheral vascular disease history [a]	• Baseline Systolic Blood Pressure
• Amputation history	○ > 120 vs ≤120 mmHg
• Neuropathy history	○ > 140 vs ≤140 mmHg
• Retinopathy history	• Baseline eGFR (ml/min/1.73m^2)
• Nephropathy history	○ < 60 vs ≥60
• Any diuretic use	○ < 45 vs ≥45
• Loop diuretic use	• Diabetes duration (< 10 vs ≥10 yrs.)
• Non-loop diuretic use	• Baseline HbA_{1c} (> 8 vs ≤8%)
Baseline Continuous Factors	
• Age (yrs.)	• eGFR (mL/min/1.73m^2)
• Diabetes duration (yrs.)	• HbA_{1c} (%)
• Systolic blood pressure (mmHg)	• Hemoglobin (g/L)

[a] Excludes amputation history

Mortality as a Competing Risk

As mortality can hinder the observation of amputation, the lower extremity atraumatic amputation risk with and without the adjustment of the competing risk of mortality will be assessed. Without considering mortality, the cumulative incidence function can be estimated by a naïve Kaplan-Meier estimate using the time to amputation data. To account for the competing risk of mortality, the amputation-specific cumulative incidence will be estimated as follows.

$$\sum_{i:t_{(i)}\le t} \left(\frac{d_{A\,i}}{n_i}\right) \hat{S}_{A,M}\left(t_{(i)}\right)$$

where $d_{A\,i}$ is the number of amputation cases at the i-th event time among n_i subjects still at risk of either amputation or mortality, and $\hat{S}_{A,M}$ is the Kaplan-Meier estimate of the probability of free from both amputation and mortality.

The estimates will be provided by treatment. The estimated amputation-specific cumulative incidence will be plotted along with the naïve Kaplan-Meier estimates. The difference in the estimates of survival probability will be evaluated by treatment.

6.2.2.8. Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) and related AEs will be identified using the list of MedDRA terms in Appendix 6. Adverse events identified by investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent Endpoint Adjudication Committee. The main analysis of the DKA events will be based on adjudicated events of DKA in the ITT analysis set. Events occurring at any time post-randomization, regardless of the timing of the last dose of study medication, will be included.

For the adjudicated DKA events, the incidence and the follow-up-adjusted incidence rate will be summarized.

A listing of all DKA events identified by the sponsor's medical monitoring team and the subset of these event that went for adjudication will be provided.

6.3. Clinical Laboratory Tests

The percentage of subjects with specific treatment-emergent laboratory values meeting pre-defined limit of change (PDLC) criteria listed in Appendix 8 will be summarized. The 95% CI for the percentage difference between canagliflozin compared to placebo group will be provided for each PDLC criterion which have at least 4 or more subjects in any treatment group; a corresponding listing will also be provided. As described above, PDLC values will be presented based on measurements on study drug and up to a maximum of 2 days after the last dose of study drug, as well as all measurements regardless of the time of the last dose of double-blind study drug. Summaries based on both standard units (SI) and conventional units will be provided.

6.4. Vital Signs

A treatment-emergent vital sign abnormality is defined as a change from baseline and subsequent post-baseline value that satisfies the criteria listed in the PDLC list (Appendix 8). For each vital sign parameter, the proportion of subjects with a treatment-emergent abnormality will be tabulated by treatment group. PDLC values will be presented based on measurements up to a maximum of 2 days after the last dose of study drug. The blood pressure measurements will be based on the average of the consecutive sitting blood pressure readings that were to be collected at each visit.

REFERENCES

1. Peto R et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. *Int. Br. J. Cancer.* 1976; 34:585-612.

2. Little R et al. The treatment of missing data in a large cardiovascular clinical outcomes study. Clin Trials. 2016;13(3):344-351.

APPENDIX 1: Summary of Operational Specifics and Key Inclusion/Exclusion Criteria

	CANVAS	CANVAS-R
N	4330	5812
Duration	Dec 2009 to 1Q2017	Jan 2014 to 1Q2017
Primary objective	MACE events	Progression of albuminuria
Key secondary objectives	Progression of albuminuria, GFR changes	MACE events, regression of albuminuria, GFR changes
Endpoint adjudication	All deaths, nonfatal MI and MI-like events, nonfatal stroke and stroke-like events, hospitalization for heart failure, VTE (only in CANVAS), fractures	
AE collection	SAEs, AEs that result in study drug discontinuation, AEs of interest	
Key inclusion criteria	Diagnosis of T2DM with HbA_{1c} level ≥7.0% to ≤10.5% at screening	
	Not currently on AHA therapy or on AHA monotherapy or combination therapy with any approved agent (except SGLT2i) (stable regimen for ≥8 weeks prior in CANVAS, due to substudies)	
	History or high risk of CV events defined on the basis of either: Age ≥30 years with documented symptomatic atherosclerotic CV disease: including stroke; MI; hospital admission for unstable angina; coronary artery bypass graft; percutaneous coronary intervention (with or without stenting); peripheral revascularization (angioplasty or surgery); symptomatic with documented hemodynamically-significant carotid or peripheral vascular disease; or amputation secondary to vascular disease Age ≥50 years with 2 or more of the following risk factors determined at the screening visit: duration of T2DM of 10 years or more, systolic blood pressure >140 mmHg (average of 3 readings) recorded at the Screening Visit, while the subject is on at least one blood pressure-lowering treatment, current daily cigarette smoker, documented micro- or macroalbuminuria, or documented HDL-C of <1 mmol/L (<39 mg/dL).	
Key exclusion criteria	History of diabetic ketoacidosis, T1DM, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy	
	Fasting fingerstick glucose at home or at investigational site >270 mg/dL (>15 mmol/L) at Baseline/Day 1 *For patients on a sulfonylurea agent or on insulin*: fasting fingerstick glucose at home or at investigational site <110 mg/dL (<6 mmol/L) at Baseline/Day 1	
	History of one or more severe hypoglycemic episode within 6 months before screening	
	Myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident within 3 months before screening, or a planned revascularization procedure, or history of New York Heart Association (NYHA) Class IV cardiac disease	
	History of hepatitis B surface antigen or hepatitis C antibody positive, or other clinically active liver disease	
	ALT levels >2.0 times the ULN or total bilirubin >1.5 times the ULN at screening	
	Any history of or planned bariatric surgery.	
	Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 at screening (provided by the central laboratory). *For subjects taking metformin*: at screening, serum creatinine ≥1.4 mg/dL (124 μmol/L) for men or ≥1.3 mg/dL (115 μmol/L) for women; no contraindication to the use of metformin (including eGFR) based on the label of the country of investigational site.	eGFR <30 mL/min/1.73m^2 at screening visit (provided by the central laboratory).

APPENDIX 2: Expanded List of the Eligibility Criteria

Note: Differences between the 2 studies are underlined.

	CANVAS	CANVAS-R
	Inclusion criteria at screening visit	**Inclusion criteria at screening visit**
Incl-1	Man or woman with a diagnosis of T2DM with HbA_{1c} level ≥7.0% to ≤10.5% at screening and be either (1) not currently on AHA therapy or (2) on AHA monotherapy or combination therapy with any approved agent: eg, sulfonylurea, metformin, pioglitazone, alpha-glucosidase inhibitor, GLP-1 analogue, DPP-4 inhibitor, or insulin.	Man or woman with a diagnosis of T2DM with HbA_{1c} level ≥7.0% to ≤10.5% at screening and be either (1) not currently on AHA therapy or (2) on AHA monotherapy or combination therapy with any approved agent: eg, sulfonylurea, metformin, pioglitazone, alpha-glucosidase inhibitor, GLP-1 analogue, DPP-4 inhibitor, or insulin.
Incl-2	History or high risk of CV events defined on the basis of either: Age ≥30 years with documented symptomatic atherosclerotic CV disease: including stroke; MI; hospital admission for unstable angina; coronary artery bypass graft; percutaneous coronary intervention (with or without stenting); peripheral revascularization (angioplasty or surgery); symptomatic with documented hemodynamically-significant carotid or peripheral vascular disease; or amputation secondary to vascular disease Age ≥50 years with 2 or more of the following risk factors determined at the screening visit: duration of T2DM of 10 years or more, systolic blood pressure >140 mmHg (average of 3 readings) recorded at the Screening Visit, while the subject is on at least one blood pressure-lowering treatment, current daily cigarette smoker, documented micro- or macroalbuminuria, or documented HDL-C of <1 mmol/L (<39 mg/dL).	History or high risk of CV events defined on the basis of either: Age ≥30 years with documented symptomatic atherosclerotic CV events: including stroke; MI; hospital admission for unstable angina; coronary artery bypass graft; percutaneous coronary intervention (with or without stenting); peripheral revascularization (angioplasty or surgery); symptomatic with documented hemodynamically-significant carotid or peripheral vascular disease; or amputation secondary to vascular disease. Age ≥50 years with 2 or more of the following risk factors determined at the screening visit: duration of T2DM of 10 years or more, systolic blood pressure >140 mmHg (average of 3 readings) recorded at the Screening Visit, while the subject is on at least one blood pressure-lowering treatment, current daily cigarette smoker, documented micro- or macroalbuminuria <u>within one year of screening</u>, or documented HDL-C of <1 mmol/L (<39 mg/dL) <u>within one year of screening</u>.

	CANVAS	CANVAS-R
Incl-3	Women must be: postmenopausal, defined as >45 years of age with amenorrhea for at least 18 months, or >45 years of age with amenorrhea for at least 6 months and less than 18 months and a serum follicle stimulating hormone (FSH) level >40 IU/L, or surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal ligation), or otherwise be incapable of pregnancy, or heterosexually active *and* practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (eg, condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), or male partner sterilization, consistent with local regulations regarding use of birth control methods for subjects participating in clinical trials, for the duration of their participation in the study, or not heterosexually active.	Women must be: postmenopausal, defined as: >45 years of age with amenorrhea for at least 18 months, or >45 years of age with amenorrhea for at least 6 months and less than 18 months and a known serum follicle stimulating hormone (FSH) level >40 IU/L, or surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal <u>occlusion</u>), or otherwise be incapable of pregnancy, or heterosexually active *and* practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (eg, condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), or male partner sterilization, consistent with local regulations regarding use of birth control methods for subjects participating in clinical trials, for the duration of their participation in the study, or not heterosexually active.
Incl-4	Subjects who are not heterosexually active at screening must agree to utilize a highly effective method of birth control if they become heterosexually active during their participation in the study. Women of childbearing potential must have a negative urine β-human chorionic gonadotropin (β-hCG) pregnancy test at screening and baseline (predose, Day 1).	Women of childbearing potential (ie, those subjects who do not meet the postmenopausal definition above, regardless of age) must have a negative urine pregnancy test at baseline (Day 1) and at screening if required by local regulations (Note: a serum pregnancy test is acceptable in lieu of a urine pregnancy test if required by local regulations)
Incl-5	Willing and able to adhere to the prohibitions and restrictions specified in this protocol.	Willing and able to adhere to the prohibitions and restrictions specified in this protocol.
Incl-6	Subjects must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study. <u>To participate in the optional pharmacogenomic component of this study, subjects must have signed the informed consent form for pharmacogenomic research indicating willingness to participate in the pharmacogenomic component of the study (where local regulations permit). Refusal to give consent for this component does not exclude a subject from participation in the clinical study.</u>	Subjects must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study. <u>*[There are no pharmacogenomic collections in CANVAS-R]*</u>
Incl-7	**Inclusion criteria at randomization** Subjects must have taken ≥80% of their single-blind placebo capsules during the 2-week run-in period at Day 1 to be eligible for randomization.	**Inclusion criteria at randomization** Subjects must have taken ≥80% of their single-blind placebo doses during the 2-weeks prior to randomization on Day 1 to be eligible for randomization.

	CANVAS	CANVAS-R
Excl-1	**Diabetes-Related/Metabolic** History of diabetic ketoacidosis, T1DM, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy On an AHA and not on a stable regimen (ie, agents and doses) for at least 8 weeks before the screening visit and through the screening/run-in period. **Note**: a stable dose of insulin is defined as no change in the insulin regimen (ie, type[s] of insulin) and ≤15% change in the total daily dose of insulin (averaged over 1 week to account for day to day variability). Fasting fingerstick glucose at home or at investigational site >270 mg/dL (>15 mmol/L) at Baseline/Day 1 *For patients on a sulfonylurea agent or on insulin*: fasting fingerstick glucose at home or at investigational site <110 mg/dL (<6 mmol/L) at Baseline/Day 1 **Note**: at the investigator's discretion, based upon an assessment of recent SMBG values, subjects meeting either of these fingerstick glucose exclusion criteria may continue the single-blind placebo and return to the investigational site within 14 days and may be randomized if the repeat fasting fingerstick value no longer meets the exclusion criterion. Subjects with fingerstick glucose >270 mg/dL (>15 mmol/L) may have their AHA regimen adjusted, and be rescreened once on a stable regimen for at least 8 weeks.	**Diabetes-Related/Metabolic** History of diabetic ketoacidosis, T1DM, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy. *[There are no substudies in CANVAS-R that required a stable prestudy dose of AHA].*
Excl-2	History of one or more severe hypoglycemic episode within 6 months before screening. Note: a severe hypoglycemic episode is defined as an event that requires the help of another person.	History of one or more severe hypoglycemic episode within 6 months before screening. Note**:** a severe hypoglycemic episode is defined as an event that requires the help of another person.
Excl-3	History of hereditary glucose-galactose malabsorption or primary renal glucosuria.	History of hereditary glucose-galactose malabsorption or primary renal glucosuria.
Excl-4	Ongoing, inadequately controlled thyroid disorder. Note: subjects on thyroid hormone replacement therapy must be on a stable dose for at least 6 weeks before Day 1.	Ongoing, inadequately controlled thyroid disorder. Note: subjects on thyroid hormone replacement therapy must be on a stable dose for at least 6 weeks before Day 1.
Excl-5	**Renal/Cardiovascular** Renal disease that required treatment with immunosuppressive therapy or a history of chronic dialysis or renal transplant. **Note**: subjects with a history of treated childhood renal disease, without sequelae, may participate.	**Renal/Cardiovascular** Renal disease that required treatment with immunosuppressive therapy or a history of chronic dialysis or renal transplant. Note: subjects with a history of treated childhood renal disease, without sequelae, may participate.

	CANVAS	CANVAS-R
Excl-6	Myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident within 3 months before screening, or a planned revascularization procedure, or history of New York Heart Association (NYHA) Class IV cardiac disease; refer to Attachment 3, New York Heart Association Classification of Cardiac Disease, for a description of the classes	Myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident within 3 months before screening, or a planned revascularization procedure, or history of New York Heart Association (NYHA) Class IV cardiac disease (The Criteria Committee of the New York Heart Association).
Excl-7	Findings on 12-lead ECG that would require urgent diagnostic evaluation or intervention (eg, new clinically important arrhythmia or conduction disturbance).	Known ECG findings within 3 months before screening that would require urgent diagnostic evaluation or intervention (eg, new clinically important arrhythmia or conduction disturbance).
Excl-8	**Gastrointestinal** History of hepatitis B surface antigen or hepatitis C antibody positive (unless associated with documented persistently stable/normal range aspartate aminotransferase [AST] and ALT levels), or other clinically active liver disease	**Gastrointestinal** Known history of hepatitis B surface antigen or hepatitis C antibody positive (unless known to be associated with documented persistently stable/normal range aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels), or other clinically active liver disease.
Excl-9	Any history of or planned bariatric surgery.	Any history of or planned bariatric surgery.
Excl-10	**Laboratory** Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 at screening (provided by the central laboratory). *For subjects taking metformin*: at screening, serum creatinine ≥1.4 mg/dL (124 μmol/L) for men or ≥1.3 mg/dL (115 μmol/L) for women; no contraindication to the use of metformin (including eGFR) based on the label of the country of investigational site.	**Laboratory** eGFR <30 mL/min/1.73m^2 at screening visit (provided by the central laboratory).
Excl-11	ALT levels >2.0 times the ULN or total bilirubin >1.5 times the ULN at screening, unless in the opinion of the investigator and as agreed upon by the sponsor's medical officer, the findings are consistent with Gilbert's disease.	ALT levels >2.0 times the upper limit of normal (ULN) or total bilirubin >1.5 times the ULN, unless in the opinion of the investigator and as agreed upon by the sponsor's medical officer, the findings are consistent with Gilbert's disease.
Excl-12	**Other conditions** History of malignancy within 5 years before screening (exceptions: squamous and basal cell carcinomas of the skin and carcinoma of the cervix in situ, or a malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence).	**Other conditions** History of malignancy within 5 years before screening (exceptions: squamous and basal cell carcinomas of the skin and carcinoma of the cervix in situ, or a malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence).
Excl-13	History of human immunodeficiency virus (HIV) antibody positive.	History of human immunodeficiency virus (HIV) antibody positive.

	CANVAS	CANVAS-R
Excl-14	Subject has a current clinically important hematological disorder (eg, symptomatic anemia, proliferative bone marrow disorder, thrombocytopenia).	Subject has a current clinically important hematological disorder (eg, symptomatic anemia, proliferative bone marrow disorder, thrombocytopenia).
Excl-15	Investigator's assessment that the subject's life expectancy is less than 1 year, or any condition that in the opinion of the investigator would make participation not in the best interest of the subject, or could prevent, limit, or confound the protocol-specified safety or efficacy assessments.	Investigator's assessment that the subject's life expectancy is less than 1 year, or any condition that in the opinion of the investigator would make participation not in the best interest of the subject, or could prevent, limit, or confound the protocol-specified safety or efficacy assessments.
Excl-16	Major surgery (ie, requiring general anesthesia) within 3 months of the screening visit or any surgery planned during the subject's expected participation in the study (except minor surgery, ie, outpatient surgery under local anesthesia).	Major surgery (ie, requiring general anesthesia) within 3 months of the screening visit or any surgery planned during the subject's expected participation in the study (except minor surgery, ie, outpatient surgery under local anesthesia).
Excl-17	Any condition that, in the opinion of the investigator, would compromise the well-being of the subject or prevent the subject from meeting or performing study requirements.	Any condition that, in the opinion of the investigator, would compromise the well-being of the subject or prevent the subject from meeting or performing study requirements.
Excl-18	**Medications/Therapies** Current use of other SGLT2 inhibitor; use of rosiglitazone within 8 weeks of screening. (Note: subjects taking rosiglitazone who are already in screening are not eligible for randomization.).	**Medications/Therapies** Current or prior use of an SGLT2 inhibitor.
Excl-19	[*See #22 below*]	Prior or current participation in another canagliflozin study.
Excl-20	Known allergies, hypersensitivity, or intolerance to canagliflozin or its excipients.	Known allergies, hypersensitivity, or intolerance to canagliflozin or its excipients.
Excl-21	Current use of a corticosteroid medication or immunosuppressive agent, or likely to require treatment with a corticosteroid medication (for longer than 2 weeks in duration) or an immunosuppressive agent. Note: subjects using inhaled, intranasal, intra-articular, or topical corticosteroids, or corticosteroids in therapeutic replacement doses may participate.	Current use of a corticosteroid medication or immunosuppressive agent, or likely to require treatment with a corticosteroid medication (for longer than 2 weeks in duration) or an immunosuppressive agent. Note: subjects using inhaled, intranasal, intra-articular, or topical corticosteroids, or corticosteroids in therapeutic replacement doses may participate.
Excl-22	Received an active investigational drug (including vaccines) or used an investigational medical device within 3 months before Day 1/baseline or received at least one dose of canagliflozin in a prior study.	Received an active investigational drug (including vaccines) or used an investigational medical device within 3 months before Day 1/baseline.
Excl-23	**General** History of drug or alcohol abuse within 3 years before screening.	**General** History of drug or alcohol abuse within 3 years before screening.

	CANVAS	CANVAS-R
Excl-24	Pregnant or breast-feeding or planning to become pregnant or breast-feed during the study.	Pregnant or breast-feeding or planning to become pregnant or breast-feed during the study.
Excl-25	Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator.	Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator.

APPENDIX 3: Number of Randomized Subjects by Region, Country, and Study

Region	Country	CANVAS	CANVAS-R	Integrated
CENTRAL/SOUTH AMERICA	Argentina	160	305	465
	Brazil		549	549
	Columbia	7		7
	Region total	(167)	(854)	(1021)
EUROPE	Belgium	21	152	173
	Czech Republic	117	139	256
	Germany	175	101	276
	Spain	209	496	705
	Estonia	44		44
	France		124	124
	United Kingdom	92	151	243
	Hungary	125	179	304
	Italy		98	98
	Luxembourg	1		1
	Netherlands	228	249	477
	Norway	109		109
	Poland	144	363	507
	Sweden	71	220	291
	Region total	(1336)	(2272)	(3608)
NORTH AMERICA	Canada	396	282	678
	Mexico	124	228	352
	United State	727	673	1400
	Region total	(1247)	(1183)	(2430)
REST OF THE WORLD	Australia	177	109	286
	China		92	92
	India	695		695
	Israel	25		25
	South Korea		167	167
	Malaysia	73	92	165
	New Zealand	74	105	179
	Russia	389	412	801
	Taiwan		76	76
	Ukraine	147	449	596
	Region total	(1580)	(1502)	(3082)
STUDY TOTAL		4330	5811	10141

APPENDIX 4: List of Key Analysis for Primary and Secondary Endpoints

Analysis Set	Dataset	Endpoint	Purpose of Analysis (related section)	Role
Primary Hypothesis				
ITT	CANVAS + CANVAS-R	MACE	Demonstrate the exclusion of 1.3 in the HR of Cana to placebo (Section 4.1.1)	Main
ITT	CANVAS + CANVAS-R	MACE	Assess PH assumption (Section 4.1.2.1)	Supportive
ITT	CANVAS + CANVAS-R	MACE	Assess the impacts of missing data on the primary conclusion via multiple imputation method (Section 4.1.2.2)	Supportive
On-Treatment	CANVAS + CANVAS-R	MACE	Demonstrate the exclusion of 1.3 in the HR of Cana to placebo (Section 4.1.2.3)	Supportive
ITT	CANVAS + CANVAS-R	MACE component	Assess the consistency of the HR estimate for each component of MACE (Section 4.1.2.4)	Supportive
ITT	CANVAS + CANVAS-R	MACE	Assess the consistency of the HR estimate for selected participant subgroups including study (Section 4.1.2.5, 4.1.2.6)	Supportive
Secondary Hypotheses				
Truncated	Truncated CANVAS + CANVAS-R	All-cause mortality	Demonstrate the superiority of Cana to placebo in the reduction of all-cause mortality (Section 4.2.1)	Main
ITT	CANVAS + CANVAS-R	All-cause mortality	Demonstrate the superiority of Cana to placebo in the reduction of all-cause mortality (Section 4.2.2.1)	Supportive
Truncated	Truncated CANVAS + CANVAS-R	All-cause mortality	Assess PH assumption (Section 4.2.2.2)	Supportive

Analysis Set	Dataset	Endpoint	Purpose of Analysis (related section)	Role
Truncated	Truncated CANVAS + CANVAS-R	All-cause mortality	Assess the impacts of missing data on the superiority conclusion via single imputation method (Section 4.2.2.3)	Supportive
Secondary Hypotheses				
Truncated	Truncated CANVAS + CANVAS-R	CV mortality	Demonstrate the superiority of Cana to placebo in the reduction of all-cause mortality (Section 4.2.1)	Main
ITT	CANVAS + CANVAS-R	CV mortality	Demonstrate the superiority of Cana to placebo in the reduction of all-cause mortality (Section 4.2.2.1)	Supportive
Truncated	Truncated CANVAS + CANVAS-R	CV mortality	Assess PH assumption (Section 4.2.2.2)	Supportive
Truncated	Truncated CANVAS + CANVAS-R	CV mortality	Assess the impacts of missing data on the superiority conclusion via single imputation method (Section 4.2.2.3)	Supportive

APPENDIX 5: Confidence Interval for Risk Ratio Based on the Log Rank Method

Let K denote the number of distinct event time in the integrated database. At each event time, the following 2x2 table can be constructed.

	Status		
Treatment	Event	No Event	Total
Canagliflozin	d_{1k}	n_{1k}-d_{1k}	n_{1k}
Placebo	d_{2k}	n_{2k}-d_{2k}	n_{2k}
Total:	d_k	n_k- d_k	n_k

The log rank statistic can be computed with the layout below.

Ordered Distinct Event Time	Observed Number of Events	Expected Number of Events	Difference	Variance
$y_{(1)}$	d_{11}	$e_{11}= n_{11}d_1/n_1$	d_{11}-e_{11}	v_{11}
$y_{(2)}$	d_{12}	$e_{12}= n_{12}d_2/n_2$	d_{12}-e_{12}	v_{12}
…	…	…	…	…
$y_{(K)}$	d_{1K}	$e_{1K}= n_{1K}d_K/n_K$	d_{1K}-e_{1K}	v_{1K}
Total:	d_1	e_1	d_1-e_1	v_1

Note: $V_{1k} = n_{1k}\, n_{2k}\, d_k\, (n_k - d_k)/[n^2_k\, (n_k - 1)]$

where $d_1 = \sum_{k=1}^{K} d_{1k}$, $e_1 = \sum_{k=1}^{K} e_{1k}$ and $v_1 = \sum_{k=1}^{K} v_{1k}$.

Peto et al. (1976) suggested that the HR can be estimated as

$$\hat{\lambda} = \exp(\frac{d_1 - e_1}{v_1})$$

The (1-α) 100% confidence interval for λ can be obtained as

$$\exp\{[(d_1 - e_1)/v_1] \pm z_{1-\alpha/2}/\sqrt{v_1}\}$$

where $z_{1-\alpha/2}$ is the 1-α/2 percentile for the standard normal distribution.

APPENDIX 6: List of Preferred Terms for Adverse event of Interest

Diabetic ketoacidosis	Female Mycotic Genital Infections	Fracture
Acidosis	Genital candidiasis	Acetabulum fracture
Acidosis aggravated	Genital infection	Ankle fracture
Acidosis diabetic	Genital infection female	Atypical femur fracture
Acidosis metabolic	Genital infection fungal	Atypical fracture
Acidosis NOS	Urogenital infection fungal	Avulsion fracture
Acute acidosis	Vaginal infection	Bone fragmentation
Anion gap acidosis	Vaginal inflammation	Cervical vertebral fracture
Blood ketone body	Vulvitis	Chance fracture
Blood ketone body increased	Vulvovaginal candidiasis	Clavicle fracture
Blood ketone body present	Vulvovaginal mycotic infection	Closed fracture manipulation
Diabetes mellitus with ketoacidosis	Vulvovaginitis	Comminuted fracture
Diabetes with hyperosmolarity		Complicated fracture
Diabetes with ketoacidosis		Compression fracture
Diabetic acidosis		Craniofacial fracture
Diabetic hyperglycemic coma		Elevation skull fracture
Diabetic hyperosmolar coma		Epiphyseal fracture
Diabetic ketoacidosis		External fixation of fracture
Diabetic ketoacidotic hyperglycemic coma		Facial bones fracture
Diabetic metabolic decompensation		Femoral neck fracture
High anion gap metabolic acidosis		Femur fracture
Hyperglycemic seizure		Fibula fracture
Hyperosmolar hyperglycemic state		Foot fracture
Hyperosmolar state		Forearm fracture
Ketoacidosis		Fracture
Ketonuria		Fracture debridement
Ketosis		Fracture delayed union
Metabolic acidosis		Fracture displacement
Metabolic acidosis exacerbated		Fracture malunion
Metabolic acidosis NOS exacerbated		Fracture nonunion
Metabolic acidosis not otherwise specified (NOS)		Fracture pain
Metabolic acidosis worsened		Fracture reduction
Type I diabetes mellitus with ketoacidosis		Fracture treatment
Type II diabetes mellitus with ketoacidosis		Fractured coccyx
		Fractured ischium
		Fractured maxilla elevation
		Fractured sacrum
		Fractured skull depressed
		Fractured zygomatic arch elevation
		Greenstick fracture
		Hand fracture
		Hip fracture
		Humerus fracture
		Ilium fracture
		Impacted fracture
		Internal fixation of fracture
		Jaw fracture
		Limb crushing injury
		Limb fracture

Diabetic ketoacidosis	Female Mycotic Genital Infections	Fracture
		Loss of anatomical alignment after fracture reduction
		Lower limb fracture
		Lumbar vertebral fracture
		Multiple fractures
		Open fracture
		Open reduction of fracture
		Open reduction of spinal fracture
		Osteochondral fracture
		Osteoporotic fracture
		Patella fracture
		Pathological fracture
		Pelvic fracture
		Periprosthetic fracture
		Pubis fracture
		Radius fracture
		Rib fracture
		Sacroiliac fracture
		Scapula fracture
		Skull fracture
		Skull fractured base
		Spinal compression fracture
		Spinal fracture
		Spinal fusion fracture
		Sternal fracture
		Stress fracture
		Thoracic vertebral fracture
		Tibia fracture
		Torus fracture
		Traumatic fracture
		Ulna fracture
		Upper limb fracture
		Wrist fracture

Hepatic Injury	Hypoglycaemia	Male Mycotic Genital Infections
Acute graft versus host disease in liver	Hypoglycaemia	Balanitis
Acute hepatic failure	Hypoglycaemic coma	Balanitis candida
Acute yellow liver atrophy	Hypoglycaemic seizure	Balanoposthitis
Allergic hepatitis		Balanoposthitis infective
Ammonia increased		Erosive balanitis
Ascites		Gangrenous balanitis
Asterixis		Genital candidiasis
Autoimmune hepatitis		Genital infection
Bacterascites		Genital infection fungal
Biliary ascites		Genital infection male
Biliary cirrhosis		Penile infection
Biliary cirrhosis primary		Posthitis
Biliary fibrosis		
Bilirubin excretion disorder		
Biopsy liver abnormal		
Child-Pugh-Turcotte score increased		
Cholaemia		
Cholestasis		

Hepatic Injury	Hypoglycaemia	Male Mycotic Genital Infections
Cholestatic liver injury		
Cholestatic pruritus		
Chronic graft versus host disease in liver		
Chronic hepatic failure		
Chronic hepatitis		
Coma hepatic		
Cryptogenic cirrhosis		
Diabetic hepatopathy		
Drug-induced liver injury		
Duodenal varices		
Focal nodular hyperplasia		
Gallbladder varices		
Gastric varices		
Gastric varices haemorrhage		
Graft versus host disease in liver		
Haemangioma of liver		
Haemorrhagic ascites		
Haemorrhagic hepatic cyst		
Hepatectomy		
Hepatic adenoma		
Hepatic atrophy		
Hepatic calcification		
Hepatic cirrhosis		
Hepatic cyst		
Hepatic cyst ruptured		
Hepatic encelalopathy		
Hepatic encephalopathy prophylaxis		
Hepatic failure		
Hepatic fibrosis		
Hepatic fibrosis marker abnormal		
Hepatic haemangioma rupture		
Hepatic hydrothorax		
Hepatic infiltration eosinophilic		
Hepatic lesion		
Hepatic necrosis		
Hepatic steatosis		
Hepatitis		
Hepatitis acute		
Hepatitis cholestatic		
Hepatitis chronic active		
Hepatitis chronic persistent		
Hepatitis fulminant		
Hepatitis toxic		
Hepatobiliary disease		
Hepatocellular foamy cell syndrome		
Hepatocellular injury		
Hepatopulmonary syndrome		
Hepatorenal failure		
Hepatorenal syndrome		
Hepatotoxicity		
Hyperbilirubinaemia		
Icterus index increased		
Intestinal varices		
Ischaemic hepatitis		

Hepatic Injury	Hypoglycaemia	Male Mycotic Genital Infections
Jaundice		
Jaundice cholestatic		
Jaundice hepatocellular		
Liver and small intestine transplant		
Liver disorder		
Liver injury		
Lupoid hepatic cirrhosis		
Lupus hepatitis		
Mixed liver injury		
Nodular regenerative hyperplasia		
Non-alcoholic steatohepatitis		
Non-cirrhotic portal hypertension		
Ocular icterus		
Oedema due to hepatic disease		
Oesophageal varices haemorrhage		
Parenteral nutrition associated liver disease		
Peripancreatic varices		
Periportal oedema		
Portal hypertension		
Portal hypertensive enteropathy		
Portal hypertensive gastropathy		
Portal triaditis		
Portal vein cavernous transformation		
Portal vein dilatation		
Portopulmonary hypertension		
Radiation hepatitis		
Renal and liver transplant		
Retrograde portal vein flow		
Reye's syndrome		
Reynold's syndrome		
Splenic varices		
Splenic varices haemorrhage		
Subacute hepatic failure		
Varices oesophageal		
Varicose veins of abdominal wall		

Malignancy Bladder Cancer	Malignancy Breast Cancer	Malignancy Phaeochromocytoma
Bladder adenocarcinoma recurrent	Apocrine breast carcinoma	Phaeochromocytoma
Bladder adenocarcinoma stage 0	Breast angiosarcoma	Phaeochromocytoma crisis
Bladder adenocarcinoma stage I	Breast angiosarcoma metastatic	Phaeochromocytoma excision
Bladder adenocarcinoma stage II	Breast cancer	Phaeochromocytoma malignant
Bladder adenocarcinoma stage III	Breast cancer female	
Bladder adenocarcinoma stage IV	Breast cancer in situ	
Bladder adenocarcinoma stage unspecified	Breast cancer male	
Bladder cancer	Breast cancer metastatic	
Bladder cancer recurrent	Breast cancer recurrent	
Bladder cancer stage 0, with cancer in situ	Breast cancer stage I	
Bladder cancer stage 0, without cancer in situ	Breast cancer stage II	
Bladder cancer stage I, with cancer in situ	Breast cancer stage III	

Malignancy Bladder Cancer	Malignancy Breast Cancer	Malignancy Phaeochromocytoma
Bladder cancer stage I, without cancer in situ	Breast cancer stage IV	
Bladder cancer stage II	Breast neoplasm	
Bladder cancer stage III	Breast sarcoma	
Bladder cancer stage IV	Breast sarcoma metastatic	
Bladder squamous cell carcinoma recurrent	Breast sarcoma recurrent	
Bladder squamous cell carcinoma stage 0	Contralateral breast cancer	
Bladder squamous cell carcinoma stage I	HER-2 positive breast cancer	
Bladder squamous cell carcinoma stage II	Hormone refractory breast cancer	
Bladder squamous cell carcinoma stage III	Inflammatory carcinoma of breast recurrent	
Bladder squamous cell carcinoma stage IV	Inflammatory carcinoma of breast stage III	
Bladder squamous cell carcinoma stage unspecified	Inflammatory carcinoma of breast stage IV	
Bladder transitional cell carcinoma	Inflammatory carcinoma of the breast	
Bladder transitional cell carcinoma metastatic	Intraductal papillary breast neoplasm	
Bladder transitional cell carcinoma recurrent	Intraductal proliferative breast lesion	
Bladder transitional cell carcinoma stage 0	Invasive breast carcinoma	
Bladder transitional cell carcinoma stage I	Invasive ductal breast carcinoma	
Bladder transitional cell carcinoma stage II	Invasive lobular breast carcinoma	
Bladder transitional cell carcinoma stage III	Invasive papillary breast carcinoma	
Bladder transitional cell carcinoma stage IV	Lobular breast carcinoma in situ	
Metastases to bladder	Malignant nipple neoplasm	
Metastatic carcinoma of the bladder	Malignant nipple neoplasm female	
Transitional cell carcinoma	Malignant nipple neoplasm male	
	Medullary carcinoma of breast	
	Metaplastic breast carcinoma	
	Metastases to breast	
	Mucinous breast carcinoma	
	Neuroendocrine breast tumour	
	Nipple neoplasm	
	Oestrogen receptor positive breast cancer	
	Paget's disease of nipple	
	Phyllodes tumour	
	Triple negative breast cancer	
	Tubular breast carcinoma	

Malignancy Renal Cell Cancer	Malignancy Testicular	Osmotic Diuresis
Clear cell renal cell carcinoma	Benign neoplasm of testis	Dry mouth
Clear cell sarcoma of the kidney	Leydig cell tumour of the testis	Dry throat
Denys-Drash syndrome	Sertoli cell testicular tumour	Micturition disorder
Hereditary leiomyomatosis renal cell carcinoma	Spermatocytic seminoma	Micturition urgency
Hereditary papillary renal carcinoma	Testicle adenoma	Nocturia
Metastatic renal cell carcinoma	Testicular cancer metastatic	Pollakiuria
Nephroblastoma	Testicular neoplasm	Polydipsia
Non-renal cell carcinoma of kidney	Testicular papilloma	Polyuria
Renal cancer	Testis cancer	Thirst
Renal cancer metastatic		Tongue dry
Renal cancer recurrent		Urine output increased
Renal cancer stage I		
Renal cancer stage II		
Renal cancer stage III		
Renal cancer stage IV		
Renal cell carcinoma		
Renal cell carcinoma recurrent		
Renal cell carcinoma stage I		
Renal cell carcinoma stage II		
Renal cell carcinoma stage III		
Renal cell carcinoma stage IV		
Rhabdoid tumour of the kidney		

Pancreatitis	Phimosis	Photosensitivity
Cullen's sign	Acquired phimosis	Actinic elastosis
Grey Turner's sign	Phimosis	Actinic prurigo
Haemorrhagic necrotic pancreatitis		Administration site photosensitivity reaction
Hereditary pancreatitis		Application site photosensitivity reaction
Ischaemic pancreatitis		Chronic actinic dermatitis
Oedematous pancreatitis		Hartnup disease
Pancreatic abscess		Implant site photosensitivity
Pancreatic haemorrhage		Infusion site photosensitivity reaction
Pancreatic necrosis		Injection site photosensitivity reaction
Pancreatic phlegmon		Juvenile spring eruption
Pancreatic pseudocyst		Medical device site photosensitivity
Pancreatic pseudocyst drainage		Photodermatosis
Pancreatitis		Photokeratitis
Pancreatitis acute		Photoonycholysis
Pancreatitis haemorrhagic		Photosensitivity reaction
Pancreatitis necrotising		Polymorphic light eruption
Pancreatitis relapsing		Solar dermatitis
Pancreatorenal syndrome		Solar urticaria
		Sunburn
		Vaccination site photosensitivity

Renal Related	Severe Hypersensitivity/Cutaneous AEs	Upper UTI
Acute kidney injury	Acute generalised exanthematous pustulosis	Bacterial pyelonephritis
Acute phosphate nephropathy	Allergic oedema	Emphysematous pyelonephritis
Acute prerenal failure	Anaphylactic reaction	Kidney infection
Anuria	Anaphylactic shock	Perinephric abscess
Azotaemia	Anaphylactic transfusion reaction	Pyelocystitis
Blood creatinine increased	Anaphylactoid reaction	Pyelonephritis
Blood urea increased	Anaphylactoid shock	Pyelonephritis acute
Continuous haemodiafiltration	Angioedema	Pyelonephritis chronic
Dialysis	Circulatory collapse	Pyelonephritis fungal
Glomerular filtration rate decreased	Circumoral oedema	Pyelonephritis mycoplasmal
Haemodialysis	Conjunctival oedema	Pyelonephritis viral
Haemofiltration	Corneal exfoliation	Pyonephrosis
Hypercreatininaemia	Corneal oedema	Renal abscess
Neonatal anuria	Cutaneous vasculitis	Renal cyst infection
Nephritis	Dermatitis bullous	Urosepsis
Nephropathy toxic	Dermatitis exfoliative	
Oliguria	Dermatitis exfoliative generalised	
Peritoneal dialysis	Drug eruption	
Prerenal failure	Drug hypersensitivity	
Renal failure	Drug reaction with eosinophilia and systemic symptoms	
Renal failure acute	Epidermal necrosis	
Renal failure neonatal	Epiglottic oedema	
Renal impairment	Erythema multiforme	
Renal impairment neonatal	Exfoliative rash	
	Eye oedema	
	Eye swelling	
	Eyelid oedema	
	Face oedema	
	First use syndrome	
	Fixed drug eruption	
	Gingival oedema	
	Gingival swelling	
	Gleich's syndrome	
	Hereditary angioedema	
	Hypersensitivity vasculitis	
	Idiopathic angioedema	
	Idiopathic urticaria	
	Kounis syndrome	
	Laryngeal dyspnoea	
	Laryngeal oedema	
	Laryngospasm	
	Laryngotracheal oedema	
	Limbal swelling	
	Lip exfoliation	
	Lip oedema	
	Lip swelling	
	Mucocutaneous ulceration	
	Mucosa vesicle	
	Mucosal erosion	
	Mucosal exfoliation	
	Mucosal necrosis	
	Mucosal ulceration	

Renal Related	Severe Hypersensitivity/Cutaneous AEs	Upper UTI
	Nikolsky's sign	
	Oculomucocutaneous syndrome	
	Oculorespiratory syndrome	
	Oedema mouth	
	Oedema mucosal	
	Oral mucosal blistering	
	Oral mucosal exfoliation	
	Orbital oedema	
	Oropharyngeal blistering	
	Oropharyngeal swelling	
	Palatal oedema	
	Penile exfoliation	
	Periorbital oedema	
	Pharyngeal oedema	
	Scleral oedema	
	Shock	
	Shock symptom	
	Skin exfoliation	
	Skin necrosis	
	Small bowel angioedema	
	Stevens-Johnson syndrome	
	Stridor	
	Swelling face	
	Swollen tongue	
	Throat tightness	
	Tongue exfoliation	
	Tongue oedema	
	Toxic epidermal necrolysis	
	Type I hypersensitivity	
	Urticaria	
	Urticaria cholinergic	
	Urticaria chronic	
	Urticaria papular	
	Urticarial vasculitis	
	Vaginal exfoliation	

UTI	Venous Thromboembolic events	Volume Depletion
Bladder candidiasis	Deep vein thrombosis	Blood pressure decreased
Cystitis	Deep vein thrombosis postoperative	Blood pressure orthostatic decreased
Cystitis bacterial	Embolism venous	Dehydration
Cystitis escherichia	Iliac vein occlusion	Diastolic hypotension
Cystitis gonococcal	Inferior vena cava syndrome	Dizziness postural
Cystitis haemorrhagic	Inferior vena caval occlusion	Hypotension
Cystitis interstitial	Jugular vein occlusion	Hypovolaemia
Cystitis klebsiella	Mesenteric vein occlusion	Hypovolaemic shock
Cystitis pseudomonal	Obstructive shock	Orthostatic hypotension
Emphysematous cystitis	Portosplenomesenteric venous thrombosis	Orthostatic intolerance
Escherichia urinary tract infection	Post procedural pulmonary embolism	Postural orthostatic tachycardia syndrome
Fungal cystitis	Postpartum venous thrombosis	Presyncope
Funguria	Pulmonary embolism	Shock
Genitourinary tract infection	Pulmonary infarction	Shock symptom
Streptococcal urinary tract	Pulmonary microemboli	Syncope

UTI	Venous Thromboembolic events	Volume Depletion
infection		
Ureter abscess	Pulmonary oil microembolism	Urine output decreased
Ureteritis	Pulmonary thrombosis	
Urethritis	Renal vein embolism	
Urethral abscess	Renal vein occlusion	
Urethral carbuncle	Subclavian vein thrombosis	
Urethral stricture post infection	Vascular occlusion	
Urinary bladder abscess	Venous thrombosis	
Urinary tract abscess	Venous thrombosis in pregnancy	
Urinary tract infection	Venous thrombosis limb	
Urinary tract infection bacterial	Visceral venous thrombosis	
Urinary tract infection enterococcal		
Urinary tract infection fungal		
Urinary tract infection pseudomonal		
Urinary tract infection staphylococcal		

APPENDIX 7: Adverse event with Potential Amputation Association

List of Selected Preferred Terms Included Within the System Organ Classes of Infections and Infestations, Vascular Disorders, Nervous System Disorders, and Skin and Subcutaneous Tissue Disorders

Infections and Infestations	Vascular Disorders	Nervous System Disorders	Skin and Subcutaneous Tissue Disorders	High Level Term (HLT) Skin and subcutaneous tissue ulcerations	
Infected skin ulcer	Arteriosclerosis	Paraesthesia	Diabetic ulcer	Penile ulceration	Medical device site erosion
Skin infection	Peripheral arterial occlusive disease	Hypoaesthesia	Neuropathic ulcer	Implant site ulcer	Ulcerated haemangioma
Staphylococcal skin infection	Peripheral vascular disorder	Diabetic neuropathy	Fungating wound	Cytomegalovirus mucocutaneous ulcer	Incision site erosion
Gangrene	Peripheral artery stenosis	Neuropathy peripheral	Diabetic foot	Skin ulcer	Incision site ulcer
Osteomyelitis	Peripheral ischaemia	Areflexia	Diabetic neuropathic ulcer	Eyelid erosion	Vaccination site ulcer
Diabetic gangrene	Arterial stenosis	Hyporeflexia	Skin erosion	Implant site erosion	Fungating wound
Localised infection	Diabetic vascular disorder	Polyneuropathy		Diabetic foot infection	Ecthyma
Wound abscess	Femoral artery occlusion	Autonomic neuropathy		Application site erosion	Perineal ulceration
Wound infection	Thrombosis	Neuropathy peripheral		Infusion site erosion	Tropical ulcer
Subcutaneous abscess	Poor peripheral circulation	Burning sensation		Mycobacterium ulcerans infection	Injection site erosion
Abscess limb	Microangiopathy	Diabetic autonomic neuropathy		Infusion site ulcer	Pyogenic sterile arthritis pyoderma gangrenosum and acne syndrome
Staphylococcal osteomyelitis	Peripheral coldness	Peripheral sensory neuropathy		Neuropathic ulcer	Scleroderma associated digital ulcer
Diabetic foot infection	Diabetic microangiopathy	Peripheral sensorimotor neuropathy		Skin ulcer haemorrhage	Vulval ulceration
Staphylococcal skin infection	Arterial occlusive disease	Sensory disturbance		Burn infection	Mucocutaneous ulceration
Soft tissue infection	Arterial thrombosis	Diabetic neuropathic ulcer		Diabetic foot	Injection site ulcer
Bone abscess	Peripheral artery thrombosis			Diabetic ulcer	Pyoderma gangrenosum
Osteitis	Arterial occlusive disease			Catheter site erosion	Scrotal ulcer
Cellulitis	Angiopathy			Pyostomatitis vegetans	Application site ulcer
Wound [a]	Intermittent claudication			Catheter site ulcer	Genital ulceration
Dry gangrene	Arterial disorder			Medical device site ulcer	Infected skin ulcer
Post-operative wound infection	Impaired healing [a]			Administration site ulcer	Diabetic neuropathic ulcer
Post-operative wound complication [a]				Instillation site erosion	Varicose ulceration
Wound dehiscence				Breast ulceration	Vaginal ulceration
Burn infection				Instillation site ulcer	Vulvovaginal ulceration
Extremity necrosis				Administration site erosion	Auditory meatus external erosion
				Vasculitic ulcer	Skin erosion
				Vaccination site erosion	

[a] Although these PTs belong in the SOC of Injury, Poisoning and Procedural Complications or in the SOC of General Disorders and Administration Site Conditions, these terms were retained for the search strategy because of their relevance

List of Preferred Terms classified as Reversible infections, Irreversible infections and Osteomyelitis

Reversible Infections	**Irreversible Infections**	**Osteomyelitis**
Abscess limb	Diabetic gangrene	Bone abscess
Burn infection	Dry gangrene	Osteitis
Cellulitis	Extremity necrosis	Osteomyelitis
Diabetic foot infection	Gangrene	Staphylococcal osteomyelitis
Infected skin ulcer		
Localised infection		
Skin infection		
Soft tissue infection		
Staphylococcal skin infection		
Subcutaneous abscess		
Wound		
Wound abscess		
Wound dehiscence		
Wound infection		

APPENDIX 8: Pre-Defined Limit of Change (PDLC) Criteria

Laboratory Test	Parameter for ANY value and LAST value
CHEMISTRY	
ALT	Absolute Value: >3X ULN
	Absolute Value: >5X ULN
	Absolute Value: >8X ULN
AST	Absolute Value: >3X ULN
	Absolute Value: >5X ULN
	Absolute Value: >8X ULN
ALT >3X ULN and Tbili >2X ULN	Composite: ALT >3X ULN and Tbili >2X ULN [with the Tbili elevation >2 X ULN within 30 days of the ALT elevation >3x ULN]
AST >3X ULN and Tbili >2X ULN	Composite: AST >3X ULN and Tbili >2X ULN [with the Tbili elevation >2 X ULN within 30 days of the AST elevation >3x ULN]
Bilirubin	Composite: >ULN and > 25% increase from BL
	Absolute Value: >2XULN
Bicarbonate	Absolute Value: <16 mEq/L
Calcium	Composite: >ULN and > 10 % increase from BL
Magnesium	Composite: >ULN and >25% increase from BL
Phosphorus	Composite: >ULN and >25% increase from BL
Potassium	Composite: <LLN and >15% decrease from BL
	Composite: >ULN and >15% increase from BL
	Absolute Value: ≥ 6.5 mEq/L
Sodium	Composite: <LLN and decrease >5 mEq/L or more from BL
	Composite: >ULN and increase>5 mEq/L or more from BL
Uric Acid	Composite: <LLN and >25% decrease from BL
HEMATOLOGY	
Hemoglobin	Change: ≥ 2 g/dl decrease from BL
	Change: ≥ 2 g/dL increase from BL
Platelets	Composite: >ULN and increase >25% from BL
White Blood Count	Composite: < LLN and >25% decrease from BL
	Composite: > ULN and >50 % increase from BL
VITAL SIGNS	
Pulse	Absolute Value: ≤50 beats per minute
	Absolute Value: ≥100 beats per minute
Systolic Blood Pressure	Composite: ≥ 20 mm Hg decrease from BL and ≤90 mm Hg
	Composite: ≥ 20 mm Hg increase from BL and ≥ 160 mm Hg
Diastolic Blood Pressure	Composite: ≥ 15 mm Hg decrease from BL and ≤ 50 mm Hg
	Composite: ≥ 15 mm Hg increase from BL and ≥ 100 mm Hg

APPENDIX 9: SAS Program for Key Analyses of Mortality Endpoints

Stratified Cox proportional hazard model

```
proc phreg data=&in;
  model &time* &censor(1)=&trtv  &covar/RL ties=efron alpha = 0.05;
      strata &STRATA;

ods output ParameterEstimates=&out1 (keep Estimate StdErr parameter
HazardRatio HRLowerCL HRUpperCL ProbChiSq rename=( parameter=VAR
HazardRatio=HR HRLowerCL=LCL HRUpperCL=UCL ProbChiSq=PRBW)
where=(VAR="&trtv"));

run;
```

Stratified log rank test

```
proc lifetest data=&in notable;
  time &time*&censor(1);
  strata    &STRATA; /group=&trtv;
  ods output HomTests=outlrt (keep= Test ChiSq ProbChiSq
where=(Test='Log-Rank') rename=( ChiSq=chi_LRT ProbChiSq=prb_LRT));
run;
```

Test of proportional hazard assumption-cox model with log –transformed time and its interaction with treatment

```
  *Test using time varying covariates--test non-zero slope of individual
covariate using wald test and global effect thru partial likely hood test ;
      proc phreg data=&datain;
        model &time* &censor(1)=&trtv &covar /RL ties=efron alpha = 0.05;
      strata &strata;
      &ttime=log(&time);
       &trtv.t=&trtv*&ttime;
       &covar.t=&covar*&ttime;
       proportionality_test: test &trtv.t &covar.t;
      ods output ParameterEstimates= est0 CensoredSummary=censor
      TestStmts=gbprpt;
 run;
```

Study stratified cox proportional hazard model with interaction term and hazard ratio by subgroup

```
   proc phreg data=&in ;
        class &clas;
         model &time* &censor(1)=&trtv &covar  &clas &trtv*&clas /RL
ties=efron alpha = 0.05;

            HAZARDRATIO &trtv/&trtby;

            strata &STRATA;
```

```
        ods output HazardRatios=HR Type3=&out2 (keep= Effect ProbChiSq
rename=(ProbChiSq=PRB_INT) where=(index(Effect,'*')>0));
     run;
```

Gail-Simon test

```
      *options to run Gail Simon test when interaction is significant;
      *the smallest prb_int will be used as the flag to trigger the G-S test;
      proc sort data=&out2 out=temp nodupkey;
            by PRB_INT;
      run;
      data _null_;
            set temp;
            if _n_=1;
            call symput('FGS', PRB_INT);
      run;
      %if %sysevalf(&FGS)<=0.05 %then
      %do;
        proc sql;
            create table gs01 as
            select
              count(&clas) as m,
               sum(((Estimate>0)*Estimate/stdErr)**2) as qplus,
               sum(((Estimate<0)*Estimate/StdErr)**2) as qminus,
               min(calculated qplus, calculated qminus) as q
               from &out1

                  ;
                  quit;

                data gs02;
                  set gs01;
                  pvalue_gs=0;
                  do i=1 to m-1;
                   pvalue_gs=pvalue_gs+pdf("binomial",i,0.5,m-1)*(1-
probchi(q,i));
                  end;
                   keep pvalue_gs;
                  label pvalue_gs="Gail-Simon Two-sided p-value";
                run;

      %end;
```

Janssen Research & Development

Statistical Analysis Plan

Cardiovascular Outcomes Clinical Program
Integrated Database of CANVAS and CANVAS-R

Protocol 28431754DIA3008
Protocol 28431754DIA4003

JNJ-28431754 (canagliflozin)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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SUMMARY OF AMENDMENT

Relative to the integrated statistical analysis plan (SAP) dated 20 September, 2016, the major amendments made in this version are summarized as follows.

Applicable Section(s)	Description of Change(s)
2.2	The On-Study analysis set was added for MACE and replaced the ITT analysis set for several adverse events of interest. The upper bound of the data period for the On-Treatment analysis set was clarified as last dose plus 2 days for laboratory parameters except ACR.
4.1.1	Consistent with the analytic approach described in the Cardiovascular Endpoint adjudication charter, it is clarified that undetermined death is considered as CV death.
4.1.2.2	Updated the multiple imputation analysis section
4.1.2.5	Added an analysis of MACE in the first 30, 60 and 90 days.
4.1.2.7 4.2.2.4	Additional subgroups were added for the analysis of MACE and the mortality endpoints.
5.1	Clarified that any adjudicated non-CV death event where the adjudication committee assigned a renal proximate cause is considered a renal death.
6.2.2.9	Added a section on the analysis of adjudicated pancreatitis.
Appendix 8	Additional lab analytes were included in the Pre-defined Limit of Change (PDLC) criteria.

SUMMARY OF AMENDMENT

Relative to the integrated statistical analysis plan (SAP) submitted in 2013, the major amendments made in this version are summarized as follows.

Applicable Section(s)	Description of Change(s)
1.3	Addition of 2 secondary objectives to demonstrate the superiority of canagliflozin to placebo in reduction of all-cause mortality and cardiovascular death.
1.4, 2.2	Proposal to evaluate the secondary objectives based on pooled CANVAS data, using the Truncated analysis set (defined in Section 2.2), with CANVAS-R.
1.4.1	Pre-specify the multiplicity adjustment for the CV Outcomes Clinical Program including the proposal to transfer alpha for the tests in CANVAS-R.
4.1.2.2	Outline the multiple imputation method for sensitivity analyses to evaluate the robustness of the conclusion due to missing data.
4.2.1	Analysis methods for the secondary endpoints.
4.2.2	Supportive analyses for the secondary endpoints including the worst case scenario analysis for missing data.
4.3	Addition of all-cause hospitalization, hospitalization for heart failure (HHF) and the composite of HHF or CV death as additional exploratory endpoints.
5	Addition of the renal endpoints as exploratory endpoints and their analysis methods.
6	Addition of the integrated safety analysis plan.

ABBREVIATION

ACM	all-cause mortality
ACR	albumin creatinine ratio
AE	adverse event
AHA	anti-hyperglycemic agent
BMI	body mass index
BP	blood pressure
Cana	canagliflozin
CANVAS	**CAN**agliflozin cardio**V**ascular **A**ssessment **S**tudy
CANVAS-R	**CAN**agliflozin cardio**V**ascular **A**ssessment **S**tudy - **R**enal
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CM	concomitant medication
CV	cardiovascular
CVD	cardiovascular death
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FDA	US Food and Drug Administration
GTED	Global Trial End Date
HF	heart failure
HR	hazard ratio
HbA1c	hemoglobin A1c
HDL-C	high-density lipoprotein cholesterol
IDMC	Independent Data Monitoring Committee
IWRS	Interactive Web Response System
ITT	Intent-to-Treat
LB	laboratory
LDL-C	low-density lipoprotein cholesterol
MACE	major adverse cardiovascular event
MH	medical history
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NI	non-inferiority
PMR	Post Marketing Requirement
PT	preferred term
SAP	statistical analysis plan
SCr	serum creatinine
SD	standard deviation
SGLT2	sodium-glucose co-transporter 2
SOC	system organ class
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TEAE	treatment emergent adverse event
VS	vital signs

1. INTRODUCTION

The canagliflozin cardiovascular (CV) outcomes clinical program consists of 2 studies 28431754DIA3008 (CANVAS) and 28431754DIA4003 (CANVAS-R) initiated in December 2009 and January 2014, respectively. Canagliflozin (Cana, JNJ-28431754) was approved for marketing in the US on 29 March 2013. It is an orally active inhibitor of the sodium-glucose co-transporter 2 (SGLT2) that has been developed as an oral anti-hyperglycemic agent (AHA) for the treatment of patients with type 2 diabetes mellitus (T2DM).

To meet the FDA guidance on assessing CV safety of AHAs, the sponsor initiated the CANVAS CV Outcomes study to supply data to support the CV safety of canagliflozin and to also evaluate whether canagliflozin reduces CV risk. As part of the marketing authorization application, the sponsor performed an integrated analysis of CV events from the Phase 2 and Phase 3 canagliflozin program using data from 9,632 subjects, which included interim data harvested on 31 January 2012 from the ongoing CANVAS CV Outcomes study of 4,330 subjects at high risk for CV disease. The primary CV endpoint for the pre-approval safety analysis was the composite of CV death, non-fatal myocardial infarction (MI), non-fatal stroke or hospitalization for unstable angina. In response to a request arising during review of the canagliflozin Marketing Authorization Application by the Committee for Medicinal Products for Human Use (CHMP), the sponsor conducted a second integrated CV analysis of the Phase 2 and Phase 3 studies, which included interim data from CANVAS harvested on 19 November 2012. Data on major adverse cardiovascular events (MACE; CV death, non-fatal MI, or non-fatal stroke) and mortality outcomes beyond 19 November 2012 have remained blinded to the sponsor and investigators.

As per the FDA guidance and following market authorization, the sponsor is required to demonstrate that the upper bound of the 2-sided 95% confidence interval (CI) of the CV risk ratio of test drug to comparator be less than 1.3. In the 19 February 2013 and 05 March 2013 teleconferences between the Agency and the sponsor, the Agency indicated that the sponsor needed to rule out 1.3 upper bound using MACE. The Agency indicated these data could be derived from a new dedicated study or from a pooled analysis including the CANVAS study along with a new CANVAS-like study (so as to accumulate sufficient events within an appropriate time period post-approval).

As a result of these discussions, the sponsor proposed to conduct a second CANVAS-like study (identified at that time as CANVAS2, now referenced as CANVAS-R) with approximately 5,700 randomized subjects. As such, the CANVAS and CANVAS-R trials are purposefully similar in design and in subject characteristics (see next section). Data from these studies are to be harvested for an integrated analysis no later than June 2017 with study reports submitted to FDA by September 2017. The integrated analysis for CV safety will use all subjects enrolled in CANVAS and CANVAS-R in an intent-to-treat (ITT) analysis to show that a canagliflozin-associated increase in the CV risk ratio, if any, was significantly less than 1.3 using the 2-sided 95% CI of the risk ratio. A previous CANVAS/CANVAS-R integrated SAP for the CV risk assessment Post Marketing Requirement (PMR) was submitted to FDA in October 2013.

The analysis plan for the integrated dataset to satisfy the CV risk assessment PMR was oriented to the role of safety evaluation; ie, to rule out a canagliflozin-associated increase in the risk ratio for MACE of 1.3 in accord with FDA Guidance. There were plans for independent SAPs for CANVAS and CANVAS-R, with separate strong control of the Type I error rate within each study. The primary endpoint of CANVAS was to evaluate whether there was a risk reduction in MACE associated with canagliflozin treatment. Due to unblinding of the interim summary results of CANVAS at the time of marketing approval, the planned expansion of enrollment in CANVAS was eliminated, and CANVAS-R was initiated to provide sufficient CV outcome data to support the CV safety PMR. The primary endpoint of CANVAS, MACE, was not changed although it was recognized that with the smaller sample size the study was substantially under-powered for the objective.

In the March 2016 submission to FDA, the sponsor proposed to modify the analysis plans for CANVAS and CANVAS-R. The new CANVAS/CANVAS-R integrated SAP would maintain, as originally planned, the use of the integrated dataset for purposes of the MACE CV safety PMR. As originally planned, this dataset would contain information from all subjects enrolled under either the CANVAS or CANVAS-R protocols, including all subject study-time before and since the 20 November 2012 CANVAS interim analysis related to the reviews for marketing approval. After the CV safety PMR is addressed, the sponsor proposed to add the endpoints to evaluate mortality benefit in this SAP revision. Key adjustments in the integrated dataset will be made for the main analysis of these additional endpoints of mortality and will be described in this document.

The CANVAS/CANVAS-R integrated SAP in this submission, which replaces the October 2013 document, specifies updated definitions of analysis sets, key derived variables and statistical methods for analysis of efficacy and safety of the canagliflozin program to evaluate CV risk for PMR and the benefit in mortality reduction.

The SAP for the integrated dataset will be the primary SAP for data from both CANVAS and CANVAS-R for purposes of maintaining strong control of the Type I error rate. Although there are separate SAP documents for the CANVAS-only and CANVAS-R-only data, these SAPs are subordinate to this SAP for the integrated dataset with regard to controlling the Type I error rate, and the relationship is further detailed in this document.

1.1. Similarity of CANVAS and CANVAS-R

The CANVAS and CANVAS-R trials are ongoing in subjects with CV disease (secondary-prevention) and subjects with at least 2 risk factors for a CV event (primary-prevention). The key design elements of the 2 trials are similar (refer to Table 1).

The similarities in study design, eligibility criteria, study population, key endpoints, etc, were done as per the PMR and in agreement with the FDA so as to support an integrated analyses of these studies. The selection criteria were virtually identical in CANVAS and CANVAS-R. The only differences were the following requirements in the CANVAS study: stable AHA regimen prior to randomization as required to evaluate glycemic efficacy in the 18-week sub studies; findings on ECG obtained at screening instead of simply “known” findings within 3 months

before screening; additional estimated glomerular filtration rate (eGFR) criterion for subjects taking metformin, and the exclusion of rosiglitazone; see Appendix 1 for a summary of operational specifics and key inclusion/exclusion criteria. An expanded list of the eligibility criteria is provided in Appendix 2.

1.2. Completion of CANVAS and CANVAS-R

The CANVAS and CANVAS-R studies will complete when the last subject randomized has approximately 78 weeks of follow-up or when 688 MACEs are accumulated between both studies (estimated to occur between January 2017 and April 2017).

All sites in CANVAS and CANVAS-R will be notified of the projected Global Trial End Date (GTED). Following announcement of the projected GTED and for subjects remaining on double-blind study drug, sites will schedule the End of Treatment visit and the 30-day off-drug follow-up visit as per the Time and Events schedule in the protocols[1]; for subjects that have prematurely discontinued study drug prior to the announcement of the projected GTED, sites will be required to make a final contact or vital status check as soon as possible after the announcement. It is estimated that there will be 6.1 and 2.3 years of median observation in CANVAS and CANVAS-R, respectively.

[1]Following the announcement of the GTED, investigators are not expected to continue collecting data for purposes of the clinical trial after the 30-day post-treatment contact.

Table 1: CANVAS and CANVAS-R: Key Design Elements

	CANVAS	CANVAS-R
Patient population	Men or women with T2DM who have inadequate glycemic control (HbA_{1c} ≥7.0 and ≤10.5%) with either known CV disease or 2 or more risk factors for CV events	
Renal function for trial entry	eGFR ≥ 30 mL/min/1.73m^2	
Renal function for study drug discontinuation	Confirmed eGFR < 15 mL/min/1.73m^2	
AHA background therapy	Drug naïve, AHA monotherapy or combination therapy	
CV risk factor management	The effects of canagliflozin will be evaluated against a background of standard of care for the treatment of hyperglycemia and CV risk factors (ie, blood pressure and lipids) with study investigators counseled to assure appropriate management according to applicable national guidelines for the care of patients with T2DM with treatment individualized as clinically appropriate.	
Governance and supporting committee	Single Academic Steering Committee, Independent Data Monitoring Committee and Endpoint Adjudication Committee. (note: consistent endpoint definitions were applied across both the CANVAS/CANVAS-R studies).	
Study treatment regime	Three arms: placebo, Cana 100 mg QD and Cana 300 mg QD	Two arms: placebo, Cana (100 mg QD for the 1st 13 weeks, with up-titration to 300 mg QD thereafter at investigator discretion and based on tolerability and glycemic needs)
Number of subjects randomized	4,330	5,812
First subject randomized	December 2009	January 2014
Last subject Randomized	March 2011	May 2015

1.3. Key Objectives of Integrated Analysis

- To demonstrate that canagliflozin is not associated with an unacceptable increase in cardiovascular risk by showing that the upper bound of the 2-sided 95% CI for the risk ratio of canagliflozin to placebo is less than 1.3 where the risk ratio is measured by hazard ratio (HR).
- To demonstrate the superiority of canagliflozin in the reduction of the following mortality endpoints relative to placebo:
  - All-cause mortality (ACM): Death from any cause
  - CV Death (CVD): Death from cardiovascular cause

1.4. Statistical Hypotheses

All hypotheses in the CV program will be tested with a Type I error strongly controlled at 5%.

Primary Hypothesis

The following statistical hypothesis is addressed by use of the entire integrated dataset (without any data truncation [see below]) and performing a non-inferiority test for the HR (all canagliflozin versus placebo) for MACE at the margin of 1.3:

H_0: The HR $\geq$1.3, versus H_1: The HR < 1.3.

The CV safety of canagliflozin will be demonstrated if, as compared to placebo, the upper bound of 95% CI of the HR is less than 1.3.

If the null hypothesis H_0 is rejected and if the upper bound of the 2-sided 95% CI of the HR is less than 1.0, then it will be concluded that canagliflozin is superior to placebo in terms of MACE reduction.

Secondary Hypotheses

The secondary objectives are to demonstrate that canagliflozin is superior to placebo in reducing all-cause mortality and CV death. Because there was an unblinded interim analysis of the CANVAS study in 2012, information from this study will be left-truncated; that is only deaths accrued from the study time from after 19 November 2012 will be used in these superiority analyses, and deaths up to the date of the interim analysis will be excluded. For these mortality endpoints, the following statistical hypothesis on the HR of canagliflozin to placebo will be tested.

H_0: The HR $\geq$ 1.0, versus H_1: The HR < 1.0

Canagliflozin will be deemed to be superior as compared to placebo if the upper bound of 95% CI of the HR is less than 1.0.

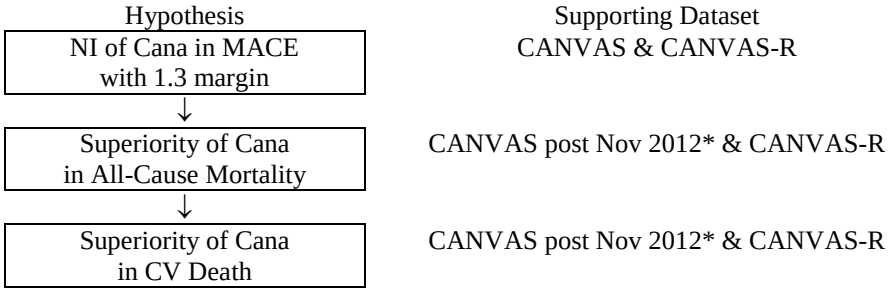
1.4.1. Control of the Type I Error Rate

The primary and the secondary hypotheses will be tested sequentially in order to strongly control the type I error at 5% (refer to Figure 1). For the primary non-inferiority MACE assessment,

canagliflozin will be tested against placebo to exclude the HR of 1.3. Testing of secondary hypotheses will proceed sequentially conditional on the statistical significance of the primary test at the 5% significance level and the testing of subsequent endpoints proceeds conditional on the statistical significance of the prior test.

If the MACE and the mortality endpoints in the integrated analysis succeed in rejecting the null hypotheses, all of the alpha for testing (ie, 5%) will pass to the CANVAS-R SAP for testing of the renal and the CV efficacy hypotheses in the CANVAS-R study. Therefore, no alpha is preserved for evaluating hypotheses in CANVAS and only nominal p-values will be reported for efficacy endpoints assessed in the CANVAS study.

Figure 1: Hypothesis Testing Sequence in Integrated Analysis



* Only subjects who were at risk for mortality after 19-Nov-2012 are included.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Analysis Populations

- Randomized subjects—subjects who are randomized via the Interactive Web Response System (IWRS);
- Treated subjects—randomized subjects who received at least one dose of double-blind study medication.

For efficacy analyses and baseline summaries, subjects will be analyzed according to their randomization assignment. For analysis of safety (eg, adverse events [AEs]) and summary of exposure, subjects will be analyzed according to the predominant treatment received (defined as the treatment to which the subject was exposed for the greatest duration), in the event that subjects receive a treatment other than the one to which they were randomized.

2.2. Analysis Sets

Analysis sets consist of 2 components: (1) analysis population (Section 2.1), which specifies the subjects included in an analysis; (2) data period, defining the time window during which data will be included in the analysis. Table 2 presents the 4 analysis sets defined for the integrated analysis with the component description. In the ITT, the On-Study, and the On-Treatment analysis sets, Day 1 is the first double blind dose date for each subject. If missing or incomplete,

the first dose date will be imputed as the randomization date (also see trial reference start date in Section 2.4.2).

All the integrated analyses are mainly based on the ITT analysis set, the On-Study analysis set, or the On-Treatment analysis set. The exception is in the testing of the treatment effects on all-cause and CV-specific mortality where the Truncated analysis set will be used.

As the results of the CV interim analysis of CANVAS (through November 2012) were known at the time of marketing approval, the inclusion of that information in analyses of the integrated dataset for the mortality endpoint tests of superiority of canagliflozin relative to placebo can raise concern of a biased analysis. Therefore, the dataset used in the analyses of secondary endpoints for the integrated dataset is adjusted to eliminate all mortality and censored cases that contributed to the 2012 CANVAS interim analysis. In the Truncated analysis set that will be used for these secondary endpoints, the CANVAS data will be left-truncated such that only the study time from after the 19 November 2012 interim analysis will be used. That is, study time from study initiation through 19 November 2012 will be excluded and Day 1 for CANVAS subjects in the Truncated analysis set will be 20 November 2012.

Table 2: Summary of Analysis set for Integrated Analysis

Analysis Set	Population	Data Period
ITT[a]	Randomized subjects	Day 1 to the last trial contact date (see Section 2.4.2) up to GTED
On-Study[a]	Treated subjects	Day 1 to the last trial contact date (see Section 2.4.2) up to GTED
On-Treatment[a]	Treated subjects	Day 1 to the last dose date plus X[b] days or the last trial contact date, whichever is earlier.
Truncated	All randomized subjects in CANVAS-R and subjects in CANVAS who were at risk for mortality after 19-Nov-2012	For CANVAS, 20-NOV-2012 to the last trial contact date (see Section 2.4.2) up to GTED. For CANVAS-R, Day 1 to the last trial contact date (see Section 2.4.2) up to GTED

[a] The same definitions of the analysis set are applied in CANVAS and CANVAS-R.
[b] X is 2 days for laboratory (except ACR) and vital sign measurements, and 30 days for CV, and mortality, endpoints and adverse events.

2.3. Data Integration

In the integrated analysis, data from CANVAS and CANVAS-R will be combined. If not otherwise specified, subjects treated with canagliflozin will be pooled as the 'All canagliflozin' group. The table below presents the projected number of randomized subjects by treatment.

	Estimated Median Duration of Follow-Up	Number of Randomized Subjects			
		Cana 100 mg	Cana 300 mg	All Cana	Placebo
CANVAS	6.1 yrs.	1445	1443	2888	1442
CANVAS-R	2.3 yrs.			2906*	2906*

* Assumption that an equal number of subjects were randomized to Cana and Placebo

2.4. Data Handling

2.4.1. Censoring Rules

For each analysis set, events that occur any time during the data period of the corresponding analysis set (see Table 2) will be considered as eligible events; otherwise subjects not experiencing an event will be censored at the earlier of the last trial contact date or end of the respective data period, if not otherwise specified.

2.4.2. Handling of Key Milestone Dates

- Trial reference start date (Day 1): the first double-blind dose date for each subject (First dose date). If missing or incomplete, the first dose date will be imputed as the randomization date. In Truncated analysis set (Section 2.2), due to the data exclusion, Day 1 for eligible CANVAS subjects is defined to be 20-Nov-2012.
- Last dose date: the date on which the last dose of double-blind study drug was taken by the subject. If only the day is missing, impute the last day of the month. If the month or the year is missing, impute the date as the date of the scheduled visit subsequent to the last visit when the study drug was dispensed. The imputed last dose date should be no later than the end of treatment visit date or the last trial contact date. In addition, the imputed last dose date should be no earlier than the first dose date. The last dose date is the date of permanent study drug discontinuation regardless of any temporary drug interruption.
- Last trial contact date: the date when the last trial-related procedure is conducted. It is defined as the latest of:
  - The date of last visit/contact (scheduled or unscheduled visit; office or phone contact), or
  - The latest known date of an AE or the study endpoint event status, concomitant medication, vital sign measurements or laboratory results as reported on their respective eCRF, or
  - The date of alternate contact made (eg, family members, relatives, friends, health care providers, public search) confirming the patient's survival status at the time of the GTED.
  - For subjects who die during the study, the last trial contact date will be defined as the date of death.

3. SUBJECT INFORMATION

3.1. Baseline Anthropometric and Demographic Characteristics

Baseline anthropometric and demographic characteristics will be summarized by treatment group. Descriptive statistics (N, mean, standard deviation [SD], median, and range) will be provided by treatment group for continuous variables at baseline such as age and body weight.

Additionally, the number and percentage of subjects in the categories of the following variables at baseline will also be summarized by treatment group based on the ITT analysis set:

- Age group: <65, ≥65 years old;
- Sex: Male, Female;
- Race: White, Black or African American, Asian, Others;
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Unknown, Not reported;
- Region: North America, Central/South America, Europe, Rest of the World (refer to Appendix 3 for list of countries in each region).

A summary for the integrated database, CANVAS, and CANVAS-R presenting in a side-by-side format will be provided. Another summary based on the ITT analysis set and the Truncated analysis set will also be presented side-by-side.

3.2. Baseline Disease Characteristics

Descriptive statistics (N, mean, SD, median, and range) will be provided by treatment group and overall for continuous variables at baseline such as duration of diabetes (in years), baseline eGFR, baseline albumin creatinine ratio (ACR), systolic blood pressure (SBP), weight, body mass index (BMI), HbA1c, LDL-C, HDL-C , triglycerides (TG), total cholesterol (TC) and LDL-C/HDL-C.

Additionally, the number and percentage of subjects will be summarized by treatment group for the following:

- Baseline BMI categories (<30, ≥30 Kg/m^2);
- Currently daily cigarette smoker: Yes/No;
- Baseline HbA_{1c} ≥8%: Yes/No;
- Duration of T2DM ≥10 years: Yes/No;
- Baseline systolic blood pressure categories (≤140, >140 mmHg);
- Baseline LDL-C categories (≤70, >70 mg/dL);
- Baseline HDL-C categories (<39, ≥39 mg/dL);
- Baseline eGFR categories (<30, 30 to <60, 60 to <90, ≥90 mL/min/1.73m^2);
- Baseline albuminuria categories: Normoalbuminuria (0 ≤ACR <30 mg/g); Microalbuminuria (ACR ≥30 mg/g and ≤300 mg/g); Macroalbuminuria (ACR >300 mg/g: ACR >300 mg/g and ≤3000 mg/g, ACR >3000 mg/g).
- History of hypertension: Yes/No ;
- History of prior CV disease: Yes/No;
- History of coronary artery disease: Yes/No;
- History of cerebrovascular disease: Yes/No;

- History of peripheral vascular disease: Yes/No;
- History of heart failure: Yes/No;
- Microvascular diabetes complications (Any, 1, 2 or 3 of retinopathy, neuropathy [diabetic or automatic neuropathy], and nephropathy)
- History of fracture: Yes/No;

A summary for the integrated database, CANVAS, and CANVAS-R presenting in a side-by-side format will be provided based on the ITT analysis set. Another summary based on the ITT analysis set and the Truncated analysis set will also be presented side-by-side.

3.3. Disposition Information

Disposition for all randomized subjects will be summarized by treatment group (all canagliflozin and placebo) using the categories listed below:

- Screen failure;
- Subjects who are randomized (ITT);
- Subjects who are treated;
- Subjects who are randomized and at risk of mortality on 20-Nov-2012 or afterward (Truncated);
- Subjects who complete the study (ie, defined as having been followed until a time point between the notification of the GTED and the GTED, or if the subject had died prior to the GTED);
- Subjects who prematurely discontinued study medication;
- Subjects without final vital status.

The reasons for non-randomization, withdrawal from study (lost to follow-up, consent withdrawal), and discontinuation from study medication will be summarized. Distribution of time to premature discontinuation of study medication will be displayed using a Kaplan-Meier plot, where one minus the survival function will be shown.

3.4. Extent of Exposure and Follow-Up

Total exposure time for each subject is defined as the number of days from Day 1 to the last dose date (inclusive), regardless of any temporary drug interruption(s). Follow-up time is defined as the number of days from Day 1 to the last contact day (inclusive) for each subject. Descriptive statistics (N, mean, standard deviation, median, and range) for total exposure or total follow-up will be presented by treatment and study.

3.5. Prior and Concomitant Medications

Medications of special interest are pre-specified and captured on the eCRF of CANVAS-R. In CANVAS, the medication usage was collected without any pre-specified categories. For the purpose of reporting, the medications in CANVAS, which are coded using World Health

Organization Drug Utilization Research Group (WHODRUG) and Anatomical Therapeutic Chemical (ATC) codes, will be aligned with the medication categories in CANVAS-R.

The number of subjects receiving medication in pre-specified categories, such as insulin, sulphonylurea, metformin, statin, anti-thrombotic, diuretic (loop and non-loop), renin angiotensin aldosterone system inhibitor, will be presented by treatment group at baseline and on-drug period. SGLT2 inhibitor use during the off-drug follow-up period will also be summarized by treatment group.

4. CARDIOVASCULAR AND MORTALITY ENDPOINTS

The primary objective to demonstrate CV safety will be assessed using data from all randomized subjects (ITT analysis set). The secondary objectives (ie, demonstration of superiority in reducing all-cause and CV mortality) will be assessed using the Truncated analysis set. Subjects treated with canagliflozin will be pooled (all canagliflozin group) for the comparison to placebo. A tabulation of the primary and the secondary analyses is presented in Appendix 4.

4.1. Primary Endpoint

The primary CV endpoint is MACE which is the composite of CV outcomes including CV death[a], non-fatal MI[b], or non-fatal stroke. Adjudication of these outcomes by the Endpoint Adjudication Committee (EAC) has been done in a blinded fashion.

4.1.1. Primary Analysis Methods

The objective of this analysis is to demonstrate that canagliflozin is not associated with an unacceptable increase in cardiovascular risk by showing that the upper bound of the 2-sided 95% CI of the HR of canagliflozin to placebo is less than 1.3.

The following statistical hypotheses on the HR (all canagliflozin versus placebo) will be tested:

H_0: The HR $\geq$1.3, versus H_1: The HR <1.3.

If the null hypothesis H_0 is rejected and if the upper bound of the 2-sided 95% CI of the HR is less than 1.0, then it will be concluded that canagliflozin is superior to placebo.

The primary analysis will be based on the time to first occurrence of MACE based on the ITT analysis set. The HR of all canagliflozin compared to placebo and its 95% CI will be estimated using a stratified Cox proportional hazards regression model with treatment (all canagliflozin and placebo) as the explanatory variable, and study (CANVAS and CANVAS-R) and prior CV disease subgroup (secondary prevention and primary prevention) as the stratification factors. P-value of stratified log rank test for treatment effect will also be reported for the primary analysis.

[a] Undetermined death is considered CV death.

[b] Silent MIs are excluded from the analysis.

The percentage of subjects who experience a MACE and the corresponding incidence rate per 1,000 patient-years will be reported. The study-combined cumulative event rate over time will be presented using a Kaplan-Meier plot showing all canagliflozin and placebo.

4.1.2. Supportive Analyses

4.1.2.1. Proportional Hazard Assumptions

The plot of the log of cumulative hazard function by treatment over time will be made and the assumption of proportional hazards will be assessed. In addition, a treatment by logarithm-transformed time interaction term will be added into the primary Cox model and tested. A p-value greater than 0.05 for the interaction term will be interpreted as no statistical evidence against the proportional hazard assumption. If the p-value is 0.05 or less, the confidence interval for the CV risk ratio will be re-estimated based on the log rank method suggested by Peto et al. (1976)[1] (refer to Appendix 5 for details).

4.1.2.2. Assessment of Missing Data

For subjects who are lost to follow up or withdrew consent before the development of a MACE in ITT analysis set, data between the last trial contact date and the GTED, will be considered missing.

The proportion of data missing, defined as the ratio of the duration of missing follow up (ie, days between last contact date + 1 day and the GTED) and the duration of intended follow up (ie, days between randomization date and the GTED) will be summarized.

Distributions of baseline demographics and other characteristics will be compared between subjects with and without missing data, to evaluate the plausibility of the assumption of non-informative censoring used in the analysis. The information among those with missing data will also be summarized by treatment groups to further evaluate any imbalance of non-informative censoring if applicable.

Multiple Imputation

The estimate of interest is the hazard ratio to develop MACE among all randomized subjects regardless of adherence to study medication over the period between randomization and the global trial end date (GTED). For subjects who are lost to follow up or withdrew consent before the development of a MACE, data between the last trial contact date and the GTED will be considered missing.

The subjects who discontinued from study medication prematurely prior to the announcement of the GTED can have a different hazard from those who stay on treatment throughout the trial, and their corresponding drop-out could be considered informative. This subpopulation is defined to be the subjects who

- discontinued from study medication prior to the announcement of the GTED, and
- for whom death is not the reason for the discontinuation of study medication.

The data used to model imputed outcomes for subjects with missing data will be those of this subpopulation including the retrieved drop-out data. The definition of the retrieved drop-out data is the follow up data between treatment discontinuation and the GTED. Subjects who developed MACE prior to the treatment discontinuation are included in the subpopulation and their time to MACE data will be used for the imputation modeling. With these subjects included, the model estimate of hazard should fully reflect the potential hazard of the subjects with missing outcome.

A Weibull parametric time to event model (the imputation model) will be fit using the observed time to MACE data from the subpopulation described above. The model will be stratified by study and prior cardiovascular disease (Yes/No), and adjusted for treatment and the following covariates potentially correlated with missing mechanism and risk of MACE so that bias due to informative censoring in the estimation of hazard could be minimized and the precision could be optimized.

- Completion of follow up to GTED: Yes/No
- Age group: <65, ≥65 years old;
- Sex: Male, Female;
- Baseline use of Metformin: Yes/No;
- History of heart failure: Yes/No;
- Baseline SBP >140 mmHg: Yes/No;
- Baseline HbA_{1c} ≥8%: Yes/No;

In case the model does not converge, covariates will be removed from the model in the descending order as listed.

For subjects with missing data, follow up time post drop-out will be imputed with random values derived from the conditional distribution of the missing data, given the observed data and the parameters estimated from the imputation model with the pre-specified covariates. If the sum of the observed time and the simulated time is less than the expected follow-up time, ie, from randomization to the GTED, an event is imputed for the corresponding subject. Otherwise, the subjects will be censored at GTED.

The imputed events and follow-up times will be integrated with the observed data. The primary efficacy model will be reanalyzed with the imputed dataset. This process will be repeated 1,000 times. The multiple analysis results will be combined into a single inferential summary (ie, HR and 95% CI) using Rubin's rules.[2]

4.1.2.3. On-Study Analysis

The primary analysis will be repeated using the On-Study analysis set which uses data from the same data period as the ITT analysis set, but is restricted to dosed subjects.

4.1.2.4. On-Treatment Analysis

The primary analysis will be repeated using the On-Treatment analysis set in which data from the first dose of study drug to 30 days after the last dose of the study drug are used.

For subjects without MACE who were lost to follow up or withdrew consent in the On-Treatment analysis set, data between the last trial contact date and last dose date plus 30 days will be considered missing. The fraction of data missing will be summarized using similar approach as described for the ITT analysis set.

4.1.2.5. MACE in the First 30, 60 and 90 Days

In addition to the Kaplan-Meier plot described in Section 4.1.1, frequency counts (n and %) of subjects experiencing the first occurrence of MACE within the first 30 days, 60 days and 90 days will be provided in the ITT analysis set.

4.1.2.6. Hazard Ratio Estimation for Individual MACE Components

A separate analysis will be performed on each component of MACE (CV death, non-fatal MI, or non-fatal stroke). Additionally, analyses of fatal/non-fatal MI as well as fatal/non-fatal stroke will be performed. In case of subjects with multiple types of events, all events will be counted towards analyses for relevant components (eg, if a subject has both non-fatal MI and non-fatal stroke, the subject will be counted as having event for both endpoints). Frequency count and percentage of subjects who have such events as well as the event rate will be summarized by treatment. The corresponding HR and its 2-sided 95% CI will also be estimated via the stratified Cox proportional hazards model in the primary analysis (refer to Section 4.1.1).

4.1.2.7. Test of Study Homogeneity

In the primary analysis, if the null hypothesis (ie, H_0: the HR $\geq$1.3) is rejected and if the upper bound of the 2-sided 95% CI of the HR is less than 1.0, an additional homogeneity assessment will be performed. A Cox proportional hazards model with treatment, study (ie, CANVAS and CANVAS-R), and treatment-by-study interaction as the explanatory variables will be fit. If the p-value for the interaction is greater than 0.05, the test result will be interpreted as a lack of statistical evidence for a difference in the treatment effect between CANVAS and CANVAS-R. The superiority of canagliflozin to placebo in MACE reduction will be claimed. Otherwise, a Gail-Simon test will be performed to assess if the interaction is quantitative or qualitative.

4.1.2.8. Subgroup Analyses

The homogeneity of treatment effects on the occurrence of the MACE across subgroups (if a total number of events is greater than 10 for two treatment groups and at least 1 event in both groups) will be examined (at a 2-sided significance level of 0.05) via a test for the treatment-by-subgroup interaction by adding this term and the subgroup as covariates (viewed as class variables) to the primary efficacy analysis (Section 4.1.1) model. Factors exhibiting interactions with $p < 0.05$ will be identified as exhibiting a possible treatment effect heterogeneity, recognizing that one or more p-values under 0.05 may be expected to be observed by chance when several subgroup factors are examined.

If a significant interaction is observed, Gail-Simon test will be used to further examine the nature of the interaction (qualitative or quantitative).

Estimates and 2-sided 95% confidence intervals for the HR (canagliflozin/placebo) will be provided for each subgroup. The analyses will be based on the primary analysis model separated for each of the following subgroups:

- Age group: <65, ≥65 years old;
- Sex: Male, Female;
- Race: White, Black or African American, Asian, Other;
- Region: Central/South America, Europe, North America, Rest of the World;
- Baseline BMI categories (<30, ≥30 kg/m^2);
- Baseline composite blood pressure categories ([SBP<140or DBP<90 mmHg] vs. [SBP ≥140 and DBP ≥90 mmHg]);
- Baseline eGFR categories (30 to <60, 60 to <90, ≥90 $mL/min/1.73m^2$);
- Baseline HbA_{1c} ≥8%: Yes/No;
- Duration of diabetes ≥10 years: Yes/No;
- History of prior CV disease: Yes/No;
- History of peripheral vascular disease: Yes/No;
- History of amputation: Yes/No;
- Baseline use of statin;
- Baseline use of anti-thrombotics;
- Baseline use of RAAS inhibitor;
- Baseline use of Beta blocker;
- Baseline use of insulin;
- Baseline use of diuretics.

4.2. Secondary Endpoints

The secondary endpoints are all-cause mortality and CV death. All mortality events are adjudicated in a blinded fashion by the EAC. The objectives of these analyses are to demonstrate that canagliflozin is superior to placebo in reducing all-cause mortality and CV death.

4.2.1. Main Analysis Method

The analysis will be based on the Truncated analysis set. For each endpoint, the following statistical hypothesis on the HR of canagliflozin over placebo will be tested.

H_0: The HR ≥1.0, versus H_1: The HR < 1.0 (*)

The HR of all canagliflozin compared to placebo will first be tested using a stratified Cox proportional hazards regression model with treatment (all canagliflozin and placebo) as the explanatory variables, and study (CANVAS and CANVAS-R) and prior CV disease subgroup (secondary and primary prevention) as the stratification factors. This base model can be expressed as follows.

$$\lambda(t) = \lambda_{0j}(t) \exp(\beta X)$$

where λ is the hazard function, λ_{0j} is the baseline hazard which is assumed to be heterogeneous for CANVAS (j=1) and CANVAS-R (j=2), and X is the indicator for the treatment of canagliflozin. With the linkage of HR = exp(β), the hypothesis in (*) can be translated in terms of the model parameter as below.

$$H_0: \beta \geq 0.0, \text{ versus } H_1: \beta < 0.0$$

The above hypothesis testing is considered final if there is no significant treatment-by-study qualitative interaction which will be evaluated by the Gail & Simon test as described below.

For each study, a proportional hazard model with term for treatment will be fit. Assuming the normality of the treatment estimate $\hat{\beta}_i \sim N(\log(\theta_i), V_i)$, i=1,2,$\hat{\beta}_i \sim N(\log(\theta_i), V_i)$ (that is valid in large samples as in CANVAS and CANVAS-R studies), where $V_i = \{I(\hat{\beta}_i)\}^{-1}$ is the inverse of the observed Fisher's observed information, the null hypothesis of no treatment-by-study qualitative interaction can be rejected in the Gail & Simon test if

$$\min\{Q^+, Q^-\} > c$$

where

$$Q^+ = \frac{\hat{\beta}_1^2}{V_1} I\{\hat{\beta}_1 > 0\} + \frac{\hat{\beta}_0^2}{V_0} I\{\hat{\beta}_0 > 0\} \text{ and } Q^- = \frac{\hat{\beta}_1^2}{V_1} I\{\hat{\beta}_1 < 0\} + \frac{\hat{\beta}_0^2}{V_0} I\{\hat{\beta}_0 < 0\}$$

with c=2.71 for type I error rate of 0.05.

If there is no significant treatment-by-study interaction, the HR estimate and the CI will be derived from the base model.

For reference, p-value of stratified log rank test for treatment effect will also be provided.

An alternative overall treatment estimate using the estimates from each study will also be reported. The estimator is the minimum variance linear combination of estimators $\hat{\beta}_1$ and $\hat{\beta}_2$ as shown below:

$$\hat{\beta} = \frac{V_2}{V_1 + V_2} \hat{\beta}_1 + \frac{V_1}{V_1 + V_2} \hat{\beta}_2 .$$

4.2.2. Supportive Analyses

4.2.2.1. Full Analysis without Data Truncation

The analysis of the 2 secondary mortality endpoints (described in Section 4.2.1) will also be conducted using the ITT analysis set (ie, without data truncation) where all subjects at risk in CANVAS and CANVAS-R are included.

4.2.2.2. Proportional Hazard Assumption

The plot of the log of cumulative hazard function by treatment over time will be made and the assumption of proportional hazards will be assessed. In addition, a treatment by logarithm-transformed time interaction term will be added into the base model for the main analysis (refer to Section 4.2.1) and tested. A p-value greater than 0.05 for the interaction term will be interpreted as no statistical evidence against the proportional hazard assumption. If the p-value is 0.05 or less and the assumption is not justified, then the p-value of the stratified log rank test will be referred.

4.2.2.3. Single Imputation for Missing Data

Every effort will be made to ascertain vital status for subjects who discontinued from full scheduled follow-up prior to the announcement of the GTED. To assess the impacts of missing follow-up data, a worst case scenario analysis will be conducted. Among subjects with unknown vital status at the study completion, those on canagliflozin will be assumed to experience mortality on the date of censoring while the placebo subjects remain censored. The stratified Cox proportional hazards model (described in Section 4.2.1) will be applied to the Truncated analysis set with the single imputation pertaining only to the canagliflozin subjects with unknown vital status. The derived HRs and CIs will be compared with the estimates from the main analysis.

4.2.2.4. Subgroup Analysis

The subgroup analysis for MACE will also be conducted for the 2 mortality endpoints using the Truncated and the ITT analysis sets. The same subgroup factors as well as analysis method described in Section 4.1.2.8 will be followed.

4.2.2.5. Consistency Analysis

The following exploratory analyses will be conducted to examine if there are components of the data that appear inconsistent:

- Hazard ratio in each of the 3 treatment regimens (CANVAS: 100 mg QD, 300 mg QD; CANVAS-R: 100 mg QD with investigator option to increase to 300 mg QD);
- Hazard ratio in the 3 separate components of the data (CANVAS prior to 20 November, 2012, CANVAS post 20 November, 2012, and CANVAS-R);
- Hazard ratio in the truncated dataset after exclusion of all subjects who had a non-fatal MACE event prior to 20 November 2012.

Forest plots will be generated to present the HRs and the CIs in these analyses.

4.3. Multiplicity Adjustment

Please refer to Section 1.4.1 for multiplicity adjustment.

4.4. Additional Endpoints

Additional endpoints are the first occurrence of the following events:

- All-cause hospitalization;
- Adjudicated hospitalization for heart failure;
- Composite of adjudicated hospitalization for heart failure or CV death.

These analyses will be done on the ITT analysis set (without truncation). The time to these CV endpoints will be analyzed using a stratified Cox proportional hazards model with treatment as the explanatory variable, and study (CANVAS and CANVAS-R) and prior CV disease subgroup (secondary prevention and primary prevention) as the stratification factors. The HRs of canagliflozin to placebo and their 95% CIs will be estimated from the model.

5. RENAL ENDPOINTS

The integrated analysis of the renal endpoints are exploratory in nature. The analysis will be based on the ITT analysis set.

5.1. Endpoints Definition

The renal endpoints of interest are:

- Progression of albuminuria;
- Regression of albuminuria;
- Renal composites:
  - 40% decrease in eGFR, renal death[a], or requirement for renal replacement therapy;
  - 40% decrease in eGFR, renal death, requirement for renal replacement therapy or CV death;
  - 40% decrease in eGFR, conversion to macroalbuminuria, renal death, or requirement for renal replacement therapy;
  - doubling of serum creatinine (SCr), renal death, or requirement for renal replacement therapy;
  - doubling of SCr, renal death, requirement for renal replacement therapy or CV death;
  - doubling of SCr, conversion to macroalbuminuria, renal death, or requirement for renal replacement therapy.

[a] Adjudicated non-CV death with a renal proximate cause is considered as renal death.

Urinary ACR is used to assess albuminuria. Subjects will be classified as having normoalbuminuria (ACR <30 mg/g), microalbuminuria (ACR ≥30 mg/g and ≤300 mg/g), or macroalbuminuria (ACR of >300 mg/g).

Albuminuria progression is the development of microalbuminuria or macroalbuminuria in a subject with baseline normoalbuminuria or the development of macroalbuminuria in a subject with baseline microalbuminuria, accompanied by an ACR value increase of greater than or equal to 30% from baseline.

Albuminuria regression is the development of normoalbuminuria in a subject with baseline microalbuminuria or macroalbuminuria or the development of microalbuminuria in a subject with baseline macroalbuminuria, accompanied by a decrease in the urinary ACR value of greater than or equal to 30% from baseline.

The onset of events of albuminuria progression/regression are based on the ACR measurements quantified by a central laboratory. The date of the progression/regression event will be defined as the visit date of the first urine sample for the potential progression/regression findings.

The components of the renal composite endpoints, such as requirement for renal replacement therapy and doubling of SCr, identified by the investigators or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent EAC.

5.2. Analysis Methods

Progression of Albuminuria

The analysis will be based on the ITT analysis set. Only subjects with baseline and at least one post-baseline ACR measures will be included in the analysis. Subjects with macroalbuminuria at baseline (ACR >300 mg/g) will also be excluded from the analysis.

At each visit, the geometric mean of the duplicate measurements (when available) will be computed and used for all subsequent analysis unless otherwise specified. For ACR values below the lower quantifiable limit, the lower quantifiable limit itself will be used in the geometric mean calculation.

The HR estimate and the CI will be derived from a stratified Cox proportional hazards model with treatment and baseline albuminuria status as the explanatory variables and study as the stratification factor.

Regression of Albuminuria

Regression of albuminuria will be analyzed in a similar fashion as progression of albuminuria based on the ITT analysis set. Only subjects with baseline and at least one post-baseline ACR measures will be included in the analysis. Subjects with normal albuminuria at baseline will be excluded. The HR estimate and the CI will be derived from a stratified Cox proportional hazards model with treatment and baseline albuminuria status as the explanatory variables and study as the stratification factor.

Renal composite endpoints

The time to each of the renal composite endpoints will be analyzed using a stratified Cox proportional hazards model with treatment as the explanatory variable, and stage of baseline chronic kidney disease, measured by eGFR (< 60, ≥60 mL/min/1.73m^2) and study as the stratification factors. The HR of canagliflozin to placebo and its 95% confidence interval, will be derived from the model.

6. SAFETY

This section describes the integration of the safety data collected in CANVAS and CANVAS-R, and the analysis methods. The main summary will be based on the On-Treatment analysis set unless otherwise specified.

Treatment groups will be canagliflozin combined doses and placebo such that the canagliflozin 100 mg and 300 mg groups in CANVAS will be pooled with the canagliflozin group in CANVAS-R. The safety for the 100 mg and the 300 mg doses will be presented in the clinical study report of CANVAS separately.

6.1. Adjudicated MACE Event

Please refer to Section 4.1 for the analysis of adjudicated MACE events.

6.2. Adverse Events

Adverse events (AEs) will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock.

A treatment-emergent adverse event (TEAE) is defined as an AE with an onset after the initiation of double-blind study medication and before the last study medication date plus 30 days. Adverse events with a start date prior to initiation of double-blind study medication which are reported to have an increase in intensity, or AEs reported to have an attribution in relationship to study medication (ie, attribution to possible, probably, very likely) after the initiation of double-blind study medication will also be considered as TEAEs. Most of the AE analysis will pertain to the TEAEs.

6.2.1. Collection of Adverse Events

CANVAS-R was started after the approval of canagliflozin. Since the safety profile of canagliflozin had been well established in the Phase 3 program, the AE collection in CANVAS-R was streamlined to include:

- serious AEs;
- AEs that resulted in study drug discontinuation;
- all AEs (serious and non-serious) for selected AEs of interest (refer Table 3 below).

After the approval of protocol amendment INT-6, the AE data collection in CANVAS was also streamlined in the same fashion as CANVAS-R.

For selected AEs of interest, additional data was collected on supplementary eCRF pages mainly for the purposes of narrative description of certain events. Table 3 lists the AEs of interest.

Table 3: Adverse Events of Interest

Section A. All AEs (serious and non-serious) listed below were collected in CANVAS through INT-6. After INT-6, only the AEs that were serious or that led to study drug discontinuation were collected. In CANVAS-R , only serious AEs or AEs that led to drug discontinuation are collected: Osmotic diuresis Volume depletion Hypoglycemia Urinary tract infection (UTI) Female mycotic genital infection Severe hypersensitivity /cutaneous reactions Pancreatitis Hepatic injury Renal related AEs (including Nephrotoxicity/ acute kidney injury)
Section B. The AEs listed below were collected regardless of whether they were serious and/or led to study drug discontinuation: Male mycotic genital infection (balanitis, phimosis, events leading to circumcision) Malignancy Renal cell cancer Bladder cancer Pheochromocytoma Leydig cell tumors Breast cancer Photosensitivity Venous thromboembolic events (VTE) Amputation Fracture Diabetic ketoacidosis

The AEs listed above will be identified using a MedDRA preferred term list (see Appendix 6).

6.2.2. Analysis Methods

The study durations of CANVAS and CANVAS-R are long relative to the rest of the canagliflozin Phase 3 program. Accordingly, the incidences of AEs (ie, proportion of subjects reporting the AEs) derived from these 2 studies are not comparable to the incidences generated in the Phase 3 program. To adjust for duration of exposure, the exposure-adjusted incidence rate will be reported in addition to the incidence. The rate is calculated as the total number of subjects with the AE divided by the on-treatment exposure in subject-years. For some particular AEs such as malignancy where the off-drug follow up is included, the follow-up-adjusted incidence rate will be estimated. The rate is calculated as the total number of subjects with the AEs divided by the follow-up time in subject-years.

For the general AEs and selected AEs of interest that are not routinely collected in CANVAS-R and CANVAS post INT-6 (refer Section A of Table 3), the main interest in the integrated summary will be the serious AEs and the AEs leading to discontinuation of study medication.

Groupings of MedDRA preferred terms used to identify events to be included in each category of AEs of interest are presented in Appendix 6.

6.2.2.1. General Adverse Events

The analysis will be based on the TEAEs in the On-Treatment analysis set. An overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- Serious AEs
- Deaths
- AEs leading to discontinuation of study medication
- Serious AEs leading to discontinuation of study medication
- Serious AEs considered drug-related
- AEs considered drug-related leading to discontinuation of study medication

SAEs by system organ class and preferred term will be summarized by treatment group using the On-Treatment analysis set. The same summary will be provided for AEs leading to discontinuation of study medication using the On-Treatment analysis set.

The incidence of all SAEs (by preferred term, grouped by SOC, and presented by treatment group) will also be summarized by the relationship to study drug, by the action taken regarding the study drug, as well as by the outcome. The relationship to study drug will be presented by 2 categories: related (which includes possibly related, probably related and very likely related, as reported by the investigator) and not related (which includes not related and doubtfully related, as reported by the investigator).

For reference, as a screening tool, the 95% CIs for incidence difference between treatment groups will be provided for the AEs (regardless of seriousness) which are reported in at least 4 or more subjects in any treatment group. Four (rule-of-4) was chosen based on the recommendation from the Safety, Planning, Evaluation, and Reporting Team (SPERT). The exclusion of “0” from the 95% CI for the between-group the treatment difference in incidence for a particular AE does not necessarily imply that the higher incidence is due to the drug. The intent of providing the 95% CIs is as a filter to identify AEs that require additional assessment. AEs are identified by the above screening procedure will be subject to further evaluation.

For AEs of interest in Section A of Table 3, a summary similar to the analysis of general AEs will be provided. The AEs will be identified using the MedDRA PTs listed in Appendix 6.

6.2.2.2. Male Mycotic Genital Infections

Balanitis and phimosis AEs will be identified using the MedDRA PTs listed in Appendix 6.

An overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- All AEs

- Serious AEs
- AEs considered drug-related (investigator assessment of possible, probable or very likely)
- AEs leading to discontinuation of study medication
- Serious AEs leading to discontinuation of study medication
- Serious AEs considered drug-related
- AEs considered drug-related leading to discontinuation of study medication

AEs by preferred term will be summarized by treatment group. A Kaplan-Meier plot for the time to first occurrence of balanitis will be provided by treatment group.

In addition, circumcision events will be identified by searching the AE, the Diagnostic or Therapeutic Procedure eCRF pages and the sponsor's pharmacovigilance database. A table will summarize the incidence and the exposure-adjusted incidence rate of TEAEs by treatment.

6.2.2.3. Selected Malignancies

The selected malignancies of interest are renal cell cancer, bladder cancer, testicular cancer (Leydig cell tumors), pheochromocytomas, and breast cancer. Selected malignancy AEs will be identified using the MedDRA PTs listed in Appendix 6, and the analyses will be based on the On-Study analysis set. For each selected malignancy of interest, an overview summary table with the incidence and the follow-up-adjusted incidence will be provided for:

- All AEs
- Serious AEs
- AEs considered drug-related (investigator assessment of possible, probable or very likely)
- AEs leading to discontinuation of study medication
- Serious AEs leading to discontinuation of study medication
- Serious AEs considered drug-related
- AEs considered drug-related leading to discontinuation of study medication

The preferred terms associated with each selected malignancy type will be summarized by treatment.

6.2.2.4. Photosensitivity

Photosensitivity AEs will be identified using the MedDRA PTs listed in Appendix 6. The integrated summary will be based on the related AEs reported in the regular AE eCRF page.

An overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- All AEs
- Serious AEs

- AEs considered drug-related (investigator assessment of possible, probable or very likely)
- AEs leading to discontinuation of study medication
- Serious AEs leading to discontinuation of study medication
- Serious AEs considered drug-related
- AEs considered drug-related leading to discontinuation of study medication

AEs by preferred term will be summarized by treatment group.

6.2.2.5. Venous Thromboembolic Events

Venous thromboembolic events will be identified using the MedDRA PTs listed in Appendix 6. The integrated summary will be based on the related AEs reported in the regular AE eCRF page.

An overview summary table with the incidence and the exposure-adjusted incidence will be provided for:

- All AEs
- Serious AEs
- AEs considered drug-related (investigator assessment of possible, probable or very likely)
- AEs leading to discontinuation of study medication
- Serious AEs leading to discontinuation of study medication
- Serious AEs considered drug-related
- AEs considered drug-related leading to discontinuation of study medication

AEs by preferred term will be summarized by treatment group.

6.2.2.6. Fracture

Fracture events identified by the investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent Fracture Adjudication Committee to confirm that events were fractures, to determine fracture location (anatomic region) and type (low trauma or not). The main analysis will be based on the adjudicated low trauma fracture and the On-Study analysis set.

An overview summary table with the incidence and the follow-up-adjusted incidence will be provided for:

- Adjudicated fractures;
- Adjudicated fractures considered serious (investigator assessment);
- Adjudicated fractures considered drug-related (investigator assessment of possible, probable or very likely);
- Adjudicated fractures leading to discontinuation of study medication;
- Adjudicated fractures considered serious and drug-related (investigator assessment);

- Adjudicated fractures considered drug-related (investigator assessment) and leading to discontinuation of study medication

A summary of adjudicated fracture stratified by sex (male and female), and anatomical region by treatment will be provided. The incidence as well as the incidence rate will be presented.

A Kaplan-Meier plot for the time to first occurrence of adjudicated fracture event will be provided by treatment group. The HR and the 95% confidence interval will be derived from a stratified Cox proportion hazards model with treatment as the explanatory variable and study as the stratification factor. The HR estimates will also be evaluated in subgroups based on sex, baseline age (<65 and ≥65 years), duration of T2DM (<10 and ≥10 years), baseline eGFR (<60 and ≥60 mL/min/1.73 m^2), and prior fracture history (yes or no).

A summary of all adjudicated fractures by anatomic location will be provided. The HR and its 95% CI as well as a Kaplan-Meier plot for the first occurrence of all adjudicated fracture will be provided using the same analysis as the low trauma fracture.

6.2.2.7. Amputation

To standardize data collection on lower extremity amputation procedures any such event identified on the AE, or Diagnostic or Therapeutic Procedure case report form pages or in the sponsor's pharmacovigilance database were to be entered on a dedicated amputation case report form page.

The main analysis of lower extremity amputations as documented in the dedicated case report form page will be based on the On-Study analysis set. An overview summary table with the incidence and the follow-up-adjusted incidence will be provided for:

- All lower limb amputations;
- Traumatic lower limb amputation;
- Atraumatic lower limb amputation.

Summary of anatomical region (toe, ankle, trans-metatarsal, below knee, above knee) of lower extremity atraumatic amputations will be reported by treatment group.

For atraumatic lower limb amputation, a Kaplan-Meier plot for the time to first occurrence of event will be provided by treatment group. The association of amputation with treatment and the baseline risk factors listed in Table 4 will be assessed via logistic regression modeling. The relationship between amputation and some post-treatment factors such as volume depletion will also be explored.

For the post-treatment AEs that may be associated with amputation, groupings of selected MedDRA preferred terms used to identify events to be included in each of the following SOC categories are presented in Appendix 7:

- Infections and Infestations;

- Vascular disorders;
- Nervous System disorders;
- Skin and subcutaneous tissue disorders.

The selected PTs in infections and infestation are further split into "Reversible Infection" and "Irreversible Infections". In addition, the preferred terms grouped under the MedDRA high level term of "skin and subcutaneous tissue ulcerations" are also of interest.

For each AE group listed above, the incidence of the respective PTs will be summarized by treatment. Stratified by treatment, the odds ratio of amputation and each AE group listed above will be estimated.

Table 4: Baseline Factors Included in the Logistic Regression Analysis

Baseline Categorical Factors	
• Gender	• Smoking
• Cardiovascular disease history	• Use of insulin
• Peripheral vascular disease history [a]	• Baseline Systolic Blood Pressure
• Amputation history	o > 120 vs ≤120 mmHg
• Neuropathy history	o > 140 vs ≤140 mmHg
• Retinopathy history	• Baseline eGFR (ml/min/1.73m^2)
• Nephropathy history	o < 60 vs ≥60
• Any diuretic use	o < 45 vs ≥45
• Loop diuretic use	• Diabetes duration (< 10 vs ≥10 yrs.)
• Non-loop diuretic use	• Baseline HbA_{1c} (> 8 vs ≤8%)
Baseline Continuous Factors	
• Age (yrs.)	• eGFR (mL/min/1.73m^2)
• Diabetes duration (yrs.)	• HbA_{1c} (%)
• Systolic blood pressure (mmHg)	• Hemoglobin (g/L)

[a] Excludes amputation history

Mortality as a Competing Risk

As mortality can hinder the observation of amputation, the lower extremity atraumatic amputation risk with and without the adjustment of the competing risk of mortality will be assessed. Without considering mortality, the cumulative incidence function can be estimated by a naïve Kaplan-Meier estimate using the time to amputation data. To account for the competing risk of mortality, the amputation-specific cumulative incidence will be estimated as follows.

$$\sum_{i:t_{(i)}\le t}\left(\frac{d_{A\,i}}{n_i}\right)\hat{S}_{A,M}\left(t_{(i)}\right)$$

where $d_{A\,i}$ is the number of amputation cases at the i-th event time among n_i subjects still at risk of either amputation or mortality, and $\hat{S}_{A,M}$ is the Kaplan-Meier estimate of the probability of free from both amputation and mortality.

The estimates will be provided by treatment. The estimated amputation-specific cumulative incidence will be plotted along with the naïve Kaplan-Meier estimates. The difference in the estimates of survival probability will be evaluated by treatment.

6.2.2.8. Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) and related AEs will be identified using the list of MedDRA terms in Appendix 6. Adverse events identified by investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent DKA Adjudication Committee. The main analysis of the DKA events will be based on adjudicated events of DKA in the On-Study analysis set. Events occurring at any time post-randomization, regardless of the timing of the last dose of study medication, will be included.

For the adjudicated DKA events, the incidence and the follow-up-adjusted incidence rate will be summarized.

A listing of all DKA events identified by the sponsor's medical monitoring team and the subset of these events that went for adjudication will be provided.

6.2.2.9. Pancreatitis

Pancreatitis and related AEs identified by the sponsor using the list of MedDRA terms pre-specified in the charter will be sent to the independent Pancreatitis Adjudication Committee. The main analysis of events will be based on adjudicated, confirmed events in the On-Treatment analysis set. Analysis based on events occurring at any time post-randomization, regardless of the timing of the last dose of study medication, will be performed. The incidence rate and proportion of adjudicated pancreatitis events by severity will be summarized. The total number of subjects with an event not confirmed by the Pancreatitis Adjudication Committee will also be summarized.

6.3. Clinical Laboratory Tests

The percentage of subjects with specific treatment-emergent laboratory values meeting pre-defined limit of change (PDLC) criteria listed in Appendix 8 will be summarized. The 95% CI for the percentage difference between canagliflozin compared to placebo group will be provided for each PDLC criterion which have at least 4 or more subjects in any treatment group; a corresponding listing will also be provided. As described above, PDLC values will be presented based on measurements on study drug and up to a maximum of 2 days after the last dose of study drug, as well as all measurements regardless of the time of the last dose of double-blind study drug. Summaries based on both standard units (SI) and conventional units will be provided.

6.4. Vital Signs

A treatment-emergent vital sign abnormality is defined as a change from baseline and subsequent post-baseline value that satisfies the criteria listed in the PDLC list (Appendix 8). For each vital sign parameter, the proportion of subjects with a treatment-emergent abnormality will be tabulated by treatment group. PDLC values will be presented based on measurements up to a maximum of 2 days after the last dose of study drug. The blood pressure measurements will be based on the average of the consecutive sitting blood pressure readings that were to be collected at each visit.

REFERENCES

1. Peto R et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. *Int. Br. J. Cancer.* 1976; 34:585-612.

2. Little R et al. The treatment of missing data in a large cardiovascular clinical outcomes study. Clin Trials. 2016;13(3):344-351.

Appendix 1: Summary of Operational Specifics and Key Inclusion/Exclusion Criteria

	CANVAS	CANVAS-R
N	4330	5812
Duration	Dec 2009 to 1Q2017	Jan 2014 to 1Q2017
Primary objective	MACE events	Progression of albuminuria
Key secondary objectives	Progression of albuminuria, GFR changes	MACE events, regression of albuminuria, GFR changes
Endpoint adjudication	All deaths, nonfatal MI and MI-like events, nonfatal stroke and stroke-like events, hospitalization for heart failure, VTE (only in CANVAS), fractures	
AE collection	SAEs, AEs that result in study drug discontinuation, AEs of interest	
Key inclusion criteria	Diagnosis of T2DM with HbA_{1c} level ≥7.0% to ≤10.5% at screening	
	Not currently on AHA therapy or on AHA monotherapy or combination therapy with any approved agent (except SGLT2i) (stable regimen for ≥8 weeks prior in CANVAS, due to substudies)	
	History or high risk of CV events defined on the basis of either: Age ≥30 years with documented symptomatic atherosclerotic CV disease: including stroke; MI; hospital admission for unstable angina; coronary artery bypass graft; percutaneous coronary intervention (with or without stenting); peripheral revascularization (angioplasty or surgery); symptomatic with documented hemodynamically-significant carotid or peripheral vascular disease; or amputation secondary to vascular disease Age ≥50 years with 2 or more of the following risk factors determined at the screening visit: duration of T2DM of 10 years or more, systolic blood pressure >140 mmHg (average of 3 readings) recorded at the Screening Visit, while the subject is on at least one blood pressure-lowering treatment, current daily cigarette smoker, documented micro- or macroalbuminuria, or documented HDL-C of <1 mmol/L (<39 mg/dL).	
Key exclusion criteria	History of diabetic ketoacidosis, T1DM, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy	
	Fasting fingerstick glucose at home or at investigational site >270 mg/dL (>15 mmol/L) at Baseline/Day 1 *For patients on a sulfonylurea agent or on insulin*: fasting fingerstick glucose at home or at investigational site <110 mg/dL (<6 mmol/L) at Baseline/Day 1	
	History of one or more severe hypoglycemic episode within 6 months before screening	
	Myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident within 3 months before screening, or a planned revascularization procedure, or history of New York Heart Association (NYHA) Class IV cardiac disease	
	History of hepatitis B surface antigen or hepatitis C antibody positive, or other clinically active liver disease	
	ALT levels >2.0 times the ULN or total bilirubin >1.5 times the ULN at screening	
	Any history of or planned bariatric surgery.	
	Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 at screening (provided by the central laboratory). *For subjects taking metformin*: at screening, serum creatinine ≥1.4 mg/dL (124 μmol/L) for men or ≥1.3 mg/dL (115 μmol/L) for women; no contraindication to the use of metformin (including eGFR) based on the label of the country of investigational site.	eGFR <30 mL/min/1.73m^2 at screening visit (provided by the central laboratory).

Appendix 2: Expanded List of the Eligibility Criteria

Note: Differences between the 2 studies are underlined.

	CANVAS	CANVAS-R
	Inclusion criteria at screening visit	**Inclusion criteria at screening visit**
Incl-1	Man or woman with a diagnosis of T2DM with HbA_{1c} level ≥7.0% to ≤10.5% at screening and be either (1) not currently on AHA therapy or (2) on AHA monotherapy or combination therapy with any approved agent: eg, sulfonylurea, metformin, pioglitazone, alpha-glucosidase inhibitor, GLP-1 analogue, DPP-4 inhibitor, or insulin.	Man or woman with a diagnosis of T2DM with HbA_{1c} level ≥7.0% to ≤10.5% at screening and be either (1) not currently on AHA therapy or (2) on AHA monotherapy or combination therapy with any approved agent: eg, sulfonylurea, metformin, pioglitazone, alpha-glucosidase inhibitor, GLP-1 analogue, DPP-4 inhibitor, or insulin.
Incl-2	History or high risk of CV events defined on the basis of either: Age ≥30 years with documented symptomatic atherosclerotic CV disease: including stroke; MI; hospital admission for unstable angina; coronary artery bypass graft; percutaneous coronary intervention (with or without stenting); peripheral revascularization (angioplasty or surgery); symptomatic with documented hemodynamically-significant carotid or peripheral vascular disease; or amputation secondary to vascular disease Age ≥50 years with 2 or more of the following risk factors determined at the screening visit: duration of T2DM of 10 years or more, systolic blood pressure >140 mmHg (average of 3 readings) recorded at the Screening Visit, while the subject is on at least one blood pressure-lowering treatment, current daily cigarette smoker, documented micro- or macroalbuminuria, or documented HDL-C of <1 mmol/L (<39 mg/dL).	History or high risk of CV events defined on the basis of either: Age ≥30 years with documented symptomatic atherosclerotic CV events: including stroke; MI; hospital admission for unstable angina; coronary artery bypass graft; percutaneous coronary intervention (with or without stenting); peripheral revascularization (angioplasty or surgery); symptomatic with documented hemodynamically-significant carotid or peripheral vascular disease; or amputation secondary to vascular disease. Age ≥50 years with 2 or more of the following risk factors determined at the screening visit: duration of T2DM of 10 years or more, systolic blood pressure >140 mmHg (average of 3 readings) recorded at the Screening Visit, while the subject is on at least one blood pressure-lowering treatment, current daily cigarette smoker, documented micro- or macroalbuminuria <u>within one year of screening</u>, or documented HDL-C of <1 mmol/L (<39 mg/dL) <u>within one year of screening</u>.
Incl-3	Women must be: postmenopausal, defined as >45 years of age with amenorrhea for at least 18 months, or >45 years of age with amenorrhea for at least 6 months and less than 18 months and a serum follicle stimulating hormone (FSH) level >40 IU/L, or surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal ligation), or otherwise be incapable of pregnancy, or heterosexually active *and* practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (eg, condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), or male partner sterilization, consistent with local regulations regarding use of birth control methods for subjects participating in clinical trials, for the duration of their participation in the study, or not heterosexually active.	Women must be: postmenopausal, defined as: >45 years of age with amenorrhea for at least 18 months, or >45 years of age with amenorrhea for at least 6 months and less than 18 months and a known serum follicle stimulating hormone (FSH) level >40 IU/L, or surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal <u>occlusion</u>), or otherwise be incapable of pregnancy, or heterosexually active *and* practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (eg, condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), or male partner sterilization, consistent with local regulations regarding use of birth control methods for subjects participating in clinical trials, for the duration of their participation in the study, or not heterosexually active.

	CANVAS	CANVAS-R
Incl-4	Subjects who are not heterosexually active at screening must agree to utilize a highly effective method of birth control if they become heterosexually active during their participation in the study. Women of childbearing potential must have a negative urine β-human chorionic gonadotropin (β-hCG) pregnancy test at screening and baseline (predose, Day 1).	Women of childbearing potential (ie, those subjects who do not meet the postmenopausal definition above, regardless of age) must have a negative urine pregnancy test at baseline (Day 1) and at screening if required by local regulations (Note: a serum pregnancy test is acceptable in lieu of a urine pregnancy test if required by local regulations)
Incl-5	Willing and able to adhere to the prohibitions and restrictions specified in this protocol.	Willing and able to adhere to the prohibitions and restrictions specified in this protocol.
Incl-6	Subjects must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study. To participate in the optional pharmacogenomic component of this study, subjects must have signed the informed consent form for pharmacogenomic research indicating willingness to participate in the pharmacogenomic component of the study (where local regulations permit). Refusal to give consent for this component does not exclude a subject from participation in the clinical study.	Subjects must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study. *[There are no pharmacogenomic collections in CANVAS-R]*
Incl-7	**Inclusion criteria at randomization** Subjects must have taken ≥80% of their single-blind placebo capsules during the 2-week run-in period at Day 1 to be eligible for randomization.	**Inclusion criteria at randomization** Subjects must have taken ≥80% of their single-blind placebo doses during the 2-weeks prior to randomization on Day 1 to be eligible for randomization.

	CANVAS	CANVAS-R
Excl-1	**Diabetes-Related/Metabolic** History of diabetic ketoacidosis, T1DM, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy On an AHA and not on a stable regimen (ie, agents and doses) for at least 8 weeks before the screening visit and through the screening/run-in period. **Note**: a stable dose of insulin is defined as no change in the insulin regimen (ie, type[s] of insulin) and ≤15% change in the total daily dose of insulin (averaged over 1 week to account for day to day variability). Fasting fingerstick glucose at home or at investigational site >270 mg/dL (>15 mmol/L) at Baseline/Day 1 *For patients on a sulfonylurea agent or on insulin*: fasting fingerstick glucose at home or at investigational site <110 mg/dL (<6 mmol/L) at Baseline/Day 1 **Note**: at the investigator's discretion, based upon an assessment of recent SMBG values, subjects meeting either of these fingerstick glucose exclusion criteria may continue the single-blind placebo and return to the investigational site within 14 days and may be randomized if the repeat fasting fingerstick value no longer meets the exclusion criterion. Subjects with fingerstick glucose >270 mg/dL (>15 mmol/L) may have their AHA regimen adjusted, and be rescreened once on a stable regimen for at least 8 weeks.	**Diabetes-Related/Metabolic** History of diabetic ketoacidosis, T1DM, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy. *[There are no substudies in CANVAS-R that required a stable prestudy dose of AHA].*
Excl-2	History of one or more severe hypoglycemic episode within 6 months before screening. Note: a severe hypoglycemic episode is defined as an event that requires the help of another person.	History of one or more severe hypoglycemic episode within 6 months before screening. Note**:** a severe hypoglycemic episode is defined as an event that requires the help of another person.
Excl-3	History of hereditary glucose-galactose malabsorption or primary renal glucosuria.	History of hereditary glucose-galactose malabsorption or primary renal glucosuria.
Excl-4	Ongoing, inadequately controlled thyroid disorder. Note: subjects on thyroid hormone replacement therapy must be on a stable dose for at least 6 weeks before Day 1.	Ongoing, inadequately controlled thyroid disorder. Note: subjects on thyroid hormone replacement therapy must be on a stable dose for at least 6 weeks before Day 1.
Excl-5	**Renal/Cardiovascular** Renal disease that required treatment with immunosuppressive therapy or a history of chronic dialysis or renal transplant. **Note**: subjects with a history of treated childhood renal disease, without sequelae, may participate.	**Renal/Cardiovascular** Renal disease that required treatment with immunosuppressive therapy or a history of chronic dialysis or renal transplant. Note: subjects with a history of treated childhood renal disease, without sequelae, may participate.

	CANVAS	CANVAS-R
Excl-6	Myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident within 3 months before screening, or a planned revascularization procedure, or history of New York Heart Association (NYHA) Class IV cardiac disease; refer to Attachment 3, New York Heart Association Classification of Cardiac Disease, for a description of the classes	Myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident within 3 months before screening, or a planned revascularization procedure, or history of New York Heart Association (NYHA) Class IV cardiac disease (The Criteria Committee of the New York Heart Association).
Excl-7	Findings on 12-lead ECG that would require urgent diagnostic evaluation or intervention (eg, new clinically important arrhythmia or conduction disturbance).	Known ECG findings within 3 months before screening that would require urgent diagnostic evaluation or intervention (eg, new clinically important arrhythmia or conduction disturbance).
Excl-8	**Gastrointestinal** History of hepatitis B surface antigen or hepatitis C antibody positive (unless associated with documented persistently stable/normal range aspartate aminotransferase [AST] and ALT levels), or other clinically active liver disease	**Gastrointestinal** Known history of hepatitis B surface antigen or hepatitis C antibody positive (unless known to be associated with documented persistently stable/normal range aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels), or other clinically active liver disease.
Excl-9	Any history of or planned bariatric surgery.	Any history of or planned bariatric surgery.
Excl-10	**Laboratory** Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 at screening (provided by the central laboratory). *For subjects taking metformin*: at screening, serum creatinine ≥1.4 mg/dL (124 μmol/L) for men or ≥1.3 mg/dL (115 μmol/L) for women; no contraindication to the use of metformin (including eGFR) based on the label of the country of investigational site.	**Laboratory** eGFR <30 mL/min/1.73m^2 at screening visit (provided by the central laboratory).
Excl-11	ALT levels >2.0 times the ULN or total bilirubin >1.5 times the ULN at screening, unless in the opinion of the investigator and as agreed upon by the sponsor's medical officer, the findings are consistent with Gilbert's disease.	ALT levels >2.0 times the upper limit of normal (ULN) or total bilirubin >1.5 times the ULN, unless in the opinion of the investigator and as agreed upon by the sponsor's medical officer, the findings are consistent with Gilbert's disease.
Excl-12	**Other conditions** History of malignancy within 5 years before screening (exceptions: squamous and basal cell carcinomas of the skin and carcinoma of the cervix in situ, or a malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence).	**Other conditions** History of malignancy within 5 years before screening (exceptions: squamous and basal cell carcinomas of the skin and carcinoma of the cervix in situ, or a malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence).
Excl-13	History of human immunodeficiency virus (HIV) antibody positive.	History of human immunodeficiency virus (HIV) antibody positive.
Excl-14	Subject has a current clinically important hematological disorder (eg, symptomatic anemia, proliferative bone marrow disorder, thrombocytopenia).	Subject has a current clinically important hematological disorder (eg, symptomatic anemia, proliferative bone marrow disorder, thrombocytopenia).

	CANVAS	CANVAS-R
Excl-15	Investigator's assessment that the subject's life expectancy is less than 1 year, or any condition that in the opinion of the investigator would make participation not in the best interest of the subject, or could prevent, limit, or confound the protocol-specified safety or efficacy assessments.	Investigator's assessment that the subject's life expectancy is less than 1 year, or any condition that in the opinion of the investigator would make participation not in the best interest of the subject, or could prevent, limit, or confound the protocol-specified safety or efficacy assessments.
Excl-16	Major surgery (ie, requiring general anesthesia) within 3 months of the screening visit or any surgery planned during the subject's expected participation in the study (except minor surgery, ie, outpatient surgery under local anesthesia).	Major surgery (ie, requiring general anesthesia) within 3 months of the screening visit or any surgery planned during the subject's expected participation in the study (except minor surgery, ie, outpatient surgery under local anesthesia).
Excl-17	Any condition that, in the opinion of the investigator, would compromise the well-being of the subject or prevent the subject from meeting or performing study requirements.	Any condition that, in the opinion of the investigator, would compromise the well-being of the subject or prevent the subject from meeting or performing study requirements.
Excl-18	**Medications/Therapies** Current use of other SGLT2 inhibitor; use of rosiglitazone within 8 weeks of screening. (Note: subjects taking rosiglitazone who are already in screening are not eligible for randomization.).	**Medications/Therapies** Current or prior use of an SGLT2 inhibitor.
Excl-19	[*See #22 below*]	Prior or current participation in another canagliflozin study.
Excl-20	Known allergies, hypersensitivity, or intolerance to canagliflozin or its excipients.	Known allergies, hypersensitivity, or intolerance to canagliflozin or its excipients.
Excl-21	Current use of a corticosteroid medication or immunosuppressive agent, or likely to require treatment with a corticosteroid medication (for longer than 2 weeks in duration) or an immunosuppressive agent. Note: subjects using inhaled, intranasal, intra-articular, or topical corticosteroids, or corticosteroids in therapeutic replacement doses may participate.	Current use of a corticosteroid medication or immunosuppressive agent, or likely to require treatment with a corticosteroid medication (for longer than 2 weeks in duration) or an immunosuppressive agent. Note: subjects using inhaled, intranasal, intra-articular, or topical corticosteroids, or corticosteroids in therapeutic replacement doses may participate.
Excl-22	Received an active investigational drug (including vaccines) or used an investigational medical device within 3 months before Day 1/baseline or received at least one dose of canagliflozin in a prior study.	Received an active investigational drug (including vaccines) or used an investigational medical device within 3 months before Day 1/baseline.
Excl-23	**General** History of drug or alcohol abuse within 3 years before screening.	**General** History of drug or alcohol abuse within 3 years before screening.
Excl-24	Pregnant or breast-feeding or planning to become pregnant or breast-feed during the study.	Pregnant or breast-feeding or planning to become pregnant or breast-feed during the study.
Excl-25	Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator.	Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator.

Appendix 3: Number of Randomized Subjects by Region, Country, and Study

Region	Country	CANVAS	CANVAS-R	Integrated
CENTRAL/SOUTH AMERICA	Argentina	160	305	465
	Brazil		549	549
	Columbia	7		7
	Region total	(167)	(854)	(1021)
EUROPE	Belgium	21	152	173
	Czech Republic	117	139	256
	Germany	175	101	276
	Spain	209	496	705
	Estonia	44		44
	France		124	124
	United Kingdom	92	151	243
	Hungary	125	179	304
	Italy		98	98
	Luxembourg	1		1
	Netherlands	228	249	477
	Norway	109		109
	Poland	144	363	507
	Sweden	71	221	292
	Region total	(1336)	(2273)	(3609)
NORTH AMERICA	Canada	396	282	678
	Mexico	124	228	352
	United State	727	673	1400
	Region total	(1247)	(1183)	(2430)
REST OF THE WORLD	Australia	177	109	286
	China		92	92
	India	695		695
	Israel	25		25
	South Korea		167	167
	Malaysia	73	92	165
	New Zealand	74	105	179
	Russia	389	412	801
	Taiwan		76	76
	Ukraine	147	449	596
	Region total	(1580)	(1502)	(3082)
STUDY TOTAL		4330	5812	10142

Appendix 4: List of Key Analysis for Primary and Secondary Endpoints

Analysis Set	Dataset	Endpoint	Purpose of Analysis (related section)	Role
Primary Hypothesis				
ITT	CANVAS + CANVAS-R	MACE	Demonstrate the exclusion of 1.3 in the HR of Cana to placebo (Section 4.1.1)	Main
ITT	CANVAS + CANVAS-R	MACE	Assess PH assumption (Section 4.1.2.1)	Supportive
ITT	CANVAS + CANVAS-R	MACE	Assess the impacts of missing data on the primary conclusion via multiple imputation method (Section 4.1.2.2)	Supportive
On-Treatment	CANVAS + CANVAS-R	MACE	Demonstrate the exclusion of 1.3 in the HR of Cana to placebo (Section 4.1.2.3)	Supportive
ITT	CANVAS + CANVAS-R	MACE component	Assess the consistency of the HR estimate for each component of MACE (Section 4.1.2.4)	Supportive
ITT	CANVAS + CANVAS-R	MACE	Assess the consistency of the HR estimate for selected participant subgroups including study (Section 4.1.2.5, 4.1.2.6)	Supportive
Secondary Hypotheses				
Truncated	Truncated CANVAS + CANVAS-R	All-cause mortality	Demonstrate the superiority of Cana to placebo in the reduction of all-cause mortality (Section 4.2.1)	Main
ITT	CANVAS + CANVAS-R	All-cause mortality	Demonstrate the superiority of Cana to placebo in the reduction of all-cause mortality (Section 4.2.2.1)	Supportive
Truncated	Truncated CANVAS + CANVAS-R	All-cause mortality	Assess PH assumption (Section 4.2.2.2)	Supportive

Analysis Set	Dataset	Endpoint	Purpose of Analysis (related section)	Role
Truncated	Truncated CANVAS + CANVAS-R	All-cause mortality	Assess the impacts of missing data on the superiority conclusion via single imputation method (Section 4.2.2.3)	Supportive
Secondary Hypotheses				
Truncated	Truncated CANVAS + CANVAS-R	CV mortality	Demonstrate the superiority of Cana to placebo in the reduction of all-cause mortality (Section 4.2.1)	Main
ITT	CANVAS + CANVAS-R	CV mortality	Demonstrate the superiority of Cana to placebo in the reduction of all-cause mortality (Section 4.2.2.1)	Supportive
Truncated	Truncated CANVAS + CANVAS-R	CV mortality	Assess PH assumption (Section 4.2.2.2)	Supportive
Truncated	Truncated CANVAS + CANVAS-R	CV mortality	Assess the impacts of missing data on the superiority conclusion via single imputation method (Section 4.2.2.3)	Supportive

Appendix 5: Confidence Interval for Risk Ratio Based on the Log Rank Method

Let K denote the number of distinct event time in the integrated database. At each event time, the following 2x2 table can be constructed.

	Status		
Treatment	Event	No Event	Total
Canagliflozin	d_{1k}	n_{1k}-d_{1k}	n_{1k}
Placebo	d_{2k}	n_{2k}-d_{2k}	n_{2k}
Total:	d_k	n_k- d_k	n_k

The log rank statistic can be computed with the layout below.

Ordered Distinct Event Time	Observed Number of Events	Expected Number of Events	Difference	Variance
$y_{(1)}$	d_{11}	$e_{11}= n_{11}d_1/n_1$	d_{11}-e_{11}	v_{11}
$y_{(2)}$	d_{12}	$e_{12}= n_{12}d_2/n_2$	d_{12}-e_{12}	v_{12}
…	…	…	…	…
$y_{(K)}$	d_{1K}	$e_{1K}= n_{1K}d_K/n_K$	d_{1K}-e_{1K}	v_{1K}
Total:	d_1	e_1	d_1-e_1	v_1

Note: $V_{1k} = n_{1k}\, n_{2k}\, d_k\, (n_k - d_k)/[n^2_k\, (n_k - 1)]$

where $d_1 = \sum_{k=1}^{K} d_{1k}$, $e_1 = \sum_{k=1}^{K} e_{1k}$ and $v_1 = \sum_{k=1}^{K} v_{1k}$.

Peto et al. (1976) suggested that the HR can be estimated as

$$\hat{\lambda} = \exp(\frac{d_1 - e_1}{v_1})$$

The (1-α) 100% confidence interval for λ can be obtained as

$$\exp\{[(d_1 - e_1)/v_1] \pm z_{1-\alpha/2}/\sqrt{v_1}\}$$

where $z_{1-\alpha/2}$ is the 1-α/2 percentile for the standard normal distribution.

Appendix 6: List of Preferred Terms for Adverse Event of Interest

Diabetic ketoacidosis	Female Mycotic Genital Infections	Fracture
Acidosis	Genital candidiasis	Acetabulum fracture
Acidosis aggravated	Genital infection	Ankle fracture
Acidosis diabetic	Genital infection female	Atypical femur fracture
Acidosis metabolic	Genital infection fungal	Atypical fracture
Acidosis NOS	Urogenital infection fungal	Avulsion fracture
Acute acidosis	Vaginal infection	Bone fragmentation
Anion gap acidosis	Vaginal inflammation	Cervical vertebral fracture
Blood ketone body	Vulvitis	Chance fracture
Blood ketone body increased	Vulvovaginal candidiasis	Clavicle fracture
Blood ketone body present	Vulvovaginal mycotic infection	Closed fracture manipulation
Diabetes mellitus with ketoacidosis	Vulvovaginitis	Comminuted fracture
Diabetes with hyperosmolarity		Complicated fracture
Diabetes with ketoacidosis		Compression fracture
Diabetic acidosis		Craniofacial fracture
Diabetic hyperglycemic coma		Elevation skull fracture
Diabetic hyperosmolar coma		Epiphyseal fracture
Diabetic ketoacidosis		External fixation of fracture
Diabetic ketoacidotic hyperglycemic coma		Facial bones fracture
Diabetic metabolic decompensation		Femoral neck fracture
High anion gap metabolic acidosis		Femur fracture
Hyperglycemic seizure		Fibula fracture
Hyperosmolar hyperglycemic state		Foot fracture
Hyperosmolar state		Forearm fracture
Ketoacidosis		Fracture
Ketonuria		Fracture debridement
Ketosis		Fracture delayed union
Metabolic acidosis		Fracture displacement
Metabolic acidosis exacerbated		Fracture malunion
Metabolic acidosis NOS exacerbated		Fracture nonunion
Metabolic acidosis not otherwise specified (NOS)		Fracture pain
Metabolic acidosis worsened		Fracture reduction
Type I diabetes mellitus with ketoacidosis		Fracture treatment
Type II diabetes mellitus with ketoacidosis		Fractured coccyx
		Fractured ischium
		Fractured maxilla elevation
		Fractured sacrum
		Fractured skull depressed
		Fractured zygomatic arch elevation
		Greenstick fracture
		Hand fracture
		Hip fracture
		Humerus fracture
		Ilium fracture
		Impacted fracture
		Internal fixation of fracture
		Jaw fracture

Diabetic ketoacidosis	Female Mycotic Genital Infections	Fracture
		Limb crushing injury
		Limb fracture
		Loss of anatomical alignment after fracture reduction
		Lower limb fracture
		Lumbar vertebral fracture
		Multiple fractures
		Open fracture
		Open reduction of fracture
		Open reduction of spinal fracture
		Osteochondral fracture
		Osteoporotic fracture
		Patella fracture
		Pathological fracture
		Pelvic fracture
		Periprosthetic fracture
		Pubis fracture
		Radius fracture
		Rib fracture
		Sacroiliac fracture
		Scapula fracture
		Skull fracture
		Skull fractured base
		Spinal compression fracture
		Spinal fracture
		Spinal fusion fracture
		Sternal fracture
		Stress fracture
		Thoracic vertebral fracture
		Tibia fracture
		Torus fracture
		Traumatic fracture
		Ulna fracture
		Upper limb fracture
		Wrist fracture

Hepatic Injury	Hypoglycaemia	Male Mycotic Genital Infections
Acute graft versus host disease in liver	Hypoglycaemia	Balanitis
Acute hepatic failure	Hypoglycaemic coma	Balanitis candida
Acute yellow liver atrophy	Hypoglycaemic seizure	Balanoposthitis
Allergic hepatitis		Balanoposthitis infective
Ammonia increased		Erosive balanitis
Ascites		Gangrenous balanitis
Asterixis		Genital candidiasis
Autoimmune hepatitis		Genital infection
Bacterascites		Genital infection fungal
Biliary ascites		Genital infection male
Biliary cirrhosis		Penile infection
Biliary cirrhosis primary		Posthitis
Biliary fibrosis		
Bilirubin excretion disorder		
Biopsy liver abnormal		
Child-Pugh-Turcotte score increased		

Hepatic Injury	Hypoglycaemia	Male Mycotic Genital Infections
Cholaemia		
Cholestasis		
Cholestatic liver injury		
Cholestatic pruritus		
Chronic graft versus host disease in liver		
Chronic hepatic failure		
Chronic hepatitis		
Coma hepatic		
Cryptogenic cirrhosis		
Diabetic hepatopathy		
Drug-induced liver injury		
Duodenal varices		
Focal nodular hyperplasia		
Gallbladder varices		
Gastric varices		
Gastric varices haemorrhage		
Graft versus host disease in liver		
Haemangioma of liver		
Haemorrhagic ascites		
Haemorrhagic hepatic cyst		
Hepatectomy		
Hepatic adenoma		
Hepatic atrophy		
Hepatic calcification		
Hepatic cirrhosis		
Hepatic cyst		
Hepatic cyst ruptured		
Hepatic encelalopathy		
Hepatic encephalopathy prophylaxis		
Hepatic failure		
Hepatic fibrosis		
Hepatic fibrosis marker abnormal		
Hepatic haemangioma rupture		
Hepatic hydrothorax		
Hepatic infiltration eosinophilic		
Hepatic lesion		
Hepatic necrosis		
Hepatic steatosis		
Hepatitis		
Hepatitis acute		
Hepatitis cholestatic		
Hepatitis chronic active		
Hepatitis chronic persistent		
Hepatitis fulminant		
Hepatitis toxic		
Hepatobiliary disease		
Hepatocellular foamy cell syndrome		
Hepatocellular injury		
Hepatopulmonary syndrome		
Hepatorenal failure		
Hepatorenal syndrome		
Hepatotoxicity		
Hyperbilirubinaemia		
Icterus index increased		

Hepatic Injury	Hypoglycaemia	Male Mycotic Genital Infections
Intestinal varices		
Ischaemic hepatitis		
Jaundice		
Jaundice cholestatic		
Jaundice hepatocellular		
Liver and small intestine transplant		
Liver disorder		
Liver injury		
Lupoid hepatic cirrhosis		
Lupus hepatitis		
Mixed liver injury		
Nodular regenerative hyperplasia		
Non-alcoholic steatohepatitis		
Non-cirrhotic portal hypertension		
Ocular icterus		
Oedema due to hepatic disease		
Oesophageal varices haemorrhage		
Parenteral nutrition associated liver disease		
Peripancreatic varices		
Periportal oedema		
Portal hypertension		
Portal hypertensive enteropathy		
Portal hypertensive gastropathy		
Portal triaditis		
Portal vein cavernous transformation		
Portal vein dilatation		
Portopulmonary hypertension		
Radiation hepatitis		
Renal and liver transplant		
Retrograde portal vein flow		
Reye's syndrome		
Reynold's syndrome		
Splenic varices		
Splenic varices haemorrhage		
Subacute hepatic failure		
Varices oesophageal		
Varicose veins of abdominal wall		

Malignancy Bladder Cancer	Malignancy Breast Cancer	Malignancy Phaeochromocytoma
Bladder adenocarcinoma recurrent	Apocrine breast carcinoma	Phaeochromocytoma
Bladder adenocarcinoma stage 0	Breast angiosarcoma	Phaeochromocytoma crisis
Bladder adenocarcinoma stage I	Breast angiosarcoma metastatic	Phaeochromocytoma excision
Bladder adenocarcinoma stage II	Breast cancer	Phaeochromocytoma malignant
Bladder adenocarcinoma stage III	Breast cancer female	
Bladder adenocarcinoma stage IV	Breast cancer in situ	
Bladder adenocarcinoma stage unspecified	Breast cancer male	
Bladder cancer	Breast cancer metastatic	
Bladder cancer recurrent	Breast cancer recurrent	
Bladder cancer stage 0, with cancer in situ	Breast cancer stage I	
Bladder cancer stage 0, without cancer in situ	Breast cancer stage II	
Bladder cancer stage I, with cancer in situ	Breast cancer stage III	

Malignancy Bladder Cancer	Malignancy Breast Cancer	Malignancy Phaeochromocytoma
Bladder cancer stage I, without cancer in situ	Breast cancer stage IV	
Bladder cancer stage II	Breast neoplasm	
Bladder cancer stage III	Breast sarcoma	
Bladder cancer stage IV	Breast sarcoma metastatic	
Bladder squamous cell carcinoma recurrent	Breast sarcoma recurrent	
Bladder squamous cell carcinoma stage 0	Contralateral breast cancer	
Bladder squamous cell carcinoma stage I	HER-2 positive breast cancer	
Bladder squamous cell carcinoma stage II	Hormone refractory breast cancer	
Bladder squamous cell carcinoma stage III	Inflammatory carcinoma of breast recurrent	
Bladder squamous cell carcinoma stage IV	Inflammatory carcinoma of breast stage III	
Bladder squamous cell carcinoma stage unspecified	Inflammatory carcinoma of breast stage IV	
Bladder transitional cell carcinoma	Inflammatory carcinoma of the breast	
Bladder transitional cell carcinoma metastatic	Intraductal papillary breast neoplasm	
Bladder transitional cell carcinoma recurrent	Intraductal proliferative breast lesion	
Bladder transitional cell carcinoma stage 0	Invasive breast carcinoma	
Bladder transitional cell carcinoma stage I	Invasive ductal breast carcinoma	
Bladder transitional cell carcinoma stage II	Invasive lobular breast carcinoma	
Bladder transitional cell carcinoma stage III	Invasive papillary breast carcinoma	
Bladder transitional cell carcinoma stage IV	Lobular breast carcinoma in situ	
Metastases to bladder	Malignant nipple neoplasm	
Metastatic carcinoma of the bladder	Malignant nipple neoplasm female	
Transitional cell carcinoma	Malignant nipple neoplasm male	
	Medullary carcinoma of breast	
	Metaplastic breast carcinoma	
	Metastases to breast	
	Mucinous breast carcinoma	
	Neuroendocrine breast tumour	
	Nipple neoplasm	
	Oestrogen receptor positive breast cancer	
	Paget's disease of nipple	
	Phyllodes tumour	
	Triple negative breast cancer	
	Tubular breast carcinoma	

Malignancy Renal Cell Cancer	Malignancy Testicular	Osmotic Diuresis
Clear cell renal cell carcinoma	Benign neoplasm of testis	Dry mouth
Clear cell sarcoma of the kidney	Leydig cell tumour of the testis	Dry throat
Denys-Drash syndrome	Sertoli cell testicular tumour	Micturition disorder
Hereditary leiomyomatosis renal cell carcinoma	Spermatocytic seminoma	Micturition urgency
Hereditary papillary renal carcinoma	Testicle adenoma	Nocturia
Metastatic renal cell carcinoma	Testicular cancer metastatic	Pollakiuria
Nephroblastoma	Testicular neoplasm	Polydipsia
Non-renal cell carcinoma of kidney	Testicular papilloma	Polyuria
Renal cancer	Testis cancer	Thirst
Renal cancer metastatic		Tongue dry
Renal cancer recurrent		Urine output increased
Renal cancer stage I		
Renal cancer stage II		
Renal cancer stage III		
Renal cancer stage IV		
Renal cell carcinoma		
Renal cell carcinoma recurrent		
Renal cell carcinoma stage I		
Renal cell carcinoma stage II		
Renal cell carcinoma stage III		
Renal cell carcinoma stage IV		
Rhabdoid tumour of the kidney		

Phimosis	Photosensitivity
Acquired phimosis	Actinic elastosis
Phimosis	Actinic prurigo
	Administration site photosensitivity reaction
	Application site photosensitivity reaction
	Chronic actinic dermatitis
	Hartnup disease
	Implant site photosensitivity
	Infusion site photosensitivity reaction
	Injection site photosensitivity reaction
	Juvenile spring eruption
	Medical device site photosensitivity
	Photodermatosis
	Photokeratitis
	Photoonycholysis
	Photosensitivity reaction
	Polymorphic light eruption
	Solar dermatitis
	Solar urticaria
	Sunburn
	Vaccination site photosensitivity

Renal Related	Severe Hypersensitivity/Cutaneous AEs	Upper UTI
Acute kidney injury	Acute generalised exanthematous pustulosis	Bacterial pyelonephritis
Acute phosphate nephropathy	Allergic oedema	Emphysematous pyelonephritis
Acute prerenal failure	Anaphylactic reaction	Kidney infection
Anuria	Anaphylactic shock	Perinephric abscess
Azotaemia	Anaphylactic transfusion reaction	Pyelocystitis
Blood creatinine increased	Anaphylactoid reaction	Pyelonephritis
Blood urea increased	Anaphylactoid shock	Pyelonephritis acute
Continuous haemodiafiltration	Angioedema	Pyelonephritis chronic
Dialysis	Circulatory collapse	Pyelonephritis fungal
Glomerular filtration rate decreased	Circumoral oedema	Pyelonephritis mycoplasmal
Haemodialysis	Conjunctival oedema	Pyelonephritis viral
Haemofiltration	Corneal exfoliation	Pyonephrosis
Hypercreatininaemia	Corneal oedema	Renal abscess
Neonatal anuria	Cutaneous vasculitis	Renal cyst infection
Nephritis	Dermatitis bullous	Urosepsis
Nephropathy toxic	Dermatitis exfoliative	
Oliguria	Dermatitis exfoliative generalised	
Peritoneal dialysis	Drug eruption	
Prerenal failure	Drug hypersensitivity	
Renal failure	Drug reaction with eosinophilia and systemic symptoms	
Renal failure acute	Epidermal necrosis	
Renal failure neonatal	Epiglottic oedema	
Renal impairment	Erythema multiforme	
Renal impairment neonatal	Exfoliative rash	
	Eye oedema	
	Eye swelling	
	Eyelid oedema	
	Face oedema	
	First use syndrome	
	Fixed drug eruption	
	Gingival oedema	
	Gingival swelling	
	Gleich's syndrome	
	Hereditary angioedema	
	Hypersensitivity vasculitis	
	Idiopathic angioedema	
	Idiopathic urticaria	
	Kounis syndrome	
	Laryngeal dyspnoea	
	Laryngeal oedema	
	Laryngospasm	
	Laryngotracheal oedema	
	Limbal swelling	
	Lip exfoliation	
	Lip oedema	
	Lip swelling	
	Mucocutaneous ulceration	
	Mucosa vesicle	
	Mucosal erosion	
	Mucosal exfoliation	
	Mucosal necrosis	
	Mucosal ulceration	

Renal Related	Severe Hypersensitivity/Cutaneous AEs	Upper UTI
	Nikolsky's sign	
	Oculomucocutaneous syndrome	
	Oculorespiratory syndrome	
	Oedema mouth	
	Oedema mucosal	
	Oral mucosal blistering	
	Oral mucosal exfoliation	
	Orbital oedema	
	Oropharyngeal blistering	
	Oropharyngeal swelling	
	Palatal oedema	
	Penile exfoliation	
	Periorbital oedema	
	Pharyngeal oedema	
	Scleral oedema	
	Shock	
	Shock symptom	
	Skin exfoliation	
	Skin necrosis	
	Small bowel angioedema	
	Stevens-Johnson syndrome	
	Stridor	
	Swelling face	
	Swollen tongue	
	Throat tightness	
	Tongue exfoliation	
	Tongue oedema	
	Toxic epidermal necrolysis	
	Type I hypersensitivity	
	Urticaria	
	Urticaria cholinergic	
	Urticaria chronic	
	Urticaria papular	
	Urticarial vasculitis	
	Vaginal exfoliation	

UTI	Venous Thromboembolic events	Volume Depletion
Bladder candidiasis	Deep vein thrombosis	Blood pressure decreased
Cystitis	Deep vein thrombosis postoperative	Blood pressure orthostatic decreased
Cystitis bacterial	Embolism venous	Dehydration
Cystitis escherichia	Iliac vein occlusion	Diastolic hypotension
Cystitis gonococcal	Inferior vena cava syndrome	Dizziness postural
Cystitis haemorrhagic	Inferior vena caval occlusion	Hypotension
Cystitis interstitial	Jugular vein occlusion	Hypovolaemia
Cystitis klebsiella	Mesenteric vein occlusion	Hypovolaemic shock
Cystitis pseudomonal	Obstructive shock	Orthostatic hypotension
Emphysematous cystitis	Portosplenomesenteric venous thrombosis	Orthostatic intolerance
Escherichia urinary tract infection	Post procedural pulmonary embolism	Postural orthostatic tachycardia syndrome
Fungal cystitis	Postpartum venous thrombosis	Presyncope
Funguria	Pulmonary embolism	Shock
Genitourinary tract infection	Pulmonary infarction	Shock symptom
Streptococcal urinary tract	Pulmonary microemboli	Syncope

UTI	Venous Thromboembolic events	Volume Depletion
infection		
Ureter abscess	Pulmonary oil microembolism	Urine output decreased
Ureteritis	Pulmonary thrombosis	
Urethritis	Renal vein embolism	
Urethral abscess	Renal vein occlusion	
Urethral carbuncle	Subclavian vein thrombosis	
Urethral stricture post infection	Vascular occlusion	
Urinary bladder abscess	Venous thrombosis	
Urinary tract abscess	Venous thrombosis in pregnancy	
Urinary tract infection	Venous thrombosis limb	
Urinary tract infection bacterial	Visceral venous thrombosis	
Urinary tract infection enterococcal		
Urinary tract infection fungal		
Urinary tract infection pseudomonal		
Urinary tract infection staphylococcal		

Appendix 7: Adverse Event with Potential Amputation Association

List of Selected Preferred Terms Included Within the System Organ Classes of Infections and Infestations, Vascular Disorders, Nervous System Disorders, and Skin and Subcutaneous Tissue Disorders

Infections and Infestations	Vascular Disorders	Nervous System Disorders	Skin and Subcutaneous Tissue Disorders	High Level Term (HLT) Skin and subcutaneous tissue ulcerations	
Infected skin ulcer	Arteriosclerosis	Paraesthesia	Diabetic ulcer	Penile ulceration	Medical device site erosion
Skin infection	Peripheral arterial occlusive disease	Hypoaesthesia	Neuropathic ulcer	Implant site ulcer	Ulcerated haemangioma
Staphylococcal skin infection	Peripheral vascular disorder	Diabetic neuropathy	Fungating wound	Cytomegalovirus mucocutaneous ulcer	Incision site erosion
Gangrene	Peripheral artery stenosis	Neuropathy peripheral	Diabetic foot	Skin ulcer	Incision site ulcer
Osteomyelitis	Peripheral ischaemia	Areflexia	Diabetic neuropathic ulcer	Eyelid erosion	Vaccination site ulcer
Diabetic gangrene	Arterial stenosis	Hyporeflexia	Skin erosion	Implant site erosion	Fungating wound
Localised infection	Diabetic vascular disorder	Polyneuropathy		Diabetic foot infection	Ecthyma
Wound abscess	Femoral artery occlusion	Autonomic neuropathy		Application site erosion	Perineal ulceration
Wound infection	Thrombosis	Neuropathy peripheral		Infusion site erosion	Tropical ulcer
Subcutaneous abscess	Poor peripheral circulation	Burning sensation		Mycobacterium ulcerans infection	Injection site erosion
Abscess limb	Microangiopathy	Diabetic autonomic neuropathy		Infusion site ulcer	Pyogenic sterile arthritis pyoderma gangrenosum and acne syndrome
Staphylococcal osteomyelitis	Peripheral coldness	Peripheral sensory neuropathy		Neuropathic ulcer	Scleroderma associated digital ulcer
Diabetic foot infection	Diabetic microangiopathy	Peripheral sensorimotor neuropathy		Skin ulcer haemorrhage	Vulval ulceration
Staphylococcal skin infection	Arterial occlusive disease	Sensory disturbance		Burn infection	Mucocutaneous ulceration
Soft tissue infection	Arterial thrombosis	Diabetic neuropathic ulcer		Diabetic foot	Injection site ulcer
Bone abscess	Peripheral artery thrombosis			Diabetic ulcer	Pyoderma gangrenosum
Osteitis	Arterial occlusive disease			Catheter site erosion	Scrotal ulcer
Cellulitis	Angiopathy			Pyostomatitis vegetans	Application site ulcer
Wound [a]	Intermittent claudication			Catheter site ulcer	Genital ulceration
Dry gangrene	Arterial disorder			Medical device site ulcer	Infected skin ulcer
Post-operative wound infection	Impaired healing [a]			Administration site ulcer	Diabetic neuropathic ulcer
Post-operative wound complication [a]				Instillation site erosion	Varicose ulceration
Wound dehiscence				Breast ulceration	Vaginal ulceration
Burn infection				Instillation site ulcer	Vulvovaginal ulceration
Extremity necrosis				Administration site erosion	Auditory meatus external erosion
				Vasculitic ulcer	Skin erosion
				Vaccination site erosion	

[a] Although these PTs belong in the SOC of Injury, Poisoning and Procedural Complications or in the SOC of General Disorders and Administration Site Conditions, these terms were retained for the search strategy because of their relevance

List of Preferred Terms classified as Reversible infections, Irreversible infections and Osteomyelitis

Reversible Infections	**Irreversible Infections**	**Osteomyelitis**
Abscess limb	Diabetic gangrene	Bone abscess
Burn infection	Dry gangrene	Osteitis
Cellulitis	Extremity necrosis	Osteomyelitis
Diabetic foot infection	Gangrene	Staphylococcal osteomyelitis
Infected skin ulcer		
Localised infection		
Skin infection		
Soft tissue infection		
Staphylococcal skin infection		
Subcutaneous abscess		
Wound		
Wound abscess		
Wound dehiscence		
Wound infection		

Appendix 8: Pre-Defined Limit of Change (PDLC) Criteria

Laboratory Test	Parameter for ANY value and LAST value
CHEMISTRY	
Albumin	Composite: <LLN and >25% decrease from BL
ALT	Absolute Value: >3X ULN
	Absolute Value: >5X ULN
	Absolute Value: >8X ULN
AST	Absolute Value: >3X ULN
	Absolute Value: >5X ULN
	Absolute Value: >8X ULN
ALT >3X ULN and Tbili >2X ULN	Composite: ALT >3X ULN and Tbili >2X ULN [with the Tbili elevation >2 X ULN within 30 days of the ALT elevation >3x ULN]
AST >3X ULN and Tbili >2X ULN	Composite: AST >3X ULN and Tbili >2X ULN [with the Tbili elevation >2 X ULN within 30 days of the AST elevation >3x ULN]
Bilirubin	Composite: >ULN and > 25% increase from BL
	Absolute Value: >2XULN
Bicarbonate	Absolute Value: <16 mEq/L
Calcium	Composite: >ULN and > 10 % increase from BL
Creatinine Kinase	Absolute Value: >1000U/L
eGFR	Composite: < 80 and decrease>30% from BL
	Change: decrease>50% from BL
Magnesium	Composite: <LLN and >25% decrease from BL
	Composite: >ULN and >25% increase from BL
Phosphorus	Composite: >ULN and >25% increase from BL
Potassium	Composite: <LLN and >15% decrease from BL
	Composite: >ULN and >15% increase from BL
	Absolute Value: ≥ 6.5 mEq/L
Sodium	Composite: <LLN and decrease >5 mEq/L or more from BL
	Composite: >ULN and increase>5 mEq/L or more from BL
Uric Acid	Composite: <LLN and >25% decrease from BL
HEMATOLOGY	
Hemoglobin	Change: ≥ 2 g/dl decrease from BL
	Change: ≥ 2 g/dL increase from BL
Platelets	Composite: >ULN and increase >25% from BL
White Blood Count	Composite: < LLN and >25% decrease from BL
	Composite: > ULN and >50 % increase from BL
VITAL SIGNS	
Pulse	Absolute Value: ≤50 beats per minute
	Absolute Value: ≥100 beats per minute
Systolic Blood Pressure	Composite: ≥ 20 mm Hg decrease from BL and ≤90 mm Hg
	Composite: ≥ 20 mm Hg increase from BL and ≥ 160 mm Hg
Diastolic Blood Pressure	Composite: ≥ 15 mm Hg decrease from BL and ≤ 50 mm Hg
	Composite: ≥ 15 mm Hg increase from BL and ≥ 100 mm Hg

Appendix 9: SAS Program for Key Analyses of Mortality Endpoints

Stratified Cox proportional hazard model

```
      proc phreg data=&in;
        model &time* &censor(1)=&trtv  &covar/RL ties=efron alpha = 0.05;
            strata &STRATA;

      ods output ParameterEstimates=&out1 (keep Estimate StdErr parameter
      HazardRatio HRLowerCL HRUpperCL ProbChiSq rename=( parameter=VAR
      HazardRatio=HR HRLowerCL=LCL HRUpperCL=UCL ProbChiSq=PRBW)
      where=(VAR="&trtv"));

     run;
```

Stratified log rank test

```
      proc lifetest data=&in notable;
        time &time*&censor(1);
        strata    &STRATA; /group=&trtv;
        ods output HomTests=outlrt (keep= Test ChiSq ProbChiSq
      where=(Test='Log-Rank') rename=( ChiSq=chi_LRT ProbChiSq=prb_LRT));
      run;
```

Test of proportional hazard assumption-cox model with log –transformed time and its interaction with treatment

```
  *Test using time varying covariates--test non-zero slope of individual
covariate using wald test and global effect thru partial likely hood test ;
      proc phreg data=&datain;
        model &time* &censor(1)=&trtv &covar /RL ties=efron alpha = 0.05;
      strata &strata;
      &ttime=log(&time);
       &trtv.t=&trtv*&ttime;
       &covar.t=&covar*&ttime;
       proportionality_test: test &trtv.t &covar.t;
      ods output ParameterEstimates= est0 CensoredSummary=censor
      TestStmts=gbprpt;
 run;
```

Study stratified cox proportional hazard model with interaction term and hazard ratio by subgroup

```
   proc phreg data=&in ;
        class &clas;
         model &time* &censor(1)=&trtv &covar  &clas &trtv*&clas /RL
ties=efron alpha = 0.05;

            HAZARDRATIO &trtv/&trtby;

            strata &STRATA;
```

```
        ods output HazardRatios=HR Type3=&out2 (keep= Effect ProbChiSq
rename=(ProbChiSq=PRB_INT) where=(index(Effect,'*')>0));
     run;
```

Gail-Simon test

```
      *options to run Gail Simon test when interaction is significant;
      *the smallest prb_int will be used as the flag to trigger the G-S test;
      proc sort data=&out2 out=temp nodupkey;
            by PRB_INT;
      run;
      data _null_;
            set temp;
            if _n_=1;
            call symput('FGS', PRB_INT);
      run;
      %if %sysevalf(&FGS)<=0.05 %then
      %do;
        proc sql;
            create table gs01 as
            select
              count(&clas) as m,
               sum(((Estimate>0)*Estimate/stdErr)**2) as qplus,
               sum(((Estimate<0)*Estimate/StdErr)**2) as qminus,
               min(calculated qplus, calculated qminus) as q
               from &out1

                  ;
                  quit;

                data gs02;
                  set gs01;
                  pvalue_gs=0;
                  do i=1 to m-1;
                   pvalue_gs=pvalue_gs+pdf("binomial",i,0.5,m-1)*(1-
probchi(q,i));
                  end;
                   keep pvalue_gs;
                  label pvalue_gs="Gail-Simon Two-sided p-value";
                run;

      %end;
```