Protocol

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

Protocol for: Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2017;377:1228-39. DOI: 10.1056/NEJMoa1612917

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes

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EXenatide Study of Cardiovascular Event Lowering Trial (EXSCEL)

Clinical Study Protocol BCB109

A RANDOMIZED, PLACEBO CONTROLLED CLINICAL TRIAL TO EVALUATE CARDIOVASCULAR OUTCOMES AFTER TREATMENT WITH EXENATIDE ONCE WEEKLY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Phase 3b/4

Original Protocol: 24 December 2009

Protocol Approved By:

24Dec2009

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Eli Lilly and Company

Throughout this protocol, unless otherwise specified, the term "Lilly" is used to refer to Eli Lilly and Company and its affiliates, acting as a representative of Amylin Pharmaceuticals, Inc. Amylin Pharmaceuticals, Inc. sponsors the Investigational New Drug Application in the US and Puerto Rico and transfers the clinical sponsor obligations to Lilly for the conduct of this study outside the US. For investigative sites outside of the US and Puerto Rico, Lilly will serve as the study sponsor. The applicable party will hereinafter be referred to as the "sponsor".

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LIST OF ABBREVIATIONS

ACS	Acute coronary syndrome
AE	Adverse Event
AHA	Antihyperglycemic agent
Alliance	Amylin/Lilly exenatide consortium
Amylin	Amylin Pharmaceuticals Inc.
ARO	Academic Research Organisation
BP	Blood Pressure
CEC	Clinical Events Committee
CHF	Congestive heart failure
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DCRI	Duke Clinical Research Institute
DSMB	Data Safety Monitoring Board
DTU	Diabetes Trials Unit
EC	Executive Committee
ECG	Electrocardiogram
EDC	Electronic Data Collection
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EQW	Exenatide once weekly
EQ 5D	EuroQol 5 Dimensions
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA_{1c}	Hemoglobin A1c
IRB	Institutional Review Board
MI	Myocardial infarction
OC	Operations Committee
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
SBP	Systolic blood pressure
T2DM	Type 2 diabetes mellitus

CLINICAL PROTOCOL

1 INTRODUCTION

1.1 Background

Type 2 diabetes mellitus is a leading public health issue. Often regarded as a mild disease, it is the fourth leading cause of death in developed countries and the number of people world wide with diabetes is predicted to exceed 300 million by the year 2025. Diabetes remains the leading cause of blindness, end stage renal disease and lower extremity amputations and confers a two to four times greater risk of heart disease and strokes.

The majority of people with type 2 diabetes mellitus (T2DM) die as a result of cardiovascular disease (CVD). Epidemiological analysis of UKPDS data from patients with newly-diagnosed T2DM showed that potentially modifiable risk factors for CVD were a raised LDL cholesterol, a low HDL cholesterol, hyperglycemia, hypertension and smoking (1). Elevated glucose levels were also the major determinant of microvascular complications. A number of trials in people with T2DM have shown that their CVD risk can be reduced by lowering LDL cholesterol (2,3), blood pressure (4,5), glycated haemoglobin (6,7) or all three risk factors (8).

1.2 Rationale for Conduct of the Study

Exenatide, a GLP-1 receptor agonist, has been shown in randomized clinical trials to improve glycemic control, augment endogenous insulin secretion, to reduce blood pressure and promote weight loss with a meta-analysis of exenatide twice-daily (BYETTA) trials (9) showing a trend to lower relative risk for CV events versus pooled comparators of 0.70 (95% confidence interval 0.38 - 1.31). BYETTA (exenatide) injection is currently available in the US and in many countries worldwide for people with type 2 diabetes who are unable to achieve good glycemic control with common oral therapies. Exenatide once weekly (EQW), a new formulation of exenatide that is administered once weekly rather than twice daily, is under development and currently being reviewed by the US FDA.

In a 30-week, randomized, open-label trial, EQW treatment resulted in a significantly greater improvement in glycemic control, as measured by hemoglobin A1c (HbA_{1c}), compared to

exenatide administered twice daily (10). Furthermore, treatment with EQW for one year (52 weeks) showed net reductions of 2.0% in HbA_{1c}, 0.06 mmol/l (2.2 mg/dl) LDL cholesterol, 6 mmHg in systolic blood pressure and 4 kg in body weight (11). Thus, EQW represents a novel therapeutic approach to the treatment of T2DM that could potentially impact the occurrence of cardiovascular events in patients mediated by improvements in multiple CV risk factors, as well as reducing glycemia.

EXSCEL (EXenatide Study of Cardiovascular Event Lowering) is a pragmatic, long-term, placebo-controlled, double-blinded trial which seeks to characterize the effects of EQW on cardiovascular-related outcomes in patients with type 2 diabetes when added to the current usual care for glycemic control in a standard care setting.

2 STUDY OBJECTIVES AND HYPOTHESES

2.1 Primary Objective

The primary objective of EXSCEL will be to evaluate the effect of EQW, used in conjunction with the current usual care for glycemic control, on major macrovascular events when administered to patients with type 2 diabetes.

Objective: To compare the impact of including EQW as part of usual care *vs.* usual care without exenatide on major CV outcomes as measured by the primary CV composite endpoint of CV-related death, nonfatal myocardial infarction (MI), or nonfatal stroke.

Hypothesis: EQW, when used as part of usual care, is superior to usual care without exenatide with regard to the risk of developing a confirmed event in the primary CV composite endpoint.

2.2 Secondary Objectives

The secondary objectives of EXSCEL are to evaluate the effect of EQW treatment used in conjunction with the current usual care for glycemic control on:

(1) All cause mortality
(2) Each of the components of the primary composite CV endpoint
(3) Hospitalization for acute coronary syndrome (ACS)
(4) Hospitalization for heart failure (CHF)

2.3 Additional Objectives

Additional objectives of EXSCEL are to evaluate the effect of EQW treatment used in conjunction with the current usual care for glycemic control on:

(1) Revascularization procedures. This will include percutaneous coronary intervention with or without stenting, coronary artery bypass grafting, revascularization and/or stenting for peripheral arterial disease, carotid endarterectomy, or carotid stenting.

(2) Time to initiation of first co-interventional agent (i.e., next AHA or chronic insulin therapy)

(3) Number of episodes of severe hypoglycemia

(4) Absolute values of and changes in markers of cardiovascular risk including:
- HbA_{1c}
- body weight
- blood pressure
- lipid profile

(5) Quality of life assessed by the EQ-5D (EuroQol 5 Dimension) questionnaire.

(6) Medical resource use and total direct medical costs.

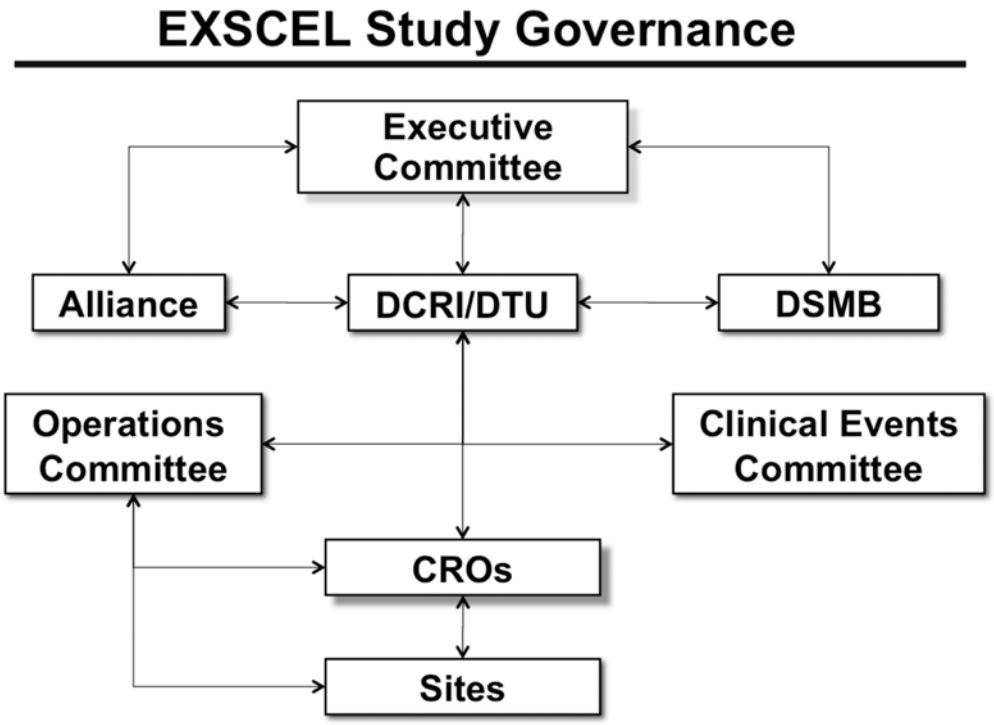
(7) Incremental cost-effectiveness analysis of exenatide once weekly as part of usual care compared with usual care without exenatide.

3 TRIAL GOVERNANCE

EXSCEL is a multinational pragmatic trial that will be conducted in approximately 400 sites worldwide. It will be run jointly by the Duke Clinical Research Institute (DCRI) and the University of Oxford Diabetes Trials Unit (DTU) Academic Research Organizations (AROs), in an academic collaboration with Amylin Pharmaceuticals Inc. (Amylin). EXSCEL will be Co-Chaired by Professors Robert Califf (Cardiologist) and Rury Holman (Endocrinologist) but sponsored and funded by Amylin on behalf of the Alliance (Amylin & Eli Lilly).

The EXSCEL Executive Committee (EC) will have overall responsibility for the oversight and management of the trial (Figure 1). The EC will consist of approximately eleven individuals, comprising nine senior independent academic representatives who are experts in their field and two Alliance representatives. It will be Co-Chaired by Professors Rob Califf and Rury Holman with other academic members comprising four further diabetologists and three further cardiologists. Geographical balance will be sought. Decision making will be by consensus.

Figure 1: EXSCEL Governance



4 TRIAL DESIGN

4.1 Design Description

EXSCEL will be a multinational, placebo-controlled, double-blind, randomized, parallel-group pragmatic clinical trial. Eligible patients will have type 2 diabetes with a glycated hemoglobin (HbA_{1c}) ≥7.0 % and ≤10.0 % on stable doses of up to three oral antihyperglycemic agents (AHAs) for at least 3 months *i.e.* no oral AHA adjustments in the past 3 months. Patients enrolled will be at a wide range of CV risk with approximately 60% having had a prior CV event.

Approximately 9500 patients meeting all enrollment criteria will be recruited in to the trial over approximately three year period, randomly allocated to treatment with either EQW 2 mg or matching placebo subcutaneous injections once weekly in a 1:1 ratio, and followed up for a minimum of four years. The trial will continue until adjudicated 1591 primary endpoint events have been accrued, or until the independent Data and Safety Monitoring Board (DSMB) advise otherwise.

The trial will assess the impact of EQW therapy upon CV outcomes in a large population from a heterogeneous group of countries and practice environments. Approximately one-third of patients will be enrolled in the Americas (North/South America & Canada), one-third in Europe and one-third in the Asia/Australasia. Given that this population will be at elevated CV risk, it is anticipated that subjects will see their usual care physicians at least twice per year for routine care. Trial follow up will consist of a blend of trial visits and phone calls during the double-blind placebo-controlled treatment period, which is expected to provide an average 5.5 patient years of follow up.

There is no requirement to achieve glycemic equipoise between randomized groups but all patients during the double-blind treatment period will have their AHA regimens adjusted as deemed necessary by their usual care physicians with the addition or substitution of other AHAs, including insulin but excluding GLP-1 receptor agonists, to achieve appropriate individualized glycemic goals in line with national guidelines. Adjustments in AHA medications are permitted any time after randomization, but usual care physicians will be asked to avoid this until HbA_{1c} levels begin to reflect the initial effect of randomized study medication. Prior to randomization, it is anticipated that all subjects will have received counseling regarding appropriate diet and level of physical activity as part of usual care for type 2 diabetes. Per usual care, HbA_{1c} values should be measured locally using a NGSP (National Glycohemoglobin Standardization Program) certified HbA_{1c} assay (12).

4.2 Trial Duration

Minimum follow up for the last patient to be randomized will be 4 years unless the trial is terminated earlier. All patients that cease study medication will be followed up, if at all possible, for the full study period. All patients that withdraw from the trial will have their vital status ascertained, if at all possible, at the end of the trial.

5 TRIAL POPULATION

5.1 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this trial.

a. Patient has type 2 diabetes mellitus

b. Patient will able to see a usual care provider at least twice a year

c. Patient has an HbA_{1c} of ≥ 7.0 % and ≤ 10.0% on stable doses of up to three oral AHAs for at least 3 months *i.e.* no oral AHA adjustments in the past 3 months.

A patients whose HbA_{1c} is > 10.0% may, at the discretion of the investigator, have their oral AHA therapy adjusted and be re-screened once for HbA_{1c} randomization eligibility (≥ 7.0 % and ≤ 10.0%) following a 3-month period on stable AHA doses.

d. Patients with any level of CV risk and meeting all other inclusion criteria may be enrolled. Recruitment will be constrained such that 40% will not have had a prior CV event and 60% will have had a prior CV event defined as *at least one of the following*:

- History of a major clinical manifestation of coronary artery disease *i.e.* myocardial infarction, surgical or percutaneous (balloon and/or stent) coronary revascularization procedure, or coronary angiography showing at least one stenosis ≥ 50% in a major epicardial artery or branch vessel.
- Ischemic cerebrovascular disease, including:
    - History of ischemic stroke. Strokes not known to be hemorrhagic will be allowed as part of this criterion;
    - History of carotid arterial disease as documented by ≥50 % stenosis documented by carotid ultrasound, magnetic resonance imaging (MRI), or angiography, with or without symptoms of neurologic deficit.
- Atherosclerotic peripheral arterial disease, as documented by objective evidence such as amputation due to vascular disease, current symptoms of intermittent claudication confirmed by an ankle-brachial pressure index or toe brachial pressure index less than 0.9, or history of surgical or percutaneous revascularization procedure.

e. Female patients must not be breast feeding and agree to use an effective method of contraception or must not otherwise be at risk of becoming pregnant.

f. Patient understands the trial procedures, alternative treatments available, the risks involved with the trial, and voluntarily agrees to participate by providing written informed consent.

g. Patient agrees to provide permission to obtain all medical records necessary for complete data ascertainment during the follow-up period, and agrees to communication between the trial site and the usual care provider in order to facilitate routine care.

h. Patient is 18 years or older at enrollment.

5.2 Exclusion Criteria

a. Patient has a diagnosis of type 1 diabetes mellitus, or a history of ketoacidosis.

b. Patient has taken insulin within 2 weeks of screening visit or for greater than 1 week within 3 months of screening visit.

c. Patient has ever been treated with an approved or investigational GLP-1 receptor agonist *e.g.* BYETTA (exenatide), EQW, VICTOZA (liraglutide), or taspoglutide.

d. Patient is enrolled in another experimental protocol which involves the use of an investigational drug or device, or an intervention that would interfere with the conduct of the trial.

e. Patient has a planned or anticipated revascularization procedure.

f. Pregnancy or planned pregnancy during the trial period.

g. Patient has medical history that indicates a life expectancy of <2 years or might limit the individual's ability to take trial treatments for the duration of the trial.

h. Patient has a history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance which, in the opinion of the investigator or coordinator, might pose an unacceptable risk to the patient, confound the results of the trial *e.g.* if patient cannot comply with requirements of the trial, or likely to interfere with the patient's participation for the full duration of the trial.

i. Patient has end-stage renal disease or an estimated glomerular filtration rate (eGFR) derived from serum creatinine (using the simple MDRD-4 formula) of <30 mL/min/1.73 m^2.

j. Patient has a known allergy or intolerance to exenatide.

k. Patient has a history of gastroparesis.

l. Personal or family history of medullary thyroid cancer or MEN2 (Multiple Endocrine Neoplasia Type 2) or calcitonin level of 100 ng/L or greater.

NOTE: Serum for calcitonin measurement will be drawn at screening. Patients may be randomized and initiate study medication prior to the results of the calcitonin measure being available. If a randomized patient is found to have an exclusionary serum calcitonin concentration, they will stop study medication and patients will continue to have follow-up for vital status and be part of the intention to treat analysis.

m. Patient has previously been enrolled in EXSCEL.

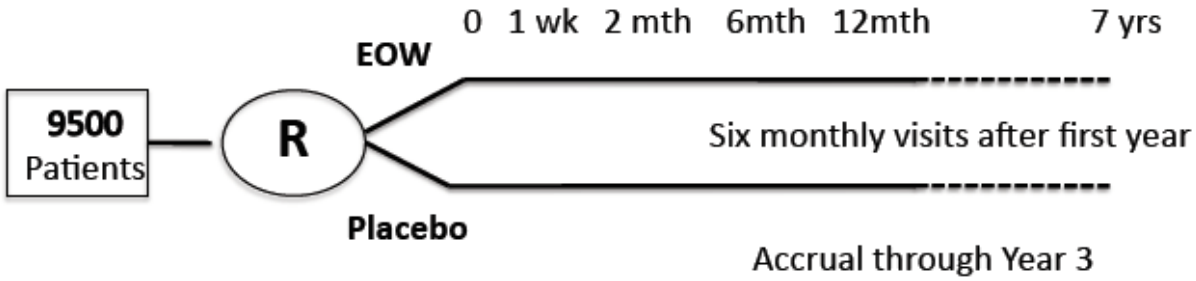
n. Patient has a history of pancreatitis.

6 TRIAL PLAN

6.1 Trial Procedures

A trial flow chart of the schedule of procedures to be performed during the trial is found in Appendix 2. The intent of this large, pragmatic, global trial is to integrate the trial-specific procedures into usual clinical care visits and to use routine clinical care assessments and laboratory values whenever possible as an efficient strategy for protocol implementation and data collection. At baseline (visit 1) patients will be provided with the patients' instruction brochure and be trained by study personnel to administer the study medication injection. Patients will be seen at one week (±3 days) and have their self-injection observed. Then patients will be seen at 2 months (± 2 weeks) after randomization to again confirm competency with dosing study medication. The next visit will be six months (±1 month) after randomization. Thereafter, patients will be seen six-monthly (±1 month) until study close out.

At all visits post randomization there will be an assessment of clinical and ancilliary events, as well as a review of concomitant medication, and adherence to study therapy. At semi-annual and annual visits, additional procedures will include blood pressure, body weight, review of routine laboratory values and dispensing of study drug as described in Appendix 2.



6.2 Pre-Enrollment and Enrollment Procedures

Informed consent, and if feasible, randomization will occur at the initial trial visit for patients satisfying all inclusion and exclusion criteria. Patients may qualify for enrollment based

on recent laboratory data *e.g.* HbA_{1c} within the last 3 months, obtained as part of usual care prior to Visit 1. For patients who require a repeat visit *e.g.* key lab data not available at Visit 1 or there is a required period after informed consent, randomization will be delayed until all information is available. It should be noted that patients may still be randomized at Visit 1 even if calcitonin results are pending from screening.

6.3 Method of Assigning Patients to Treatment Groups (Visit 1)

An Interactive Voice Response System (IVRS) will be used to enroll those patients satisfying all inclusion and exclusion criteria. This automated system will assign a unique allocation number to eligible patients and dispense double-blind trial medication. Each site will be given an identification number and a password to access the IVRS. Patients will be randomly allocated at Visit 1 in a 1:1 ratio, stratified by whether or not they have had a prior CV event, to receive one of the following two interventions:

Treatment 1: EQW 2 mg subcutaneous injection, administered once weekly

Treatment 2: Matching placebo subcutaneous injection, administered once weekly

The generation of the randomized allocation schedule for trial treatment assignment will be the responsibility of the IVRS provider. Prior to database lock, these codes will be provided in strict confidence only to the facility packaging trial medication and to the DSMB independent statistical group. Immediately upon database lock the codes will be transmitted to the DTU and DCRI data management groups for incorporation into the trial database.

6.4 Treatments Administered

In accordance with standard guidelines for care in all countries participating in the trial, it is anticipated that all patients will receive counseling about appropriate diet and exercise interventions as part of usual care.

EQW and matching placebo will be supplied as subcutaneous injections and will be administered once weekly.

As exenatide is not recommended for use in patients with end-stage renal disease or severe renal impairment, trial medication must be discontinued if a patient's eGFR drops below 30

mL/min/1.73 m^2, based on two consecutive serum creatinine determinations. As part of standard of care, serum creatinine should be among labs drawn annually. If serum creatinine has not been performed on an annual basis, then study personnel should prompt usual care providers to perform serum creatinine measurement. If serum creatinine remains unavailable, then it should be performed at the next visit by study personnel. If the trial physician recognizes that the eGFR has decreased sufficiently to necessitate trial drug cessation, he/she should determine whether or not repeat/confirmatory testing has occurred and undertake this if necessary. If the need for drug discontinuation is confirmed, the patient will be invited back to the trial site for an unscheduled visit to explain the situation, to stop the study drug and to encourage the patient to continue follow up off study drug until the end of the trial. Drug discontinuation will be managed at the trial site through the IVRS system. Drug discontinuation visit procedures should be followed as outlined in Section 6.11 – 6.14.

6.5 Concomitant Therapy

Concomitant medications will be used at the discretion of the usual care physician (or investigator if also the usual care physician), who will be informed of the participant's enrollment in the trial, the use of blinded trial medication, and that use of GLP-1 receptor agonists is contraindicated during the trial period. If an open-label GLP-1 receptor agonist therapy is started whilst on study medication, then the investigator will inform the usual care physician about the possibility of double dosing and encourage the discontinuation of open-label GLP-1 agonist therapy. However, if an open-label GLP-1 receptor agonist therapy remains, then study drug should be discontinued to avoid potential double dosing. Usual care physicians will be encouraged to follow guidelines for care based upon local and institutional practice patterns and any relevant published practice guidelines. AHAs will be captured by name and total daily dose at the time of study visits, while other relevant concomitant medications may be collected only as drug classes.

During the double-blind treatment period, trial investigators are expected to monitor patients' AHA regimens and communicate with usual care physicians, who will be responsible for adjusting the AHA regimen in order to achieve locally-appropriate HbA_{1c} goals. These goals will be individualized, with the understanding that currently applicable glycemic guidelines may vary among different geographic regions. With adherence to local custom and laws (including

privacy regulations such as HIPAA), types of communication may be informal *e.g.* email or telephone exchanges, to enhance frequency and ease of two-way communication. In addition, the degree of locally-appropriate HbA_{1c} goal-attainment at each site will be monitored centrally and sites with unusually low goal attainment will be advised accordingly.

Usual care providers should be notified that adjustments to the AHA regimen are not recommended until HbA_{1c} levels begin reflect the effect of randomized therapy. Any AHA agent, with the exception of GLP-1 receptor agonists, is acceptable. If HbA_{1c} goals are not met following adjustment with oral AHAs, an insulin regimen may be initiated, preferably without discontinuing or down-titrating some or all of the existing AHAs, as clinically appropriate. Ideally, patients should generally remain on the baseline AHA therapies throughout the course of the trial, unless the baseline AHA is no longer clinically appropriate. However, this should be at the discretion of the usual care provider. In addition, patients should be reminded to keep taking their blinded trial drug following initiation of insulin.

6.6 Precautions to Minimize Rates of Hypoglycemia

At the screening/enrollment visit and all subsequent visits, the symptoms and appropriate management of hypoglycemia will be reviewed with participants. Patients who experience severe hypoglycemia will be asked to notify both their usual care physician, as well as trial personnel. Usual care physicians will be responsible for the adjustment of non-trial AHA medications in order to prevent or minimize the occurrence of further hypoglycemia. All episodes of severe hypoglycemia will be reviewed and recorded. Severe hypoglycemia (hypoglycemia requiring assistance) refers to instances in which the patient was sufficiently disoriented or incapacitated as to require help from either a family member or from medical personnel (whether or not this assistance was actually provided). For example, if a family member or other bystander brought the patient a snack or drink to help raise his blood sugar even though the patient was capable of doing this himself, the episode would not be considered severe.

6.7 Laboratory and Anthropometric Measurements

Laboratory values *i.e.* HbA_{1c} serum creatinine, lipid panel [LDL-C, TC, TG, HDL-C]) will be obtained where available as per the patient's usual care assessments. Blood pressure,

heart rate, height, and body weight will be collected by study personnel as indicated in the flow chart.

6.8 Genetic and Biomarker Sample Collection

In a subset of sites, patients enrolled in the trial will be asked to consent separately to provide a whole blood sample for future pharmacogenomic analyses. The objective of collecting blood samples from which genetic analyses can be performed is to investigate the relationships between genetic make-up and clinical events. These samples will be drawn at baseline, or at any point in the trial at which consent is obtained from the patient.

Patients enrolled in the trial will be asked to consent separately to provide two blood and two urine samples for future biomarker analyses. These fasting specimens will be obtained at baseline (prior to drug exposure), and either at one year of treatment or at the time of drug discontinuation (if occurring within the first year).

6.9 Resource Utilization Quality of Life Data for Economic Evaluation

As part of this trial, data will be collected to inform cost-effectiveness analyses that are relevant to major health care systems around the world. The economic analyses will be undertaken by a team led by Professor Alastair Gray, Health Economic Research Centre (HERC), University of Oxford and Professor Kevin Schulman, Duke University. Resource use information will be collected from case report forms on number, type and duration of hospitalizations, number of outpatient physician visits, and use of antihyperglycemic and cardiovascular agents. The EQ-5D instrument, consisting of 5 questions, will be used to measure health utilities which are essential to estimating quality-adjusted survival for the cost-effectiveness analysis. This instrument will be administered at baseline, at 6 months and annually thereafter.

An outline statistical analysis plan for this evaluation is reported in Section 9.12; a detailed analysis plan and study report will be developed and reported separately.

6.10 End of Trial Visit and Post trial Telephone Contact

Investigators will be informed by the DCRI and DTU Coordinating Centres as to when the final trial visit is to be completed, and will schedule all patients for the **End of Trial Visit**.

The window of time for scheduling the visit will be based on a final projection of when the requisite 1591 adjudicated events will have been accrued. For procedural details, refer to the trial flow chart (Appendix 2).

NOTE: ***All patients should have an End of Trial Visit. (Patients who have discontinued trial drug must, at minimum, have an End of Trial telephone contact visit.)***

If a patient fails to return or otherwise becomes difficult to contact, it is the investigator's responsibility to make every effort to maintain contact so that at the end of the trial the patient can be located to determine status and to obtain necessary information for serious adverse experience reporting and/or endpoint adjudication.

After the end of the trial (or after earlier discontinuation of trial drug when appropriate), patients will be contacted by telephone to check for any serious adverse experiences and hospitalizations that occurred within 90 days after the administration of the last dose of trial medication.

6.11 Early Discontinuation of Trial Medication

Following randomization, it is expected that patients will remain on study medication for the duration of trial participation. However, it is recognized that patients may need to discontinue trial medication, in some cases permanently, for protocol-specified reasons (Section 6.13), due to the judgment of the primary investigator or because the patient withdraws consent. The Trial Hotline should be contacted whenever a site is considering interrupting or discontinuing trial drug (Section 6.16).

Unless resumption of trial medication is considered unsafe or is refused by the participant, the patient will be expected to resume regular use of the blinded trial medication. Should a participant stop taking trial medication, either permanently or temporarily, the reasons for discontinuation and length of time the patient stopped taking trial medication will be assessed and recorded. All randomized patients who permanently discontinue trial medication should have a medication discontinuation visit (as described in Section 6.12) as soon as possible after stopping the trial drug. All efforts should be made to reinforce with patients that this would be a medication discontinuation visit, not a trial discontinuation visit. Unless consent to follow the patient is specifically withdrawn, patients should continue to be followed as outlined in Section

6.14 until the end of the trial. When a patient withdraws consent prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at that time.

6.12 Permanent Discontinuation of Study Medication Visit Procedures

All randomized patients who permanently discontinue trial medication should have a medication discontinuation visit as soon as possible after stopping the trial drug. Necessary procedures are indicated in the Flow Chart. All efforts should be made to reinforce with patients that this would be a medication discontinuation visit, not a trial discontinuation visit. Patients will be asked to continue with all other trial follow up until the completion of the trial, including annual in-person visits and telephone calls. IVRS should be contacted to register the patient as discontinued only after all efforts have been exhausted to get patients back on trial drug if appropriate.

6.13 Permanent Discontinuation of Trial Drug Per Protocol

Reasons for protocol-specified discontinuation from the trial drug are listed below**.** All patients will be followed until resolution *i.e.* return to baseline values or diagnosis determined, or new stable state established, based on investigator assessment, for any adverse event or laboratory safety test abnormality resulting in discontinuation.

a) Severe Hypoglycemia: repeated (2 or more) episodes since the prior trial visit of severe hypoglycemia *i.e.* in which patient required medical assistance, despite down-titration or interruption/discontinuation of non-trial AHAs.

***Note**: The patient and the Investigator will notify the usual care provider of severe hypoglycemic events. The usual care provider should make a thorough attempt to down-titrate and/or modify co-interventional and baseline therapies that may contribute to hypoglycemia before discontinuing blinded trial drug for hypoglycemia. The usual care provider will be provided with standard guidance on down-titrating AHAs in the presence of hypoglycemia.*

b) Pregnancy, as confirmed by serum pregnancy test.

Patient must stop taking blinded trial medication, and be followed if she becomes pregnant during the trial (Section 10.4)

c) Any medical condition or personal circumstance which, in the opinion of the investigator, exposes the patient to additional risk by continuing in the trial or does not allow the patient to adhere to the requirements of the protocol.

d) Severe, irreversible renal dysfunction (eGFR <30 ml/min/1.73m^2) or renal replacement therapy.

6.14 Follow-up for Patients who Permanently Discontinue Trial Drug

Patients who discontinue trial drug prior to the **End of Trial Visit** will be followed according to the regular visit schedule to obtain information about potential trial endpoints and to confirm contact information. These patients will be encouraged to attend all scheduled trial visits in person, including the End of Trial Visit, and participate in all scheduled telephone contacts. If patients cannot attend visits in person, they will be followed via telephone contact for all subsequent visits outlined in the trial protocol.

6.15 Breaking the Blind

The IVRS will be used to unblind patients to the randomized treatment assignment only if absolutely necessary. Disclosure envelopes will not be supplied with the clinical supplies. Drug identification information is to be unmasked ONLY if necessary for the welfare of the patient. Prior to unblinding, the investigator is required to speak with a trial hotline physician (Section 6.16).

6.16 Trial Hotline

Clinicians at DCRI and DTU operate the trial hotline. It is available at all times to answer urgent clinical questions from sites concerning enrolled patients as well as questions to determine whether a particular patient qualifies for enrollment or performance of study procedures.

7 TRIAL MEDICATIONS

7.1 Trial Medication Supply

Investigational Materials will be provided by the Sponsor as EQW 2mg and matching placebo.

7.2 Formulation, Packaging, and Storage

EQW (formulation AC2993 F17) is an extended release formulation of exenatide and consists of 5% exenatide, sucrose, and 50:50 poly D,L lactic-co-glycolic acid (PLG). The vial containing the white to off white dry powder (2.8 mg of EQW microspheres) must be stored in a

refrigerator between 2ºC and 8ºC (36°F and 46°F) and protected from light. EQW matching placebo is the identical formulation with the active ingredient omitted.

The Microsphere Diluent for suspension of the EQW and matching placebo microspheres contains carboxymethylcellulose low viscosity, polysorbate 20, sodium chloride, and water for injection. The Microsphere Diluent must be stored between 2°C and 27°C (36°F and 81°F). The EQW or matching placebo dose is prepared by reconstitution of the microspheres in the diluent provided. Specific instructions for dose preparation of the injection will be provided in the Directions For Use (DFU). The reconstituted dose of study medication (EQW or matching placebo) should not be stored for future use. The injection must be administered immediately after preparation of the dose.

7.3 Dispensing of Trial Medication

Study materials will be provided to subjects by the investigator or medically qualified subinvestigator named on Form FDA 1572, or other qualified study-site personnel. Under no circumstance will the investigator or subinvestigators allow the study medication to be used other than as directed by the protocol or to be administered to any persons other than subjects participating in the study.

A supply of study medication will be dispensed for each subject, according to their assigned treatment group (EQW or Placebo). A 6 month supply of study medication will be distributed to subjects at the study site during Visit 1 and at subsequent visits indicated in Appendix 2. Patients should bring used and unused study medication vials to the site at each visit so medication compliance can be assessed.

7.4 Dose Administration Procedures, Route, and Schedule

Doses of EQW or matching placebo are to be injected into subcutaneous (SC) tissue of the abdomen. The site of injection should be rotated on a regular basis so that the same site is not used repeatedly.

At Visit 1 (Day 0), a medically qualified staff member will demonstrate the preparation of EQW or matching placebo for the subject or a designated caregiver and will administer the

first dose of study medication. Subjects will subsequently self administer study medication (or have it administered by a caregiver) once weekly (± 2 days) relative to the date of the first dose of EQW or matching placebo (Visit 1 [Day 0]). Subjects will be seen one week as well as one month after randomization to confirm competency with study medication. On weeks with no scheduled study-site visits, subjects may opt to return to the study site to have the injection procedure monitored by study-site personnel, although such visits will not be required. During scheduled study visits, subjects must bring their study medication treatment kit with them to the clinic and will self administer EQW or matching placebo as directed by study-site personnel.

Adjustments to dosing regimens are not permitted. If a subject is unable to tolerate study medication (e.g., subject experiences adverse events that are judged by the investigator to be unacceptable), the termination of study medication can be considered. Subjects who terminate study medication will be followed for the remainder of the study for the assessment of clinical events unless the subject opts to withdraw consent.

7.5 Randomization Schedule and Blinding Procedures

Subjects who meet all study requirements based on inclusion and exclusion criteria will be randomized at Visit 1 (Day 0). Subjects will be randomly assigned to 1 of 2 treatment groups (EQW or Matching placebo). Randomization will be in the ratio of 1:1 (EQW:Matching placebo) and will be carried out centrally in a manner blocked within site to achieve a balanced distribution of subjects across treatment groups.

Sufficient study medication will be provided to the study site for enrollment of all subjects. Study medication kits will be labeled with unique package numbers (this is not the subject randomization number). At Visit 1 (Day 0), study site personnel must contact the interactive voice response system (IVRS) to randomly assign subjects. The study-site personnel must call the IVRS at all subsequent visits (except Study Termination) to record the visit and confirm the kit assignment. The calls to the IVRS will ensure the resupply of additional kits required for upcoming visits. If medication is allocated to a subject incorrectly, the sponsor must be notified. At Study Termination or Early Termination, the site must call the IVRS to record study termination. The sponsor, the study-site personnel, and the subjects will be blinded to treatment allocation.

7.6 Drug Accountability

Drug accountability will be the responsibility of the study-site personnel. Upon receipt of study medication, study site personnel should open the shipment, verify that the amount and identity of the contents match that stated on the enclosed shipping form, indicate the condition of the contents on the form, and then sign and date the form. The study-site personnel should make a copy of the shipping form for the site's file, and return the original completed form to the sponsor (or designee). In addition, the study-site personnel will contact IVRS to verify receipt of study medication. The sponsor (or designee) should be notified immediately about any irregularities, discrepancies, or damage.

A drug disposition form will be provided to record all study medication dispensed to or returned from each subject. Upon completion of the study, all used and unused remaining EQW or matching placebo, empty containers, and copies of completed drug disposition forms should be returned to the sponsor (or designee). A clinical supplies return authorization form will be prepared by the clinical research associate at the closeout visit. The clinical supplies return form should be enclosed with the return drug shipment. The study site personnel must maintain documentation of any missing or unreturned study medication.

8 EFFICACY ASSESSMENTS

Trial endpoints will be defined based on clinical standards, regulatory precedent, and historical trials. These definitions will be provided in a separate document, along with the description of the Clinical Events Classification Committee (CEC). Patients will be asked at each trial visit about procedures and hospitalizations which have taken place since they were last seen.

8.1 Primary Efficacy Endpoint

- **Time to first confirmed CV event in the primary composite CV endpoint**
  Defined as the time from randomization to first confirmed CV-related death, nonfatal MI or nonfatal stroke.

8.2 Secondary Efficacy Endpoints

- **Time to all-cause mortality**
  Defined as time from randomization to death due to any cause.

- **Time to first confirmed CV event for each component of the primary composite endpoint**
  Defined as time from randomization to a confirmed CV-related death, nonfatal MI or nonfatal stroke.

- **Time to hospitalization for acute coronary syndrome**
  Defined as time from randomization to a confirmed hospital admission for unstable angina, ST-elevation myocardial infarction or non-ST-elevation myocardial infarction

- **Time to hospitalization for heart failure**
  Defined as time from randomization to hospital admission for congestive heart failure requiring treatment with intravenous diuretics, inotropes, or vasodilator therapy.

8.3 Additional Efficacy Endpoints

- **Time to revascularization procedure**
  Defined as time from randomization to time of first cardiovascular or peripheral revascularization procedure. This will include percutaneous coronary intervention with or without stenting, coronary artery bypass grafting, revascularization and/or stenting for peripheral arterial disease, carotid endarterectomy, or carotid stenting.

- **Time to initiation of first co-interventional agent**
  - Additional AHA
  - Chronic insulin therapy

- **Number of episodes of severe hypoglycemia requiring medical assistance**

- **Absolute values and change from baseline in:**

  - HbA_{1c}
  - Body weight
  - Blood pressure
  - Lipid profile

- **Quality of life assessed by the EQ-5D (EuroQol 5 Dimension) questionnaire.**

- **Medical resource use and total direct medical costs.**

- **Incremental cost-effectiveness analysis of exenatide once weekly as part of usual care compared with usual care without exenatide.**

9 STATISTICAL METHODS

This section outlines the statistical analysis strategy related to the primary and secondary study objectives with the full details given in a separate Statistical Analysis Plan (SAP). If any

substantive changes are made to these objectives or the statistical methods after the study has begun then the protocol will be amended, provided that it is prior to any unblinding, consistent with ICH Guideline E-9. The study database will only be locked and unblinded once medical/scientific review has been performed, protocol violations have been identified and the data have been declared final and complete. The statistical analyses for this study will be the responsibility of the University of Oxford Diabetes Trials Unit.

9.1 Baseline Characteristics

Demographic characteristics *e.g.* gender, age, ethnicity, body weight, will be summarized for each treatment group. In addition, duration of diabetes, alcohol intake, smoking status, cardiovascular medical history, baseline laboratory results and concomitant medications will be summarized by treatment group.

9.2 Sample Size

The planned sample size for this study is 9500 patients, randomized 1:1 to each of the two treatment arms assuming:

- An annual composite cardiovascular primary endpoint event rate estimated to be 3.8% per year for the population to be enrolled.
- A planned accrual period of 3 years
- A minimum treatment period of 4 years
- An estimated annual lost-to-follow up rate of 1%
- An anticipated treatment discontinuation rate of 5% per year

The number of cardiovascular primary endpoint events required is commensurate with a 90% power to detect a 15% relative risk decrease in the EQW group, *i.e.* a true hazard ratio of 0.85 relative to placebo, with a two-sided alpha=0.05. For an exponential maximum likelihood test of equality of survival curves, a total of 1591 composite cardiovascular events were calculated to be required using nQuery.

9.3 Randomization

Randomization via an Interactive Voice Response System (IVRS) will be 1:1 EQW to placebo, blocked within each site, and stratified by whether a participant has or has not had a prior cardiovascular event (i.e. prior myocardial infarction, surgical or percutaneous coronary revascularization).

9.4 Primary Hypothesis

The primary hypothesis is that EQW will be superior to placebo with respect to the primary composite cardiovascular outcome, with the participants analyzed according to their allocated treatment (intention to treat).

9.5 Secondary Hypothesis

The secondary hypothesis is that EQW will be non-inferior to placebo with respect to the primary composite cardiovascular outcome, with participants analyzed according to their allocated treatment (intention to treat). For the primary composite cardiovascular outcome a non-inferiority test will be applied (one-sided alpha=0.025) to confirm the hypothesis that the hazard ratio comparing the EQW and placebo groups falls below and excludes a 1.30 upper bound of the 95% confidence interval, *i.e.* if the upper limit of the 95% confidence interval of the hazard ratio is less than 1.30, non- inferiority will be concluded. A sensitivity analysis using a *per* protocol population will also be conducted.

9.6 Primary Analysis

Statistical analyses will be based upon adjudicated outcomes with subjects who discontinue prematurely from treatment followed until the end of the study, *i.e*. until the requisite number of primary composite events has been accrued. Analysis of the primary composite cardiovascular outcome will be based on the time from randomization to the occurrence of the first event, with participants analyzed according to their allocated treatment (intention to treat).

A logrank test will be performed first, with Kaplan-Meier curves for time to event used to depict the accumulation of events over time for the EQW and placebo treatment groups. The hazard ratio for the time of occurrence of the composite endpoint for the EQW and placebo treated groups and its 95% confidence interval will then be estimated using a Cox proportional

hazards model without covariate adjustment. Secondary Cox proportional hazards model analyses using covariate adjustments will also be performed as detailed in the SAP.

9.7 Secondary Analyses

Secondary analyses will be conducted with participants analyzed according to their allocated treatment (intention to treat) with a Hochberg adjustment for multiple testing. These analyses will examine:

1. All cause mortality
2. Fatal or nonfatal myocardial infarction
3. Fatal or nonfatal stroke
4. Hospitalization for acute coronary syndrome (ACS)
5. Hospitalization for heart failure (CHF)

9.8 Analysis Populations

The three predefined analysis populations are:

1) The Intent to Treat Population (ITT)

2) The Per Protocol Population (PP)

3) The Safety Population (SP).

9.8.1 Intent To Treat Population

The ITT population consists of all randomized patients. Evaluation will include all events which occurred from randomization to the date of final post-study telephone contact, regardless of the time interval between patient discontinuation of study drug and final contact. Patients who do not have any events during the study will be censored at the date of their final post-study telephone contact. Every effort will be made to collect CV events to study termination even in those who have discontinued the study. For the ITT population, any patient found to have taken a study medication for the entire duration of the study that is different from that to which he/she was randomized will be counted in the treatment group of the drug to which he/she was randomized.

9.8.2 Per Protocol Population

The Per-Protocol population consists of all randomized patients who have taken at least one dose of study medication and will include in their analysis all data collected prior to any major protocol violations such as:

- Initiation of an open-label prohibited medication *i.e.* a GLP-1 receptor agonist. Evaluation will include all data up to the day of the initiation of the prohibited medication.
- Discontinuation from study medication. Evaluation will include events which occurred from randomization to 90 days after the last dose of study medication.
- Taking incorrect study medication for more than three months

All such protocol violations will be identified prior to unblinding of the data. Events that occurred after protocol violation will be excluded from the analysis. If a patient is found to have taken a study medication for the entire duration of the study that is different from that to which he/she was randomized then the patient is counted in the treatment group of the drug he/she actually received. Patients who do not have any events during the study will be censored 90 days after the last dose of study medication.

9.8.3 Safety Population

The safety population consists of all randomized patients who received at least 1 dose of study therapy; in addition, if a patient is found to have taken a study therapy for the entire duration of the study, different from that to which he/she was randomized, then the patient is counted in the treatment group of the drug he/she actually received. Serious AEs and AEs leading to discontinuation of study medication, any of which occurred within 90 days after the last dose of study medication, will be collected. For continuous safety parameters, at least one post-randomization measurement is required for inclusion in the analysis. To assess change from baseline, a baseline measurement is also required.

9.9 Safety Data Analysis

Safety parameters will be summarized and presented in tables for the safety population. Serious adverse events will be listed by high level group terms (HGLT), as assigned by the MedDRA dictionary.

9.10 Subgroup Analyses

Subgroup analyses for the primary CV composite endpoint will be performed on the ITT population in order to explore whether the treatment effects on the risk of developing CV events are consistent across subgroups. The subgroups will be divided by categories or by the tertiles for continuous variables. Prespecified subgroups are as follows:

- Class of AHA therapy at entry (mono or combination)
- Race (Black, Caucasian, Asian, Other)
- Region (North/South America or Canada, Europe or South Africa, ROW)
- Gender (Male, Female)
- Age (<65 or ≥65)
- Baseline HbA_{1c} (<8.0% or ≥8/0%)
- Baseline BMI (<30 or ≥30 kg/m^2)
- Duration of diabetes (<5 years or ≥5 years)
- Baseline eGFR (<60 mL/min or ≥60 mL/min)
- History of previous cardiovascular event (e.g., previous MI or stroke)

The hazard ratios, 95% CIs, and appropriate summary statistics for each of the subgroups (by treatment group) will be provided and the hazard ratios examined for interaction effects. The interaction effect would be treatment*stratified variable, in additive format with treatment + stratified variable. For example, the stratified variable means the categorical variable 'Region'.

9.11 Interim Analyses

The DSMB will review available data every 6 months or more frequently if the committee deems it appropriate as outlined in the DSMB Charter. Stopping guidelines will be detailed in the DSMB Charter. The overall alpha=0.05 will be preserved by limiting the number of interim superiority analyses conducted as detailed in the DSMB Charter. The DSMB may, however, advise stopping the study before the minimum follow-up of 4 years has been achieved on ethical or safety grounds.

9.12 Economic Analysis

The primary objective of the economic analysis is to collect sufficient data from the trial participants on resource use and quality of life to undertake cost-effectiveness analyses that are

relevant to the major countries taking part in the study. Resource use data on hospitalizations, visits and medications will be combined with appropriate national unit costs to calculate a cost per patient per year in the study. Quality of life data from the EQ-5D will be combined with survival data to calculate quality adjusted time in the trial per patient.

Cost-effectiveness analyses will report the incremental cost per major CV outcome averted, CV-related death averted, life-year gained and quality-adjusted life year gained, of including exenatide once weekly as part of usual care *vs.* usual care without exenatide. Analyses will be conducted within trial and using a lifetime perspective, with lifetime extrapolation performed using the UKPDS Outcomes Model or all patients still alive at the end of the study, using risk factor characteristics from the last available visit. A full analysis plan for the economic analysis will be prepared and reported separately from this protocol.

10 SAFETY ASSESSMENTS

10.1 Definitions

Adverse Event (AE)

An adverse event is defined as any unfavorable and unintended sign, symptom, disease or change in the structure, function, or chemistry of the body temporally associated with the use of the investigational product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the investigational product, is also an adverse event. Adverse events include those reported spontaneously by the patient or as the result of non-directed questioning from study site personnel. Changes as a result of normal growth and development which do not vary significantly in frequency or severity from expected levels are not to be considered adverse events (e.g. the onset of menopause occurring at a physiologically appropriate time).

Serious Adverse Event (SAE)

This is defined as any untoward medical occurrence or effect in a patient treated on a study protocol which does not necessarily have a causal relationship with the study treatment, that also, at any dose:

- Results in death

- Is life-threatening
- Results in persistent or significant or disability/incapacity
- Requires in-patient hospitalization or prolongs existing hospitalization
- Results in a congenital anomaly or birth defect
- Is otherwise medically significant (i.e. withdrawal reactions, all accidental or intentional overdoses whether they result in an adverse event or not, or any event which the investigator considers significant but which is not covered by the above.)

Events meeting the above definition as SAEs and will be recorded in the safety trial database as either Clinical or Ancillary Events (definitions and criteria are summarized in Table 1).

Suspected Unexpected Serious Adverse Reaction (SUSAR)

This is defined as a serious adverse reaction, the nature or severity of which is not consistent with the known study treatment information.

10.2 Adverse Event Assessment

Adverse events will be monitored over the course of the trial, starting from the time of randomization and through the duration of the subject's participation, including the 90 day post-trial drug follow-up period or withdrawal. Adverse events reported by the patient will be evaluated by the investigator to determine if a given event meets the criteria for a serious event (described in Section 10.1.1). Any adverse event that does not meet the definition of a serious event will be considered non-serious and will not be recorded.

10.3 Classification and Reporting of Adverse Events

The classification of an SAE as a Clinical or Ancillary event is dependent on if the SAE is included in the Clinical Events List (Appendix 1). The Clinical Events List is inclusive of SAEs that are: (1) components of the primary or secondary composite cardiovascular endpoints, (2) other trial endpoints, (3) potential components of the CV endpoint that are included among terms sent for review by the CEC; (4) expected sequelae of type 2 diabetes; (5) expected events based on information noted in the exenatide investigator brochure. SAE which meet these criteria will be reported in the **Clinical Events eCRF module**. SAE which are not included on

the Clinical Events List will be considered Ancillary events and will be reported in the **Ancillary Events eCRF module**.

The Clinical Events List will be reviewed and the eCRF will be completed during every visit to determine if a patient has experienced one or more of the listed events. SAE should be reviewed for all patients randomized regardless of whether the patient is currently on trial medication.

Table 1 Adverse event definitions and reporting modules

Serious Adverse Event:
An adverse event that results in any of the following:
death, life-threatening situation, inpatient hospitalization (or prolongation of hospitalization), persistent or significant disability or incapacity, congenital anomaly or birth defect, or important medical events that require medical or surgical intervention to prevent one of the preceding outcomes.

SAE category	Description	Reporting Module
Clinical Event*	SAEs that are: 1. components of the primary or secondary composite cardiovascular endpoints 2. other trial endpoints 3. potential components of the CV endpoint that are included among terms sent for review by the CEC 4. expected sequelae of type 2 diabetes 5. expected events based on information noted in the exenatide investigator brochure	Clinical Event eCRF
Ancillary Event	Adverse events which meet the criteria for a serious event but are not noted on the clinical events list	Ancillary SAE eCRF

Non-serious adverse events:
Any adverse event which does not meet a criterion to be classified as a SAE. These events will not be recorded.

*The clinical events list is noted in Appendix 1.

SAE recorded on the Clinical Events eCRF represent those events which are components of the composite CV endpoint, other trial endpoints, potential components of the CV endpoint that require adjudication, expected sequelae of T2DM, or are expected based on information provided in the exenatide investigator brochure. Clinical events will be monitored by the DSMB and **will not** require expedited reporting to the sponsor even though they may be considered possibly, probably or definitely drug-related and meet SAE criteria. ***Regardless of relationship to trial drug, Clinical Events will not be reported by the sponsor to regulatory agencies or ethics committees in an expedited manner, nor in the format of a line listing as part of an Annual Safety Report.*** Events reported via this module will be regularly monitored by the DSMB and those which may be associated with a trial endpoint will be adjudicated by the CEC.

As described in Section 10.1.1 all SAEs that are not included in the Clinical Events List will be recorded by the investigator as Ancillary Events. These events must be recorded in this module within **1 day** of a trial site becoming aware of the event. Brief information on the clinical course of the event, treatment, and relevant diagnostic, laboratory or other investigations will be collected on the eCRF. Episodes of pancreatitis, diagnoses of thyroid carcinoma and pancreatic cancer will be collected and reported as Ancillary Events. All Ancillary Events will be reported to the appropriate regulatory agencies in a manner and timeframe consistent with all applicable laws and regulations (Section 10.3.1).

Additionally, any SAE considered by an investigator who is a qualified physician to be possibly, probably, or definitely related to the investigational product that is brought to the attention of the investigator after study closeout must be reported within the above timeline to Amylin/Eli Lilly. All patients with serious adverse events must be followed to assess outcome until resolution or until designated permanent.

10.3.1 Sponsor Responsibility for Reporting Serious Adverse Events

The Sponsor will ensure that all appropriate regulatory agencies confirm that the approach for monitoring Clinical Events, described in the Safety Assessments section is acceptable to them. All Ancillary SAE will be reported to regulatory agencies, IRB/IECs, and investigators in accordance with all applicable global laws and regulations.

10.4 Overdose

10.4.1 Definition of an Overdose for This Protocol

An overdose is defined as a subject taking more than 1 dose of study medication in the same day. In the event of an overdose, medical treatment may be needed since severe nausea and vomiting are possible. The patient should be instructed to contact the investigational site, and/or healthcare provider in the event of an overdose 1 day of the trial site becoming aware of the event.

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10.4.2 Reporting of Overdose

If an adverse experience(s) is associated with ("results from") the overdose of test drug, the adverse experience(s) is reported as a serious adverse experience, even if no other criteria for seriousness are met.

If a dose of test drug meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse experience must be reported within 1 day of the site's knowledge of the event.

10.5 Reporting of Pregnancy

Although not considered an adverse experience, it is the responsibility of investigators or their designees to report any pregnancy in a patient (spontaneously reported to them) which occurs during the trial or within 90 days of completing the trial. All patients who become pregnant must stop taking blinded trial medication and be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported.

11 ETHICAL AND LEGAL ASPECTS

11.1 General Informed Consent

The investigator must obtain written documented consent to participate in the trial from each potential patient in his/her native language. Consent must be documented by the patient's dated signature on a Consent Form along with the dated signature of the person conducting the consent discussion. If the patient is illiterate, an impartial witness should be present during the entire informed consent reading and discussion. Afterward, the patient should sign and date the informed consent, if capable. The impartial witness should also sign and date the informed consent along with the individual who read and discussed the informed consent (i.e., trial staff personnel). A copy of the signed and dated consent form should be given to the patient at time of randomization.

The initial informed consent form, any subsequent revised written informed consent forms, and any written information provided to the patient must receive the IRB/IECs approval/favorable opinion in advance of use. The patient or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form.

The informed consent form will describe the regular two-way exchange of information that is expected to occur between trial physicians and the usual care physicians. The informed consent form will also include a request that the patient provide permission for the collection of medical records and copies of relevant reports necessary for complete data collection even if trial medication is discontinued beforehand.

11.2 Consent and Collection of Specimens for Genetic and Genomic Analysis

Patients providing informed consent will have a whole blood specimen collected for potential future genetic research. This is an optional activity, and only those patients who have consented to having this genetic sample collected may have this blood sample drawn. The approval of the consent form for analysis and the associated protocol procedures (e.g., collection of a blood sample) may, in some cases, proceed independently through Institutional Review Boards, Ethical Review Boards, Independent Ethical Review Committees (ERCs), Privacy Committees, etc., from the associated clinical trial.

11.3 Consent and Collection of Biomarker Specimens

Patients providing informed consent will have a fasting blood sample collected at baseline (prior to drug exposure), and either at one year of treatment or at the time of drug discontinuation (if occurring within the first year). Biomarker samples will be stored in at least two aliquots for potential future proteomic and/or metabolomic analysis. This is an optional activity, and only those patients who have consented to having this biomarker sample collected may have this blood sample drawn. The approval of the consent form for analysis and the associated protocol procedures (e.g., collection of a blood sample) may, in some cases, proceed

independently through Institutional Review Boards, Ethical Review Boards, Independent Ethical Review Committees (ERCs), Privacy Committees, etc., from the associated clinical trial.

11.4 Ethics Committee or Institutional Review Board

Documented approval from appropriate Ethics Committee(s) or Institutional Review Board(s) must be obtained for all participating centers prior to study start, according to Good Clinical Practice (GCP), local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the Ethics Committee approval must also be obtained. Ethics Committees, upon request, may be required to provide a list of the Ethics Committee members involved in the vote and a statement to confirm that the Ethics Committee is organized and operates according to GCP and applicable laws and regulations. Modifications to the study protocol will not be implemented without the agreement of the Executive Committee and appropriate ethical approval.

11.5 Ethical Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by GCP Guidelines. The study will also be carried out in keeping with applicable local law(s) and regulation(s). This may include an inspection by the sponsor representatives and/or Regulatory Authority representatives at any time. The investigator must agree to the inspection of study-related records by the Regulatory Authority/sponsor representatives, and must allow direct access to source documents to the Regulatory Authority/sponsor representatives.

11.6 Regulatory Authority Approvals/Authorizations

Regulatory Authority approvals/authorizations/notifications, where required, must be in place and fully documented prior to study start

11.7 Confidentiality

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. The patient will be identified only by a unique patient ID number on the eCRF. All documents will be stored securely and kept in strict confidence in compliance with the Data Protection Act.

Study findings stored on a computer will be stored in accordance with local data protection laws. The patients will be informed in writing that representatives of the sponsor, Ethical Committees, Institutional Review Boards or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

When the results of the study are published, the patient's identity will remain confidential. The investigator will maintain a list to enable patients' records to be identified

12 TRIAL MANAGEMENT/GOVERNANCE COMMITTEES

12.1 Executive Committee (EC)

The EC will be responsible for overall management and oversight of the trial. The EC will be composed of approximately eleven individuals consisting of nine senior independent academic representatives who are experts in their field and two representatives from the Alliance. The Committee will be co-chaired by Professors Robert Califf (cardiologist) and Rury Holman (endocrinologist). The other academic members will comprise four further diabetologists and three further cardiologists. Geographical balance will be sought. Decision making will be by consensus. An EC charter will delineate operating procedures.

The Executive Committee is the main decision-making body for EQW and is charged with the overall scientific, professional, and operational conduct of the trial.

<u>The primary functions of the Executive Committee are to:</u>

1. Review and approve the trial protocol and all protocol amendments.
2. Supervise the conduct of the trial in accordance with its responsibilities described in the trial protocol.
3. Review and approve the Statistical Analysis Plan.
4. Oversee all trial subcommittees, including but not limited to:

    - Clinical Endpoint Committee

- Data Safety Monitoring Board
- Operations Committee

5. Review and consider recommendations from the Data Safety Monitoring Board DSMB).

6. The Executive Committee will determine the time to terminate the trial, based on recommendations from the DSMB and other available information. The Executive Committee may also find it necessary to terminate the trial under certain circumstances, including but not limited to the following reasons:

   - Animal, human or toxicological test results, in the reasonable determination of the Executive Committee, support termination of the trial
   - Ethical or patient safety issues occur that the Executive Committee feels support termination of the trial
   - Extraordinary scientific, regulatory or other events that negatively impact the rationale for the trial such that the Executive Committee agrees it is appropriate to terminate the trial

7. Review all sub-study requests and approve where appropriate.

8. Consider, authorize as appropriate and prioritize requests for access to EQW trial data and genetic and biomarker samples for academic or other collaborations. After the Executive Committee disbands, DCRI, DTU and the sponsor will assume this responsibility.

9. Approve the communication strategy on how to best communicate information about the progress of the trial.

10. Ensure accurate, uniform, timely, and high quality reporting of the main trial and all approved sub-studies.

11. Serve as the writing group who will prepare and submit for publication the primary manuscript describing the main trial results. All members of the Executive Committee will

have access, in confidence to the draft manuscript describing the primary results paper.

12. Assume the role of publications committee and review, authorize and prioritize proposals for publications which require trial or sub study data samples, or genetic material and assign writing groups.

13. Review and comment on any independent publications by the Alliance reporting results from the trial following the primary publication.

12.2 Operations Committee (OC)

The Operations Committee (OC) is composed of Country Leads selected by the Executive Committee from investigators in each country with appropriate clinical trial experience. The OC will be co-chaired by the clinical coordinators from the Duke Clinical Research Institute (DCRI) and the Diabetes Trials Unit (DTU). Balance will be sought between cardiologists and endocrinologists. The primary role of the OC is to serve as the interface between the EC and the trial sites, and to assist in the progress of the trial at the regional level. Committee members will be instrumental in serving as ambassadors of the trial to encourage recruitment as well as ensure trial compliance by working with study personnel and mediating in country-specific issues. The committee will provide a means of transmitting any identified needs, concerns, or suggestions from the sites to the EC and assist in disseminating clinical or operational information to the sites. The functions and operating procedures of the OC are delineated in a charter.

12.2.1 Remit of Operations Committee

Specific functions of the OC will include the following:

1. All members will serve as regional leaders for site investigators.
2. All members will serve as advocates for the trial.
3. Country Leads will:
   a. Communicate with investigators in the Lead's country to review country specific progress reports, including but not limited to recruitment/retention of patients, event reporting and data collection, and communication between sites and usual care providers.

b. Liaise with the academic coordinating centers and global Contract Research Organizations (CROs) to review and attempt to resolve any operational issues raised within a region
c. Support regulatory submissions, as needed in collaboration with the Sponsor's Regulatory Affairs Department.

4. Committee Co-Chairs will:
   a. Compile country-specific performance metrics for presentation to the Executive Committee.
   b. Liaise with Country Leads, academic coordinating centers (DCRI and DTU project teams), sponsors and global AROs/CROs to implement trial policies

12.3 Data Safety Monitoring Board (DSMB)

The DSMB will be composed of five senior academic individuals, including the DSMB Chair. There will be at least one member with high-level expertise for each of cardiology, endocrinology, and statistics. An Independent Statistician (not affiliated with the DCRI, DTU, or the Sponsor) will also be in attendance. All of these individuals will have long-standing experience in the operational, medical, and biostatistical aspects of international clinical trials. The DTU senior statistician assigned to the EQW trial will oversee the provision of interim masked data sets for use by the DSMB and the DCRI/DTU trial coordinating centers. DTU will transfer pre-agreed masked datasets to the Independent Statistician who will then prepare unmasked confidential reports for the DSMB, using treatment codes provided in advance by the Sponsor. During the Open Session of the DSMB meetings, representatives of the Executive Committee may present updates on the trial status or the safety profile of exenatide, but will not be privy to discussions of the unmasked data conducted during the Closed Sessions and will not vote. Proceedings and minutes of the Closed Session will be held in strict confidence and will not be shared outside the DSMB while the trial is ongoing.

The DSMB will be responsible for the interests of the patients and, to this end, will undertake regular reviews of the safety data. The DSMB will have access to an agreed subset of the trial data as listed in the DSMB charter (updated as necessary during the trial) in an unblinded fashion throughout the trial duration. In addition, the DSMB will evaluate interim analyses of the data every six months (or on an ad hoc basis if needed) to determine if it believes

either the trial should be terminated early because the exenatide arm (with respect to the placebo arm) demonstrates (a) clear inferiority, i.e., it is not in patient's best interest to continue taking blinded therapy; or (b) clear superiority, i.e., it is not in patient's best interest to continue taking blinded placebo.

If the DSMB finds it necessary to recommend actions regarding interruption of the trial or changes to the protocol based on medical rationale that would make it unethical to continue the trial in its present form, those recommendations will be forwarded to the EC. The details of the DSMB's functions and the early stopping rules will be delineated in a separate DSMB charter.

12.4 Clinical Events Committee (CEC)

The events which constitute the principal endpoints of this trial will be adjudicated by the Clinical Events Classification Committee (CEC), coordinated through the Duke Clinical Research Institute (DCRI), which will be comprised of approximately 5-7 physicians and a coordinator. The specific endpoints to be adjudicated include: cause of death (cardiovascular-related vs. non-cardiovascular), MI, stroke, acute coronary syndrome, and CHF requiring hospitalization. Clinical reviewers will be board certified or board eligible endocrinologists, cardiologists, neurologists, gastroenterologists, or physicians with clinical expertise and prior clinical event classification experience. The CEC will review clinical data and adjudicate safety and efficacy endpoints. The CEC will adjudicate clinical events using pre-specified criteria and definitions for the diagnoses of MI, stroke, acute coronary syndrome, and CHF requiring hospitalization. The CEC will be blinded to the assigned trial drug. Sites will provide clinical information via the eCRF and also provide supplemental information from medical records, when needed. The CEC operations and endpoint criteria will be described in a separate charter.

13 DISCLOSURE OF DATA AND PUBLICATIONS

During the Trial all data derived from the Trial will be held by the AROs but with access for Sponsor to any data required for safety and regulatory purposes. At the time database lock occurs, the IVRS provider will provide the AROs with an electronic file containing the full randomization codes for upload to the electronic database. The ARO will undertake the planned analyses and prepare and submit manuscripts for publication and presentation to academic

meetings agreed by the Executive Committee. The Sponsor will have the right to comment on these but the final editorial control remains with the Executive Committee. Following submission for publication of the main trial results, a copy of the database will be transferred to the Sponsor. The Executive Committee, which includes the principal investigators, Sponsor representatives, academic cardiologists and academic endocrinologists, will draft the manuscript describing the main study results, and oversee publications requiring trial data, samples, or genetic material.

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APPENDIX 1

CLINICAL EVENTS LIST (TO BE INCORPORATED INTO ECRF)

The following list of events would be recorded in the eCRF at the time of the trial visit, ***but not reported to the Sponsor or regulatory agencies urgently*** regardless of relationship to trial drug. Included are trial endpoints as well as events that are expected to occur in this trial population.

I. Primary or Secondary Trial Endpoints

A. **Obvious trial endpoints** (These events will prompt the investigator to complete an endpoint package which will then be adjudicated according to the Clinical Events Classification [CEC] charter)

Death
- Cardiovascular (CV) Death (i.e., fatal myocardial infarction [MI]/cerebrovascular accident [CVA]/ congestive heart failure [CHF]/arrhythmia, cardiac arrest, death following CV intervention)
- Non-CV Death

Nonfatal MI
Acute coronary syndrome
Nonfatal CVA
CHF requiring hospitalization

B. **Cardiovascular Events of Interest** (some of these events will result in prompts to answer additional questions in the eCRF – these questions will be designed to determine whether or not a primary or secondary outcome of interest has occurred)

Atrial fibrillation/Atrial flutter
Ventricular fibrillation/tachycardia requiring intervention
Deep Vein Thrombosis (DVT)
Pulmonary embolism
Percutaneous Coronary Intervention (PCI)
Coronary Artery Bypass Graft (CABG)
Coronary catheterization
Stress test
Abdominal aortic aneurysm/repair
Carotid endarterectomy/Carotid angioplasty and/or stenting
Any hospitalization due to cardiovascular events (i.e., whether or not the hospitalization was for an obvious trial endpoint)
Shock/hypotension
Accelerated or malignant hypertension/hypertensive urgency
Transient Ischemic Attack (TIA)
Syncope
Renal artery angioplasty and/or stenting
Other arterial angioplasty and/or stenting

II. Expected Events and Diabetic Complications (subcategories indicate potential additional information to be captured, usually as an indication of severity)

A. Peripheral Vascular Disease (PVD)
- Limb PCI
- Vascular surgery
- Amputation
- Surgical debridement of ulcer

B. Gangrene

C. Hypoglycemia / Hyperglycemia /Diabetic ketoacidosis / Hyperosmolar hyperglycemic nonketotic coma

D. Diabetic eye disease
- Photocoagulation or other laser therapy
- Cataract extraction
- Blindness
- Enucleation
- Steroid/Avastin injection
- Scleral buckling or other retinal fixation procedure

E. Diabetic neuropathy (including distal sensorimotor, focal/multifocal, or autonomic)
- Foot ulcer

F. Diabetic nephropathy
- Microalbuminuria
- Proteinuria

G. Renal failure/peritoneal or hemodialysis/renal transplant (including creation of fistula or other vascular access for hemodialysis)

H. Any hospitalization due to complications of DM

I. Infections
- Osteomyelitis
  - IV antibiotic therapy vs. debridement
- Cellulitis
  - Oral vs. IV antibiotic therapy
- Mucormycosis
- Pneumonia
  - Community acquired vs. hospital acquired
  - Oral vs. IV antibiotic therapy

- Bacteremia
- Sepsis
- Infected joints
    - Prosthetic joint
- Complicated or serious urinary tract infection (UTI)/Pyelonephritis
    - requiring hospitalization
- Malignant external otitis

J. Gastrointestinal (GI) conditions
- Abdominal pain
- Nausea / vomiting
- Diarrhea
- Fatty liver disease / Nonalcoholic steatohepatitis (NASH)
- Cholecystitis / cholelithiasis
- Elevated liver enzymes

K. Metabolic Conditions Associated with Diabetes
- Hyperlipidemia / dyslipidemia
- Hypertension
- Gout

III. Terms listed in the exenatide Investigator Brochure

A. Allergic/Hypersensitivity Reactions
- Injection site reactions
- Pruritis and/or urticaria
- Rash
- Angioedema
- Anaphylactic reaction

B. Gastrointestinal reactions
- Nausea
- Vomiting and/or diarrhea resulting in dehydration
- Abdominal distension or pain
- Eructation
- Constipation
- Flatulence
- Diarrhea

C. Renal and Urinary Disorders
- Altered renal function, including acute or worsened chronic renal failure
- Renal impairment
- Increased serum creatinine

D. Development of antibodies to exenatide

E. For all other terms please refer to the current Investigator Brochure

APPENDIX 2 TRIAL PLAN (Protocol BCB109)

		Treatment Initiation		Follow-up [4]		Drug or Study Termination	
Evaluation	**Screening Day -1**	**Randomization Day 0 Visit 1 [1]**	**Week 1 and Month 2 Visit 2 and 3**	**Semi-Annual**	**Annual**	**Drug Termination [5]**	**Trial/Early Termination**
Informed Consent/HIPAA [2] and Stored Blood Sample Authorization	X						
Medical History	X						
Physical Examination	X						
Height	X						
Blood pressure	X	X		X	X	X	X
Body Weight	X	X		X	X	X	X
Calcitonin measurement	X						
Collect and review available information including most recent HbA_{1c}, serum creatinine and lipid profile	X			X	X	X	X
Randomization		X					
If consent obtained, collect blood sample for genetic and genomic analysis	X						
Blood sample (serum and plasma) and urine sample for archive	X				Month 12 only		
Drug Dispensation		X		X	X		
Used/Unused Vial Assessment				X	X	X	X
Clinical and Ancillary Event Assessment		X	X	X	X	X	X
Conmed Assessment	X	X	X	X	X	X	X
Confirm competency with injections [3]			X				
EQ-5D Completion		X		Month 6 only	X	X	X

[1] Wherever possible the screening and randomization visit should be combined.
[2] Informed Consent Form and if applicable, authorization to use and disclose protected health information.
[3] Patients will return approximately 1 week (±3 days) as well as 2 months (± 2 weeks) after Day 0 to perform a self-injection under the observation of the clinical site to confirm competency with injection. An additional visit can be considered at ~1 month if the patient is not able to adequately inject themselves.
[4] Semi-annual (±1 month) and Annual Follow-up (±1 month) Visits will occur in reference to Visit 1 Day 0 for the duration of participation in the trial.
[5] Patients who terminate study medication are required to have a Drug Termination Visit as soon as possible following the cessation of study medication. Patients will continue to be observed following the Drug Termination visit according to their planned visit schedule for the remainder of the trial. All procedures for remaining Semi-annual and Annual Visits are to be followed with the exception of Drug Dispensation.

EXenatide Study of Cardiovascular Event Lowering Trial (EXSCEL)
Clinical Study Protocol D5551C00003, BCB109

A RANDOMIZED, PLACEBO CONTROLLED CLINICAL TRIAL TO EVALUATE CARDIOVASCULAR OUTCOMES AFTER TREATMENT WITH EXENATIDE ONCE WEEKLY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Phase 3b/4

Original Protocol:	24 December 2009
Amendment 01:	11 November 2010
Amendment 02:	10 May 2011
Amendment 03:	23 April 2012
Amendment 04:	12 September 2012
Amendment 05:	25 October 2013
Amendment 06	09 March 2016

Protocol Approved By:

13-JUN-2016

Stephanie Gustavson, MD, PhD — Date

Director - CVMD Global Medicines Department

Telephone: +

IND Number: 67,092

EUDRACT: 2010-021069-63

SPONSOR:

Amylin Pharmaceuticals, LLC (a wholly owned subsidiary of AstraZeneca)

1800 Concord Pike

Wilmington, Delaware 19897-0001

United States

Amylin Pharmaceuticals, LLC sponsors the Investigational New Drug Application

PROTOCOL AMENDMENT 06: SUMMARY OF CHANGES

Exenatide QW Clinical Study Protocol D5551C00003, BCB109

PROTOCOL TITLE: A RANDOMIZED, PLACEBO CONTROLLED CLINICAL TRIAL TO EVALUATE CARDIOVASCULAR OUTCOMES AFTER TREATMENT WITH EXENATIDE ONCE WEEKLY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Protocol Number: **D5551C00003, BCB109**

Amendment Number: **06**

Amendment Purpose: **Date: 09 March 2016**

The purpose of this non-substantial amendment is two-fold:

1. to update the protocol based on US Food and Drug Administration (FDA) recommendation for the study analysis, and
2. to update the procedures for handling all Clinical Events (as defined in Protocol Appendix 1) to be consistent throughout the study.

As per the protocol, the EXenatide Study of Cardiovascular Event Lowering Trial (EXSCEL) Executive Committee will monitor the accrual of the aggregate number of adjudicated primary endpoint events (confirmed cardiovascular-related death, nonfatal myocardial infarction or nonfatal stroke) and will determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued). The primary statistical analysis was initially planned to include all adjudicated cardiovascular events with onset dates up to and including the primary endpoint event cut-off date. As per FDA recommendation, the primary statistical analysis has been updated to include all adjudicated primary endpoint events with onset dates up to and including the Trial Termination Visit date (rather than the primary endpoint event cut-off date). Any events occurring between the Trial Termination Visit and the safety follow-up phone call (scheduled 70 days after last dose of study medication) will not be adjudicated and will not be included in the primary analysis, as agreed by the FDA. The FDA also made recommendations for updating the censoring strategy, which has been incorporated in the protocol amendment.

The procedure for serious adverse event (SAE) reporting described in Protocol Section 10.3.1 and Protocol Appendix 1 will be updated to reflect that Clinical Events (as defined in Protocol Appendix 1) occurring after the primary endpoint event cut-off date (e.g., during either the time period up to the Trial Termination Visit or during the safety follow-up period) will continue to be collected and reported in the same way as they have been throughout the study. There will be no switch to collecting and managing Clinical Events as SAEs after the primary endpoint cut-off date as previously described in the protocol.

This amendment will also address administrative changes in the study.

Administrative Changes:

- To inform that as of January 2015, the EXSCEL Executive Committee co-chair, Professor Robert Califf, has been replaced by Dr Adrian Felipe Hernandez, MD., Professor of Medicine, Member in the Duke Clinical Research Institute.
- To inform that while Amylin LLC remains the sponsor for the study, as of 1 February 2014, Amylin LLC is wholly owned by AstraZeneca.
- To inform that as part of the ownership transfer of Amylin, a new study code D5551C00003 was generated to comply with AstraZeneca internal procedures. Trial reference codes H80-MC-GWDQ, BCB109 and D5551C00003 refer to the same clinical study, known as EXSCEL.

In the table below, the changes in individual sections are presented in the revised text with all deletions addressed as a strikethrough and all additions shown in bold.

SECTION	AMENDMENT 05 TEXT	AMENDMENT 06 TEXT
3 Trial Governance	EXSCEL is a multinational pragmatic trial that will be conducted at approximately 800 sites worldwide. It will be run jointly by the Duke Clinical Research Institute (DCRI) and the University of Oxford Diabetes Trials Unit (DTU) Academic Research Organizations (AROs), in an academic collaboration with Amylin Pharmaceuticals, LLC (Amylin), a wholly owned subsidiary of Bristol-Myers Squibb. EXSCEL will be Co-Chaired by Professors Robert Califf (Cardiologist) and Rury Holman (Endocrinologist) and sponsored and funded by Amylin. The EXSCEL Executive Committee (EC) will have overall responsibility for the oversight and management of the trial (Figure 1). The EC will consist of senior independent academic representatives who are experts in their field and sponsor representatives. It will be Co-Chaired by Professors Robert Califf and Rury Holman (see Section 12.1).	EXSCEL is a multinational pragmatic trial that will be conducted at approximately 800 sites worldwide. It will be run jointly by the Duke Clinical Research Institute (DCRI) and the University of Oxford Diabetes Trials Unit (DTU) Academic Research Organizations (AROs), in an academic collaboration with Amylin Pharmaceuticals, LLC (Amylin), a wholly owned subsidiary of **AstraZeneca** ~~Bristol Myers Squibb~~. EXSCEL will be Co-Chaired by Professors **Adrian Hernandez** ~~Robert Califf~~ (Cardiologist) and Rury Holman (Endocrinologist) and sponsored and funded by Amylin. The EXSCEL Executive Committee (EC) will have overall responsibility for the oversight and management of the trial (Figure 1). The EC will consist of senior independent academic representatives who are experts in their field and sponsor representatives. It will be Co-Chaired by Professors **Adrian Hernandez** ~~Robert Califf~~ and Rury Holman (see Section 12.1).
4.1 Design Description Paragraph 2	Approximately 14,000 patients meeting all enrollment criteria will be recruited in to the trial over approximately a five year period, randomly allocated to treatment with either EQW 2 mg or matching placebo subcutaneous injections once weekly in a 1:1 ratio, and followed until the requisite number of primary endpoint events have been reported. The trial is planned to continue until 1360 patients with positively adjudicated primary endpoint events have been accrued, or until the independent Data Safety Monitoring Board (DSMB) advises otherwise. It is anticipated that the EXSCEL Executive Committee will monitor the accrual of the aggregate number of adjudicated primary endpoint events and will determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued); all patients will be expected to have follow-up through this date (see Section 6).	Approximately 14,000 patients meeting all enrollment criteria will be recruited in to the trial over approximately a five year period, randomly allocated to treatment with either EQW 2 mg or matching placebo subcutaneous injections once weekly in a 1:1 ratio, and followed until the requisite number of primary endpoint events have been reported. The trial is planned to continue until 1360 patients with positively adjudicated primary endpoint events have been accrued, or until the independent Data Safety Monitoring Board (DSMB) advises otherwise. It is anticipated that the EXSCEL Executive Committee will monitor the accrual of the aggregate number of adjudicated primary endpoint events and will determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued). **Based on the primary endpoint event cut-off date, a window of time for conduct of the Trial Termination Visit will be established**; all patients will be expected to have follow-up ~~through this date~~ **until the Trial Termination Visit** (see Section 6).

SECTION	AMENDMENT 05 TEXT	AMENDMENT 06 TEXT
4.2 Trial Duration	It is anticipated that enrollment will occur over approximately a five year period, and that an additional 2 to 3 years may be required to accumulate the requisite number of patients with positively adjudicated primary endpoint events, for a total duration of up to approximately 7.5 years, unless the trial is terminated earlier. All patients who discontinue study medication, but have not withdrawn consent to participate in the study, will be followed up, if possible, for the full study period and will have their vital status ascertained, if possible, as of the data cut-off date for primary endpoint events.	It is anticipated that enrollment will occur over approximately a ~~five~~ **5-**year period, and that an additional 2 to 3 years may be required to accumulate the requisite number of patients with positively adjudicated primary endpoint events, for a total duration of up to approximately 7.5 years, unless the trial is terminated earlier. All patients who discontinue study medication, but have not withdrawn consent to participate in the study, will be followed up, if possible, for the full study period and will have their vital status ascertained, if possible, as of the **Trial Termination Visit** ~~data cut-off date for primary endpoint events~~.
6.1 Trial Procedures - Overview	Paragraph 3: The trial is planned to continue until 1360 patients with positively adjudicated primary endpoint events have been accrued. It is anticipated that the EXSCEL Executive Committee will monitor the accrual of the aggregate number of adjudicated primary endpoint events and will determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued; all patients will be expected to have follow-up through this date). Based on the primary endpoint event cut-off date, a window of time for conduct of the Trial Termination Visit will be established.	Paragraph 3: The trial is planned to continue until 1360 patients with positively adjudicated primary endpoint events have been accrued. It is anticipated that the EXSCEL Executive Committee will monitor the accrual of the aggregate number of adjudicated primary endpoint events and will determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued)~~- all patients will be expected to have follow-up through this date)~~. Based on the primary endpoint event cut-off date, a window of time for conduct of the Trial Termination Visit will be established. **All patients will be expected to have follow-up until this visit.**

SECTION	AMENDMENT 05 TEXT	AMENDMENT 06 TEXT
	Paragraphs 5 and 6: After the Trial Termination Visit patients will be contacted by telephone to check for any serious adverse experiences and hospitalizations that occurred within 70 days after the administration of the last dose of trial medication. Patients who have discontinued trial medication 70 or more days prior to the Trial Termination Visit will not need to have the telephone contact visit performed. These patients will have their final assessment of serious adverse experiences and hospitalizations completed at the Trial Termination Visit. Note that all serious adverse experiences, hospitalizations, and reportable study events with an onset date after the primary endpoint event cut-off date established by the study Executive Committee will be managed as serious adverse experiences (see Section 10.3.1).	Paragraphs 5 and 6: After the Trial Termination Visit patients will be contacted by telephone to check for any **Clinical Events**, serious adverse experiences and hospitalizations that occurred within 70 days after the administration of the last dose of trial medication. **Note that any events occurring between the Trial Termination Visit and the safety follow-up phone call will not be adjudicated and will not be included in the primary analysis**. Patients who have discontinued trial medication 70 or more days prior to the Trial Termination Visit will not need to have the **safety follow-up** telephone contact visit performed. These patients will have their final assessment of **Clinical Events**, serious adverse experiences and hospitalizations completed at the Trial Termination Visit. **Clinical Events (as defined in Protocol Appendix 1) will continue to be collected and reported in the same way as they have been throughout the entire study (i.e., prior to the cut-off date)** ~~Note that all serious adverse experiences, hospitalizations, and reportable study events with an onset date after the primary endpoint event cut-off date established by the study Executive Committee will be managed as serious adverse experiences~~ (see Section 10.3.1).

SECTION	AMENDMENT 05 TEXT	AMENDMENT 06 TEXT
6.13 Trial Termination Visit	Investigators will be informed by the DCRI and DTU Coordinating Centers as to when the Trial Termination Visit is to be completed, and will schedule **all** patients for the Trial Termination Visit. Based on the primary endpoint event cut-off date, a window of time for conduct of the Trial Termination Visits will be established; this window will be a period of time following the primary endpoint event cut-off date. At the Trial Termination Visit, all patients must be discontinued from trial medication; the investigator should ensure that the patient receives appropriate standard of care. For procedural details of the Trial Termination Visit, refer to Appendix 2. …. If a patient fails to return or otherwise becomes difficult to contact, it is the investigator's responsibility to make every effort to maintain contact so that at the end of the trial the patient can be located to determine status and to obtain necessary information for serious adverse experience reporting and/or endpoint adjudication as of the primary endpoint event cut-off date.	Investigators will be informed by the DCRI and DTU Coordinating Centers as to when the Trial Termination Visit is to be completed, and will schedule **all** patients for the Trial Termination Visit. Based on the primary endpoint event cut-off date, a window of time for conduct of the Trial Termination Visits will be established; this window will be a period of time following the primary endpoint event cut-off date. **All patients will be expected to have follow-up until this visit.** At the Trial Termination Visit, all patients must be discontinued from trial medication; the investigator should ensure that the patient receives appropriate standard of care. For procedural details of the Trial Termination Visit, refer to Appendix 2. …. If a patient fails to return or otherwise becomes difficult to contact, it is the investigator's responsibility to make every effort to maintain contact so that at the end of the trial the patient can be located to determine status and to obtain necessary information for serious adverse experience reporting and/or endpoint adjudication as of the **Trial Termination Visit** ~~primary endpoint event cut-off date~~.
6.14 Post-Treatment Telephone Contact	After the Trial Termination Visit, patients will be contacted by telephone to check for any serious adverse experiences and hospitalizations that occurred within 70 days after the administration of the last dose of trial medication. For patients who have been discontinued from trial medication for more than 70 days as of the Trial Termination Visit, the Trial Termination Visit will be the final study follow-up. Note that all serious adverse experiences, hospitalizations, and reportable study events with an *onset* date after the primary endpoint event cut-off date established by the study Executive Committee will be managed as serious adverse experiences (see Section 10.3.1).	After the Trial Termination Visit, patients will be contacted by telephone to check for any **Clinical Events**, serious adverse experiences and hospitalizations that occurred within 70 days after the administration of the last dose of trial medication. For patients who have been discontinued from trial medication for more than 70 days as of the Trial Termination Visit, the Trial Termination Visit will be the final study follow-up. **Clinical Events (as defined in Protocol Appendix 1) will continue to be collected and reported in the same way as they have been throughout the entire study (i.e., prior to the cut-off date)** ~~Note that all serious adverse experiences, hospitalizations, and reportable study events with an *onset* date after the primary endpoint event cut-off date established by the study Executive Committee will be managed as serious adverse experiences~~ (see Section 10.3.1).
8.3 Additional Efficacy Endpoints	• Number of episodes of severe hypoglycemia requiring medical assistance.	• ~~Number of episodes of severe hypoglycemia requiring medical assistance.~~

SECTION	AMENDMENT 05 TEXT	AMENDMENT 06 TEXT
9.5 Primary Analysis	The primary statistical analysis will be based upon adjudicated CV events with patients who discontinue prematurely from treatment followed until the end of the study, *i.e.* until the requisite number of primary composite events has been accrued. It is anticipated that the Executive Committee will monitor the accrual of the aggregate number of primary composite CV events to determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued). All patients will be expected to have follow-up through this date. Analysis of the primary composite cardiovascular outcome will be based on the time from randomization to the occurrence of the first event, with patients analyzed according to their randomized treatment. The primary analysis will include all adjudicated CV events with onset dates up to and including the primary endpoint event cut-off date.	The primary statistical analysis will be based upon adjudicated CV events with patients who discontinue prematurely from treatment followed until the end of the study, *i.e*. **the Trial Termination Visit and** until the requisite number of primary composite events has been accrued. It is anticipated that the Executive Committee will monitor the accrual of the aggregate number of primary composite CV events to determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued). **Based on the primary endpoint event cut-off date, a window of time for conduct of the Trial Termination Visit will be established.** All patients will be expected to have follow-up ~~through this date~~ **until this visit**. Analysis of the primary composite cardiovascular outcome will be based on the time from randomization to the occurrence of the first event, with patients analyzed according to their randomized treatment. The primary analysis will include all adjudicated CV events with onset dates up to and including the **Trial Termination Visit** ~~primary endpoint event cut-off~~ date. **Note that any event occurring between the Trial Termination Visit and the safety follow-up date (70 days after the administration of the last dose of trial medication) will not be adjudicated and will not be included in the primary analysis. Events occurring during this period will be summarized descriptively.**
9.7.1 Intent-To-Treat Population	The ITT population consists of all randomized patients. Evaluation will include all events which occurred from randomization to the primary endpoint event cut-off date, regardless of the time interval between patient discontinuation of study drug and final contact. Patients who do not have any events during the study will be censored at the primary endpoint event cut-off date. Every effort will be made to collect CV events through the primary endpoint event cut-off date even in those who have discontinued study medication or the study. For the ITT population, patients will be analyzed as randomized.	The ITT population consists of all randomized patients. Evaluation will include all events which occurred from randomization to the **Trial Termination Visit** ~~primary endpoint event cut-off~~ date, regardless of the time interval between patient discontinuation of study drug and final contact. Patients who do not have any events during the study will be censored at the **Trial Termination Visit** ~~primary endpoint event cut-off~~ date. Every effort will be made to collect CV events ~~through~~ **until** the **Trial Termination Visit** ~~primary endpoint event cut-off date~~ even in those who have discontinued study medication or the study. For the ITT population, patients will be analyzed as randomized.

SECTION	AMENDMENT 05 TEXT	AMENDMENT 06 TEXT
9.7.1.1 On-Treatment Analysis	An on-treatment analysis using the ITT population will be performed for the primary and secondary analyses as sensitivity analyses. This analysis will include only those events that occurred within 70 days of the last dose of study medication or the primary endpoint event cut-off date, whichever occurs first. The patients will be analyzed according to the treatment group to which they were randomized.	An on-treatment analysis using the ITT population will be performed for the primary and some secondary endpoints as sensitivity analyses. This analysis will include only those events that occurred **through** ~~within 70 days of~~ the last dose of study medication or the **Trial Termination Visit** ~~primary endpoint event cutoff~~ date, whichever occurs first. The patients will be analyzed according to the treatment group to which they were randomized. **The on-treatment censoring scheme will also be applied for analysis for on-treatment + n days, where n=7, 30, and 70.**
9.7.2 Per-Protocol Population	The Per-Protocol population consists of all randomized patients who have taken at least one dose of study medication and will include in their analysis all data collected prior to any major protocol violations (or primary endpoint event cut-off date, whichever occurs first), such as: • Initiation of an open-label prohibited medication, i.e. a GLP-1 receptor agonist. Evaluation will include all data up to the day of the initiation of the prohibited medication. • Early discontinuation from study medication. Evaluation will include events which occurred from randomization to 70 days after the last dose of study medication or the primary endpoint event cut-off date, whichever occurs first.	The Per-Protocol population consists of all randomized patients who have taken at least one dose of study medication and will include in their analysis all data collected prior to any major protocol violations (or **the Trial Termination Visit** ~~primary endpoint event cut-off~~ date, whichever occurs first), such as: • Initiation of an open-label prohibited medication, i.e. a GLP-1 receptor agonist. Evaluation will include all data up to the day of the initiation of the prohibited medication. • Early discontinuation from study medication. Evaluation will include events which occurred from randomization to 70 days after the last dose of study medication or the **Trial Termination Visit** ~~primary endpoint event cut-off~~ date, whichever occurs first.
9.8 Safety Data Analysis	Safety parameters will be summarized and presented in tables for the safety population. Serious adverse events will be listed and tabulated by high level group terms (HGLT), as assigned by the MedDRA dictionary.	Safety parameters will be summarized and presented in tables for the safety population. Serious adverse events will be listed and tabulated **as described in the SAP** ~~by high level group terms (HGLT), as assigned by the MedDRA dictionary~~.

SECTION	AMENDMENT 05 TEXT	AMENDMENT 06 TEXT
9.9 Subgroup Analyses	Subgroup analyses for the primary CV composite endpoint will be performed on the ITT population in order to explore whether the treatment effect on the risk of developing CV events is consistent across subgroups. The following subgroups will be assessed: • Class of AHA therapy at entry (mono or combination) • Race (Black, Caucasian, Asian, Other) • Region (North/South America, Europe or South Africa, Rest of world) • Gender (Male, Female) • Age (<65 or ≥65) • Baseline HbA1c (<8.0% or ≥8/0%) • Baseline BMI (<30 or ≥30 kg/m^2) • Duration of diabetes (<5 years or ≥5 years) • Baseline eGFR (<60 mL/min or ≥60 mL/min) • History of previous cardiovascular event (e.g., previous MI or stroke)	Subgroup analyses for the primary CV composite endpoint will be performed on the ITT population in order to explore whether the treatment effect on the risk of developing CV events is consistent across subgroups. The following subgroups will be assessed: • Class of AHA therapy at entry (mono or combination) • Race (**Indian [American] or Alaska Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Hispanic, Other** ~~(Black, Caucasian, Asian, Other~~) • **Geographic** region (**North America, Latin America, Europe and Asia Pacific)** (~~North/South America, Europe or South Africa, Rest of world~~) • Gender (Male, Female) • Age (<65 or ≥65) • Baseline HbA1c (<8.0% or ≥8.~~/~~0%) • Baseline BMI (<30 or ≥30 kg/m^2) • Duration of diabetes (<5, **5-14, ≥15 years** ~~or ≥5 years~~) • **eGFR groups (in mL/min/1.73 m^2)** – **(<60 or ≥60)** – **Stage 1: 90+, Stage 2: 60-89, Stage 3: 30-59, Stage 3a: 45-59, Stage 3b: 30-44, Stage 4: 15-29, Stage 5: <15** ~~Baseline eGFR (<60 mL/min or ≥60 mL/min)~~ • History of previous cardiovascular event (e.g., previous MI or stroke)

SECTION	AMENDMENT 05 TEXT	AMENDMENT 06 TEXT
9.11 Economic Analysis	The primary objective of the economic analysis is to collect sufficient data from the trial participants on resource use and quality of life to undertake cost-effectiveness analyses that are relevant to the major countries taking part in the study. Resource use data on hospitalizations, visits and medications will be combined with appropriate national unit costs to calculate a cost per patient per year in the study. Quality of life data from the EQ-5D will be combined with survival data to calculate quality adjusted time in the trial per patient. Cost-effectiveness analyses will report the incremental cost per major CV outcome averted, CV related death averted, life-year gained and quality-adjusted life year gained, of including EQW in addition to usual care vs. usual care without EQW. Analyses will be conducted within trial and using a lifetime perspective, with lifetime extrapolation performed using the UKPDS Outcomes Model or all patients still alive at the end of the study, using risk factor characteristics from the last available visit. A full analysis plan for the economic analysis will be prepared and reported separately from this protocol.	The primary objective of the economic analysis is to collect sufficient data from the trial participants on resource use and quality of life to undertake cost-effectiveness analyses that are relevant to the major countries taking part in the study. Resource use data on hospitalizations, visits and medications will be combined with appropriate national unit costs to calculate a cost per patient per year in the study. Quality of life data from the EQ-5D will be combined with survival data to calculate quality adjusted time in the trial per patient. Cost-effectiveness analyses will report the incremental cost per major CV outcome averted, CV related death averted, life-year gained and quality-adjusted life year gained, of including EQW in addition to usual care vs. usual care without EQW. Analyses will be conducted within trial and using a lifetime perspective, with lifetime extrapolation performed using the UKPDS Outcomes Model or all patients still alive at the end of the study, using risk factor characteristics from the last available visit. A full analysis plan for the economic analysis will be prepared and reported separately from this protocol. **For the main clinical study report (CSR), the quality of life data will be summarized descriptively for baseline and changes from baseline by treatment.**

<table>
<tr><th>SECTION</th><th>AMENDMENT 05 TEXT</th><th>AMENDMENT 06 TEXT</th></tr>
<tr><td>10.3.1 Recording Adverse Events</td><td>SAEs will be recorded in the Clinical Events or SAE eCRF modules as appropriate (see Table 1) through the primary endpoint event cut-off date; ALL SAEs with onset dates AFTER the primary endpoint event cut-off date will be recorded in the SAE eCRF module. Guidelines for events which qualify as Clinical Events are provided in Appendix 1. Events to be recorded in the Clinical Events eCRF module include SAEs that are: (1) Obvious trial endpoints, (2) Cardiovascular Events of Interest, (3) Expected Events and Diabetic Complications.

<table>
<tr><th>Table 1</th><th>List of events to be recorded in each eCRF reporting module*</th></tr>
<tr><td>eCRF reporting module to be used</td><td>List of events to be recorded in this eCRF reporting module:</td></tr>
<tr><td>Clinical Event eCRF (events with onset date up to and including the primary endpoint event cut-off date)</td><td>- Clinical Events that meet the criteria of an SAE (i.e. serious adverse event) and are listed in Appendix 1
- All non-serious (or serious) events of percutaneous coronary intervention (PCI), stress tests, severe hypoglycemia, diabetic eye disease, foot ulcer, microalbuminuria, macroalbuminuria, hyperlipidemia/dyslipidemia, hypertension, or gout
- All neoplasia events
- All pancreatitis events</td></tr>
<tr><td>SAE eCRF</td><td>- Any event meeting the criteria of an SAE (see Section 10.1 for definition of SAE) that are <u>not</u> listed in Appendix 1 and all events above with an onset date after the primary endpoint event cut-off date
- All episodes of pancreatitis
- All episodes of any type of neoplasia/cancer
- Any AE or SAE resulting from an overdose of study drug
- Any event that is recorded in the Clinical Event eCRF, that the investigator considers a SUSAR, with the exception of possible Primary or Secondary trial endpoints (i.e. all events listed in Appendix 1, Section I)</td></tr>
<tr><td colspan="2">* Trial sites will be provided with an ‘EXSCEL Event Reporting’ flow chart that can be referenced to help identify which events should be reported in which eCRF reporting module.</td></tr>
</table></td><td>SAEs will be recorded in the Clinical Events or SAE eCRF modules as appropriate (see Table 1) throughout the trial (including the 70 day safety wash-out period after last dose of study medication) <s>through primary endpoint event cut-off date; ALL SAEs with onset dates AFTER the primary endpoint event cut-off date will be recorded in the SAE eCRF module</s>. Guidelines for events which qualify as Clinical Events are provided in Appendix 1. Events to be recorded in the Clinical Events eCRF module include SAEs that are: (1) Obvious trial endpoints, (2) Cardiovascular Events of Interest, (3) Expected Events and Diabetic Complications.

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- All episodes of any type of neoplasia/cancer
- Any AE or SAE resulting from an overdose of study drug
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</table></td></tr>
</table>

SECTION	AMENDMENT 05 TEXT	AMENDMENT 06 TEXT
10.3.2 Safety Reporting	The DSMB will monitor the totality of collected safety data (i.e. events recorded on both the Clinical Events and SAE eCRFs) on a semi-annual basis regardless of event classification. SAEs recorded on the Clinical Events eCRF represent those events which are components of the composite CV endpoint, other trial endpoints, potential components of the CV endpoint that require adjudication or are expected sequelae of T2DM. SAEs recorded as Clinical Events, including death related to an event in the Clinical Events List, ***will not be reported to the Sponsor, regulatory agencies or ethics committees, regardless of relationship to trial medication*** even though they may be considered possibly, probably or definitely drug-related and meet SAE criteria. In addition to the un-blinded review by the DSMB, events reported via this module that may be associated with a trial endpoint will be adjudicated by the CEC. As described above, all SAEs that are not included in the Clinical Events List and "Clinical Events" with onset dates after the primary endpoint event cut-off date will be recorded by the investigator in the SAE eCRF module. These events must be recorded in this module (or faxed to the number provided on the SAE report form if EDC is unavailable) within **24 hours** of a trial site becoming aware of the event. Any SAEs meeting the definition of a SUSAR will be subject to expedited reporting as per current legislation. Brief information on the clinical course of the event, treatment, and relevant diagnostic, laboratory or other investigations will be collected on the eCRF. All episodes of pancreatitis and neoplasia will be treated as SAEs and will be collected and reported in the SAE eCRF module. All events recorded in the SAE eCRF module will be reported to the appropriate regulatory agencies in a manner and timeframe consistent with all applicable laws and regulations (Section 10.3.3). **All SUSARS** will be reported in an expedited manner with the exception of possible trial endpoints as detailed in Section I of Appendix 1, which will be handled as Clinical Events.	The DSMB will monitor the totality of collected safety data (i.e. events recorded on both the Clinical Events and SAE eCRFs) on a semi-annual basis regardless of event classification. SAEs recorded on the Clinical Events eCRF represent those events which are components of the composite CV endpoint, other trial endpoints, potential components of the CV endpoint that require adjudication or are expected sequelae of T2DM. SAEs recorded as Clinical Events, including death related to an event in the Clinical Events List, ***will not be reported to the Sponsor, regulatory agencies or ethics committees, regardless of relationship to trial medication*** even though they may be considered possibly, probably or definitely drug-related and meet SAE criteria. **This will be applicable throughout the duration of trial including the 70 day wash-out period**. **There will be no switch to collecting and reporting Clinical Events as SAEs. Thus, the exemption from routine SAE reporting of events listed in Protocol Appendix 1 will remain for the entire trial duration, including the safety wash-out phase.** In addition to the un-blinded review by the DSMB, events reported via this module that may be associated with a trial endpoint will be adjudicated by the CEC. As described above, all SAEs that are not included in the Clinical Events List ~~and "Clinical Events" with onset dates after the primary endpoint event cut-off date~~ will be recorded by the investigator in the SAE eCRF module. These events must be recorded in this module (or faxed to the number provided on the SAE report form if EDC is unavailable) within **24 hours** of a trial site becoming aware of the event. Any SAEs meeting the definition of a SUSAR will be subject to expedited reporting as per current legislation. Brief information on the clinical course of the event, treatment, and relevant diagnostic, laboratory or other investigations will be collected on the eCRF. All episodes of pancreatitis and neoplasia will be treated as SAEs and will be collected and reported in the SAE eCRF module. All events recorded in the SAE eCRF module will be reported to the appropriate regulatory agencies in a manner and timeframe consistent with all applicable laws and regulations (Section 10.3.3). **All SUSARS** will be reported in an expedited manner with the exception of possible trial endpoints as detailed in Section I of Appendix 1, which will be handled as Clinical Events.

SECTION	AMENDMENT 05 TEXT	AMENDMENT 06 TEXT
12.1 Executive Committee (EC)	The EC will be responsible for overall management and oversight of the trial. The EC will be composed of senior independent academic representatives who are experts in their field and representatives from the sponsor. The Committee will be co-chaired by Professors Robert Califf (cardiologist) and Rury Holman (endocrinologist). An EC charter will outline the committee membership and structure and delineate operating procedures.	The EC will be responsible for overall management and oversight of the trial. The EC will be composed of senior independent academic representatives who are experts in their field and representatives from the sponsor. The Committee will be co-chaired by Professors **Adrian Hernandez** ~~Robert Califf~~ (cardiologist) and Rury Holman (endocrinologist). An EC charter will outline the committee membership and structure and delineate operating procedures.
Appendix 2 TRIAL PLAN (PROTOCOL BCB109)	Table 1 Footnote 9: [9] Patients will be contacted by telephone to check for any serious adverse experiences and hospitalizations that occurred within 70 days after the administration of the last dose of trial medication. Note that all serious adverse experiences, hospitalizations, and reportable study events with an onset date after the primary endpoint event cut-off date established by the study Executive Committee will be managed as serious adverse experiences (see Section 10.3.1).	Table 1 Footnote 9: [9] Patients will be contacted by telephone to check for any **Clinical Events**, serious adverse experiences and hospitalizations that occurred within 70 days after the administration of the last dose of trial medication. ~~Note that all serious adverse experiences, hospitalizations, and reportable study events with an onset date after the primary endpoint event cut-off date established by the study Executive Committee will be managed as serious adverse experiences~~ (see Section 10.3.1).

LIST OF ABBREVIATIONS

ACS	Acute coronary syndrome
AE	Adverse Event
AHA	Antihyperglycemic agent
Amylin	Amylin Pharmaceuticals, LLC
ARO	Academic Research Organization
BP	Blood Pressure
CEC	Clinical Events Committee
CHF	Congestive heart failure
CI	Confidence Interval
CRO	Contract Research Organization
CSR	Clinical Study Report
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DCRI	Duke Clinical Research Institute
DSMB	Data Safety Monitoring Board
DTU	Diabetes Trials Unit
EC	Executive Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EQW	Exenatide once weekly
EQ-5D	EuroQol 5 Dimensions
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA_{1c}	Hemoglobin A1c
HLGT	High level group term
IFU	Instructions for use
IRB	Institutional Review Board
ITT	Intent-to-Treat
MDRD	Modification of Diet in Renal Disease Study Group method for eGFR
MI	Myocardial infarction
OC	Operations Committee
PCI	Percutaneous coronary intervention
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
SBP	Systolic blood pressure
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TG	Triglycerides
TIA	Transient ischemic attack
UKPDS	United Kingdom Prospective Diabetes Study

CLINICAL STUDY PROTOCOL

1 INTRODUCTION

1.1 Background

Type 2 diabetes mellitus is a leading public health issue. Often regarded as a mild disease, it is the fourth leading cause of death in developed countries and the number of people worldwide with diabetes is predicted to exceed 300 million by the year 2025.[1] Diabetes remains the leading cause of blindness, end stage renal disease, and lower extremity amputations and confers a two to four times greater risk of heart disease and strokes.

The majority of people with type 2 diabetes mellitus (T2DM) die as a result of cardiovascular disease (CVD). Epidemiological analysis of UKPDS data from patients with newly-diagnosed T2DM showed that potentially modifiable risk factors for CVD were a raised LDL cholesterol, a low HDL cholesterol, hyperglycemia, hypertension, and smoking.[2] Elevated glucose levels were also the major determinant of microvascular complications. A number of trials in people with T2DM have shown that their CVD risk can be reduced by lowering LDL cholesterol,[3,4] blood pressure,[5,6] glycated hemoglobin,[7,8] or all three risk factors.[9]

1.2 Rationale for Conduct of the Study

Exenatide, a GLP-1 receptor agonist, has been shown in randomized clinical trials to improve glycemic control, augment endogenous insulin secretion, to reduce blood pressure and promote weight loss with a meta-analysis of exenatide twice-daily (BYETTA) trials[10] showing a trend to lower relative risk for CV events versus pooled comparators of 0.70 (95% confidence interval 0.38 - 1.31). BYETTA (exenatide) injection is currently available in the US and in many countries worldwide for people with type 2 diabetes who are unable to achieve good glycemic control with common oral therapies. The addition of BYETTA to titrated basal insulin therapy has also been demonstrated to improve glycemic control without an increased risk of hypoglycemia in patients receiving concomitant diet/exercise, metformin, or metformin+pioglitazone therapy (exenatide enhances insulin secretion in a glucose-dependent manner, thus minimizing the risk of hypoglycemia in the absence of an insulin secretagogue).[11]

Exenatide once weekly (EQW; BYDUREON), is an extended release formulation of exenatide that is administered once weekly rather than twice daily. EQW has been approved by the US FDA as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and in the European Union as an adjunct to metformin, a sulfonylurea (SU), a thiazolidinedione (TZD), a combination of metformin and SU, or a combination of metformin and TZD therapy to improve glycemic control in adult patients with type 2 diabetes mellitus.

In a 30-week, randomized, open-label trial, EQW treatment resulted in a significantly greater improvement in glycemic control, as measured by glycated hemoglobin (HbA_{1c}), compared to exenatide administered twice daily.[12] Furthermore, treatment with EQW for one year (52 weeks) showed net reductions of 2.0% in HbA_{1c}, 0.06 mmol/l (2.2 mg/dl) LDL cholesterol, 6 mmHg in systolic blood pressure and 4 kg in body weight.[13] Thus, EQW represents a novel therapeutic

approach to the treatment of T2DM that could potentially impact the occurrence of cardiovascular events in patients mediated by improvements in multiple CV risk factors, as well as reducing glycemia.

EXSCEL (EXenatide Study of Cardiovascular Event Lowering) is a pragmatic, long-term, placebo-controlled, double-blinded trial which seeks to characterize the effects of EQW on cardiovascular-related outcomes in patients with type 2 diabetes when added to the current usual care for glycemic control in a standard care setting.

2 STUDY OBJECTIVES AND HYPOTHESES

2.1 Primary Objective

The primary objective of EXSCEL will be to evaluate the effect of EQW, used in addition to the current usual care for glycemic control, on major macrovascular events when administered to patients with type 2 diabetes.

Objective: To compare the impact of including EQW in addition to usual care *vs.* usual care without EQW on major CV outcomes as measured by the primary CV composite endpoint of CV-related death, nonfatal myocardial infarction (MI), or nonfatal stroke.

Hypotheses:

Efficacy: EQW, when used in addition to usual care, is superior to usual care without EQW with regard to the risk of developing a confirmed event in the primary CV composite endpoint.

Safety: EQW, when used in addition to usual care, is non-inferior to usual care without EQW with regard to the risk of developing a confirmed event in the primary CV composite endpoint.

2.2 Secondary Objectives

The secondary objectives of EXSCEL are to evaluate the effect of EQW treatment used in addition to the current usual care for glycemic control on:

1) All cause mortality
2) Each of the components of the primary composite CV endpoint
3) Hospitalization for acute coronary syndrome (ACS)
4) Hospitalization for congestive heart failure (CHF)

2.3 Additional Objectives

Additional objectives of EXSCEL are to evaluate the effect of EQW treatment used in addition to the current usual care for glycemic control on:

1) Revascularization procedures. This will include percutaneous coronary intervention (PCI) with or without stenting, coronary artery bypass grafting, revascularization and/or stenting for peripheral arterial disease, carotid endarterectomy, or carotid stenting
2) Time to initiation of first co-interventional agent (i.e., next antihyperglycemic agent [AHA] or chronic insulin therapy)
3) Number of episodes of severe hypoglycemia

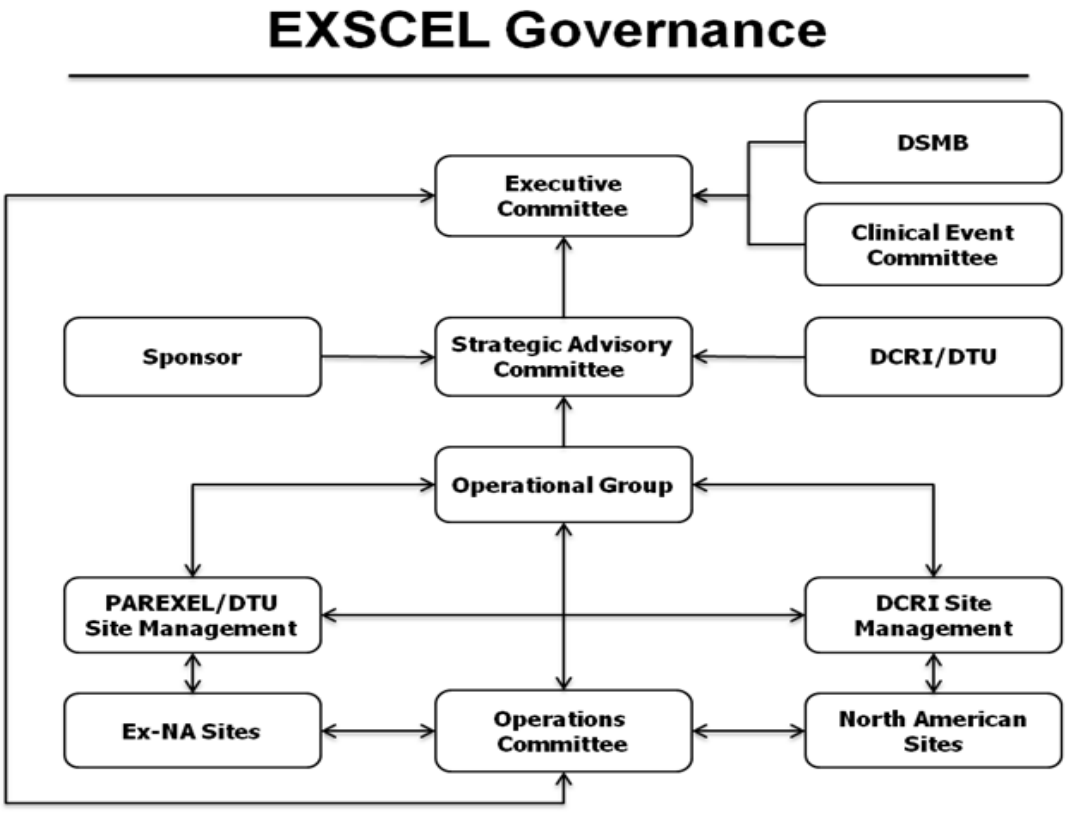
4) Absolute values of and changes in markers of cardiovascular risk including: HbA_{1c}, body weight, blood pressure, lipid profile
5) Quality of life assessed by the EQ-5D (EuroQol 5 Dimension) questionnaire
6) Medical resource use and total direct medical costs
7) Incremental cost-effectiveness analysis of exenatide once weekly as part of usual care compared with usual care without exenatide

3 TRIAL GOVERNANCE

EXSCEL is a multinational pragmatic trial that will be conducted at approximately 800 sites worldwide. It will be run jointly by the Duke Clinical Research Institute (DCRI) and the University of Oxford Diabetes Trials Unit (DTU) Academic Research Organizations (AROs), in an academic collaboration with Amylin Pharmaceuticals, LLC (Amylin), a wholly owned subsidiary of AstraZeneca. EXSCEL will be Co-Chaired by Professors Adrian Hernandez (Cardiologist) and Rury Holman (Endocrinologist) and sponsored and funded by Amylin.

The EXSCEL Executive Committee (EC) will have overall responsibility for the oversight and management of the trial (Figure 1). The EC will consist of senior independent academic representatives who are experts in their field and sponsor representatives. It will be Co-Chaired by Professors Adrian Hernandez and Rury Holman (see Section 12.1).

Figure 1: EXSCEL Governance



4 TRIAL DESIGN

4.1 Design Description

EXSCEL will be a multinational, placebo-controlled, double-blind, randomized, parallel-group pragmatic clinical trial. Eligible patients will have type 2 diabetes with an HbA_{1c} ≥6.5% and ≤10.0 % on up to three (i.e., 0-3) oral antihyperglycemic agents (AHAs) or insulin either alone or in combination with up to 2 (i.e., 0-2) oral AHAs. Patients enrolled will be at a wide range of CV risk with approximately 70% having had a prior CV event (see Section 6.3).

Approximately 14,000 patients meeting all enrollment criteria will be recruited in to the trial over approximately a five year period, randomly allocated to treatment with either EQW 2 mg or matching placebo subcutaneous injections once weekly in a 1:1 ratio, and followed until the requisite number of primary endpoint events have been reported. The trial is planned to continue until 1360 patients with positively adjudicated primary endpoint events have been accrued, or until the independent Data Safety Monitoring Board (DSMB) advises otherwise. It is anticipated that the EXSCEL Executive Committee will monitor the accrual of the aggregate number of adjudicated primary endpoint events and will determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued). Based on the primary endpoint event cut-off date, a window of time for the conduct of the Trial Termination Visit will be established; all patients will be expected to have follow-up until the Trial Termination Visit (see Section 6).

The trial will assess the impact of EQW therapy upon CV outcomes in a large population from a heterogeneous group of countries and practice environments; patients will be enrolled in the Americas (North/South America), Europe and Asia/Australasia. Given that this population will be at elevated CV risk, it is anticipated that patients will see their usual care provider at least twice per year for routine care. Trial follow up will consist of a blend of trial visits and phone calls during the double-blind placebo-controlled treatment period.

There is no requirement to achieve glycemic equipoise between randomized groups but all patients during the double-blind treatment period will have their AHA regimens adjusted as deemed necessary by their usual care provider with the addition or substitution of other AHAs, including insulin, but excluding GLP-1 receptor agonists, to achieve appropriate individualized glycemic goals in line with national guidelines. Adjustments in AHA medications are permitted any time after randomization, but usual care providers will be asked to avoid this until HbA_{1c} levels begin to reflect the initial effect of randomized study medication. Prior to randomization, it is anticipated that all patients will have received counseling regarding appropriate diet and level of physical activity as part of usual care for type 2 diabetes. Per usual care, HbA_{1c} values should be measured locally. An NGSP (National Glycohemoglobin Standardization Program) certified HbA_{1c} assay[14] should be used if available.

4.2 Trial Duration

It is anticipated that enrollment will occur over approximately a 5-year period, and that an additional 2 to 3 years may be required to accumulate the requisite number of patients with positively adjudicated primary endpoint events, for a total duration of up to approximately 7.5

years, unless the trial is terminated earlier. All patients who discontinue study medication, but have not withdrawn consent to participate in the study, will be followed up, if possible, for the full study period and will have their vital status ascertained, if possible, as of the Trial Termination Visit.

4.3 Post Trial Access to Therapy

At the end of the trial, the sponsor will not continue to supply study drug to patients/investigators. The investigator should ensure that the patient receives appropriate standard of care to treat the condition under study according to national treatment guidelines.

5 TRIAL POPULATION

5.1 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this trial.

a) Patient has type 2 diabetes mellitus

b) Patient will be able to see a usual care provider at least twice a year

c) Patient has an HbA_{1c} of ≥6.5 % and ≤10.0% and is currently using one of the following treatment regimens:

- Treatment with up to three (i.e., 0-3) oral AHAs (concomitant use of DPP-4 inhibitors is permitted)
- Insulin therapy, either alone or in combination with up to two (i.e., 0-2) oral AHAs (use of basal and prandial insulins is permitted in any combination of individual or premixed insulins)

All patients should be on a stable diabetes management regimen, as assessed by the investigator, at the time of enrollment.

HbA1c values must be from within the 3 months prior to randomization. If multiple values are available, the most recent reported value should be used. A patient whose HbA_{1c} is >10.0% may, at the discretion of the investigator, have their oral AHA or insulin therapy adjusted and be re-screened once for HbA_{1c} randomization eligibility (≥6.5 % and ≤10.0%).

d) Patients with any level of CV risk and meeting all other inclusion criteria may be enrolled. Recruitment will be constrained (see Section 6.3) such that approximately 30% will not have had a prior CV event and 70% will have had a prior CV event

A prior CV event is defined as *at least one of the following*:

- History of a major clinical manifestation of coronary artery disease *i.e.* myocardial infarction, surgical or percutaneous (balloon and/or stent) coronary revascularization procedure, or coronary angiography showing at least one stenosis ≥50% in a major epicardial artery or branch vessel
- Ischemic cerebrovascular disease, including:
  - History of ischemic stroke; strokes not known to be hemorrhagic will be allowed as part of this criterion; transient ischemic attacks (TIAs) are not included

  - History of carotid arterial disease as documented by ≥50 % stenosis documented by carotid ultrasound, magnetic resonance imaging (MRI), or angiography, with or without symptoms of neurologic deficit
- Atherosclerotic peripheral arterial disease, as documented by objective evidence such as amputation due to vascular disease, current symptoms of intermittent claudication confirmed by an ankle-brachial pressure index or toe brachial pressure index less than 0.9, or history of surgical or percutaneous revascularization procedure

e) Female patients must not be breast feeding and agree to use an effective method of contraception or must not otherwise be at risk of becoming pregnant

f) Patient understands the trial procedures, alternative treatments available, the risks involved with the trial, and voluntarily agrees to participate by providing written informed consent

g) Patient agrees to provide permission to obtain all medical records necessary for complete data ascertainment during the follow-up period, and agrees to communication between the trial site and the usual care provider in order to facilitate routine care

h) Patient is 18 years or older at enrollment

5.2 Exclusion Criteria

Each patient meeting any of the following criteria will be excluded from this trial.

a) Patient has a diagnosis of type 1 diabetes mellitus, or a history of ketoacidosis

b) Patient has a history (≥2 episodes) of severe hypoglycemia within 12 months of enrollment

c) Patient has ever been treated with an approved or investigational GLP-1 receptor agonist e.g., BYETTA (exenatide), BYDUREON (EQW), VICTOZA (liraglutide), LYXUMIA (lixisenatide), albiglutide, taspoglutide, or dulaglutide

d) Patient is enrolled in another experimental protocol which involves the use of an investigational drug or device, or an intervention that would interfere with the conduct of the trial

e) Patient has a planned or anticipated revascularization procedure

f) Pregnancy or planned pregnancy during the trial period

g) Patient has medical history that indicates a life expectancy of <2 years or might limit the individual's ability to take trial treatments for the duration of the trial

h) Patient has a history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance which, in the opinion of the investigator or coordinator, might pose an unacceptable risk to the patient, confound the results of the trial e.g. if patient cannot comply with requirements of the trial, or likely to interfere with the patient's participation for the full duration of the trial

i) Patient has end-stage renal disease or an estimated glomerular filtration rate (eGFR) derived from serum creatinine (using the simple MDRD-4 formula) of <30 mL/min/1.73m^2 (see Appendix 2)

j) Patient has a known allergy or intolerance to exenatide

k) Patient has a history of gastroparesis

l) Personal or family history of medullary thyroid cancer or MEN2 (Multiple Endocrine Neoplasia Type 2) or calcitonin level of > 40 ng/L at baseline

NOTE: Serum for calcitonin measurement will be drawn at baseline. Patients may be randomized and initiate study medication prior to the results of the calcitonin measure being available. If a randomized patient is found to have an exclusionary serum calcitonin concentration, they will stop study medication and patients will continue to have follow-up and be part of the Intent-to-Treat analysis.

m) Patient has previously been randomized in EXSCEL
n) Patient has a history of pancreatitis
o) Is an employee of Amylin Pharmaceuticals, LLC, Bristol-Myers Squibb Company, or AstraZeneca

Eligibility criteria for this study have been carefully considered to ensure the safety of the study patients and that the results of the study can be used. It is imperative that patients fully meet all eligibility criteria.

6 TRIAL PLAN

6.1 Trial Procedures - Overview

A schedule of procedures to be performed during the trial is found in Appendix 2. The intent of this large, pragmatic, global trial is to integrate the trial-specific procedures into usual clinical care visits and to use routine clinical care assessments and laboratory values whenever possible as an efficient strategy for protocol implementation and data collection. At randomization (Visit 1) patients will be provided with the patients' instruction for use (IFU) and will be trained by study personnel to administer the study medication injection. Patients will be seen at one week (±3 days) and have their self-injection observed. Then patients will be seen at 2 months (± 2 weeks) after randomization to again confirm competency with dosing study medication. The next visit will be six months (±1 month) after randomization. Thereafter, patients will be seen every six months (±1 month) until study close out (Figure 2).

At all visits post randomization there will be an assessment of Clinical Events and Serious Adverse Events (see Section 10.3.1), as well as a review of concomitant medication, and adherence to study therapy. At semi-annual and annual visits, additional procedures will include blood pressure, body weight, heart rate, review of laboratory values and dispensing of study drug as described in Appendix 2.

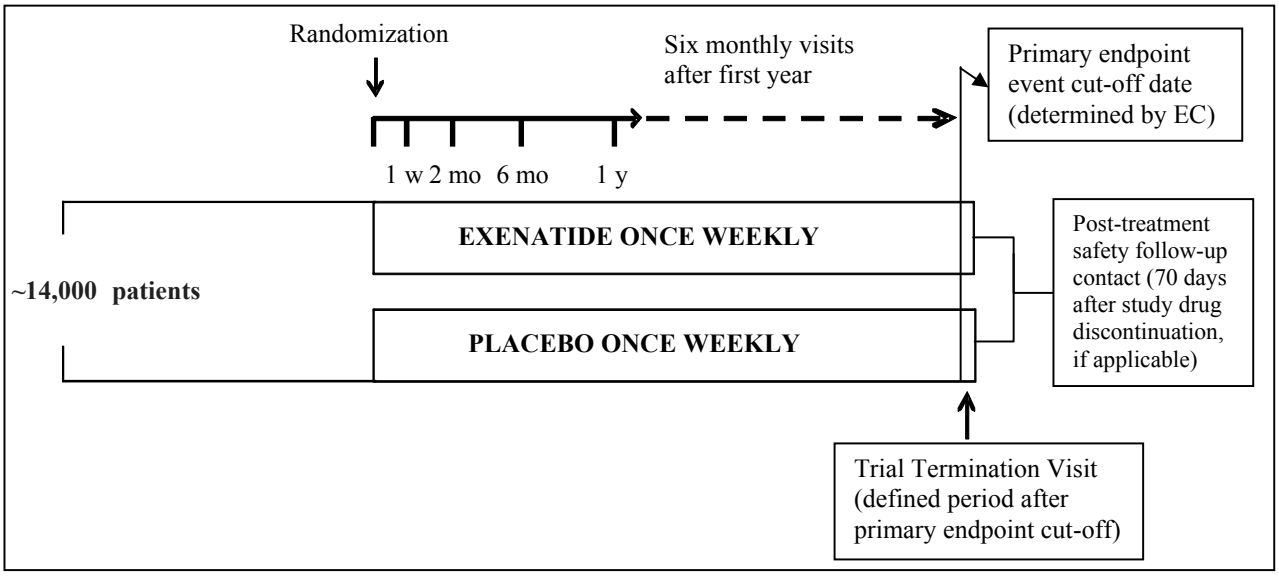
The trial is planned to continue until 1360 patients with positively adjudicated primary endpoint events have been accrued. It is anticipated that the EXSCEL Executive Committee will monitor the accrual of the aggregate number of adjudicated primary endpoint events and will determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued). Based on the primary endpoint event cut-off date, a window of time for conduct of the Trial Termination Visit will be established. All patients will be expected to have follow-up until this visit.

NOTE: Patients who have temporarily or permanently discontinued trial medication should continue with their regular visit schedule. **ALL** patients should have a Trial Termination Visit (including patients who have previously discontinued trial medication).

After the Trial Termination Visit patients will be contacted by telephone to check for any Clinical Events, serious adverse experiences and hospitalizations that occurred within 70 days after the administration of the last dose of trial medication. Note that any events occurring between the Trial Termination Visit and the safety follow-up phone call will not be adjudicated and will not be included in the primary analysis. Patients who have discontinued trial medication 70 or more days prior to the Trial Termination Visit will not need to have the safety follow-up telephone contact visit performed. These patients will have their final assessment of Clinical Events, serious adverse experiences and hospitalizations completed at the Trial Termination Visit.

Clinical Events (as defined in Protocol Appendix 1) will continue to be collected and reported in the same way as they have been throughout the entire study (i.e., prior to the cut-off date) (see Section 10.3.1).

Figure 2: EXSCEL Study Design



6.2 Pre-Enrollment and Enrollment Procedures

Informed consent, and if feasible, randomization will occur at the initial trial visit for patients satisfying all inclusion and exclusion criteria. Patients may qualify for enrollment based on recent laboratory data *e.g.* HbA_{1c} within the last 3 months, obtained as part of usual care prior to Visit 1 (recommended guidance for management of serum creatinine values will be provided to each site). For patients who require a repeat visit *e.g.* key lab data not available at Visit 1, randomization will be delayed until all information is available. It should be noted that patients may still be randomized at Visit 1 even if calcitonin results are pending.

6.3 Method of Assigning Patients to Treatment Groups (Visit 1)

An Interactive Voice Response System (IVRS) will be used to enroll those patients satisfying all inclusion and exclusion criteria. This automated system will randomize eligible patients and dispense double-blind trial medication. Each site user will be given an identification number and a password to access the IVRS. Patients will be randomly allocated at Visit 1 in a 1:1 ratio, stratified by whether or not they have had a prior CV event, to receive one of the following t wo interventions:

Treatment 1: EQW 2 mg subcutaneous injection, administered once weekly

Treatment 2: Matching placebo subcutaneous injection, administered once weekly

The IVRS will be programmed to ensure the expected overall proportion of randomized patients with a prior CV event is approximately 70%. With transition to Amylin-labeled trial medication (beginning in 2013), the IVRS was programmed to ensure at least 80% of newly randomized patients have a history of a prior CV event (previously was programmed to ensure approximately 60% of patients had a prior CV event).

The generation of the randomized allocation schedule for trial treatment assignment will be the responsibility of the IVRS provider. Prior to database lock, these codes will be provided in strict confidence only to the facility packaging trial medication and to the DSMB independent statistical group. Immediately upon database lock the codes will be transmitted to the DTU and DCRI data management groups for incorporation into the trial database.

6.4 Treatments Administered

In accordance with standard guidelines for care in all countries participating in the trial, it is anticipated that all patients will receive counseling about appropriate diet and exercise interventions as part of usual care.

EQW and matching placebo will be supplied as subcutaneous injections and will be administered once weekly.

As exenatide is not recommended for use in patients with end-stage renal disease or severe renal impairment, trial medication must be discontinued if a patient's eGFR drops below 30 mL/min/1.73 m^2, based on two consecutive serum creatinine determinations (See Section 6.12). As part of standard of care, serum creatinine should be, at minimum, among labs drawn annually. If serum creatinine has not been performed on an annual basis, then study personnel should prompt usual care providers to perform serum creatinine measurement. If serum creatinine remains unavailable, then it should be performed at the next visit by study personnel. If the investigator recognizes that the eGFR has decreased sufficiently to necessitate trial medication cessation, he/she should determine whether or not repeat/confirmatory testing has occurred and undertake this if necessary. If the need for drug discontinuation is confirmed, the situation will be explained to the patient and the patient will be asked to stop the study drug and encouraged to continue follow up off study drug until the end of the trial. If deemed necessary by the investigator, an unscheduled visit can be performed to discuss study drug discontinuation and the importance of subsequent follow up. Drug discontinuation will be managed at the trial

site through the IVRS system. Drug discontinuation visit procedures should be followed as outlined in Section 6.11.

6.5 Concomitant Therapy

Concomitant medications will be used at the discretion of the usual care provider (or investigator if also the usual care provider), who will be informed of the patient's enrollment in the trial, the use of blinded trial medication, and that use of GLP-1 receptor agonists is contraindicated during the trial period. If an open-label GLP-1 receptor agonist therapy is started whilst on study medication, then the investigator will inform the usual care provider about the possibility of double dosing and encourage the discontinuation of open-label GLP-1 agonist therapy. However, if an open-label GLP-1 receptor agonist therapy remains, then study drug should be discontinued to avoid potential double dosing. Usual care providers will be encouraged to follow guidelines for care based upon local and institutional practice patterns and any relevant published practice guidelines. AHAs will be captured by name and total daily dose at the time of study visits, while other relevant concomitant medications may be collected only as drug classes.

During the double-blind treatment period, investigators are expected to monitor patients' AHA regimens and communicate with usual care providers, who will be responsible for adjusting the AHA regimen in order to achieve locally-appropriate HbA_{1c} goals based on clinical care practice guidelines published by national and international societies. These goals will be individualized, with the understanding that currently applicable glycemic guidelines may vary among different geographic regions. With adherence to local custom and laws (including privacy regulations such as HIPAA), types of communication may be informal *e.g.* email or telephone exchanges, to enhance frequency and ease of two-way communication.

Usual care providers should be notified that adjustments to the AHA regimen are not recommended until HbA_{1c} levels begin to reflect the effect of randomized therapy. Any AHA agent, with the exception of GLP-1 receptor agonists, is acceptable. If HbA_{1c} goals are not met following adjustment with oral AHAs in patients not receiving insulin, an insulin regimen may be initiated, preferably without discontinuing or down-titrating some or all of the existing AHAs, as clinically appropriate. Patients already receiving insulin therapy may up-titrate insulin during the trial if necessary. Ideally, patients should generally remain on the baseline AHA therapies throughout the course of the trial, unless the baseline AHA is no longer clinically appropriate. However, this should be at the discretion of the usual care provider. In addition, patients should be reminded to keep taking their blinded trial medication following initiation of insulin.

6.6 Precautions to Minimize Rates of Hypoglycemia

At the screening/randomization visit and all subsequent visits, the symptoms and appropriate management of hypoglycemia will be reviewed with patients. Patients who experience severe hypoglycemia will be asked to notify both their usual care provider, as well as trial personnel. Usual care providers will be responsible for the adjustment of non-trial AHA medications in order to prevent or minimize the occurrence of further hypoglycemia.

All episodes of severe hypoglycemia will be reviewed and recorded. Severe hypoglycemia (hypoglycemia requiring assistance) refers to instances in which the patient was sufficiently

disoriented or incapacitated as to require help from either a family member or from medical personnel (whether or not this assistance was actually provided). For example, if a family member or other bystander brought the patient a snack or drink to help raise his blood sugar even though the patient was capable of doing this himself, the episode would not be considered severe.

Combination therapies with insulin and sulfonylurea have an increased risk of hypoglycemia. To minimize this risk, patients whose diabetes is well controlled may require a reduction in the insulin or sulfonylurea dose when allocated study medication. EXSCEL will employ both patient- and investigator-directed education to minimize the risk of hypoglycemia. Patients receiving sulfonylurea/insulin combinations will be explicitly reminded of the symptoms and proper management of hypoglycemia before starting study drug.

6.7 Laboratory and Anthropometric Measurements

Laboratory values *i.e.* HbA_{1c}, serum creatinine, lipid profile [LDL-C, TC, TG, HDL-C]) will be obtained where available as per the patient's usual care assessments. Blood pressure, heart rate, height, and body weight will be collected by study personnel as indicated in Appendix 2.

6.8 Calcitonin Sample Collection

Serum calcitonin concentrations will be monitored throughout the patient's participation in the trial (See Section 10.4). Samples will be collected at baseline, annually and at the Trial Termination visit.

6.9 Genetic and Biomarker Sample Collection

In a subset of sites, patients enrolled in the trial will be asked to consent separately to provide a whole blood sample for future pharmacogenomic analyses. The objective of collecting blood samples from which genetic analyses can be performed is to investigate the relationships between genetic make-up and clinical events. These samples will be drawn at baseline, or at any point in the trial at which consent is obtained from the patient.

In addition, a subset of patients enrolled in the trial will be asked to consent separately to provide one serum sample, one plasma sample, and one urine sample for future biomarker analyses. These specimens (preferably fasting) will be obtained at baseline (prior to drug exposure), year 1 and at the Trial Termination visit.

6.10 Resource Utilization Quality of Life Data for Economic Evaluation

As part of this trial, data will be collected to inform cost-effectiveness analyses that are relevant to major health care systems around the world. The economic analyses will be undertaken by a team led by the University of Oxford and Duke University. Resource use information will be collected from case report forms on number, type and duration of hospitalizations, number of outpatient physician visits, and use of antihyperglycemic and cardiovascular agents. The EQ-5D instrument, consisting of 5 questions, will be used to measure health utilities which are essential to estimating quality-adjusted survival for the cost-effectiveness analysis. This instrument will be administered at baseline, at 6 months, at subsequent annual visits, and at the Trial Termination visit.

An outline statistical analysis plan for this evaluation is reported in Section 9.11; a detailed analysis plan and study report will be developed and reported separately.

6.11 Temporary or Permanent Discontinuation of Trial Medication

Following randomization, it is expected that patients will remain on study medication for the duration of trial participation. However, it is recognized that patients may need to discontinue trial medication, in some cases permanently, for when protocol-specified reasons apply (Section 6.12), due to the judgment of the primary investigator or the decision of the patient. The Trial Hotline should be contacted whenever a site is considering interrupting or discontinuing trial medication (Section 6.18).

Unless resumption of trial medication is considered unsafe or is refused by the patient, the patient will be expected to resume regular use of the blinded trial medication after a period of temporary discontinuation. Should a patient stop taking trial medication, either permanently or temporarily, the reasons for discontinuation and length of time the patient stopped taking trial medication will be assessed and recorded.

All randomized patients who permanently discontinue trial medication should have a drug termination visit as part of their next scheduled study visit (unless a separate drug termination visit at that point is deemed necessary by the investigator). Necessary procedures are indicated in Appendix 2. All efforts should be made to reinforce with patients that this would be a medication discontinuation visit, not a trial discontinuation visit; patients should continue with their regular visit schedule until the end of the trial, including semi-annual in-person visits, as well as the annual calcitonin measurement. If patients cannot attend visits in person, they will be followed via telephone contact for all subsequent visits.

NOTE: *After trial medication is discontinued due to pregnancy, re-initiation of study medication can be considered following completion of the pregnancy and breastfeeding (if applicable).*

6.12 Permanent Discontinuation of Trial Medication Per Protocol

Reasons for protocol-specified discontinuation from the trial medication are listed below**.** All patients will be followed until resolution *i.e.* return to baseline values or diagnosis determined, or new stable state established, based on investigator assessment, for any adverse event or laboratory safety test abnormality resulting in discontinuation.

a) Severe Hypoglycemia: repeated (2 or more) episodes since the prior trial visit of severe hypoglycemia *i.e.* in which patient required medical assistance, despite down-titration or interruption/discontinuation of non-trial AHAs.

- ***Note****: The patient and the Investigator will notify the usual care provider of severe hypoglycemic events. The usual care provider should make a thorough attempt to down-titrate and/or modify co-interventional and baseline therapies that may contribute to hypoglycemia before discontinuing blinded trial medication for hypoglycemia.*

b) Any medical condition or personal circumstance which, in the opinion of the investigator, exposes the patient to additional risk by continuing in the trial or does not allow the patient to adhere to the requirements of the protocol.

c) Severe, irreversible renal dysfunction (confirmed by two consecutive eGFR <30 ml/min/1.73m^2) or renal replacement therapy.

d) Annual calcitonin measurement ≥50 ng/L

6.13 Trial Termination Visit

Investigators will be informed by the DCRI and DTU Coordinating Centers as to when the Trial Termination Visit is to be completed, and will schedule **all** patients for the Trial Termination Visit. Based on the primary endpoint event cut-off date, a window of time for conduct of the Trial Termination Visits will be established; this window will be a period of time following the primary endpoint event cut-off date. All patients will be expected to have follow-up until this visit. At the Trial Termination Visit, all patients must be discontinued from trial medication; the investigator should ensure that the patient receives appropriate standard of care. For procedural details of the Trial Termination Visit, refer to Appendix 2.

NOTE: ***All patients should have a Trial Termination Visit. Patients who have discontinued trial medication prior to the end of the trial must, at minimum, have a Trial Termination telephone contact.***

If a patient fails to return or otherwise becomes difficult to contact, it is the investigator's responsibility to make every effort to maintain contact so that at the end of the trial the patient can be located to determine status and to obtain necessary information for serious adverse experience reporting and/or endpoint adjudication as of the Trial Termination Visit.

6.14 Post-Treatment Telephone Contact

After the Trial Termination Visit, patients will be contacted by telephone to check for any Clinical Events, serious adverse experiences and hospitalizations that occurred within 70 days after the administration of the last dose of trial medication. For patients who have been discontinued from trial medication for more than 70 days as of the Trial Termination Visit, the Trial Termination Visit will be the final study follow-up. Clinical Events (as defined in Protocol Appendix 1) will continue to be collected and reported in the same way as they have been throughout the entire study (i.e., prior to the cut-off date) (see Section 10.3.1).

6.15 Withdrawal of Consent

Patients who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a patient explicitly withdraws consent for any further contact with him/her or persons previously authorized by patient to provide this information.

Patients should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator and entered on the appropriate eCRF page. In the event that vital status (whether the patient is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

When a patient withdraws consent from future follow-up prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at that time (Section 6.13).

6.16 Lost to Follow-Up

All reasonable efforts must be made to locate patients to determine and report their ongoing status. This includes follow-up with persons authorized by the patient as noted above as well as the usual care provider. Lost to follow-up is defined by the inability to reach the patient after a minimum of three documented phone calls, as well as lack of response by patient to one registered mail letter. All attempts should be documented in the patient's medical records. If it is determined that the patient has died, the site will use permissible local methods to obtain the date and cause of death.

If an investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the patient's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining patient's contact information or other public vital status data necessary to complete the follow-up portion of the study. Where specific consent has been obtained from the participant, the site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the patient remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the patient's medical records.

6.17 Breaking the Blind

The IVRS will be used to unblind patients to the randomized treatment assignment only if absolutely necessary. Disclosure envelopes will not be supplied with the clinical supplies. Drug identification information is to be unmasked ONLY if necessary for the welfare of the patient. Prior to unblinding, the investigator is required to speak with a trial hotline physician (Section 6.18). Patients whose treatment has been unblinded can continue to receive trial medication and can continue to be followed in the trial as described in this protocol.

6.18 Trial Hotline

Clinicians at DCRI and DTU operate the trial hotline. It is available at all times to answer urgent clinical questions from sites concerning enrolled patients as well as questions to determine whether a particular patient qualifies for enrollment or performance of study procedures.

7 TRIAL MEDICATIONS

7.1 Trial Medication Supply

Investigational Materials will be provided by the Sponsor as EQW 2 mg and matching placebo.

7.2 Formulation, Packaging, and Storage

EQW (formulation AC2993 F17) is an extended release formulation of exenatide and consists of 5% exenatide, sucrose, and 50:50 poly D,L lactic-co-glycolic acid (PLG). The vial containing the white to off white dry powder (2.8 mg of exenatide in EQW microspheres to deliver 2 mg of exenatide) must be stored in a refrigerator between 2ºC and 8ºC (36°F and 46°F) and protected

from light. EQW matching placebo is the identical formulation with the active ingredient omitted.

The Microsphere Diluent for suspension of the EQW and matching placebo microspheres contains carboxymethylcellulose low viscosity, polysorbate 20, sodium chloride, and water for injection. The Microsphere Diluent must be stored between 2°C and 25°C (36°F and 77°F). The EQW or matching placebo dose is prepared by reconstitution of the microspheres in the diluent provided. Specific instructions for dose preparation of the injection will be provided in the Instructions for Use (IFU). The reconstituted dose of study medication (EQW or matching placebo) should not be stored for future use. The injection must be administered immediately after preparation of the dose.

7.3 Dispensing of Trial Medication

Study materials will be provided to patients by the investigator, medically qualified subinvestigator, or other qualified study-site personnel. Under no circumstance will the investigator or subinvestigators allow the study medication to be used other than as directed by the protocol or to be administered to any persons other than patients participating in the study.

A supply of study medication will be dispensed for each patient, according to their assigned treatment group (EQW or Placebo). A 6 month supply of study medication will be distributed to patients at the study site during Visit 1 and at subsequent visits indicated in Appendix 2. Patients should bring used and unused study medication vials to the site at each visit so medication compliance can be assessed.

7.4 Dose Administration Procedures, Route, and Schedule

Doses of EQW or matching placebo are to be injected into subcutaneous (SC) tissue of the abdomen, thigh, or back of the upper arm. The site of injection should be rotated on a regular basis so that the same site is not used repeatedly. The same anatomical region can be used for the injection but the site should be rotated (e.g. different quadrants of the abdomen can be used in a weekly rotation).

At Visit 1 (Day 0), a medically qualified staff member will demonstrate the preparation of EQW or matching placebo for the patient or a designated caregiver and will administer the first dose of study medication. Patients will subsequently self administer study medication (or have it administered by a caregiver) once weekly (± 3 days) relative to the date of the first dose of EQW or matching placebo (Visit 1 [Day 0]). Patients will be seen one week as well as two months after randomization to confirm competency with study medication. On weeks with no scheduled study-site visits, patients may opt to return to the study site to have the injection procedure monitored by study-site personnel, although such visits will not be required. During scheduled study visits, patients must bring their study medication treatment kit with them to the clinic and will self administer EQW or matching placebo as directed by study-site personnel.

Adjustments to dosing regimens are not permitted. If a patient is unable to tolerate study medication (e.g., patient experiences adverse events that are judged by the investigator to be unacceptable) the termination of study medication can be considered. Patients who terminate

study medication will be followed up, per the protocol, for the remainder of the study unless the patient opts to withdraw consent for further follow-up.

7.5 Randomization Schedule and Blinding Procedures

Patients who meet all study requirements based on inclusion and exclusion criteria will be randomized at Visit 1 (Day 0). Patients will be randomly assigned to 1 of 2 treatment groups (EQW or Placebo). Randomization will be in the ratio of 1:1 (EQW:Placebo) and will be carried out centrally in a manner blocked within site and stratified by whether a participant has or has not had a prior cardiovascular event, to achieve a balanced distribution of patients across treatment groups.

Sufficient study medication will be provided to the study site for enrollment of all patients. Study medication kits will be labeled with unique package numbers (this is not the patient randomization number). At Visit 1 (Day 0), study site personnel must contact the interactive voice response system (IVRS) to randomly assign patients. The study-site personnel must call the IVRS at all subsequent visits (except Visits 2, 3 and Trial Termination) to record the visit and confirm the kit assignment. The calls to the IVRS will ensure the resupply of additional kits required for upcoming visits. If medication is allocated to a patient incorrectly, the sponsor must be notified. At Trial Termination, the site must call the IVRS to record study termination. The sponsor, the study-site personnel, and the patients will be blinded to treatment allocation.

7.6 Drug Accountability

Drug accountability will be the responsibility of the study-site personnel. Upon receipt of study medication, study site personnel should open the shipment, verify that the amount and identity of the contents match that stated on the enclosed shipping form, indicate the condition of the contents on the form, and then sign and date the form. In addition, the study-site personnel must contact IVRS to verify receipt of study medication. The sponsor (or designee) should be notified immediately about any irregularities, discrepancies, or damage.

A drug accountability log will be provided to record all study medication dispensed to or returned from each patient. Upon completion of the study, all used and unused EQW or matching placebo vials and copies of completed drug accountability logs should be returned to the sponsor (or designee). A clinical supplies return authorization form will be prepared by the clinical research associate at the closeout visit. The clinical supplies return form should be enclosed with the return drug shipment; however, if the site manager/CRA approves, the site can destroy the material instead of returning the used and unused study drug. The study site personnel must maintain documentation of any missing or unreturned study medication.

8 EFFICACY ASSESSMENTS

Trial endpoints will be defined based on clinical standards, regulatory precedent, and historical trials. The definitions of the events to be adjudicated by the Clinical Events Classification Committee (CEC) and the committee procedures will be included in the CEC Charter (Section 12.4). Patients will be asked at each trial visit about procedures and hospitalizations which have taken place since they were last seen.

8.1 Primary Efficacy Endpoint

- **Time to first confirmed CV event in the primary composite CV endpoint**
  Defined as the time from randomization to first confirmed CV-related death, nonfatal MI or nonfatal stroke.

8.2 Secondary Efficacy Endpoints

- **Time to all-cause mortality**
  Defined as time from randomization to death due to any cause.
- **Time to first confirmed CV event for each component of the primary composite endpoint**
  Defined as time from randomization to a confirmed CV-related death, fatal or nonfatal MI, or fatal or nonfatal stroke.
- **Time to hospitalization for acute coronary syndrome**
  Defined as time from randomization to a confirmed hospital admission for unstable angina, ST-elevation myocardial infarction or non-ST-elevation myocardial infarction.
- **Time to hospitalization for heart failure**
  Defined as time from randomization to hospital admission for congestive heart failure requiring treatment with increased oral or intravenous diuretics, inotropes, or vasodilator therapy.

8.3 Additional Efficacy Endpoints

- **Time to revascularization procedure**
  Defined as time from randomization to time of first cardiovascular or peripheral revascularization procedure. This will include percutaneous coronary intervention with or without stenting, coronary artery bypass grafting, revascularization and/or stenting for peripheral arterial disease, carotid endarterectomy, or carotid stenting.
- **Time to initiation of first co-interventional agent**
  - Additional AHA
  - Chronic insulin therapy
- **Absolute values and change from baseline in:**
  - HbA1c
  - Body weight
  - Blood pressure
  - Lipid profile
- **Quality of life assessed by the EQ-5D (EuroQol 5 Dimension) questionnaire**
- **Medical resource use and total direct medical costs**
- **Incremental cost-effectiveness analysis of exenatide once weekly as part of usual care compared with usual care without exenatide**

9 STATISTICAL METHODS

This section outlines the statistical analysis strategy related to the primary and secondary study objectives with the full details given in a separate Statistical Analysis Plan (SAP). If any substantive changes are made to these objectives or the statistical methods after the study has begun then the protocol will be amended, provided that it is prior to any unblinding, consistent with ICH Guideline E9. The study database will only be locked and unblinded once medical/scientific review has been performed, protocol violations have been identified and the data have been declared final and complete. The statistical analyses for this study will be the responsibility of the University of Oxford Diabetes Trials Unit.

9.1 Baseline Characteristics

Demographic characteristics *e.g.* gender, age, race, body weight, will be summarized for each treatment group. In addition, duration of diabetes, alcohol intake, smoking status, cardiovascular medical history, baseline laboratory results and concomitant medications will be summarized by treatment group.

9.2 Sample Size

The primary endpoint is the time from randomization to the first confirmed CV event defined as a CV-related death, nonfatal MI or nonfatal stroke. The study is designed to assess the primary efficacy objective of superiority of EQW to placebo through the following hypothesis:

H0: upper limit of the 95% CI of the HR [exenatide:placebo] ≥ 1

versus

H1: upper limit of the 95% CI of the HR [exenatide:placebo] <1

In order to test the above hypothesis with 85% power and 2-sided $\alpha=0.05$, a total number of 1360 composite CV events are required assuming a risk reduction of 15% on EQW compared with placebo. With this number of events, the power will be much larger than 90% to assess the primary safety objective of non-inferiority of EQW compared with placebo.

In addition, with the following assumptions made for this study,

- An annual composite cardiovascular primary endpoint event rate estimated to be around 2.2% per year for the population to be enrolled
- A planned accrual period of 5-6 years
- An estimated annual lost-to-follow up rate of 1%
- An anticipated treatment discontinuation rate of 5% per year

it is expected that a total of 14000 patients need to be randomized in a 1:1 ratio into EQW and placebo to achieve the targeted 1360 confirmed composite CV events.

9.3 Randomization

Randomization via an Interactive Voice Response System (IVRS) will be 1:1 EQW to Placebo, blocked within each site, and stratified by whether a participant has or has not had a prior cardiovascular event (see Section 5.1).

9.4 Primary Hypothesis

The primary efficacy hypothesis is that EQW will be superior to placebo with respect to the primary composite cardiovascular endpoint, defined as the time from randomization to the first confirmed CV-related death, nonfatal MI or nonfatal stroke with the patients analyzed as randomized.

The primary safety hypothesis is that EQW will be non-inferior to placebo with respect to the primary composite cardiovascular endpoint, with patients analyzed as randomized.

9.5 Primary Analysis

The primary statistical analysis will be based upon adjudicated CV events with patients who discontinue prematurely from treatment followed until the end of the study, *i.e*. the Trial Termination Visit and until the requisite number of primary composite events has been accrued. It is anticipated that the Executive Committee will monitor the accrual of the aggregate number of primary composite CV events to determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued). Based on the primary endpoint event cut-off date, a window of time for conduct of the Trial Termination Visit will be established. All patients will be expected to have follow-up until this visit. Analysis of the primary composite cardiovascular outcome will be based on the time from randomization to the occurrence of the first event, with patients analyzed according to their randomized treatment. The primary analysis will include all adjudicated CV events with onset dates up to and including the Trial Termination Visit date. Note that any event occurring between the Trial Termination Visit and the safety follow-up date (70 days after the administration of the last dose of trial medication) will not be adjudicated and will not be included in the primary analysis. Events occurring during this period will be summarized descriptively.

Kaplan-Meier curves for time to the first occurrence of a primary composite endpoint event will be used to depict the accumulation of events over time for the EQW and placebo treatment groups. The hazard ratio for the time to first occurrence of the primary composite endpoint event for the EQW treated group to that of the placebo treated group and its 95% confidence interval will then be estimated using a Cox proportional hazards model stratified by baseline CV risk group (prior CV event or no prior CV event) and using treatment group as covariate.

The primary safety hypothesis will be assessed by a non-inferiority analysis with the non-inferiority margin of 1.30, i.e., non-inferiority will be concluded if the upper limit of the confidence interval is less than 1.30.

The primary efficacy hypothesis of superiority will be then assessed by the 95% confidence interval for the hazard ratio of EQW to placebo, i.e., superiority will be concluded if the 95% confidence interval does not include 1 (upper limit of 95% confidence interval < 1).

9.6 Secondary Efficacy Analyses

The secondary efficacy endpoints are the time to confirmed occurrence of:

1) All cause mortality

2) CV-related death
3) Fatal or nonfatal myocardial infarction
4) Fatal or nonfatal stroke
5) Hospitalization for acute coronary syndrome (ACS)
6) Hospitalization for congestive heart failure (CHF)

Details of the testing strategy of the secondary efficacy endpoints will be provided in the Statistical Analysis Plan (SAP).

9.7 Analysis Populations

The three predefined analysis populations are:

1) The Intent to Treat (ITT) Population
2) The Per Protocol Population
3) The Safety Population

9.7.1 Intent-To-Treat Population

The ITT population consists of all randomized patients. Evaluation will include all events which occurred from randomization to the Trial Termination Visit date, regardless of the time interval between patient discontinuation of study drug and final contact. Patients who do not have any events during the study will be censored at the Trial Termination Visit date. Every effort will be made to collect CV events until the Trial Termination Visit date even in those who have discontinued study medication or the study. For the ITT population, patients will be analyzed as randomized.

9.7.1.1 On-Treatment Analysis

An on-treatment analysis using the ITT population will be performed for the primary and secondary analyses as sensitivity analyses. This analysis will include only those events that occurred through the last dose of study medication or the Trial Termination Visit date, whichever occurs first. The patients will be analyzed according to the treatment group to which they were randomized. The on-treatment censoring scheme will also be applied for analysis for on-treatment + n days, where n=7, 30, and 70.

9.7.2 Per-Protocol Population

The Per-Protocol population consists of all randomized patients who have taken at least one dose of study medication and will include in their analysis all data collected prior to any major protocol violations (or the Trial Termination Visit date, whichever occurs first), such as:

- Initiation of an open-label prohibited medication, i.e. a GLP-1 receptor agonist. Evaluation will include all data up to the day of the initiation of the prohibited medication.
- Early discontinuation from study medication. Evaluation will include events which occurred from randomization to 70 days after the last dose of study medication or the Trial Termination Visit date, whichever occurs first.
- Taking incorrect study medication for more than three months.

All protocol violations will be specified in the statistical analysis plan prior to unblinding of the data. Events that occurred after protocol violation will be excluded from the analysis. Patients will be analyzed as randomized.

The primary safety and primary efficacy analyses will be repeated with the per-protocol population as sensitivity analyses.

9.7.3 Safety Population

The safety population consists of all randomized patients who received at least 1 dose of study therapy; in addition, if a patient is found to have taken a study therapy for the entire duration of the study, different from that to which he/she was randomized, then the patient is counted in the treatment group of the drug he/she actually received. Serious AEs, including those which lead to discontinuation of study medication, occurring between randomization and 70 days after the last dose of study medication, will be summarized. For continuous safety parameters, at least one post-randomization measurement is required for inclusion in the analysis. To assess change from baseline, a baseline measurement is also required.

9.8 Safety Data Analysis

Safety parameters will be summarized and presented in tables for the safety population. Serious adverse events will be listed as described in the SAP.

9.9 Subgroup Analyses

Subgroup analyses for the primary CV composite endpoint will be performed on the ITT population in order to explore whether the treatment effect on the risk of developing CV events is consistent across subgroups. The following subgroups will be assessed:

- Class of AHA therapy at entry (mono or combination)
- Race (Indian [American] or Alaska Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Hispanic, Other)
- Geographic region (North America, Latin America, Europe and Asia Pacific)
- Gender (Male, Female)
- Age (<65 or ≥65)
- Baseline HbA_{1c} (<8.0% or ≥8/0%)
- Baseline BMI (<30 or ≥30 kg/m^2)
- Duration of diabetes (<5, 5-14, ≥15 years)
- eGFR groups (in mL/min/1.73 m^2)
  - (<60 or ≥60)
  - Stage 1: 90+, Stage 2: 60-89, Stage 3: 30-59, Stage 3a: 45-59, Stage 3b: 30-44, Stage 4: 15-29, Stage 5: <15
- History of previous cardiovascular event (e.g., previous MI or stroke)

The hazard ratios, 95% CIs, and appropriate summary statistics for each of the subgroups (by treatment group) will be provided and the hazard ratios examined for interaction effects. The

interaction effect would be treatment × stratified variable, in additive format with treatment + stratified variable. For example, the stratified variable means the categorical variable 'Region'.

9.10 Interim Analyses

The DSMB will undertake safety reviews of all available data every 6 months or more frequently if the committee deems it appropriate.

Two formal interim efficacy analyses are planned after approximately 453 and 906 primary composite CV events are adjudicated, corresponding to one-third and two-thirds, respectively, of the targeted 1360 primary composite CV events. The analyses will test for superiority using a Haybittle-Peto spending function where the study termination guideline for overwhelming superiority will be p-value < 0.0001 for the first interim analysis and p-value <0.001 for the second interim analysis. This will ensure a significance level of 0.0499 for the final analysis.

If the stopping boundary for efficacy is met at either of the interim analyses, the DSMB may recommend terminating the study earlier than planned. The DSMB may, however, also advise terminating the study early for safety or ethical reasons.

The interim analyses will be performed by an independent statistical group. Further details of the interim analyses are provided in the DSMB Charter.

9.11 Economic Analysis

The primary objective of the economic analysis is to collect sufficient data from the trial participants on resource use and quality of life to undertake cost-effectiveness analyses that are relevant to the major countries taking part in the study. Resource use data on hospitalizations, visits and medications will be combined with appropriate national unit costs to calculate a cost per patient per year in the study. Quality of life data from the EQ-5D will be combined with survival data to calculate quality adjusted time in the trial per patient.

Cost-effectiveness analyses will report the incremental cost per major CV outcome averted, CV-related death averted, life-year gained and quality-adjusted life year gained, of including EQW in addition to usual care *vs.* usual care without EQW. Analyses will be conducted within trial and using a lifetime perspective, with lifetime extrapolation performed using the UKPDS Outcomes Model or all patients still alive at the end of the study, using risk factor characteristics from the last available visit. A full analysis plan for the economic analysis will be prepared and reported separately from this protocol.

For the main clinical study report (CSR), the quality of life data will be summarized descriptively for baseline and changes from baseline by treatment.

10 SAFETY ASSESSMENTS

10.1 Definitions

Adverse Event (AE)

An adverse event is defined as any unfavorable and unintended sign, symptom, disease or change in the structure, function, or chemistry of the body temporally associated with the use of the investigational product, whether or not considered related to the use of the product. Any

worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the investigational product, is also an adverse event. Adverse events include those reported spontaneously by the patient or as the result of non-directed questioning from study site personnel. Changes as a result of normal growth and development which do not vary significantly in frequency or severity from expected levels are not to be considered adverse events (e.g. the onset of menopause occurring at a physiologically appropriate time).

Serious Adverse Event (SAE)

This is defined as any untoward medical occurrence or effect in a patient treated on a study protocol which does not necessarily have a causal relationship with the study treatment, that also, at any dose:

- Results in death
- Is life-threatening
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Requires in-patient hospitalization or prolongs existing hospitalization
- Results in a congenital anomaly or birth defect
- Is otherwise medically significant (i.e. withdrawal reactions, all accidental or intentional overdoses of study medication whether they result in an adverse event or not, or any event which the investigator considers significant but which is not covered by the above)

Suspected Unexpected Serious Adverse Reaction (SUSAR)

This is defined as a serious adverse event, the nature or severity of which is not consistent with the known study treatment information.

10.2 Adverse Event Assessment

Adverse events will be monitored over the course of the trial, starting from the time of randomization and through the duration of the patient's participation, including the 70 day post-trial medication follow-up period. Adverse events reported by the patient will be evaluated by the investigator to determine if a given event meets the criteria for a serious event (described in Section 10.1). Any adverse event that does not meet the definition of a serious event will be considered non-serious and will not be recorded in the eCRF, with the exception of events noted in Section 10.3.

10.3 Recording and Reporting Adverse Events

10.3.1 Recording Adverse Events

SAEs will be recorded in the **Clinical Events or SAE eCRF** modules as appropriate (see Table 1) throughout the trial (including the 70 day safety wash-out period after last dose of study medication). Guidelines for events which qualify as Clinical Events are provided in Appendix 1. Events to be recorded in the **Clinical Events eCRF** module include SAEs that are: (1) Obvious

trial endpoints, (2) Cardiovascular Events of Interest, (3) Expected Events and Diabetic Complications.

In addition, non-serious adverse events of percutaneous coronary intervention (PCI), stress tests, severe hypoglycemia, diabetic eye disease, foot ulcer, microalbuminuria, macroalbuminurea, hyperlipidemia/dyslipidemia, hypertension, or gout also will be recorded in the **Clinical Events eCRF** module (see Appendix 1).

Any SAE which is not included among the expected events on the Clinical Events List will be recorded in the **SAE eCRF** module.

Events of neoplasia and pancreatitis should be reported on the **SAE eCRF** even if the event does not meet seriousness criteria.

Note: The events listed in Appendix 1 are Clinical Events that are trial endpoints or expected events for this population, and do not generally fit the definition of a SUSAR, including those events with an outcome of death. However, if the investigator's assessment of an event is that it meets SUSAR criteria despite being listed as a Clinical Event, the event may be reported as a SUSAR via the **SAE eCRF** as long as it is not any of the **possible trial endpoints** listed in Appendix 1, Section I).

Table 1: List of events to be recorded in each eCRF reporting module*

eCRF reporting module to be used	**List of events to be recorded in this eCRF reporting module:**
Clinical Event eCRF	- Clinical Events that meet the criteria of an SAE (i.e. serious adverse event) and are listed in Appendix 1 - All **non-serious** (or serious) events of percutaneous coronary intervention (PCI), stress tests, severe hypoglycemia, diabetic eye disease, foot ulcer, microalbuminuria, macroalbuminuria, hyperlipidemia/dyslipidemia, hypertension, or gout - All neoplasia events - All pancreatitis events
SAE eCRF	- Any event meeting the criteria of an SAE (see Section 10.1 for definition of SAE) that are **not** listed in Appendix 1 - All episodes of pancreatitis - All episodes of any type of neoplasia/cancer - Any AE or SAE resulting from an overdose of study drug - Any event that is recorded in the Clinical Event eCRF, that the investigator considers a SUSAR, with the exception of possible Primary or Secondary trial endpoints (i.e. all events listed in Appendix 1, Section I)
*** Trial sites will be provided with an 'EXSCEL Event Reporting' flow chart that can be referenced to help identify which events should be reported in which eCRF reporting module.**	

The Clinical Events List will be reviewed and the eCRF will be completed during every visit to determine if a patient has experienced one or more of the listed events. SAEs should be

reviewed for all patients randomized regardless of whether the patient is currently on trial medication.

10.3.2 Safety Reporting

The DSMB will monitor the totality of collected safety data (i.e. events recorded on both the Clinical Events and SAE eCRFs) on a semi-annual basis regardless of event classification. SAEs recorded on the Clinical Events eCRF represent those events which are components of the composite CV endpoint, other trial endpoints, potential components of the CV endpoint that require adjudication or are expected sequelae of T2DM. SAEs recorded as Clinical Events, including death related to an event in the Clinical Events List, ***will not be reported to the Sponsor, regulatory agencies or ethics committees, regardless of relationship to trial medication*** even though they may be considered possibly, probably or definitely drug-related and meet SAE criteria. This will be applicable throughout the duration of trial including the 70 day wash-out period. There will be no switch to collecting and reporting Clinical Events as SAEs. Thus, the exemption from routine SAE reporting of events listed in Protocol Appendix 1 will remain for the entire trial duration, including the safety wash-out phase. In addition to the un-blinded review by the DSMB, events reported via this module that may be associated with a trial endpoint will be adjudicated by the CEC. As described above, all SAEs that are not included in the Clinical Events List will be recorded by the investigator in the SAE eCRF module. These events must be recorded in this module (or faxed to the number provided on the SAE report form if EDC is unavailable) within **24 hours** of a trial site becoming aware of the event. Any SAEs meeting the definition of a SUSAR will be subject to expedited reporting as per current legislation. Brief information on the clinical course of the event, treatment, and relevant diagnostic, laboratory or other investigations will be collected on the eCRF. All episodes of pancreatitis and neoplasia will be treated as SAEs and will be collected and reported in the SAE eCRF module. All events recorded in the SAE eCRF module will be reported to the appropriate regulatory agencies in a manner and timeframe consistent with all applicable laws and regulations (Section 10.3.3). **All SUSARS** will be reported in an expedited manner with the exception of possible trial endpoints as detailed in Section I of Appendix 1, which will be handled as Clinical Events.

Note that pancreatitis and pancreatic neoplasms / malignancies are events of special interest for GLP-1 based therapies, such as exenatide. As described above, all events of pancreatitis and all neoplasms (including pancreatic cancer) are to be reported on both the Clinical Events eCRF and the SAE eCRF, even if the event does not meet seriousness criteria. These events are reviewed by the DSMB and adjudicated by the CEC.

Additionally, any SAE considered by an investigator who is a qualified physician to be possibly, probably, or definitely related to the investigational product that is brought to the attention of the investigator after study closeout must be reported within the above timeline. All patients with serious adverse events must be followed to assess outcome until resolution or until designated permanent.

10.3.3 Sponsor Responsibility for Reporting Serious Adverse Events

The Sponsor will ensure that all appropriate regulatory agencies confirm that the approach for monitoring Clinical Events, described in the Safety Assessments Section is acceptable to them. SAEs that are not recorded as Clinical Events will be reported to regulatory agencies, IRB/IECs, and investigators in accordance with all applicable global laws and regulations.

10.4 Calcitonin Monitoring

Studies in rodents have indicated an increased incidence of thyroid C-cell tumors (adenomas, carcinomas) with EQW treatment. The relevance of these findings to human safety is currently unknown and is being investigated. In clinical studies, there was no difference between exenatide (BID or once weekly) and comparators with respect to thyroid neoplasms. A detailed summary of findings in rodents and clinical studies is available in the Exenatide Investigator Brochure. Measurement of calcitonin has been added to newly initiating clinical trials of EQW to characterize any effects of exenatide or comparator treatment on calcitonin levels over time to better assess evidence of a biologic effect on c-cells. In clinical trials, no difference in calcitonin was observed between exenatide and comparators.

Calcitonin concentrations will be monitored at baseline, annually and at the Trial Termination visit. Investigators and participants will be blinded to calcitonin values. If the baseline value exceeds 40 ng/L, the site will be informed and directed to have the patient terminate study medication. If a concerning calcitonin value (≥50 ng/L) is identified during trial follow-up, the site investigator will be notified and they should call the Trial Hotline for advice, where they will be instructed to alert the usual care provider and permanently discontinue study medication. Calcitonin concentrations will be monitored by the DSMB, which will include a thyroid expert.

10.5 Overdose

10.5.1 Definition of an Overdose for This Protocol

An overdose is defined as a patient taking more than 1 dose of study medication in the same day. In the event of an overdose, medical treatment may be needed since severe nausea and vomiting are possible. The patient should be instructed to contact the investigational site, and/or healthcare provider in the event of an overdose.

10.5.2 Reporting of Overdose

If an adverse experience(s) is associated with ("results from") the overdose of study medication, the adverse experience(s) is collected as a serious adverse experience, even if no other criteria for seriousness are met.

If a dose of study drug meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as an Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse experience must be reported within 1 day of the site's knowledge of the event.

10.6 Reporting of Pregnancy

Although not considered an adverse experience, it is the responsibility of investigators or their designees to report any pregnancy in a patient (spontaneously reported to them) which occurs during the trial or within 70 days of completing the trial. All patients who become pregnant must stop taking blinded trial medication and be followed to the completion/termination of the pregnancy. All occurrences of pregnancy must be reported via the Pregnancy Surveillance Form. If the pregnancy continues to term, the outcome (health of infant) must also be reported.

10.7 Unblinding

Breaking the blind is strongly discouraged and should only be requested if it is deemed necessary for the wellbeing or safety of the patient. Any Investigator requesting the unblinding of a patient will be asked to contact the trial hotline physician, available 24hrs/day to discuss the case and determine the course of action; however, it is the prerogative of the treating physician to insist that their patient should be unblinded. Patients whose treatment has been unblinded can continue to receive trial medication and can continue to be followed in the trial as described in this protocol.

11 ETHICAL AND LEGAL ASPECTS

11.1 General Informed Consent

The investigator must obtain written documented consent to participate in the trial from each potential patient in his/her native language. Consent must be documented by the patient's dated signature on a Consent Form along with the dated signature of the person conducting the consent discussion. If the patient is illiterate, an impartial witness should be present during the entire informed consent reading and discussion. Afterward, the patient should sign and date the informed consent, if capable. The impartial witness should also sign and date the informed consent along with the individual who read and discussed the informed consent (i.e., trial staff personnel). A copy of the signed and dated consent form should be given to the patient.

The initial informed consent form, any subsequent revised written informed consent forms, and any written information provided to the patient must receive the IRB/IECs approval/ favorable opinion in advance of use. The patient or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the patient’s willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form.

The informed consent form will describe the regular two-way exchange of information that is expected to occur between trial physicians and the usual care physicians. The informed consent form will also include a request that the patient provide permission for the collection of medical records and copies of relevant reports necessary for complete data collection even if trial medication is discontinued beforehand.

11.2 Consent and Collection of Specimens for Genetic and Genomic Analysis

Patients providing informed consent will have a whole blood specimen collected for potential future genetic research. This is an optional activity, and only those patients who have consented to having this genetic sample collected may have this blood sample drawn. The approval of the consent form for analysis and the associated protocol procedures (e.g., collection of a blood sample) may, in some cases, proceed independently through Institutional Review Boards, Ethical Review Boards, Independent Ethical Review Committees (ERCs), Privacy Committees, etc., from the associated clinical trial.

11.3 Consent and Collection of Biomarker Specimens

Patients providing informed consent will have blood and urine samples, preferably fasting, collected at baseline (prior to drug exposure), Year 1, and at the Trial Termination visit. Biomarker samples will be stored in at least two aliquots for potential future proteomic and/or metabolomic analysis. This is an optional activity, and only those patients who have consented to having this biomarker sample collected may have this blood sample drawn. The approval of the consent form for analysis and the associated protocol procedures (e.g., collection of a blood sample) may, in some cases, proceed independently through Institutional Review Boards, Ethical Review Boards, Independent Ethical Review Committees (ERCs), Privacy Committees, etc., from the associated clinical trial.

11.4 Ethics Committee or Institutional Review Board

Documented approval from appropriate Ethics Committee(s) or Institutional Review Board(s) must be obtained for all participating centers prior to study start, according to Good Clinical Practice (GCP), local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the Ethics Committee approval must also be obtained. Ethics Committees, upon request, may be required to provide a list of the Ethics Committee members involved in the vote and a statement to confirm that the Ethics Committee is organized and operates according to GCP and applicable laws and regulations. Modifications to the study protocol will not be implemented without the agreement of the Executive Committee and appropriate ethical approval.

11.5 Ethical Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by GCP Guidelines. The study will also be carried out in keeping with applicable local law(s) and regulation(s). This may include an inspection by the sponsor representatives and/or Regulatory Authority representatives at any time. The investigator must agree to the inspection of study-related records by the Regulatory Authority/sponsor representatives, and must allow direct access to source documents to the Regulatory Authority/sponsor representatives. The investigator must notify the sponsor promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to the sponsor.

All potential serious breaches must be reported to the sponsor immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the patients of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

11.6 Regulatory Authority Approvals/Authorizations

Regulatory Authority approvals/authorizations/notifications, where required, must be in place and fully documented prior to study start.

11.7 Confidentiality

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. The patient will be identified only by a unique patient ID number on the eCRF. All documents will be stored securely and kept in strict confidence in compliance with the Data Protection Act.

Study findings stored on a computer will be stored in accordance with local data protection laws. The patients will be informed in writing that representatives of the sponsor, Ethical Committees, Institutional Review Boards or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

When the results of the study are published, the patient's identity will remain confidential. The investigator will maintain a list to enable patients' records to be identified.

11.8 Records

11.8.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact the sponsor prior to destroying any records associated with the study.

The sponsor will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Notice of such transfer will be given in writing to the sponsor.

11.8.2 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and

reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet training requirements and must only access the electronic data capture tool using their unique user account. User accounts are not to be shared or reassigned to other individuals.

12 TRIAL MANAGEMENT/GOVERNANCE COMMITTEES

12.1 Executive Committee (EC)

The EC will be responsible for overall management and oversight of the trial. The EC will be composed of senior independent academic representatives who are experts in their field and representatives from the sponsor. The Committee will be co-chaired by Professors Adrian Hernandez (cardiologist) and Rury Holman (endocrinologist). An EC charter will outline the committee membership and structure and delineate operating procedures.

The Executive Committee is the main decision-making body for the EXSCEL trial and is charged with the overall scientific, professional, and operational conduct of the trial.

<u>The primary functions of the Executive Committee are to:</u>

1. Review and approve the trial protocol and all protocol amendments.
2. Supervise the conduct of the trial in accordance with its responsibilities described in the trial protocol and committee charter.
3. Review and approve the Statistical Analysis Plan.
4. Oversee all trial subcommittees, including but not limited to:

- Clinical Endpoint Committee
- Data Safety Monitoring Board
- Operations Committee
- Strategic Advisory Committee

5. Review and consider recommendations from the Data Safety Monitoring Board (DSMB).
6. The Executive Committee will determine the time to terminate the trial, based on recommendations from the DSMB and other available information. The Executive Committee may also find it necessary to terminate the trial under certain circumstances, including but not limited to the following reasons:

- Animal, human or toxicological test results, in the reasonable determination of the Executive Committee, support termination of the trial
- Ethical or patient safety issues occur that the Executive Committee feels support termination of the trial
- Extraordinary scientific, regulatory or other events that negatively impact the rationale for the trial such that the Executive Committee agrees it is appropriate to terminate the trial

7. Review all sub-study requests and approve where appropriate.

8. Consider, authorize as appropriate and prioritize requests for access to trial data and/or genetic and biomarker samples for academic or other collaborations. After the Executive Committee disbands, DCRI, DTU and the sponsor will assume this responsibility.

9. Approve the communication strategy on how to best communicate information about the progress of the trial.

10. Ensure accurate, uniform, timely, and high quality reporting of the main trial and all approved sub-studies.

11. Serve as the writing group who will prepare and submit for publication the primary manuscript describing the main trial results. All members of the Executive Committee will have access, in confidence to the draft manuscript describing the primary results paper.

12. Assume the role of publications committee and review, authorize and prioritize proposals for publications which require trial or sub study data, samples, or genetic material and assign writing groups.

13. Review and comment on any independent publications reporting results from the trial following the primary publication.

12.2 Operations Committee (OC)

The Operations Committee (OC) is composed of Country Leads selected by the Executive Committee from investigators in each country with appropriate clinical trial experience. The OC will be co-chaired by the clinical coordinators from the Duke Clinical Research Institute (DCRI) and the Diabetes Trials Unit (DTU). Balance will be sought between cardiologists and endocrinologists. The primary role of the OC is to serve as the interface between the EC and the trial sites, and to assist in the progress of the trial at the regional level. Committee members will be instrumental in serving as ambassadors of the trial to encourage recruitment as well as ensure trial compliance by working with study personnel and mediating in country-specific issues. The committee will provide a means of transmitting any identified needs, concerns, or suggestions from the sites to the EC and assist in disseminating clinical or operational information to the sites. The functions and operating procedures of the OC are delineated in a charter.

12.2.1 Remit of Operations Committee

Specific functions of the OC will include the following:

1. All members will serve as regional leaders for site investigators.
2. All members will serve as advocates for the trial.
3. Country Leads will:

a) Communicate with investigators in the Lead's country to review country specific progress reports, including but not limited to recruitment/retention of patients, event reporting and data collection, and communication between sites and usual care providers.
b) Liaise with the academic coordinating centers and global Contract Research Organizations (CROs) to review and attempt to resolve any operational issues raised within a region.
c) Support regulatory submissions, as needed in collaboration with the Sponsor's Regulatory Affairs Department.

4. Committee Co-Chairs will:
   a) Compile country-specific performance metrics for presentation to the Executive Committee.
   b) Liaise with Country Leads, academic coordinating centers (DCRI and DTU project teams), sponsors and global AROs/CROs to implement trial policies.

12.3 Data Safety Monitoring Board (DSMB)

The DSMB will be composed of six senior academic individuals, including the DSMB Chair. There will be at least one member with high-level expertise for each of cardiology, endocrinology, and statistics. An Independent Statistician (not affiliated with the DCRI, DTU, or the Sponsor) will also be in attendance. All of these individuals will have long-standing experience in the operational, medical, and biostatistical aspects of international clinical trials. The DTU senior statistician assigned to the trial will oversee the provision of interim masked data sets for use by the DSMB and the DCRI/DTU trial coordinating centers. DTU will transfer pre-agreed masked datasets to the Independent Statistician who will then prepare unmasked confidential reports for the DSMB, using treatment codes provided in advance by the IVRS vendor. During the Open Session of the DSMB meetings, representatives of the Executive Committee may present updates on the trial status or the safety profile of exenatide, but will not be privy to discussions of the unmasked data conducted during the Closed Sessions and will not vote. Proceedings and minutes of the Closed Session will be held in strict confidence and will not be shared outside the DSMB while the trial is ongoing.

The DSMB will be responsible for the interests of the patients and, to this end, will undertake regular reviews of the safety data. The DSMB will have access to an agreed subset of the trial data as listed in the DSMB charter (updated as necessary during the trial) in an unblinded fashion throughout the trial duration. In addition, the DSMB will evaluate two interim analyses after approximately one-third and two-thirds of the total targeted number of primary composite CV events (see Sec 9.10 for details).

If the DSMB finds it necessary to recommend actions regarding interruption of the trial or changes to the protocol based on medical rationale that would make it unethical to continue the trial in its present form, those recommendations will be forwarded to the EC. The details of the DSMB's functions and the early stopping rules will be delineated in a separate DSMB charter.

12.4 Clinical Events Committee (CEC)

The events which constitute the principal endpoints of this trial will be adjudicated by the Clinical Events Classification Committee (CEC), coordinated through the Duke Clinical Research Institute (DCRI), which will be comprised of approximately 5-7 physicians and a coordinator. The specific endpoints to be adjudicated include: cause of death (cardiovascular-related vs. non-cardiovascular), MI, stroke, acute coronary syndrome, pancreatitis, neoplasm, ventricular fibrillation/tachycardia, and CHF requiring hospitalization. Clinical reviewers will be board certified or board eligible endocrinologists, cardiologists, neurologists, gastroenterologists, or physicians with clinical expertise and prior clinical event classification experience. The CEC will review clinical data and adjudicate safety and efficacy endpoints. The CEC will adjudicate clinical events using pre-specified criteria and definitions. The CEC will be blinded to the assigned trial medication. Sites will provide clinical information via the eCRF and also provide supplemental information from medical records, when needed. The CEC operations and endpoint criteria will be described in a separate charter.

12.5 Strategic Advisory Committee

The Strategic Advisory Committee will provide oversight for the operational conduct of the study across all participating institutions. It will be composed of senior management from the Sponsors, AROs and contracted CROs, who are experts in the operational aspects of the conduct of clinical trials and the EXSCEL Clinical Leads.

13 DISCLOSURE OF DATA, PUBLICATIONS, AND CLINICAL STUDY REPORT

During the Trial all data derived from the Trial will be held by the AROs but with access for Sponsor to any data required for safety and regulatory purposes. At the time database lock occurs, the IVRS provider will provide the AROs with an electronic file containing the full randomization codes for upload to the electronic database. The ARO will undertake the planned analyses and prepare and submit manuscripts for publication and presentation to academic meetings agreed by the Executive Committee. The Sponsor will have the right to comment on these but the final editorial control remains with the Executive Committee. The Executive Committee will draft the manuscript describing the main study results, and oversee publications requiring trial data, samples, or genetic material.

In addition, a CSR will be prepared for regulatory purposes. The Signatory Investigator responsible for signing the CSR will be selected by the Sponsor in conjunction with the Executive Committee.

14 REFERENCES

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APPENDIX 1 CLINICAL EVENTS LIST

Any clinical event listed in this appendix that meets the criteria of an SAE (unless indicated otherwise below) must be reported in the Clinical Event eCRF reporting module.

I. Obvious Trial Endpoints

(These events will prompt the investigator to complete an endpoint package which will then be adjudicated according to the Clinical Events Classification [CEC] charter)

Death

- Cardiovascular (CV) Death (i.e., fatal myocardial infarction [MI] / cerebrovascular accident [CVA] / congestive heart failure [CHF] / arrhythmia, cardiac arrest, death following CV intervention)
- Non-CV Death

Nonfatal MI

Acute coronary syndrome

Nonfatal CVA

CHF requiring hospitalization

II. Cardiovascular Events of Interest

(Some of these events will result in prompts to answer additional questions in the eCRF – these questions will be designed to determine whether or not a primary or secondary outcome of interest has occurred)

Atrial fibrillation/Atrial flutter

Ventricular fibrillation/tachycardia requiring intervention

Deep Vein Thrombosis (DVT)

Pulmonary embolism

Percutaneous Coronary Intervention (PCI) – (including non-serious events)

Coronary Artery Bypass Graft (CABG)

Coronary catheterization

Stress test (including non-serious events)

Abdominal aortic aneurysm/repair

Carotid endarterectomy/Carotid angioplasty and/or stenting

Any hospitalization due to cardiovascular events (i.e., whether or not the hospitalization was for an obvious trial endpoint)

Shock/hypotension

Accelerated or malignant hypertension/hypertensive urgency

Transient Ischemic Attack (TIA)

Syncope

Renal artery angioplasty and/or stenting

Other arterial angioplasty and/or stenting

III. Expected Events and Diabetic Complications

(Subcategories indicate potential additional information to be captured, usually as an indication of severity)

A. Peripheral Vascular Disease (PVD)

- Limb PCI
- Vascular surgery

- Amputation
- Surgical debridement of ulcer

B. Gangrene

C. Severe hypoglycemia (including non-serious events) / Hyperglycemia / Diabetic ketoacidosis / Hyperosmolar hyperglycemic nonketotic coma

D. Diabetic eye disease (including non-serious events)

- Photocoagulation or other laser therapy
- Cataract extraction
- Blindness
- Enucleation
- Steroid/Avastin injection
- Scleral buckling or other retinal fixation procedure

E. Diabetic neuropathy (including distal sensorimotor, focal/multifocal, or autonomic) (including non-serious events)

- Foot ulcer

F. Diabetic nephropathy (including non-serious events)

- Microalbuminuria
- Macroalbuminuria

G. Renal failure

- Acute renal failure, requiring or associated with hospitalization
- Chronic renal failure, requiring peritoneal or hemodialysis, including creation of fistula or other vascular access for hemodialysis
- Renal transplant

H. Any hospitalization due to complications of DM

I. Infections

- Osteomyelitis
  - IV antibiotic therapy vs. debridement
- Cellulitis
  - Oral vs. IV antibiotic therapy
- Mucormycosis
- Pneumonia
  - Community acquired vs. hospital acquired
  - Oral vs. IV antibiotic therapy
- Bacteremia
- Sepsis
- Infected joints
  - Prosthetic joint
- Complicated or serious urinary tract infection (UTI) / Pyelonephritis
  - Requiring hospitalization
- Malignant external otitis

J. Gastrointestinal (GI) conditions

- Abdominal pain
- Nausea / vomiting
- Diarrhea
- Fatty liver disease / Nonalcoholic steatohepatitis (NASH)
- Cholecystitis / cholelithiasis
- Elevated liver enzymes

K. Metabolic Conditions Associated with Diabetes (including non-serious events)

- Hyperlipidemia / dyslipidemia
- Hypertension
- Gout

APPENDIX 2 TRIAL PLAN (PROTOCOL BCB109)

Table 1: Trial Plan

		Treatment Initiation		Follow-up [4]		Drug or Study Termination		
Evaluation	**Screening Day -1**	**Randomization Day 0 Visit 1 [1]**	**Week 1 and Month 2 Visit 2 and 3**	**Semi-Annual**	**Annual**	**Drug Termination [5]**	**Trial Termination [8]**	**Post-Treatment Follow-up Contact [9]**
Informed Consent/HIPAA [2] and Stored Blood Sample Authorization	X							
Medical History	X							
Physical Examination	X							
Height	X							
Blood Pressure, Heart Rate and Body Weight	X	X		X	X	X	X	
Calcitonin Blood Sample		X			X		X	
Collect and review available information including most recent HbA_{1c}, serum creatinine and lipid profile	X [6]			X	X	X	X	
Randomization		X						
If consent obtained, collect blood sample for genetic and genomic analysis		X [7]						
If consent obtained, blood sample (serum and plasma) and urine sample for archive		X			Year 1 only		X	
Drug Dispensation		X		X	X			
Used/Unused Vial Assessment				X	X	X	X	
Clinical and SAE Event Assessment		X	X	X	X	X	X	X
Conmed Assessment	X	X	X	X	X	X	X	
Confirm competency with injections [3]			X					
EQ-5D Completion		X		Month 6 only	X		X	

[1] Wherever possible the screening and randomization visit should be combined.

[2] Informed Consent Form and if applicable, authorization to use and disclose protected health information.

[3] Patients will return approximately 1 week (±3 days) as well as 2 months (± 2 weeks) after Day 0 to perform a self-injection under the observation of the clinical site to confirm competency with injection. An additional visit can be considered at ~1 month if the patient is not able to adequately inject themselves.

[4] Semi-annual (±1 month) and Annual Follow-up (±1 month) Visits will occur in reference to Visit 1 Day 0 for the duration of participation in the trial.

[5] Patients who terminate study medication are required to have a Drug Termination Visit as part of their next scheduled study visit (unless a separate drug termination visit at that point is deemed necessary by the investigator). Patients will continue to be observed following the Drug Termination visit according to their planned visit schedule for the remainder of the trial. All procedures for remaining Semi-annual and Annual Visits are to be followed with the exception of Drug Dispensation.

[6] It is recommended that serum creatinine value draw dates be within 3 months of randomization but up to 12 months is acceptable (however, if > 6 months old and value is between 30-40mL/min/1.73m^2 it is recommended that a new serum creatinine value is obtained as part of usual care).

[7] Blood sample for genetic and genomic analysis may be collected at any time during the trial after consent is obtained.

[8] For patients who have been discontinued from trial medication for more than 70 days as of the Trial Termination Visit, the Trial Termination Visit will be the final study follow-up.

[9] Patients will be contacted by telephone to check for any Clinical Events, serious adverse experiences and hospitalizations that occurred within 70 days after the administration of the last dose of trial medication. (see Section 10.3.1).

APPENDIX 3 PROTOCOL AMENDMENT 01: SUMMARY OF CHANGES

Exenatide QW Clinical Study Protocol BCB109

PROTOCOL TITLE: A RANDOMIZED, PLACEBO CONTROLLED CLINICAL TRIAL TO EVALUATE CARDIOVASCULAR OUTCOMES AFTER TREATMENT WITH EXENATIDE ONCE WEEKLY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Protocol Number: **BCB109**

Amendment Number: **01**

Amendment Purpose: **Date: 11 November 2010**

The purpose of Amendment 1 is to add annual and study termination calcitonin assessments and monitoring to the conduct of the trial. Additional clarifications and edits are included. Notable changes are detailed in the table below.

SECTION	ORIGINAL PROTOCOL TEXT	AMENDMENT 01 TEXT
Title Page	Amylin Pharmaceuticals, Inc. sponsors the Investigational New Drug Application in the US and Puerto Rico and transfers the clinical sponsor obligations to Lilly for the conduct of this study outside the US. For investigative sites outside of the US and Puerto Rico, Lilly will serve as the study sponsor.	Amylin Pharmaceuticals, Inc. sponsors the Investigational New Drug Application in the US and Puerto Rico and will serve as the sponsor for the Clinical Trial Application in Canada. Amylin Pharmaceuticals, Inc. transfers the clinical sponsor obligations to Lilly for the conduct of this study outside the US, Puerto Rico and Canada. For investigative sites outside of the US, Puerto Rico and Canada, Lilly will serve as the study sponsor.
4.1 Design Description	Eligible patients will have type 2 diabetes with a glycated hemoglobin (HbA_{1c}) ≥7.0 % and ≤10.0 % on stable doses of up to three oral antihyperglycemic agents (AHAs) for at least 3 months *i.e.* no oral AHA adjustments in the past 3 months.	Eligible patients will have type 2 diabetes with a glycated hemoglobin (HbA1c) ≥7.0 % and ≤10.0 % on stable doses of up to three (i.e. 0-3) oral antihyperglycemic agents (AHAs) for at least 3 months i.e. no oral AHA adjustments in the past 3 months.
5.1 Inclusion Criteria	c. Patient has an HbA_{1c} of ≥ 7.0 % and ≤ 10.0% on stable doses of up to three oral AHAs for at least 3 months *i.e.* no oral AHA adjustments in the past 3 months. *A patients whose HbA_{1c} is > 10.0% may, at the discretion of the investigator, have their oral AHA therapy adjusted and be re-screened once for HbA_{1c} randomization eligibility (≥ 7.0 % and ≤ 10.0%) following a 3-month period on stable AHA doses.*	c. Patient has an HbA_{1c} of ≥ 7.0 % and ≤ 10.0% on stable doses of up to three (i.e. 0-3) oral AHAs for at least 3 months *i.e.* no oral AHA adjustments in the past 3 months. Concomitant use of DPP-4 inhibitors is permitted. *HbA1c values must be from within the 3 months prior to randomization. If multiple values are available, the most recent reported value should be used. A patient whose HbA_{1c} is > 10.0% may, at the discretion of the investigator, have their oral AHA therapy adjusted and be re-screened once for HbA_{1c} randomization eligibility (≥ 7.0 % and ≤ 10.0%) following a 3-month period on stable AHA doses.*
5.1 Inclusion Criteria	d. Patients with any level of CV risk and meeting all other inclusion criteria may be enrolled. Recruitment will be constrained such that 40% will not have had a prior CV event and 60% will have	d. Patients with any level of CV risk and meeting all other inclusion criteria may be enrolled. Recruitment will be constrained such that approximately 40% will not have had a prior CV event and 60% will have had

SECTION	ORIGINAL PROTOCOL TEXT	AMENDMENT 01 TEXT
	had a prior CV event defined as at least one of the following:	a prior CV event defined as at least one of the following:
6.1 Trial Procedures	*Study Design Figure*	The study design figure has been updated
6.3 Method of Assigning Patients to Treatment Groups (Visit 1)	This automated system will assign a unique allocation number to eligible patients and dispense double-blind trial medication.	This automated system will randomize eligible patients and dispense double-blind trial medication.
6.8 Calcitonin Sample Collection	(*this is a new subsection; subsequent subsections have been renumbered accordingly*)	Serum calcitonin concentrations will be monitored throughout the patient's participation in the trial. Samples will be collected at baseline, annually and trial/early termination.
6.9 Genetic and Biomarker Sample Collection (*previously Section 6.8*)	These fasting specimens will be obtained at baseline (prior to drug exposure), and either at one year of treatment or at the time of drug discontinuation (if occurring within the first year).	These specimens (preferably fasting) will be obtained at baseline (prior to drug exposure), annually and trial/early termination.
6.12 Early Discontinuation of Trial Medication (*previously Section 6.11*)	Unless consent to follow the patient is specifically withdrawn, patients should continue to be followed as outlined in Section 6.14 until the end of the trial. When a patient withdraws consent prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at that time.	Unless consent to follow the patient is specifically withdrawn, patients should continue with their regular visit schedule as outlined in Section 6.15 until the end of the trial. When a patient withdraws consent prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at that time.
7.2 Formulation, Packaging, and Storage	The Microsphere Diluent must be stored between 2°C and 27°C (36°F and 81°F). The EQW or matching placebo dose is prepared by reconstitution of the microspheres in the diluent provided. Specific instructions for dose preparation of the injection will be provided in the Directions For Use (DFU).	The Microsphere Diluent must be stored between 2°C and 25°C (36°F and 77°F). The EQW or matching placebo dose is prepared by reconstitution of the microspheres in the diluent provided. Specific instructions for dose preparation of the injection will be provided in the Patient Instructions For Use (PIU).
7.3 Dispensing of Trial Medication	Study materials will be provided to subjects by the investigator or medically qualified subinvestigator named on Form FDA 1572, or other qualified study-site personnel. Under no circumstance will the investigator or subinvestigators allow the study medication to be used other than as directed by the protocol or to be administered to any persons other than subjects participating in the study.	Study materials will be provided to subjects by the investigator, medically qualified subinvestigator or other qualified study-site personnel. Under no circumstance will the investigator or subinvestigators allow the study medication to be used other than as directed by the protocol or to be administered to any persons other than subjects participating in the study.

SECTION	ORIGINAL PROTOCOL TEXT	AMENDMENT 01 TEXT
7.4 Dose Administration Procedure, Route and Schedule	Doses of EQW or matching placebo are to be injected into subcutaneous (SC) tissue of the abdomen. The site of injection should be rotated on a regular basis so that the same site is not used repeatedly.	Doses of EQW or matching placebo are to be injected into subcutaneous (SC) tissue of the abdomen, thigh or back of the upper arm. The site of injection should be rotated on a regular basis so that the same site is not used repeatedly. The same anatomical region can be used for the injection but the site should be rotated (e.g. different quadrants of the abdomen can be used in a weekly rotation).
7.4 Dose Administration Procedure, Route and Schedule	Subjects will be seen one week as well as one month after randomization to confirm competency with study medication.	Subjects will be seen one week as well as two months after randomization to confirm competency with study medication.
7.5 Randomization Schedule and Blinding Procedures	The study-site personnel must call the IVRS at all subsequent visits (except Study Termination) to record the visit and confirm the kit assignment.	The study-site personnel must call the IVRS at all subsequent visits (except Visits 2, 3 and Study Termination) to record the visit and confirm the kit assignment
7.6 Drug Accountability	Drug accountability will be the responsibility of the study-site personnel. Upon receipt of study medication, study site personnel should open the shipment, verify that the amount and identity of the contents match that stated on the enclosed shipping form, indicate the condition of the contents on the form, and then sign and date the form. The study-site personnel should make a copy of the shipping form for the site's file, and return the original completed form to the sponsor (or designee). In addition, the study-site personnel will contact IVRS to verify receipt of study medication.	Drug accountability will be the responsibility of the study-site personnel. Upon receipt of study medication, study site personnel should open the shipment, verify that the amount and identity of the contents match that stated on the enclosed shipping form, indicate the condition of the contents on the form, and then sign and date the form. In addition, the study-site personnel will contact IVRS to verify receipt of study medication.
9.8.3 Safety Population	Serious AEs and AEs leading to discontinuation of study medication, any of which occurred within 90 days after the last dose of study medication, will be collected.	Serious AEs, including those which lead to discontinuation of study medication, occurring between randomization and 90 days after the last dose of study medication, will be collected.
10.1 Definitions	• Is otherwise medically significant (i.e. withdrawal reactions, all accidental or intentional overdoses whether they result in an adverse event or not, or any event which the investigator considers significant but which is not covered by the above.)	• Is otherwise medically significant (i.e. withdrawal reactions, all accidental or intentional overdoses of study medication whether they result in an adverse event or not, or any event which the investigator considers significant but which is not covered by the above.)
10.3 Classification and Reporting of Adverse Events	Table 1. (*additional footnote included to clarify collection of pancreatitis and neoplasia*)	** All episodes of pancreatitis and neoplasia will be treated as SAEs and will be collected and reported as Ancillary Events.
10.3 Classification and Reporting of Adverse Events	As described in Section 10.1.1 all SAEs that are not included in the Clinical Events List will be recorded by the investigator as Ancillary Events. These events must be recorded in this module within 1 day of a trial site becoming aware of the event. Brief	As described above, all SAEs that are not included in the Clinical Events List will be recorded by the investigator as Ancillary Events. These events must be recorded in this module (or faxed to Lilly if EDC is unavailable) within 1 day of a trial site

SECTION	ORIGINAL PROTOCOL TEXT	AMENDMENT 01 TEXT
	information on the clinical course of the event, treatment, and relevant diagnostic, laboratory or other investigations will be collected on the eCRF. Episodes of pancreatitis, diagnoses of thyroid carcinoma and pancreatic cancer will be collected and reported as Ancillary Events. All Ancillary Events will be reported to the appropriate regulatory agencies in a manner and timeframe consistent with all applicable laws and regulations (Section 10.3.1). Additionally, any SAE considered by an investigator who is a qualified physician to be possibly, probably, or definitely related to the investigational product that is brought to the attention of the investigator after study closeout must be reported within the above timeline to Amylin/Eli Lilly. All patients with serious adverse events must be followed to assess outcome until resolution or until designated permanent.	becoming aware of the event. Brief information on the clinical course of the event, treatment, and relevant diagnostic, laboratory or other investigations will be collected on the eCRF. All episodes of pancreatitis and neoplasia will be treated as SAEs and will be collected and reported as Ancillary Events. All Ancillary Events will be reported to the appropriate regulatory agencies in a manner and timeframe consistent with all applicable laws and regulations (Section 10.3.1). **Note**: Events which meet the criteria to be classified as an Ancillary Event which result in death and are deemed to be possibly related to study drug will be collected and reported as Ancillary Events. Additionally, any SAE considered by an investigator who is a qualified physician to be possibly, probably, or definitely related to the investigational product that is brought to the attention of the investigator after study closeout must be reported within the above timeline to Amylin/Eli Lilly. All patients with serious adverse events must be followed to assess outcome until resolution or until designated permanent.
10.4 Calcitonin Monitoring	(*this is a new subsection; subsequent subsections have been renumbered accordingly*)	Studies in rodents have indicated an increased incidence of thyroid C-cell tumors (adenomas, carcinomas) with EQW treatment. The relevance of these findings to human safety is currently unknown and is being investigated. In clinical studies, there was no difference between exenatide (BID or once weekly) and comparators with respect to thyroid neoplasms. A detailed summary of findings in rodents and clinical studies is available in the Exenatide Investigator Brochure. Measurement of calcitonin has recently been added to newly initiating clinical trials of EQW to characterize any effects of exenatide or comparator treatment on calcitonin levels over time to better assess evidence of a biologic effect on c-cells. In clinical trials, no difference in calcitonin was observed between exenatide and comparators. Calcitonin concentrations will be monitored at baseline, annually and at trial/early termination. Investigators and participants will be blinded to calcitonin values. If the baseline value exceeds 100 ng/L, the site will be informed and directed to have the patient terminate study medication. If a concerning calcitonin value is identified during trial follow-up, the site investigator will

SECTION	ORIGINAL PROTOCOL TEXT	AMENDMENT 01 TEXT
		be notified and will alert the usual care physician. Calcitonin concentrations will be monitored by the DSMB, which will include a thyroid expert.
10.5.2 Reporting of Overdose (previously section 10.4.2)	If an adverse experience(s) is associated with ("results from") the overdose of test drug, the adverse experience(s) is reported as a serious adverse experience, even if no other criteria for seriousness are met.	If an adverse experience(s) is associated with ("results from") the overdose of study medication, the adverse experience(s) is collected as a serious adverse experience, even if no other criteria for seriousness are met.
10.6 Reporting of Pregnancy (previously Section 10.5)	All patients who become pregnant must stop taking blinded trial medication and be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported.	All patients who become pregnant must stop taking blinded trial medication and be followed to the completion/termination of the pregnancy. All occurrences of pregnancy must be reported via the Lilly Pregnancy/Breastfeeding Exposure Form. If the pregnancy continues to term, the outcome (health of infant) must also be reported.
11.3 Consent and Collection of Biomarker Specimens	Patients providing informed consent will have a fasting blood sample collected at baseline (prior to drug exposure), and either at one year of treatment or at the time of drug discontinuation (if occurring within the first year).	Patients providing informed consent will have a blood and urine samples, preferably fasting, collected at baseline (prior to drug exposure), annually, and at the time of trial termination.
12.3 Data Safety Monitoring Board (DSMB)	The DSMB will be composed of five senior academic individuals, including the DSMB Chair.	The DSMB will be composed of six senior academic individuals, including the DSMB Chair.
12.5 Strategic Advisory Committee	(*this is a new subsection*)	The Strategic Advisory Committee will provide oversight for the operational conduct of the study across all participating institutions. It will be composed of senior management from the Sponsors, AROs and the contracted CRO, who are experts in the operational aspects of the conduct of clinical trials and the EXSCEL Clinical Leads.
Appendix 2 Trial Plan (Protocol BCB109)	Please refer to Appendix 2 for specific changes.	Please refer to Appendix 2 for specific changes. Significant changes are summarized below: • Calcitonin samples will be collected annually and at trial/early termination visits. • Heart rate will be measured at randomization, all six-monthly visits (e.g. semi-annual and annual), and drug or trial/early termination visits. • Clarification that consent is required for the biomarker assessment • Samples for future biomarker assessments will now be collected annually trial/early termination rather than at one year only.

APPENDIX 4 PROTOCOL AMENDMENT 02: SUMMARY OF CHANGES

Exenatide QW Clinical Study Protocol BCB109

PROTOCOL TITLE: A RANDOMIZED, PLACEBO CONTROLLED CLINICAL TRIAL TO EVALUATE CARDIOVASCULAR OUTCOMES AFTER TREATMENT WITH EXENATIDE ONCE WEEKLY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Protocol Number: **BCB109**

Amendment Number: **02**

Amendment Purpose: **Date: 10 May 2011**

The purpose of Amendment 02 is to allow insulin use prior to randomization, lower the calcitonin exclusion threshold to >40 ng/L, define the calcitonin exit threshold to be ≥50 ng/L, and clarify reporting of Clinical Events, Serious Adverse Events, and deaths. Additional clarifications and edits are included. Notable changes are detailed in the table below.

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
Title Page		IND Number added
1.2 Rationale for Conduct of the Study	Exenatide, a GLP-1 receptor agonist, has been shown in randomized clinical trials to improve glycemic control, augment endogenous insulin secretion, to reduce blood pressure and promote weight loss with a meta-analysis of exenatide twice-daily (BYETTA) trials (9) showing a trend to lower relative risk for CV events versus pooled comparators of 0.70 (95% confidence interval 0.38 - 1.31). BYETTA (exenatide) injection is currently available in the US and in many countries worldwide for people with type 2 diabetes who are unable to achieve good glycemic control with common oral therapies.	Exenatide, a GLP-1 receptor agonist, has been shown in randomized clinical trials to improve glycemic control, augment endogenous insulin secretion, to reduce blood pressure and promote weight loss with a meta-analysis of exenatide twice-daily (BYETTA) trials (9) showing a trend to lower relative risk for CV events versus pooled comparators of 0.70 (95% confidence interval 0.38 - 1.31). BYETTA (exenatide) injection is currently available in the US and in many countries worldwide for people with type 2 diabetes who are unable to achieve good glycemic control with common oral therapies. The addition of BYETTA to titrated basal insulin therapy (not currently an approved indication) has also been demonstrated to improve glycemic control without an increased risk of hypoglycemia in patients receiving concomitant diet/exercise, metformin, or metformin+pioglitazone therapy (exenatide enhances insulin secretion in a glucose-dependent manner, thus minimizing the risk of hypoglycemia in the absence of an insulin secretagogue) (13).

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
4.1 Design Description	EXSCEL will be a multinational, placebo-controlled, double-blind, randomized, parallel-group pragmatic clinical trial. Eligible patients will have type 2 diabetes with a glycated hemoglobin (HbA1c) ≥7.0% and ≤10.0 % on stable doses of up to three (i.e. 0-3) oral antihyperglycemic agents (AHAs) for at least 3 months i.e. no oral AHA adjustments in the past 3 months. Patients enrolled will be at a wide range of CV risk with approximately 60% having had a prior CV event.	EXSCEL will be a multinational, placebo-controlled, double-blind, randomized, parallel-group pragmatic clinical trial. Eligible patients will have type 2 diabetes with a glycated hemoglobin (HbA1c) ≥7.0 % and ≤10.0 % on stable doses of up to three (i.e. 0-3) oral antihyperglycemic agents (AHAs) for at least 3 months i.e. no oral AHA adjustments in the past 3 months. A stable dose of insulin (±20% of the scheduled total daily insulin dose), either alone or in combination with a stable dose of metformin for at least 3 months, will also be permitted. Patients enrolled will be at a wide range of CV risk with approximately 60% having had a prior CV event.
5.1 Inclusion Criteria	c. Patient has an HbA_{1c} of ≥ 7.0 % and ≤ 10.0% on stable doses of up to three (i.e. 0-3) oral AHAs for at least 3 months *i.e.* no oral AHA adjustments in the past 3 months. Concomitant use of DPP-4 inhibitors is permitted. *HbA1c values must be from within the 3 months prior to randomization. If multiple values are available, the most recent reported value should be used. A patient whose HbA_{1c} is > 10.0% may, at the discretion of the investigator, have their oral AHA therapy adjusted and be re-screened once for HbA_{1c} randomization eligibility (≥ 7.0 % and ≤ 10.0%) following a 3-month period on stable AHA doses.*	c. Patient has an HbA_{1c} of ≥ 7.0 % and ≤ 10.0% • A stable dose of up to three (i.e. 0-3) oral AHAs for at least 3 months will be allowed (i.e. no oral AHA adjustments in the past 3 months). o Concomitant use of DPP-4 inhibitors is permitted. o A stable dose of insulin (±20% of the scheduled total daily insulin dose) either alone or in combination with a stable dose of metformin for at least 3 months is permitted. The use of basal and prandial insulins is permitted in any combination of individual or premixed insulins. If the prescribed insulin regimen includes adjustments, the total dose should not vary by more than 20% from day to day over the preceding 3 months. *HbA1c values must be from within the 3 months prior to randomization. If multiple values are available, the most recent reported value should be used. A patient whose HbA1c is>10.0% may, at the discretion of the investigator, have their oral AHA or insulin therapy adjusted and be re-screened once for HbA1c randomization eligibility (≥ 7.0 % and ≤ 10.0%) following a 3-month period on stable AHA doses.*

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
5.2 Exclusion Criteria	b. Patient has taken insulin within 2 weeks of screening visit or for greater than 1 week within 3 months of screening visit.	b. Patient has a history (≥ 2 episodes) of severe hypoglycemia within 12 months of enrollment.
	l. Personal or family history of medullary thyroid cancer or MEN2 (Multiple Endocrine Neoplasia Type 2) or calcitonin level of 100 ng/L or greater.	l. Personal or family history of medullary thyroid cancer or MEN2 (Multiple Endocrine Neoplasia Type 2) or calcitonin level > 40 ng/L at baseline.
	o. *No original protocol text; new to this version*	o. Is an employee of Eli Lilly and Company or Amylin Pharmaceuticals

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
6.5 Concomitant Therapy	During the double-blind treatment period, trial investigators are expected to monitor patients' AHA regimens and communicate with usual care physicians, who will be responsible for adjusting the AHA regimen in order to achieve locally-appropriate HbA_{1c} goals. These goals will be individualized, with the understanding that currently applicable glycemic guidelines may vary among different geographic regions. With adherence to local custom and laws (including privacy regulations such as HIPAA), types of communication may be informal *e.g.* email or telephone exchanges, to enhance frequency and ease of two-way communication. In addition, the degree of locally-appropriate HbA_{1c} goal-attainment at each site will be monitored centrally and sites with unusually low goal attainment will be advised accordingly. Usual care providers should be notified that adjustments to the AHA regimen are not recommended until HbA1c levels begin reflect the effect of randomized therapy. Any AHA agent, with the exception of GLP-1 receptor agonists, is acceptable. If HbA1c goals are not met following adjustment with oral AHAs in patients not receiving insulin, an insulin regimen may be initiated, preferably without discontinuing or down-titrating some or all of the existing AHAs, as clinically appropriate. Ideally, patients should generally remain on the baseline AHA therapies throughout the course of the trial, unless the baseline AHA is no longer clinically appropriate. However, this should be at the discretion of the usual care provider. In addition, patients should be reminded to keep taking their blinded trial drug following initiation of insulin.	During the double-blind treatment period, trial investigators are expected to monitor patients' AHA regimens and communicate with usual care physicians, who will be responsible for adjusting the AHA regimen in order to achieve locally-appropriate HbA_{1c} goals. The Executive Committee (EC) and Operations Committee (OC) will provide a brief list of guidelines for usual care based on clinical care practice guidelines published by national and international societies that will be updated as knowledge about T2DM evolves over the course of the trial. These goals will be individualized, with the understanding that currently applicable glycemic guidelines may vary among different geographic regions. With adherence to local custom and laws (including privacy regulations such as HIPAA), types of communication may be informal *e.g.* email or telephone exchanges, to enhance frequency and ease of two-way communication. In addition, the degree of locally-appropriate HbA_{1c} goal-attainment at each site will be monitored centrally and sites with unusually low goal attainment will be advised accordingly. Usual care providers should be notified that adjustments to the AHA regimen are not recommended until HbA1c levels begin reflect the effect of randomized therapy. Any AHA agent, with the exception of GLP-1 receptor agonists, is acceptable. If HbA1c goals are not met following adjustment with oral AHAs in patients not receiving insulin, an insulin regimen may be initiated, preferably without discontinuing or down-titrating some or all of the existing AHAs, as clinically appropriate. Patients already receiving insulin therapy may up-titrate insulin during the trial if necessary. Ideally, patients should generally remain on the baseline AHA therapies throughout the course of the trial, unless the baseline AHA is no longer clinically appropriate. However, this should be at the discretion of the usual care provider. In addition, patients should be reminded to keep taking their blinded trial drug following initiation of insulin.

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
6.9 Genetic and Biomarker Sample Collection	In a subset of sites, patients enrolled in the trial will be asked to consent separately to provide a whole blood sample for future pharmacogenomic analyses. The objective of collecting blood samples from which genetic analyses can be performed is to investigate the relationships between genetic make-up and clinical events. These samples will be drawn at baseline, or at any point in the trial at which consent is obtained from the patient. Patients enrolled in the trial will be asked to consent separately to provide two blood and two urine samples for future biomarker analyses. These specimens (preferably fasting) will be obtained at baseline (prior to drug exposure), annually and trial/early termination.	In a subset of sites, patients enrolled in the trial will be asked to consent separately to provide a whole blood sample for future pharmacogenomic analyses. The objective of collecting blood samples from which genetic analyses can be performed is to investigate the relationships between genetic make-up and clinical events. These samples will be drawn at baseline, or at any point in the trial at which consent is obtained from the patient. Patients enrolled in the trial will be asked to consent separately to provide one serum sample, one plasma sample, and one urine sample for future biomarker analyses. These specimens (preferably fasting) will be obtained at baseline (prior to drug exposure), annually and trial/early termination. All samples will be divided and stored in 2 aliquots at the Laboratory Corporation of America facility in Kannapolis, North Carolina, USA.
6.11 End of Trial Visit and Post Trial Telephone Contact	**NOTE:** ***All patients should have an End of Trial Visit. (Patients who have discontinued trial drug must, at minimum, have an End of Trial telephone contact visit.)***	**NOTE:** ***All patients should have an End of Trial Visit. (Patients who have discontinued trial drug prior to the end of the trial must, at minimum, have an End of Trial telephone contact visit.)***
6.12 Early Discontinuation of Trial Medication	Following randomization, it is expected that patients will remain on study medication for the duration of trial participation. However, it is recognized that patients may need to discontinue trial medication, in some cases permanently, for protocol-specified reasons (Section 6.14), due to the judgment of the primary investigator or because the patient withdraws consent. The Trial Hotline should be contacted whenever a site is considering interrupting or discontinuing trial drug (Section 6.17).	Following randomization, it is expected that patients will remain on study medication for the duration of trial participation. However, it is recognized that patients may need to discontinue trial medication, in some cases permanently, for protocol-specified reasons (Section 6.14), due to the judgment of the primary investigator or the decision of the patient. The Trial Hotline should be contacted whenever a site is considering interrupting or discontinuing trial drug (Section 6.17).
6.14 Permanent Discontinuation of Trial Drug Per Protocol	*No original text*	e) Annual calcitonin measurement ≥ 50 ng/L

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
7.6 Drug Accountability	A drug disposition form will be provided to record all study medication dispensed to or returned from each subject. Upon completion of the study, all used and unused remaining EQW or matching placebo, empty containers, and copies of completed drug disposition forms should be returned to the sponsor (or designee). A clinical supplies return authorization form will be prepared by the clinical research associate at the closeout visit. The clinical supplies return form should be enclosed with the return drug shipment. The study site personnel must maintain documentation of any missing or unreturned study medication.	A drug disposition form will be provided to record all study medication dispensed to or returned from each subject. Upon completion of the study, all used and unused remaining EQW or matching placebo, empty containers, and copies of completed drug disposition forms should be returned to the sponsor (or designee). A clinical supplies return authorization form will be prepared by the clinical research associate at the closeout visit. The clinical supplies return form should be enclosed with the return drug shipment; however, if the site manager/CRA approves, the site can destroy the material instead of returning the used and unused study drug. The study site personnel must maintain documentation of any missing or unreturned study medication.
10.1 Definitions	Events meeting the above definition as SAEs and will be recorded in the safety trial database as either Clinical or Ancillary Events (definitions and criteria are summarized in Table 1). Serious Adverse Event (SAE) This is defined as any untoward medical occurrence or effect in a patient treated on a study protocol which does not necessarily have a causal relationship with the study treatment, that also, at any dose: • Results in death • Is life-threatening • Results in persistent or significant or disability/incapacity • Requires in-patient hospitalization or prolongs existing hospitalization • Results in a congenital anomaly or birth defect • Is otherwise medically significant (i.e. withdrawal reactions, all accidental or intentional overdoses of study medication whether they result in an adverse event or not, or any event which the investigator considers significant but which is not covered by the above.)	*Text removed* Serious Adverse Event (SAE) This is defined as any untoward medical occurrence or effect in a patient treated on a study protocol which does not necessarily have a causal relationship with the study treatment, that also, at any dose: • Results in death • Is life-threatening • Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions • Requires in-patient hospitalization or prolongs existing hospitalization • Results in a congenital anomaly or birth defect • Is otherwise medically significant (i.e. withdrawal reactions, all accidental or intentional overdoses of study medication whether they result in an adverse event or not, or any event which the investigator considers significant but which is not covered by the above.)

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
10.2 Adverse Events Assessment	Adverse events will be monitored over the course of the trial, starting from the time of randomization and through the duration of the subject's participation, including the 90 day post-trial drug follow-up period or withdrawal. Adverse events reported by the patient will be evaluated by the investigator to determine if a given event meets the criteria for a serious event (described in Section 10.1). Any adverse event that does not meet the definition of a serious event will be considered non-serious and will not be recorded.	Adverse events will be monitored over the course of the trial, starting from the time of randomization and through the duration of the subject's participation, including the 90 day post-trial drug follow-up period or withdrawal. Adverse events reported by the patient will be evaluated by the investigator to determine if a given event meets the criteria for a serious event (described in Section 10.1). Any adverse event that does not meet the definition of a serious event will be considered non-serious and will not be recorded in the eCRF, with the exception of events noted in Section 10.3.
10.3 Recording and Reporting Adverse Events	Original section structure 10.3 Classification and Reporting Adverse Events 10.3.1 Sponsor Responsibility for Reporting Serious Adverse Events	New section structure 10.3 Recording and Reporting Adverse Events 10.3.1 Recording Adverse Events 10.3.2 Safety Reporting 10.3.3 Sponsor Responsibility for Reporting Serious Adverse Events

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
10.3.1 Recording Adverse Events	The classification of an SAE as a Clinical or Ancillary event is dependent on if the SAE is included in the Clinical Events List (Appendix 1). The Clinical Events List is inclusive of SAEs that are: (1) components of the primary or secondary composite cardiovascular endpoints, (2) other trial endpoints, (3) potential components of the CV endpoint that are included among terms sent for review by the CEC; (4) expected sequelae of type 2 diabetes; (5) expected events based on information noted in the exenatide investigator brochure. SAE which meet these criteria will be reported in the **Clinical Events eCRF module**. SAE which are not included on the Clinical Events List will be considered Ancillary events and will be reported in the **Ancillary Events eCRF module**. The Clinical Events List will be reviewed and the eCRF will be completed during every visit to determine if a patient has experienced one or more of the listed events. SAE should be reviewed for all patients randomized regardless of whether the patient is currently on trial medication.	SAEs will be recorded in the **Clinical Events or SAE eCRF** modules. Guidelines for events which qualify as Clinical Events are provided in Appendix 1. Events to be recorded in the **Clinical Events eCRF** module include SAEs that are: (1) components of the primary or secondary composite cardiovascular endpoints, (2) other trial endpoints, (3) potential components of the CV endpoint that are included among terms sent for review by the CEC; (4) expected sequelae of type 2 diabetes (Table 1). These events represent trial outcomes and expected events for this population. In addition, non-serious adverse events of stress tests, severe hypoglycemia, diabetic eye disease, foot ulcer, microalbuminurea, proteinuria, hyperlipidemia / dyslipidemia, hypertension, and gout also will be recorded in the **Clinical Events eCRF** module (see Appendix I). Any SAE which is not included among the expected events on the Clinical Events List will be recorded in the **SAE eCRF** module. Events of neoplasia and pancreatitis should be reported on the **SAE eCRF** even if the event does not meet serious criteria. Note: The events listed in Appendix 1 are Clinical Events that are trial endpoints or expected events for this population, and do not generally fit the definition of a SUSAR, <u>including those events with an outcome of death</u>. However, if the investigator's assessment of an event is that it meets SUSAR criteria despite being listed as a Clinical Event, the event may be reported as a SUSAR as long as it does not require adjudication. If the investigator feels that a Clinical Event meets SUSAR criteria the **SAE eCRF** should be used to report the event. The Clinical Events List will be reviewed and the eCRF will be completed during every visit to determine if a patient has experienced one or more of the listed events. SAE should be reviewed for all patients randomized regardless of whether the patient is currently on trial medication.

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
10.3.2 Safety Reporting	*(Formerly Section 10.3)* SAE recorded on the Clinical Events eCRF represent those events which are components of the composite CV endpoint, other trial endpoints, potential components of the CV endpoint that require adjudication, expected sequelae of T2DM, or are expected based on information provided in the exenatide investigator brochure. Clinical events will be monitored by the DSMB and **will not** require expedited reporting to the sponsor even though they may be considered possibly, probably or definitely drug-related and meet SAE criteria. ***Regardless of relationship to trial drug, Clinical Events will not be reported by the sponsor to regulatory agencies or ethics committees in an expedited manner, nor in the format of a line listing as part of an Annual Safety Report.*** Events reported via this module will be regularly monitored by the DSMB and those which may be associated with a trial endpoint will be adjudicated by the CEC. As described above, all SAEs that are not included in the Clinical Events List will be recorded by the investigator as Ancillary Events. These events must be recorded in this module (or faxed to Lilly if EDC is unavailable) within **1 day** of a trial site becoming aware of the event. Brief information on the clinical course of the event, treatment, and relevant diagnostic, laboratory or other investigations will be collected on the eCRF. All episodes of pancreatitis and neoplasia will be treated as SAEs and will be collected and reported as Ancillary Events. All Ancillary Events will be reported to the appropriate regulatory agencies in a manner and timeframe consistent with all applicable laws and regulations (Section 10.3.1). **Note:** Events which meet the criteria to be classified as an Ancillary Event which result in death and are deemed to be possibly related to study drug will be collected and reported as Ancillary Events.	The DSMB will monitor the totality of collected safety data (i.e. events recorded on both the Clinical Events and SAE eCRFs) on a semi-annual basis regardless of event classification. SAE recorded on the Clinical Events eCRF represent those events which are components of the composite CV endpoint, other trial endpoints, potential components of the CV endpoint that require adjudication or are expected sequelae of T2DM. SAE recorded as Clinical Events, including death related to an event in the Clinical Events List, and ***will not be reported to the Sponsor, regulatory agencies or ethics committees, regardless of relationship to trial drug*** even though they may be considered possibly, probably or definitely drug-related and meet SAE criteria. In addition to the un-blinded review by the DSMB, events reported via this module that may be associated with a trial endpoint will be adjudicated by the CEC. As described above, all SAEs that are not included in the Clinical Events List will be recorded by the investigator in the SAE eCRF module. These events must be recorded in this module (or faxed to Lilly if EDC is unavailable) within **1 day** of a trial site becoming aware of the event. Any SAEs meeting the definition of a SUSAR will be subject to expedited reporting as per current legislation. Brief information on the clinical course of the event, treatment, and relevant diagnostic, laboratory or other investigations will be collected on the eCRF. All episodes of pancreatitis and neoplasia will be treated as SAEs and will be collected and reported in the SAE eCRF module. All events recorded in the SAE eCRF module will be reported to the appropriate regulatory agencies in a manner and timeframe consistent with all applicable laws and regulations (Section 10.3.2). **All SUSARS** will be reported in an expedited manner with the exception of those fulfilling the criterion of an efficacy endpoint (as detailed in Section 1 of Appendix 1: Primary or Secondary Trial Endpoints) which will be handled as Clinical Events.

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
10.3.3 Sponsor Responsibility for Reporting Serious Adverse Events	(*Formerly Section 10.3.1)* The Sponsor will ensure that all appropriate regulatory agencies confirm that the approach for monitoring Clinical Events, described in the Safety Assessments Section is acceptable to them. All Ancillary SAE will be reported to regulatory agencies, IRB/IECs, and investigators in accordance with all applicable global laws and regulations.	The Sponsor will ensure that all appropriate regulatory agencies confirm that the approach for monitoring Clinical Events, described in the Safety Assessments Section is acceptable to them. SAE that are not recorded as Clinical Events will be reported to regulatory agencies, IRB/IECs, and investigators in accordance with all applicable global laws and regulations.
10.4 Calcitonin Monitoring	Calcitonin concentrations will be monitored at baseline, annually and at trial/early termination. Investigators and participants will be blinded to calcitonin values. If the baseline value exceeds 100 ng/L, the site will be informed and directed to have the patient terminate study medication. If a concerning calcitonin value is identified during trial follow-up, the site investigator will be notified and will alert the usual care physician. Calcitonin concentrations will be monitored by the DSMB, which will include a thyroid expert.	Calcitonin concentrations will be monitored at baseline, annually and at trial/early termination. Investigators and participants will be blinded to calcitonin values. If the baseline value exceeds 40 ng/L, the site will be informed and directed to have the patient terminate study medication. If a concerning calcitonin value (≥50 ng/L) is identified during trial follow-up, the site investigator will be notified and will alert the usual care physician and study medication will be discontinued. Calcitonin concentrations will be monitored by the DSMB, which will include a thyroid expert.
10.7 Un-blinding	*No original text*	Breaking the blind is strongly discouraged and should only be requested if it is deemed necessary for the wellbeing or safety of the patient. Any Investigator requesting the unblinding of a patient will be asked to contact the trial hotline physician, available 24hrs/day to discuss the case and determine the course of action; however, it is the prerogative of the treating physician to insist that their patient should be unblinded.

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
12.4 Clinical Events Committee (CEC)	The events which constitute the principal endpoints of this trial will be adjudicated by the Clinical Events Classification Committee (CEC), coordinated through the Duke Clinical Research Institute (DCRI), which will be comprised of approximately 5-7 physicians and a coordinator. The specific endpoints to be adjudicated include: cause of death (cardiovascular-related vs. non-cardiovascular), MI, stroke, acute coronary syndrome, and CHF requiring hospitalization. Clinical reviewers will be board certified or board eligible endocrinologists, cardiologists, neurologists, gastroenterologists, or physicians with clinical expertise and prior clinical event classification experience. The CEC will review clinical data and adjudicate safety and efficacy endpoints. The CEC will adjudicate clinical events using pre-specified criteria and definitions for the diagnoses of MI, stroke, acute coronary syndrome, and CHF requiring hospitalization. The CEC will be blinded to the assigned trial drug. Sites will provide clinical information via the eCRF and also provide supplemental information from medical records, when needed. The CEC operations and endpoint criteria will be described in a separate charter.	The events which constitute the principal endpoints of this trial will be adjudicated by the Clinical Events Classification Committee (CEC), coordinated through the Duke Clinical Research Institute (DCRI), which will be comprised of approximately 5-7 physicians and a coordinator. The specific endpoints to be adjudicated include: cause of death (cardiovascular-related vs. non-cardiovascular), MI, stroke, acute coronary syndrome, pancreatitis, neoplasm, ventricular fibrillation/tachycardia, and CHF requiring hospitalization. Clinical reviewers will be board certified or board eligible endocrinologists, cardiologists, neurologists, gastroenterologists, or physicians with clinical expertise and prior clinical event classification experience. The CEC will review clinical data and adjudicate safety and efficacy endpoints. The CEC will adjudicate clinical events using pre-specified criteria and definitions. The CEC will be blinded to the assigned trial drug. Sites will provide clinical information via the eCRF and also provide supplemental information from medical records, when needed. The CEC operations and endpoint criteria will be described in a separate charter.
References	*No original text*	13. Buse JB, Bergenstal RM, Glass LC, Heilmann CR, Lewis MS, Kwan AY, Hoogwerf BJ, Rosenstock J. Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. Ann Intern Med. 2011;154(2):103-112.
Appendix 1	**CLINICAL EVENTS LIST (TO BE INCORPORATED INTO ECRF)** The following list of events would be recorded in the eCRF at the time of the trial visit, *but not reported to the Sponsor or regulatory agencies urgently* regardless of relationship to trial drug. Included are trial endpoints as well as events that are expected to occur in this trial population.	**CLINICAL EVENTS LIST (TO BE RECORDED IN THE CLINICAL EVENTS eCRF)** *Deleted existing text*

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
Appendix 1	**I. A. Obvious trial endpoints** (These events will prompt the investigator to complete an endpoint package which will then be adjudicated according to the Clinical Events Classification [CEC] charter) Death • Cardiovascular (CV) Death (i.e., fatal myocardial infarction [MI]/cerebrovascular accident [CVA]/ congestive heart failure [CHF]/arrhythmia, cardiac arrest, death following CV intervention) • Non-CV Death	**I.A. Obvious trial endpoints** (These events will prompt the investigator to complete an endpoint package which will then be adjudicated according to the Clinical Events Classification [CEC] charter) Death • Cardiovascular (CV) Death (i.e., fatal myocardial infarction [MI]/cerebrovascular accident [CVA]/ congestive heart failure [CHF]/arrhythmia, cardiac arrest, death following CV intervention) • *Deleted existing text*
Appendix 1	**Section II. C.** Hypoglycemia / Hyperglycemia /Diabetic ketoacidosis / Hyperosmolar hyperglycemic nonketotic coma	**Section II. C.** Severe hypoglycemia / Hyperglycemia /Diabetic ketoacidosis / Hyperosmolar hyperglycemic nonketotic coma
Appendix 1	*No original text*	Added the term "(including non-serious events)" to the existing events: -stress test -diabetic eye disease -diabetic neuropathy -diabetic nephropathy -metabolic conditions associated with diabetes

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
Appendix 1	III. Terms listed in the exenatide Investigator Brochure A. Allergic/Hypersensitivity Reactions • Injection site reactions • Pruritis and/or urticaria • Rash • Angioedema • Anaphylactic reaction B. Gastrointestinal reactions • Nausea • Vomiting and/or diarrhea resulting in dehydration • Abdominal distension or pain • Eructation • Constipation • Flatulence • Diarrhea C. Renal and Urinary Disorders • Altered renal function, including acute or worsened chronic renal failure • Renal impairment • Increased serum creatinine D. Development of antibodies to exenatide E. For all other terms please refer to the current Investigator Brochure	*Deleted Section III.*

APPENDIX 5 PROTOCOL AMENDMENT 03: SUMMARY OF CHANGES

Exenatide QW Clinical Study Protocol BCB109

PROTOCOL TITLE: A RANDOMIZED, PLACEBO CONTROLLED CLINICAL TRIAL TO EVALUATE CARDIOVASCULAR OUTCOMES AFTER TREATMENT WITH EXENATIDE ONCE WEEKLY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Protocol Number: BCB109

Amendment Number: 03

Amendment Purpose: **Date: 23 April 2012**

The purpose of Amendment 03 is to alter inclusion criteria to allow patients with an HbA1c ≥6.5% and using insulin, alone or in combination with oral antihyperglycemic medications, to be eligible to enroll in the study. In addition, the requirement for patients to have been on a stable dose of oral antihyperglycemic medication has been removed. Additional safety language regarding hypoglycemia has been included for patients using concomitant insulin and/or sulfonylurea. In addition, patients discontinued due to pregnancy can resume study medication following completion of the pregnancy and cessation of breastfeeding (if applicable). Finally, clarifications regarding events requiring adjudications were added. Minor editorial changes have also been included to improve clarity and consistency. Notable changes are detailed in the table below.

SECTION	AMENDMENT 02 TEXT	AMENDMENT 03 TEXT
Title Page	**Lisa Porter, MD** **Vice President, Clinical Development** **Amylin Pharmaceuticals, Inc.**	**Lisa Porter, MD** **Vice President, Medical Research and Development ~~Clinical Development~~** **Amylin Pharmaceuticals, Inc.**
List of Abbreviations	*None*	CRO Contract Research Organization HLGT High level group term IFU Instructions for use ITT Intent-to-Treat PCI Percutaneous coronary intervention TC Total cholesterol TG Triglycerides TIA Transient ischemic attack
List of Abbreviations	EDC Electronic Data Collection	EDC Electronic Data Capture ~~Collection~~

SECTION	AMENDMENT 02 TEXT	AMENDMENT 03 TEXT
Section 1.2 Rationale for Conduct of the Study	The addition of BYETTA to titrated basal insulin therapy (not currently an approved indication) has also been demonstrated to improve glycemic control without an increased risk of hypoglycemia in patients receiving concomitant diet/exercise, metformin, or metformin+pioglitazone therapy (exenatide enhances insulin secretion in a glucose-dependent manner, thus minimizing the risk of hypoglycemia in the absence of an insulin secretagogue) (13). Exenatide once weekly (EQW), a new formulation of exenatide that is administered once weekly rather than twice daily, is under development and currently being reviewed by the US FDA.	The addition of BYETTA to titrated basal insulin therapy ~~(not currently an approved indication)~~ has also been demonstrated to improve glycemic control without an increased risk of hypoglycemia in patients receiving concomitant diet/exercise, metformin, or metformin+pioglitazone therapy (exenatide enhances insulin secretion in a glucose-dependent manner, thus minimizing the risk of hypoglycemia in the absence of an insulin secretagogue) (13). Exenatide once weekly (EQW), a new formulation of exenatide that is administered once weekly rather than twice daily, has been approved by the US FDA as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and in the European Union as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea but have not achieved adequate glycemic control. ~~is under development and currently being reviewed by the US FDA~~.
Section 2.2 Secondary Objectives	(4) Hospitalization for heart failure (CHF)	(4) Hospitalization for congestive heart failure (CHF)
Section 3 Trial Governance	The EC will consist of approximately eleven individuals, comprising nine senior independent academic representatives who are experts in their field and two Alliance representatives.	The EC will consist of approximately eleven individuals, comprising nine senior independent academic representatives who are experts in their field and two ~~Alliance~~ sponsor representatives.
Figure 1		*Figure updated to clarify groups involved*
Section 4.1 Design Description	Eligible patients will have type 2 diabetes with a glycated hemoglobin (HbA_{1c}) ≥7.0 % and ≤10.0 % on stable doses of up to three (i.e. 0-3) oral antihyperglycemic agents (AHAs) for at least 3 months *i.e.* no oral AHA adjustments in the past 3 months. A stable dose of insulin (±20% of the scheduled total daily insulin dose), either alone or in combination with a stable dose of metformin for at least 3 months, will also be permitted.	Eligible patients will have type 2 diabetes with ~~a glycated hemoglobin (HbA_{1c}) ≥7.0 %~~ an HbA_{1c} ≥6.5% and ≤10.0 % on ~~stable doses of~~ up to three (i.e., 0-3) oral ~~antihyperglycemic agents (~~AHAs~~) for at least 3 months *i.e.* no oral AHA adjustments in the past 3 months. A stable dose of~~ or insulin either alone or in combination with up to 2 (i.e., 0-2) oral AHAs. ~~(±20% of the scheduled total daily insulin dose), either alone or in combination with a stable dose of metformin for at least 3 months, will also be permitted.~~
Section 4.1 Design Description	Per usual care, HbA_{1c} values should be measured locally using a NGSP (National Glycohemoglobin Standardization Program) certified HbA_{1c} assay (12).	Per usual care, HbA_{1c} values should be measured locally. ~~using a~~ An NGSP (National Glycohemoglobin Standardization Program) certified HbA_{1c} assay should be used if available (12).

SECTION	AMENDMENT 02 TEXT	AMENDMENT 03 TEXT
Section 4.2 Trial Duration	All patients that cease study medication will be followed up, if at all possible, for the full study period. All patients that withdraw from the trial will have their vital status ascertained, if at all possible, at the end of the trial.	All patients that discontinue ~~cease~~ study medication, but have not withdrawn consent to participate in the study, will be followed up, if possible, for the full study period ~~All patients that withdraw from the trial~~ and will have their vital status ascertained, if possible, at the end of the trial.
Section 5.1 Inclusion Criteria	c. Patient has an HbA_{1c} of ≥ 7.0 % and ≤10.0% • A stable dose of up to three (i.e., 0-3) oral AHAs for at least 3 months will be allowed (*i.e.* no oral AHA adjustments in the past 3 months). o Concomitant use of DPP-4 inhibitors is permitted. o A stable dose of insulin (±20% of the scheduled total daily insulin dose) either alone or in combination with a stable dose of metformin for at least 3 months is permitted. The use of basal and prandial insulins is permitted in any combination of individual or premixed insulins. If the prescribed insulin regimen includes adjustments, the total dose should not vary by more than 20% from day to day over the preceding 3 months. *HbA1c values must be from within the 3 months prior to randomization. If multiple values are available, the most recent reported value should be used. A patient whose HbA_{1c} is>10.0% may, at the discretion of the investigator, have their oral AHA or insulin therapy adjusted and be re-screened once for HbA_{1c} randomization eligibility (≥7.0 % and ≤10.0%) following a 3-month period on stable AHA doses.*	c. Patient has an HbA_{1c} of ≥6.5 % ~~≥ 7.0 %~~ and ≤10.0% and is currently using one of the following treatment regimens: • Treatment with up to three (i.e., 0-3) oral AHAs (concomitant use of DPP-4 inhibitors is permitted). • Insulin therapy, either alone or in combination with up to two (ie., 0-2) oral AHAs (use of basal and prandial insulins is permitted in any combination of individual or premixed insulins) *All patients should be on a stable diabetes management regimen, as assessed by the investigator, at the time of enrollment.* ~~• A stable dose of up to three (i.e., 0-3) oral AHAs for at least 3 months will be allowed (*i.e.* no oral AHA adjustments in the past 3 months).~~ ~~o Concomitant use of DPP-4 inhibitors is permitted.~~ ~~o A stable dose of insulin (±20% of the scheduled total daily insulin dose) either alone or in combination with a stable dose of metformin for at least 3 months is permitted. The use of basal and prandial insulins is permitted in any combination of individual or premixed insulins. If the prescribed insulin regimen includes adjustments, the total dose should not vary by more than 20% from day to day over the preceding 3 months.~~ *HbA1c values must be from within the 3 months prior to randomization. If multiple values are available, the most recent reported value should be used. A patient whose HbA_{1c} is>10.0% may, at the discretion of the investigator, have their oral AHA or insulin therapy adjusted and be re-screened once for HbA_{1c} randomization eligibility (≥6.5 % ~~≥7.0 %~~ and ≤10.0%). ~~following a 3-month period on stable AHA doses~~*

SECTION	AMENDMENT 02 TEXT	AMENDMENT 03 TEXT
Section 5.1 Inclusion Criteria	○ History of ischemic stroke. Strokes not known to be hemorrhagic will be allowed as part of this criterion;	○ History of ischemic stroke; strokes not known to be hemorrhagic will be allowed as part of this criterion; transient ischemic attacks (TIAs) are not included
Section 5.2 Exclusion Criteria	*None*	Each patient meeting any of the following criteria will be excluded from this trial.
Section 5.2 Exclusion Criteria	i. Patient has end-stage renal disease or an estimated glomerular filtration rate (eGFR) derived from serum creatinine (using the simple MDRD-4 formula) of <30 mL/min/1.73 m^2.	i. Patient has end-stage renal disease or an estimated glomerular filtration rate (eGFR) derived from serum creatinine (using the simple MDRD-4 formula) of <30 mL/min/1.73 m^2 (see Appendix 2).
Section 5.2 Exclusion Criteria	**NOTE:** Serum for calcitonin measurement will be drawn at baseline. Patients may be randomized and initiate study medication prior to the results of the calcitonin measure being available. If a randomized patient is found to have an exclusionary serum calcitonin concentration, they will stop study medication and patients will continue to have follow-up for vital status and be part of the intention to treat analysis.	**NOTE:** Serum for calcitonin measurement will be drawn at baseline. Patients may be randomized and initiate study medication prior to the results of the calcitonin measure being available. If a randomized patient is found to have an exclusionary serum calcitonin concentration, they will stop study medication and patients will continue to have follow-up and be part of the Intent-to-Treat ~~intention to treat~~ analysis.
Section 6.1 Trial Procedures	At baseline (Visit 1) patients will be provided with the patients' instruction brochure and be trained by study personnel to administer the study medication injection.	At randomization ~~baseline~~ (Visit 1) patients will be provided with the patients' instruction for use (IFU) ~~brochure~~ and be trained by study personnel to administer the study medication injection.
Section 6.1 Trial Procedures	At semi-annual and annual visits, additional procedures will include blood pressure, body weight, review of routine laboratory values and dispensing of study drug as described in Appendix 2.	At semi-annual and annual visits, additional procedures will include blood pressure, body weight, heart rate, review of laboratory values and dispensing of study drug as described in Appendix 2.
Section 6.2 Pre-Enrollment and Enrollment Procedures	Patients may qualify for enrollment based on recent laboratory data *e.g.* HbA_{1c} within the last 3 months, obtained as part of usual care prior to Visit 1.	Patients may qualify for enrollment based on recent laboratory data *e.g.* HbA_{1c} within the last 3 months, obtained as part of usual care prior to Visit 1 (recommended guidance for management of serum creatinine values will be provided to each site).
Section 6.4 Treatments Administered	As part of standard of care, serum creatinine should be among labs drawn annually.	As part of standard of care, serum creatinine should be, at minimum, among labs drawn annually.

SECTION	AMENDMENT 02 TEXT	AMENDMENT 03 TEXT
Section 6.4 Treatments Administered	If the need for drug discontinuation is confirmed, the patient will be invited back to the trial site for an unscheduled visit to explain the situation, to stop the study drug and to encourage the patient to continue follow up off study drug until the end of the trial.	If the need for drug discontinuation is confirmed, the situation will be explained to the patient and the patient will be asked to stop the study drug and encouraged ~~the patient will be invited back to the trial site for an unscheduled visit to explain the situation, to stop the study drug and to encourage the patient~~ to continue follow up off study drug until the end of the trial. If deemed necessary by the investigator, an unscheduled visit can be performed to discuss study drug discontinuation and the importance of subsequent follow up.
Section 6.6 Precautions to Minimize Rates of Hypoglycemia	At the screening/enrollment visit and all subsequent visits, the symptoms and appropriate management of hypoglycemia will be reviewed with participants.	At the screening/randomization ~~enrollment~~ visit and all subsequent visits, the symptoms and appropriate management of hypoglycemia will be reviewed with patients. ~~participants~~
Section 6.6 Precautions to Minimize Rates of Hypoglycemia	*None*	Combination therapies with insulin and sulfonylurea have an increased risk of hypoglycemia. To minimize this risk, patients whose diabetes is well controlled may require a reduction in the insulin or sulfonylurea dose when allocated study medication. EXSCEL will employ both patient- and investigator-directed education to minimize the risk of hypoglycemia. Patients receiving sulfonylurea/insulin combinations will be explicitly reminded of the symptoms and proper management of hypoglycemia before starting study drug. The EXSCEL study team will also provide investigators with training materials to demonstrate best practice for minimizing hypoglycemia risk in these patients.
Section 6.7 Laboratory and Anthropometric Measurements	Blood pressure, heart rate, height, and body weight will be collected by study personnel as indicated in the flow chart.	Blood pressure, heart rate, height, and body weight will be collected by study personnel as indicated in Appendix 2. ~~in the flow chart~~
Section 6.10 Resource Utilization Quality of Life Data for Economic Evaluation	This instrument will be administered at baseline, at 6 months and annually thereafter.	This instrument will be administered at baseline, at 6 months, at subsequent annual visits, and at the trial/early termination visit. ~~and annually thereafter~~
Section 6.11 Trial/Early Termination Visit and Post Trial Telephone Contact	Section 6.11 End of Trial Visit and Post Trial Telephone Contact	Section 6.11 ~~End of Trial~~ Trial/Early Termination Visit and Post Trial Telephone Contact

SECTION	AMENDMENT 02 TEXT	AMENDMENT 03 TEXT
Section 6.11 Trial/Early Termination Visit and Post Trial Telephone Contact	End of Trial Visit	~~End of Trial~~ Trial/Early Termination Visit
Section 6.12 Temporary Discontinuation of Trial Medication	Section 6.12 Early Discontinuation of Trial Medication	Section 6.12 ~~Early~~ Temporary Discontinuation of Trial Medication
Section 6.12 Temporary Discontinuation of Trial Medication	Unless resumption of trial medication is considered unsafe or is refused by the participant, the patient will be expected to resume regular use of the blinded trial medication. Should a participant stop taking trial medication, either permanently or temporarily, the reasons for discontinuation and length of time the patient stopped taking trial medication will be assessed and recorded. All randomized patients who permanently discontinue trial medication should have a medication discontinuation visit (as described in Section 6.13) as soon as possible after stopping the trial drug.	Unless resumption of trial medication is considered unsafe or is refused by the patient, ~~participant~~ the patient will be expected to resume regular use of the blinded trial medication after a period of temporary discontinuation. Should a patient ~~participant~~ stop taking trial medication, either permanently or temporarily, the reasons for discontinuation and length of time the patient stopped taking trial medication will be assessed and recorded. All randomized patients who permanently discontinue trial medication should have a drug termination ~~medication discontinuation~~ visit (as described in Section 6.13) as part of their next scheduled study visit (unless a separate drug termination visit at that point is deemed necessary by the investigator). ~~as soon as possible after stopping the trial drug.~~
Section 6.12 Early Discontinuation of Trial Medication	*None*	**NOTE:** After trial medication is discontinued due to pregnancy, re-initiation of study medication can be considered following completion of the pregnancy and breastfeeding (if applicable).

SECTION	AMENDMENT 02 TEXT	AMENDMENT 03 TEXT
Section 6.13 Permanent Discontinuation of Trial Medication Visit Procedures	All randomized patients who permanently discontinue trial medication should have a medication discontinuation visit as soon as possible after stopping the trial drug. Necessary procedures are indicated in the Flow Chart. All efforts should be made to reinforce with patients that this would be a medication discontinuation visit, not a trial discontinuation visit. Patients will be asked to continue with all other trial follow up until the completion of the trial, including annual in-person visits and telephone calls, as well as the annual calcitonin measurement. IVRS should be contacted to register the patient as discontinued only after all efforts have been exhausted to get patients back on trial drug if appropriate.	All randomized patients who permanently discontinue trial medication should have a drug termination ~~medication discontinuation~~ visit as part of their next scheduled visit (unless a separate drug termination visit is deemed necessary by the investigator). ~~soon as possible after stopping the trial drug.~~ Necessary procedures are indicated in Appendix 2. ~~the Flow Chart.~~ All efforts should be made to reinforce with patients that this would be a medication discontinuation visit, not a trial discontinuation visit. Patients will be asked to continue with all other trial follow up until the completion of the trial, including semi-annual in-person visits and/or telephone calls, as well as the annual calcitonin measurement. IVRS should be contacted to register the patient as having discontinued study medication only after all efforts have been exhausted to get patients back on trial medication ~~drug~~ if appropriate.
Section 6.14 Permanent Discontinuation of Trial Medication Per Protocol	b) Pregnancy, as confirmed by serum pregnancy test. Patient must stop taking blinded trial medication, and be followed if she becomes pregnant during the trial (Section 10.6)	*Deleted; remaining items in list renumbered*
Section 6.14 Permanent Discontinuation of Trial Medication Per Protocol	*The usual care provider will be provided with standard guidance on down-titrating AHAs in the presence of hypoglycemia.*	*The usual care provider will be provided with standard guidance by the trial investigator on down-titrating AHAs in the presence of hypoglycemia.*
Section 6.14 Permanent Discontinuation of Trial Medication Per Protocol	d) Severe, irreversible renal dysfunction (eGFR <30 ml/min/1.73m^2) or renal replacement therapy.	c) Severe, irreversible renal dysfunction (confirmed by two consecutive eGFR <30 ml/min/1.73m^2) or renal replacement therapy.
Section 6.15 Follow-up for Patients who Permanently Discontinue Trial Medication	End of Trial Visit	~~End of Trial~~ Trial/Early Termination Visit
Section 7.2 Formulation, Packaging, and Storage	Specific instructions for dose preparation of the injection will be provided in the Patient Instructions for Use (PIU).	Specific instructions for dose preparation of the injection will be provided in the ~~Patient~~ Instructions for Use (IFU ~~PIU~~).

SECTION	AMENDMENT 02 TEXT	AMENDMENT 03 TEXT
Section 7.4 Dose Administration Procedures, Route, and Schedule	Subjects who terminate study medication will be followed for the remainder of the study for the assessment of clinical events unless the subject opts to withdraw consent.	Patients ~~Subjects~~ who terminate study medication will be followed up, per the protocol, for the remainder of the study unless the patient ~~subject~~ opts to withdraw consent.
Section 7.6 Drug Accountability	A drug disposition form will be provided to record all study medication dispensed to or returned from each subject. Upon completion of the study, all used and unused remaining EQW or matching placebo, empty containers, and copies of completed drug disposition forms should be returned to the sponsor (or designee).	A drug accountability log ~~disposition form~~ will be provided to record all study medication dispensed to or returned from each patient ~~subject~~. Upon completion of the study, all used and unused EQW or matching placebo vials ~~empty containers,~~ and copies of completed drug accountability logs ~~disposition forms~~ should be returned to the sponsor (or designee).
Section 9.7 Secondary Analyses	5. Hospitalization for heart failure (CHF)	5. Hospitalization for congestive heart failure (CHF)
Section 9.8.1 Intent-To-Treat Population	Every effort will be made to collect CV events to study termination even in those who have discontinued the study.	Every effort will be made to collect CV events to study termination even in those who have discontinued study medication or the study.
Section 9.8.2 Per Protocol Population	If a patient is found to have taken a study medication for the entire duration of the study that is different from that to which he/she was randomized then the patient is counted in the treatment group of the drug he/she actually received.	If a patient is found to have taken a study medication for any ~~the entire~~ duration of the study that is different from that to which he/she was randomized, then the patient is counted in the treatment group of the drug he/she actually received.
Section 9.10 Subgroup Analyses	• Region (North/South America or Canada, Europe or South Africa, ROW)	• Region (North/South America or Canada, Europe or South Africa, Rest of world ~~ROW~~)
Section 10.3.1 Recording Adverse Events	SAEs will be recorded in the **Clinical Events or SAE eCRF** modules.	SAEs will be recorded in the **Clinical Events or SAE eCRF** modules as appropriate (see Table 1).
Section 10.3.1 Recording Adverse Events	In addition, non-serious adverse events of stress tests, severe hypoglycemia, diabetic eye disease, foot ulcer, microalbuminurea, proteinuria, hyperlipidemia/dyslipidemia, hypertension, and gout also will be recorded in the **Clinical Events eCRF** module (see Appendix I).	In addition, non-serious adverse events of percutaneous coronary intervention (PCI), stress tests, severe hypoglycemia, diabetic eye disease, foot ulcer, microalbuminuria, ~~proteinuria,~~ macroalbuminuria, hyperlipidemia/ dyslipidemia, hypertension, or ~~and~~ gout also will be recorded in the **Clinical Events eCRF** module (see Appendix 1).

SECTION	AMENDMENT 02 TEXT	AMENDMENT 03 TEXT
Section 10.3.1 Recording Adverse Events	**Note:** The events listed in Appendix 1 are Clinical Events that are trial endpoints or expected events for this population, and do not generally fit the definition of a SUSAR, including those events with an outcome of death. However, if the investigator's assessment of an event is that it meets SUSAR criteria despite being listed as a Clinical Event, the event may be reported as a SUSAR as long as it does not require adjudication. If the investigator feels that a Clinical Event meets SUSAR criteria the **SAE eCRF** should be used to report the event.	**Note:** The events listed in Appendix 1 are Clinical Events that are trial endpoints or expected events for this population, and do not generally fit the definition of a SUSAR, including those events with an outcome of death. However, if the investigator's assessment of an event is that it meets SUSAR criteria despite being listed as a Clinical Event, the event may be reported as a SUSAR via the **SAE eCRF** as long as it is not a **possible Primary or Secondary trial endpoint** (i.e. all events listed in Appendix 1 Section I). ~~If the investigator feels that a Clinical Event meets SUSAR criteria the **SAE eCRF** should be used to report the event.~~
Table 1		***Table format updated for clarity***
Section 10.3.2 Safety Reporting	**All SUSARS** will be reported in an expedited manner with the exception of those fulfilling the criterion of an efficacy endpoint (as detailed in Section I of Appendix 1: Primary or Secondary Trial Endpoints) which will be handled as Clinical Events.	**All SUSARS** will be reported in an expedited manner with the exception of Primary and Secondary trial endpoints as detailed in Section I of Appendix 1, which will be handled as Clinical Events. ~~fulfilling the criterion of an efficacy endpoint (as detailed in Section I of Appendix 1: Primary or Secondary Trial Endpoints) which will be handled as Clinical Events.~~
Section 10.4 Calcitonin Monitoring	If a concerning calcitonin value (≥50 ng/L) is identified during trial follow-up, the site investigator will be notified and will alert the usual care physician and study medication will be discontinued.	If a concerning calcitonin value (≥50 ng/L) is identified during trial follow-up, the site investigator will be notified and they should call the Trial Hotline for advice, where they will be instructed to alert the usual care provider and permanently discontinue study medication. ~~and will alert the usual care physician and study medication will be discontinued.~~
Section 10.5.1 Definition of an Overdose for This Protocol	The patient should be instructed to contact the investigational site, and/or healthcare provider in the event of an overdose 1 day of the trial site becoming aware of the event.	The patient should be instructed to contact the investigational site, and/or healthcare provider in the event of an overdose ~~1 day of the trial site becoming aware of the event~~.
Section 13 Disclosure of Data and Publications	The Executive Committee, which includes principal investigators, Sponsor representatives, academic cardiologists and academic endocrinologists, will draft the manuscript describing the main study results, and oversee publications requiring trial data, samples, or genetic material.	The Executive Committee~~, which includes principal investigators, Sponsor representatives, academic cardiologists and academic endocrinologists,~~ will draft the manuscript describing the main study results, and oversee publications requiring trial data, samples, or genetic material.
Appendix 1	**CLINICAL EVENTS LIST (TO BE RECORDED IN THE CLINICAL EVENTS eCRF)**	**CLINICAL EVENTS LIST ~~(TO BE RECORDED IN THE CLINICAL EVENTS eCRF)~~** Any clinical event listed in this appendix that meets the criteria of an SAE (unless indicated otherwise below) must be reported in the Clinical Event eCRF reporting module.

SECTION	AMENDMENT 02 TEXT	AMENDMENT 03 TEXT
Appendix 1	Percutaneous Coronary Intervention (PCI)	Percutaneous Coronary Intervention (PCI) – including non-serious events
Appendix 1	C. Severe hypoglycemia / Hyperglycemia /Diabetic ketoacidosis / Hyperosmolar hyperglycemic nonketotic coma	C. Severe hypoglycemia (including non-serious events) / Hyperglycemia /Diabetic ketoacidosis / Hyperosmolar hyperglycemic nonketotic coma
Appendix 1	F. Diabetic nephropathy (including non-serious events) • Microalbuminuria • Proteinuria	F. Diabetic nephropathy (including non-serious events) • Microalbuminuria • Macroalbuminuria ~~Proteinuria~~
Appendix 1	G. Renal failure/peritoneal or hemodialysis/renal transplant (including creation of fistula or other vascular access for hemodialysis)	G. Renal failure~~/peritoneal or hemodialysis/renal transplant (including creation of fistula or other vascular access for hemodialysis)~~ • Acute renal failure, requiring or associated with hospitalization • Chronic renal failure, requiring peritoneal hemodialysis, including creation of fistula or other vascular access for hemodialysis • Renal transplant
Appendix 2	[5] Patients who terminate study medication are required to have a Drug Termination Visit as soon as possible following the cessation of study medication. Patients will continue to be observed following the Drug Termination visit according to their planned visit schedule for the remainder of the trial. All procedures for remaining Semi-annual and Annual Visits are to be followed with the exception of Drug Dispensation.	[5] Patients who terminate study medication are required to have a Drug Termination Visit as part of their next scheduled study visit (unless a separate drug termination visit at that point is deemed necessary by the investigator). ~~as soon as possible following the cessation of study medication.~~ Patients will continue to be observed following the Drug Termination visit according to their planned visit schedule for the remainder of the trial. All procedures for remaining Semi-annual and Annual Visits are to be followed with the exception of Drug Dispensation.
Appendix 2	*None*	[6] It is recommended that serum creatinine value draw dates be within 3 months of randomization but up to 12 months is acceptable (however, if > 6 months old and value is between 30-40mL/min/1.73m^2 it is recommended that a new serum creatinine value is obtained as part of usual care).
Appendix 2	*None*	[7] Blood sample for genetic and genomic analysis may be collected at any time during the trial after consent is obtained.
Appendix 4	*None*	*Added Protocol Amendment 02 Summary of Changes*

APPENDIX 6 PROTOCOL AMENDMENT 04: SUMMARY OF CHANGES

Exenatide QW Clinical Study Protocol BCB109

PROTOCOL TITLE: A RANDOMIZED, PLACEBO CONTROLLED CLINICAL TRIAL TO EVALUATE CARDIOVASCULAR OUTCOMES AFTER TREATMENT WITH EXENATIDE ONCE WEEKLY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Protocol Number: BCB109

Amendment Number: 04

Amendment Purpose: Date: 12 September 2012

The purpose of Amendment 04 is to change the sponsorship to include only Amylin Pharmaceuticals, LLC. In addition, minor changes have been included in the safety section to clarify reporting of serious adverse events, given the change in sponsorship. Notable changes are detailed in the table below.

SECTION	AMENDMENT 03 TEXT	AMENDMENT 04 TEXT
Global Change	Amylin Pharmaceuticals, Inc.	Amylin Pharmaceuticals, LLC
Title Page	Eli Lilly and Company	
Title Page	Throughout this protocol, unless otherwise specified, the term "Lilly" is used to refer to Eli Lilly and Company and its affiliates, acting as a representative of Amylin Pharmaceuticals, Inc. Amylin Pharmaceuticals, Inc. sponsors the Investigational New Drug Application in the US and Puerto Rico and will serve as the sponsor for the Clinical Trial Application in Canada. Amylin Pharmaceuticals, Inc. transfers the clinical sponsor obligations to Lilly for the conduct of this study outside the US, Puerto Rico and Canada. For investigative sites outside of the US, Puerto Rico and Canada, Lilly will serve as the study sponsor. The applicable party will hereinafter be referred to as the "sponsor".	Amylin Pharmaceuticals, LLC sponsors the Investigational New Drug Application.
List of Abbreviations	Alliance Amylin/Lilly exenatide consortium Amylin Amylin Pharmaceuticals, Inc.	Amylin Amylin Pharmaceuticals, LLC
Section 3 Trial Governance	The EC will consist of approximately eleven individuals, comprising nine senior independent academic representatives who are experts in their field and two sponsor representatives.	The EC will consist of approximately eleven individuals, comprising nine senior independent academic representatives who are experts in their field and sponsor representatives.
Section 3 Trial Governance	EXSCEL will be Co-Chaired by Professors Robert Califf (Cardiologist) and Rury Holman (Endocrinologist) but sponsored and funded by Amylin on behalf of the Alliance (Amylin & Eli Lilly).	EXSCEL will be Co-Chaired by Professors Robert Califf (Cardiologist) and Rury Holman (Endocrinologist) but sponsored and funded by Amylin.
Section 5.2 Exclusion Criteria	o. Is an employee of Eli Lilly and Company or Amylin Pharmaceuticals	o. Is an employee of Amylin Pharmaceuticals, LLC

SECTION	AMENDMENT 03 TEXT	AMENDMENT 04 TEXT
Section 10.3.2 Safety Reporting	These events must be recorded in this module (or faxed to Lilly if EDC is unavailable) within **24 hours** of a trial site becoming aware of the event.	These events must be recorded in this module (or faxed to the number provided on the SAE report form if EDC is unavailable) within **24 hours** of a trial site becoming aware of the event.
Section 10.3.2 Safety Reporting	Additionally, any SAE considered by an investigator who is a qualified physician to be possibly, probably, or definitely related to the investigational product that is brought to the attention of the investigator after study closeout must be reported within the above timeline to Amylin/Eli Lilly.	Additionally, any SAE considered by an investigator who is a qualified physician to be possibly, probably, or definitely related to the investigational product that is brought to the attention of the investigator after study closeout must be reported within the above timeline.
Section 10.6 Reporting of Pregnancy	All occurrences of pregnancy must be reported via the Lilly Pregnancy/Breastfeeding Exposure Form.	All occurrences of pregnancy must be reported via the Pregnancy/Breastfeeding Exposure Form.
Appendix 5	*None*	*Added Protocol Amendment 03 Summary of Changes*

APPENDIX 7 PROTOCOL AMENDMENT 05: SUMMARY OF CHANGES

Exenatide QW Clinical Study Protocol BCB109

PROTOCOL TITLE: A RANDOMIZED, PLACEBO CONTROLLED CLINICAL TRIAL TO EVALUATE CARDIOVASCULAR OUTCOMES AFTER TREATMENT WITH EXENATIDE ONCE WEEKLY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Protocol Number: BCB109

Amendment Number: 05

Amendment Purpose: **Date: 25 October 2013**

Based on blinded review of accrued data, the event rate for the primary composite CV endpoint is approximately 2.2 per 100 patient-year, which is less than the anticipated rate of 3.8 per 100 patient-year. To achieve completion of the study within the commitment date of the FDA Post-Marketing Request, a number of measures will be taken in protocol amendment 05:

1. The power of the study to achieve the primary objective of superiority of exenatide once weekly versus placebo with regard to the primary composite CV endpoint has been reduced from 90% to 85% resulting in a reduction of the targeted number of events from 1591 to 1360.

2. The total number of patients to be enrolled in order to achieve the targeted number of events is being increased from 9500 to 14000.

3. The proportion of patients enrolled with a prior history of a CV event is being increased from 60% to 80% (for newly enrolled patients). Since more than 7000 patients have been enrolled under the 60:40 scheme, it is anticipated that the ratio of patients with prior history of CV event to those with no prior CV event will be approximately 70:30 at study end. It is anticipated that more than 4000 patients (around 30%) without any prior CV history will be enrolled in the study.

In addition, the following changes are being made throughout this protocol amendment:

4. The secondary hypothesis of non-inferiority of exenatide once weekly compared with placebo with regard to the primary composite CV endpoint is updated to a primary safety hypothesis.

5. The end of study procedures have been clarified.

6. Clarifications have been made to the specifications around withdrawal of consent, lost-to-follow-up procedures, and the follow-up phone call for safety purposes after end-of-study discontinuation of study treatment.

7. Update to planned interim analyses as specified in the DSMB charter.

8. Administrative changes, such as, requirements for reporting of a potential serious breach of GCP, record retention, source documentation, case report form completion and the Clinical Study Report have been made.

Notable changes are detailed in the table below.

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
Throughout	Trial / Early Termination Visit	Trial Termination Visit
1.2 Rationale for Conduct of the Study	Exenatide once weekly (EQW), a new formulation of exenatide that is administered once weekly rather than twice daily, has been approved by the US FDA as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and in the European Union as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea but have not achieved adequate glycemic control.	Exenatide once weekly (EQW; BYDUREON), is an extended release formulation of exenatide that is administered once weekly rather than twice daily. EQW has been approved by the US FDA as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and in the European Union as an adjunct to metformin, a sulfonylurea (SU), a thiazolidinedione (TZD), a combination of metformin and SU, or a combination of metformin and TZD therapy to improve glycemic control in adult patients with type 2 diabetes mellitus.
2.1 Primary Objective	The primary objective of EXSCEL will be to evaluate the effect of EQW, used in conjunction with the current usual care for glycemic control, on major macrovascular events when administered to patients with type 2 diabetes. Objective: To compare the impact of including EQW as part of usual care vs. usual care without exenatide on major CV outcomes as measured by the primary CV composite endpoint of CV related death, nonfatal myocardial infarction (MI), or nonfatal stroke. Hypothesis: EQW, when used as part of usual care, is superior to usual care without exenatide with regard to the risk of developing a confirmed event in the primary CV composite endpoint.	The primary objective of EXSCEL will be to evaluate the effect of EQW, used in addition to the current usual care for glycemic control, on major macrovascular events when administered to patients with type 2 diabetes. Objective: To compare the impact of including EQW in addition to usual care vs. usual care without EQW on major CV outcomes as measured by the primary CV composite endpoint of CV related death, nonfatal myocardial infarction (MI), or nonfatal stroke. Hypotheses: Efficacy: EQW, when used in addition to usual care, is superior to usual care without EQW with regard to the risk of developing a confirmed event in the primary CV composite endpoint. Safety: EQW, when used in addition to usual care, is non-inferior to usual care without EQW with regard to the risk of developing a confirmed event in the primary CV composite endpoint.
2.2 Secondary Objectives	The secondary objectives of EXSCEL are to evaluate the effect of EQW treatment used in conjunction with the current usual care for glycemic control on:	The secondary objectives of EXSCEL are to evaluate the effect of EQW treatment used in addition to the current usual care for glycemic control on:
2.3 Additional Objectives	Additional objectives of EXSCEL are to evaluate the effect of EQW treatment used in conjunction with the current usual care for glycemic control on:	Additional objectives of EXSCEL are to evaluate the effect of EQW treatment used in addition to the current usual care for glycemic control on:

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
3 Trial Governance	EXSCEL is a multinational pragmatic trial that will be conducted in approximately 500 sites worldwide. It will be run jointly by the Duke Clinical Research Institute (DCRI) and the University of Oxford Diabetes Trials Unit (DTU) Academic Research Organizations (AROs), in an academic collaboration with Amylin Pharmaceuticals, LLC (Amylin). EXSCEL will be Co Chaired by Professors Robert Califf (Cardiologist) and Rury Holman (Endocrinologist) but sponsored and funded by Amylin.	EXSCEL is a multinational pragmatic trial that will be conducted in approximately 800 sites worldwide. It will be run jointly by the Duke Clinical Research Institute (DCRI) and the University of Oxford Diabetes Trials Unit (DTU) Academic Research Organizations (AROs), in an academic collaboration with Amylin Pharmaceuticals, LLC (Amylin), a wholly owned subsidiary of Bristol-Myers Squibb. EXSCEL will be Co Chaired by Professors Robert Califf (Cardiologist) and Rury Holman (Endocrinologist) and sponsored and funded by Amylin.
	The EXSCEL Executive Committee (EC) will have overall responsibility for the oversight and management of the trial (Figure 1). The EC will consist of approximately eleven individuals, comprising nine senior independent academic representatives who are experts in their field and two sponsor representatives. It will be Co-Chaired by Professors Robert Califf and Rury Holman with other academic members comprising four further diabetologists and three further cardiologists. Geographical balance will be sought. Decision making will be by consensus.	The EXSCEL Executive Committee (EC) will have overall responsibility for the oversight and management of the trial (Figure 1). The EC will consist of senior independent academic representatives who are experts in their field and sponsor representatives. It will be Co-Chaired by Professors Robert Califf and Rury Holman (see Section 12.1).

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
4.1 Design Description	EXSCEL will be a multinational, placebo-controlled, double-blind, randomized, parallel group pragmatic clinical trial. Eligible patients will have type 2 diabetes with an HbA1c ≥6.5% and ≤10.0 % on up to three (i.e., 0-3) oral AHAs or insulin either alone or in combination with up to 2 (i.e., 0-2) oral AHAs. Patients enrolled will be at a wide range of CV risk with approximately 60% having had a prior CV event. Approximately 9500 patients meeting all enrollment criteria will be recruited in to the trial over an approximately three year period, randomly allocated to treatment with either EQW 2 mg or matching placebo subcutaneous injections once weekly in a 1:1 ratio, and followed up for a minimum of four years. The trial will continue until adjudicated 1591 primary endpoint events have been accrued, or until the independent Data Safety Monitoring Board (DSMB) advises otherwise. The trial will assess the impact of EQW therapy upon CV outcomes in a large population from a heterogeneous group of countries and practice environments. Approximately one-third of patients will be enrolled in the Americas (North/South America & Canada), one-third in Europe and one-third in the Asia/Australasia. Given that this population will be at elevated CV risk, it is anticipated that patients will see their usual care provider at least twice per year for routine care. Trial follow up will consist of a blend of trial visits and phone calls during the double-blind placebo-controlled treatment period, which is expected to provide an average 5.5 patient years of follow up.	EXSCEL will be a multinational, placebo-controlled, double-blind, randomized, parallel group pragmatic clinical trial. Eligible patients will have type 2 diabetes with an HbA1c ≥6.5% and ≤10.0 % on up to three (i.e., 0-3) oral antihyperglycemic agents (AHAs) or insulin either alone or in combination with up to 2 (i.e., 0-2) oral AHAs. Patients enrolled will be at a wide range of CV risk with approximately 70% having had a prior CV event (see Section 6.3). Approximately 14,000 patients meeting all enrollment criteria will be recruited in to the trial over approximately a five year period, randomly allocated to treatment with either EQW 2 mg or matching placebo subcutaneous injections once weekly in a 1:1 ratio, and followed until the requisite number of primary endpoint events have been reported. The trial is planned to continue until 1360 patients with positively adjudicated primary endpoint events have been accrued, or until the independent Data Safety Monitoring Board (DSMB) advises otherwise. It is anticipated that the EXSCEL Executive Committee will monitor the accrual of the aggregate number of adjudicated primary endpoint events and will determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued); all patients will be expected to have follow-up through this date (Section 6). The trial will assess the impact of EQW therapy upon CV outcomes in a large population from a heterogeneous group of countries and practice environments; patients will be enrolled in the Americas (North/South America), Europe and Asia/Australasia. Given that this population will be at elevated CV risk, it is anticipated that patients will see their usual care provider at least twice per year for routine care. Trial follow up will consist of a blend of trial visits and phone calls during the double-blind placebo-controlled treatment period.

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
4.2 Trial Duration	Minimum follow up for the last patient randomized will be 4 years unless the trial is terminated earlier. All patients that discontinue study medication, but have not withdrawn consent to participate in the study, will be followed up if possible, for the full study period and will have their vital status ascertained, if possible, at the end of the trial.	It is anticipated that enrollment will occur over approximately a five year period, and that an additional 2 to 3 years may be required to accumulate the requisite number of patients with positively adjudicated primary endpoint events, for a total duration of up to approximately 7.5 years, unless the trial is terminated earlier. All patients who discontinue study medication, but have not withdrawn consent to participate in the study, will be followed up, if possible, for the full study period and will have their vital status ascertained, if possible, as of the data cut-off date for primary endpoint events.
4.3 Post Trial Access to Therapy	New Section in Amendment 05	At the end of the trial, the sponsor will not continue to supply study drug to patients/investigators. The investigator should ensure that the patient receives appropriate standard of care to treat the condition under study according to national treatment guidelines.
5.1 Inclusion Criteria	d. Patients with any level of CV risk and meeting all other inclusion criteria may be enrolled. Recruitment will be constrained such that approximately 40% will not have had a prior CV event and 60% will have had a prior CV event	d. Patients with any level of CV risk and meeting all other inclusion criteria may be enrolled. Recruitment will be constrained (see Section 6.3) such that approximately 30% will not have had a prior CV event and 70% will have had a prior CV event
5.2 Exclusion Criteria	c. Patient has ever been treated with an approved or investigational GLP-1 receptor agonist e.g., BYETTA (exenatide), EQW, VICTOZA (liraglutide),or taspoglutide o. Is an employee of Amylin Pharmaceuticals, LLC.	c. Patient has ever been treated with an approved or investigational GLP-1 receptor agonist e.g., BYETTA (exenatide), BYDUREON (EQW), VICTOZA (liraglutide), LYXUMIA (lixisenatide), albiglutide, taspoglutide, or dulaglutide o. Is an employee of Amylin Pharmaceuticals, LLC, Bristol-Myers Squibb Company, or AstraZeneca
5 Trial Population	New addition in Amendment 05	Eligibility criteria for this study have been carefully considered to ensure the safety of the study patients and that the results of the study can be used. It is imperative that patients fully meet all eligibility criteria.

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
6.1 Trial Procedures - Overview	New addition in Amendment 05	The trial is planned to continue until 1360 patients with positively adjudicated primary endpoint events have been accrued. It is anticipated that the EXSCEL Executive Committee will monitor the accrual of the aggregate number of adjudicated primary endpoint events and will determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued; all patients will be expected to have follow-up through this date). Based on the primary endpoint event cut-off date, a window of time for conduct of the Trial Termination Visit will be established. NOTE: Patients who have temporarily or permanently discontinued trial medication should continue with their regular visit schedule. ALL patients should have a Trial Termination Visit (including patients who have previously discontinued trial medication). After the Trial Termination Visit patients will be contacted by telephone to check for any serious adverse experiences and hospitalizations that occurred within 70 days after the administration of the last dose of trial medication. Patients who have discontinued trial medication 70 or more days prior to the Trial Termination Visit will not need to have the telephone contact visit performed. These patients will have their final assessment of serious adverse experiences and hospitalizations completed at the Trial Termination Visit. Note that all serious adverse experiences, hospitalizations, and reportable study events with an onset date after the primary endpoint event cut-off date established by the study Executive Committee will be managed as serious adverse experiences (see Section 10.3.1).
6.3 Method of Assigning Patients to Treatment Groups (Visit 1)	New addition in Amendment 05	The IVRS will be programmed to ensure the expected overall proportion of randomized patients with a prior CV event is approximately 70%. With transition to Amylin-labeled trial medication (beginning in 2013), the IVRS was programmed to ensure at least 80% of newly randomized patients have a history of a prior CV event (previously was programmed to ensure approximately 60% of patients had a prior CV event).

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
6.5 Concomitant Therapy	During the double-blind treatment period, investigators are expected to monitor patients' AHA regimens and communicate with usual care providers, who will be responsible for adjusting the AHA regimen in order to achieve locally-appropriate HbA1c goals. The Executive Committee (EC) and Operations Committee (OC) will provide a brief list of guidelines for usual care based on clinical care practice guidelines published by national and international societies that will be updated as knowledge about T2DM evolves over the course of the trial.	During the double-blind treatment period, investigators are expected to monitor patients' AHA regimens and communicate with usual care providers, who will be responsible for adjusting the AHA regimen in order to achieve locally-appropriate HbA1c goals based on clinical care practice guidelines published by national and international societies.
6.5 Concomitant Therapy	In addition, the degree of locally-appropriate HbA1c goal-attainment at each site will be monitored centrally and sites with unusually low goal attainment will be advised accordingly.	~~In addition, the degree of locally-appropriate HbA1c goal-attainment at each site will be monitored centrally and sites with unusually low goal attainment will be advised accordingly.~~
6.6 Precautions to Minimize Rates of Hypoglycemia	The EXSCEL study team will also provide investigators with training materials to demonstrate best practice for minimizing hypoglycemia risk in these patients.	~~The EXSCEL study team will also provide investigators with training materials to demonstrate best practice for minimizing hypoglycemia risk in these patients.~~
6.9 Genetic and Biomarker Sample Collection	Patients enrolled in the trial will be asked to consent separately to provide one serum sample, one plasma sample, and one urine sample for future biomarker analyses. These specimens (preferably fasting) will be obtained at baseline (prior to drug exposure), annually and trial/early termination. All samples will be divided and stored in 2 aliquots at the Laboratory Corporation of America facility in Kannapolis, North Carolina, USA.	In addition, a subset of patients enrolled in the trial will be asked to consent separately to provide one serum sample, one plasma sample, and one urine sample for future biomarker analyses. These specimens (preferably fasting) will be obtained at baseline (prior to drug exposure), year 1 and at the Trial Termination visit.

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
6.11 Temporary or Permanent Discontinuation of Trial Medication	Amendment 04 Section 6.12 Temporary Discontinuation of Trial Medication, Section 6.13 Permanent Discontinuation of Trial Medication Visit Procedures, and Section 6.15 Follow-up for Patients who Permanently Discontinue Trial Medication, were combined in Amendment 05 Section 6.11	Following randomization, it is expected that patients will remain on study medication for the duration of trial participation. However, it is recognized that patients may need to discontinue trial medication, in some cases permanently, for when protocol-specified reasons apply (Section 6.12), due to the judgment of the primary investigator or the decision of the patient. The Trial Hotline should be contacted whenever a site is considering interrupting or discontinuing trial medication (Section 6.18). Unless resumption of trial medication is considered unsafe or is refused by the patient, the patient will be expected to resume regular use of the blinded trial medication after a period of temporary discontinuation. Should a patient stop taking trial medication, either permanently or temporarily, the reasons for discontinuation and length of time the patient stopped taking trial medication will be assessed and recorded. All randomized patients who permanently discontinue trial medication should have a drug termination visit as part of their next scheduled study visit (unless a separate drug termination visit at that point is deemed necessary by the investigator). Necessary procedures are indicated in Appendix 2. All efforts should be made to reinforce with patients that this would be a medication discontinuation visit, not a trial discontinuation visit; patients should continue with their regular visit schedule until the end of the trial, including semi-annual in-person visits, as well as the annual calcitonin measurement. If patients cannot attend visits in person, they will be followed via telephone contact for all subsequent visits. NOTE: After trial medication is discontinued due to pregnancy, re-initiation of study medication can be considered following completion of the pregnancy and breastfeeding (if applicable).
6.12 Permanent Discontinuation of Trial Medication Per Protocol	Note: The patient and the Investigator will notify the usual care provider of severe hypoglycemic events. The usual care provider should make a thorough attempt to down-titrate and/or modify co-interventional and baseline therapies that may contribute to hypoglycemia before discontinuing blinded trial medication for hypoglycemia. The usual care provider will be provided with standard guidance by the trial investigator on down-titrating AHAs in the presence of hypoglycemia.	Note: The patient and the Investigator will notify the usual care provider of severe hypoglycemic events. The usual care provider should make a thorough attempt to down-titrate and/or modify co-interventional and baseline therapies that may contribute to hypoglycemia before discontinuing blinded trial medication for hypoglycemia.

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
6.13 Trial Termination Visit 6.14 Post-Treatment Telephone Contact	Amendment 04 Section 6.11 Trial/Early Termination Visit and Post-Trial Telephone Contact was separated into sections 6.13 and 6.14 in Amendment 05. In addition, the timing of the post-treatment telephone contact was modified from 90 days to 70 days after the administration of the last dose of trial medication, if applicable.	6.13 Trial Termination Visit Investigators will be informed by the DCRI and DTU Coordinating Centers as to when the Trial Termination Visit is to be completed, and will schedule all patients for the Trial Termination Visit. Based on the primary endpoint event cut-off date, a window of time for conduct of the Trial Termination Visits will be established; this window will be a period of time following the primary endpoint event cut-off date. At the Trial Termination Visit, all patients must be discontinued from trial medication; the investigator should ensure that the patient receives appropriate standard of care. For procedural details of the Trial Termination Visit, refer to Appendix 2. NOTE: All patients should have a Trial Termination Visit. (Patients who have discontinued trial medication prior to the end of the trial must, at minimum, have a Trial Termination telephone contact.) If a patient fails to return or otherwise becomes difficult to contact, it is the investigator's responsibility to make every effort to maintain contact so that at the end of the trial the patient can be located to determine status and to obtain necessary information for serious adverse experience reporting and/or endpoint adjudication as of the primary endpoint event cut-off date. 6.14 Post-Treatment Telephone Contact After the Trial Termination Visit, patients will be contacted by telephone to check for any serious adverse experiences and hospitalizations that occurred within 70 days after the administration of the last dose of trial medication. For patients who have been discontinued from trial medication for more than 70 days as of the Trial Termination Visit, the Trial Termination Visit will be the final study follow-up. Note that all serious adverse experiences, hospitalizations, and reportable study events with an onset date after the primary endpoint event cut-off date established by the study Executive Committee will be managed as serious adverse experiences (see Section 10.3.1).

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
6.15 Withdrawal of Consent	New Section in Amendment 05	Patients who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a patient explicitly withdraws consent for any further contact with him/her or persons previously authorized by patient to provide this information. Patients should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator and entered on the appropriate eCRF page. In the event that vital status (whether the patient is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law. When a patient withdraws consent from future follow-up prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at that time (Section 6.13).

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
6.16 Lost to Follow-Up	New Section in Amendment 05	All reasonable efforts must be made to locate patients to determine and report their ongoing status. This includes follow-up with persons authorized by the patient as noted above as well as the usual care provider. Lost to follow-up is defined by the inability to reach the patient after a minimum of three documented phone calls, as well as lack of response by patient to one registered mail letter. All attempts should be documented in the patient's medical records. If it is determined that the patient has died, the site will use permissible local methods to obtain the date and cause of death. If an investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the patient's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining patient's contact information or other public vital status data necessary to complete the follow-up portion of the study. Where specific consent has been obtained from the participant, the site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the patient remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the patient's medical records.
6.17 Breaking the Blind AND 10.7 Unblinding	New addition in Amendment 05	Patients whose treatment has been unblinded can continue to receive trial medication and can continue to be followed in the trial as described in this protocol.
8 Efficacy Assessments	Trial endpoints will be defined based on clinical standards, regulatory precedent, and historical trials. These definitions will be provided in a separate document, along with the description of the Clinical Events Classification Committee (CEC). Patients will be asked at each trial visit about procedures and hospitalizations which have taken place since they were last seen.	Trial endpoints will be defined based on clinical standards, regulatory precedent, and historical trials. The definitions of the events to be adjudicated by the Clinical Events Classification Committee (CEC) and the committee procedures will be included in the CEC Charter (Section 12.4). Patients will be asked at each trial visit about procedures and hospitalizations which have taken place since they were last seen.
8.2 Secondary Efficacy Endpoints	Time to first confirmed CV event for each component of the primary composite endpoint Defined as time from randomization to a confirmed CV-related death, nonfatal MI or nonfatal stroke.	Time to first confirmed CV event for each component of the primary composite endpoint Defined as time from randomization to a confirmed CV-related death, fatal or nonfatal MI, or fatal or nonfatal stroke.

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
8.2 Secondary Efficacy Endpoints	Time to hospitalization for heart failure Defined as time from randomization to hospital admission for congestive heart failure requiring treatment with intravenous diuretics, inotropes, or vasodilator therapy.	Time to hospitalization for heart failure Defined as time from randomization to hospital admission for congestive heart failure requiring treatment with increased oral or intravenous diuretics, inotropes, or vasodilator therapy.
9.2 Sample Size	The planned sample size for this study is 9500 patients, randomized 1:1 to each of the two treatment arms assuming: • An annual composite cardiovascular primary endpoint event rate estimated to be 3.8% per year for the population to be enrolled. • A planned accrual period of 3 years • A minimum treatment period of 4 years • An estimated annual lost-to-follow up rate of 1% • An anticipated treatment discontinuation rate of 5% per year The number of cardiovascular primary endpoint events required is commensurate with a 90% power to detect a 15% relative risk decrease in the EQW group, i.e. a true hazard ratio of 0.85 relative to placebo, with a two-sided alpha=0.05. For an exponential maximum likelihood test of equality of survival curves, a total of 1591 composite cardiovascular events were calculated to be required using nQuery.	The primary endpoint is the time from randomization to the first confirmed CV event defined as a CV-related death, nonfatal MI or nonfatal stroke. The study is designed to assess the primary efficacy objective of superiority of EQW to placebo through the following hypothesis: H0: upper limit of the 95% CI of the HR [exenatide:placebo] ≥ 1 versus H1: upper limit of the 95% CI of the HR [exenatide:placebo] < 1 In order to test the above hypothesis with 85% power and 2-sided α=0.05, a total number of 1360 composite CV events are required assuming a risk reduction of 15% on EQW compared with placebo. With this number of events, the power will be much larger than 90% to assess the primary safety objective of non-inferiority of EQW compared with placebo. In addition, with the following assumptions made for this study, • An annual composite cardiovascular primary endpoint event rate estimated to be around 2.2% per year for the population to be enrolled • A planned accrual period of 5-6 years • An estimated annual lost-to-follow up rate of 1% • An anticipated treatment discontinuation rate of 5% per year it is expected that a total of 14000 patients need to be randomized in a 1:1 ratio into EQW and placebo to achieve the targeted 1360 confirmed composite CV events.

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
9.4 Primary Hypothesis	The primary hypothesis is that EQW will be superior to placebo with respect to the primary composite cardiovascular outcome, with the participants analyzed according to their allocated treatment (intention to treat).	The primary efficacy hypothesis is that EQW will be superior to placebo with respect to the primary composite cardiovascular endpoint, defined as the time from randomization to the first confirmed CV-related death, nonfatal MI or nonfatal stroke with the patients analyzed as randomized. The primary safety hypothesis is that EQW will be non-inferior to placebo with respect to the primary composite cardiovascular endpoint, with patients analyzed as randomized.
Secondary Hypothesis	This section (9.5) from Amendment 04 was deleted	Not applicable

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
9.5 Primary Analysis	Statistical analyses will be based upon adjudicated outcomes with patients who discontinue prematurely from treatment followed until the end of the study, i.e. until the requisite number of primary composite events has been accrued. Analysis of the primary composite cardiovascular outcome will be based on the time from randomization to the occurrence of the first event, with participants analyzed according to their allocated treatment (intention to treat). A log rank test will be performed first, with Kaplan-Meier curves for time to event used to depict the accumulation of events over time for the EQW and placebo treatment groups. The hazard ratio for the time of occurrence of the composite endpoint for the EQW and placebo treated groups and its 95% confidence interval will then be estimated using a Cox proportional hazards model without covariate adjustment. Secondary Cox proportional hazards model analyses using covariate adjustments will also be performed as detailed in the SAP.	The primary statistical analysis will be based upon adjudicated CV events with patients who discontinue prematurely from treatment followed until the end of the study, i.e. until the requisite number of primary composite events has been accrued. It is anticipated that the Executive Committee will monitor the accrual of the aggregate number of primary composite CV events to determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued). All patients will be expected to have follow-up through this date. Analysis of the primary composite cardiovascular outcome will be based on the time from randomization to the occurrence of the first event, with patients analyzed according to their randomized treatment. The primary analysis will include all adjudicated CV events with onset dates up to and including the primary endpoint event cut-off date. Kaplan-Meier curves for time to the first occurrence of a primary composite endpoint event will be used to depict the accumulation of events over time for the EQW and placebo treatment groups. The hazard ratio for the time to first occurrence of the primary composite endpoint event for the EQW treated group to that of the placebo treated group and its 95% confidence interval will then be estimated using a Cox proportional hazards model stratified by baseline CV risk group (prior CV event or no prior CV event) and using treatment group as covariate. The primary safety hypothesis will be assessed by a non-inferiority analysis with the non-inferiority margin of 1.30, i.e., non-inferiority will be concluded if the upper limit of the confidence interval is less than 1.30. The primary efficacy hypothesis of superiority will be then assessed by the 95% confidence interval for the hazard ratio of EQW to placebo, i.e., superiority will be concluded if the 95% confidence interval does not include 1 (upper limit of 95% confidence interval < 1).

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
9.6 Secondary Efficacy Analyses	Secondary analyses will be conducted with participants analyzed according to their allocated treatment (intention to treat) with a Hochberg adjustment for multiple testing. These analyses will examine: 1. All cause mortality 2. Fatal or nonfatal myocardial infarction 3. Fatal or nonfatal stroke 4. Hospitalization for acute coronary syndrome (ACS) 5. Hospitalization for congestive heart failure (CHF)	The secondary efficacy endpoints are the time to confirmed occurrence of: 1. All cause mortality 2. CV-related death 3. Fatal or nonfatal myocardial infarction 4. Fatal or nonfatal stroke 5. Hospitalization for acute coronary syndrome (ACS) 6. Hospitalization for congestive heart failure (CHF) Details of the testing strategy of the secondary efficacy endpoints will be provided in the Statistical Analysis Plan (SAP).
9.7.1 Intent-To-Treat Population	The ITT population consists of all randomized patients. Evaluation will include all events which occurred from randomization to the date of final post-study telephone contact, regardless of the time interval between patient discontinuation of study drug and final contact. Patients who do not have any events during the study will be censored at the date of their final post-study telephone contact. Every effort will be made to collect CV events to study termination even in those who have discontinued study medication or the study. For the ITT population, any patient found to have taken a study medication for the entire duration of the study that is different from that to which he/she was randomized will be counted in the treatment group of the drug to which he/she was randomized.	The ITT population consists of all randomized patients. Evaluation will include all events which occurred from randomization to the primary endpoint event cut-off date, regardless of the time interval between patient discontinuation of study drug and final contact. Patients who do not have any events during the study will be censored at the primary endpoint event cut-off date. Every effort will be made to collect CV events through the primary endpoint event cut-off date even in those who have discontinued study medication or the study. For the ITT population, patients will be analyzed as randomized.
9.7.1.1 On-Treatment Analysis	New addition in Amendment 05	An on-treatment analysis using the ITT population will be performed for the primary and secondary analyses as sensitivity analyses. This analysis will include only those events that occurred within 70 days of the last dose of study medication or the primary endpoint event cut-off date, whichever occurs first. The patients will be analyzed according to the treatment group to which they were randomized.

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
9.7.2 Per-Protocol Population	The Per-Protocol population consists of all randomized patients who have taken at least one dose of study medication and will include in their analysis all data collected prior to any major protocol violations such as: • Initiation of an open-label prohibited medication i.e. a GLP-1 receptor agonist. Evaluation will include all data up to the day of the initiation of the prohibited medication. • Discontinuation from study medication. Evaluation will include events which occurred from randomization to 90 days after the last dose of study medication. • Taking incorrect study medication for more than three months. All such protocol violations will be identified prior to unblinding of the data. Events that occurred after protocol violation will be excluded from the analysis. If a patient is found to have taken a study medication for any duration of the study that is different from that to which he/she was randomized, then the patient is counted in the treatment group of the drug he/she actually received. Patients who do not have any events during the study will be censored 90 days after the last dose of study medication.	The Per-Protocol population consists of all randomized patients who have taken at least one dose of study medication and will include in their analysis all data collected prior to any major protocol violations (or primary endpoint event cut-off date, whichever occurs first), such as: • Initiation of an open-label prohibited medication i.e. a GLP-1 receptor agonist. Evaluation will include all data up to the day of the initiation of the prohibited medication. • Early discontinuation from study medication. Evaluation will include events which occurred from randomization to 70 days after the last dose of study medication or the primary endpoint event cut-off date, whichever occurs first. • Taking incorrect study medication for more than three months. All protocol violations will be specified in the statistical analysis plan prior to unblinding of the data. Events that occurred after protocol violation will be excluded from the analysis. Patients will be analyzed as randomized. The primary safety and primary efficacy analyses will be repeated with the per-protocol population as sensitivity analyses.
9.7.3 Safety Population	Serious AEs, including those which lead to discontinuation of study medication, occurring between randomization and 90 days after the last dose of study medication, will be collected.	Serious AEs, including those which lead to discontinuation of study medication, occurring between randomization and 70 days after the last dose of study medication, will be summarized.
9.9 Subgroup Analyses	The subgroups will be divided by categories or by the tertiles for continuous variables.	~~The subgroups will be divided by categories or by the tertiles for continuous variables.~~

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
9.10 Interim Analyses	The DSMB will review available data every 6 months or more frequently if the committee deems it appropriate as outlined in the DSMB Charter. Stopping guidelines will be detailed in the DSMB Charter. The overall alpha=0.05 will be preserved by limiting the number of interim superiority analyses conducted as detailed in the DSMB Charter. The DSMB may, however, advise stopping the study before the minimum follow-up of 4 years has been achieved on ethical or safety grounds.	The DSMB will undertake safety reviews of all available data every 6 months or more frequently if the committee deems it appropriate. Two formal interim efficacy analyses are planned after approximately 453 and 906 primary composite CV events are adjudicated, corresponding to one-third and two-thirds, respectively, of the targeted 1360 primary composite CV events. The analyses will test for superiority using a Haybittle-Peto spending function where the study termination guideline for overwhelming superiority will be p-value < 0.0001 for the first interim analysis and p-value <0.001 for the second interim analysis. This will ensure a significance level of 0.0499 for the final analysis. If the stopping boundary for efficacy is met at either of the interim analyses, the DSMB may recommend terminating the study earlier than planned. The DSMB may, however, also advise terminating the study early for safety or ethical reasons. The interim analyses will be performed by an independent statistical group. Further details of the interim analyses are provided in the DSMB Charter.
10.2 Adverse Event Assessment	Adverse events will be monitored over the course of the trial, starting from the time of randomization and through the duration of the patient's participation, including the 90 day post trial medication follow-up period or withdrawal.	Adverse events will be monitored over the course of the trial, starting from the time of randomization and through the duration of the patient's participation, including the 70 day post trial medication follow-up period.
10.3.1 Recording Adverse Events	SAEs will be recorded in the Clinical Events or SAE eCRF modules as appropriate (see Table 1). Guidelines for events which qualify as Clinical Events are provided in Appendix 1. Events to be recorded in the Clinical Events eCRF module include SAEs that are: (1) components of the primary or secondary composite cardiovascular endpoints, (2) other trial endpoints, (3) potential components of the CV endpoint that are included among terms sent for review by the CEC; (4) expected sequelae of type 2 diabetes (Table 1). These events represent trial outcomes and expected events for this population.	SAEs will be recorded in the Clinical Events or SAE eCRF modules as appropriate (see Table 1) through the primary endpoint event cut-off date; ALL SAEs with onset dates AFTER the primary endpoint event cut-off date will be recorded in the SAE eCRF module. Guidelines for events which qualify as Clinical Events are provided in Appendix 1. Events to be recorded in the Clinical Events eCRF module include SAEs that are: (1) Obvious trial endpoints, (2) Cardiovascular Events of Interest, (3) Expected Events and Diabetic Complications.
Table 1: List of events to be recorded in each eCRF reporting module	SAE eCRF: Any event meeting the criteria of an SAE (see Section 10.1 for definition of SAE) that are not listed in Appendix 1	SAE eCRF: Any event meeting the criteria of an SAE (see Section 10.1 for definition of SAE) that are not listed in Appendix 1 and all events above with an onset date after the primary endpoint event cut-off date

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
10.3.2 Safety Reporting	As described above, all SAEs that are not included in the Clinical Events List will be recorded by the investigator in the SAE eCRF module.	As described above, all SAEs that are not included in the Clinical Events List and "Clinical Events" with onset dates after the primary endpoint event cut-off date will be recorded by the investigator in the SAE eCRF module.
10.3.2 Safety Reporting	New addition in Amendment 05	Note that pancreatitis and pancreatic neoplasms / malignancies are events of special interest for GLP-1 based therapies, such as exenatide. As described above, all events of pancreatitis and all neoplasms (including pancreatic cancer) are to be reported on both the Clinical Events eCRF and the SAE eCRF, even if the event does not meet seriousness criteria. These events are reviewed by the DSMB and adjudicated by the CEC.
10.6 Reporting of Pregnancy	Although not considered an adverse experience, it is the responsibility of investigators or their designees to report any pregnancy in a patient (spontaneously reported to them) which occurs during the trial or within 90 days of completing the trial.	Although not considered an adverse experience, it is the responsibility of investigators or their designees to report any pregnancy in a patient (spontaneously reported to them) which occurs during the trial or within 70 days of completing the trial.
11.3 Consent and Collection of Biomarker Specimens	Patients providing informed consent will have a blood and urine samples, preferably fasting, collected at baseline (prior to drug exposure), annually, and at the time of trial termination.	Patients providing informed consent will have blood and urine samples, preferably fasting, collected at baseline (prior to drug exposure), Year 1, and at the Trial Termination visit.
11.5 Ethical Conduct of the Study	New addition in Amendment 05	The investigator must notify the sponsor promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to the sponsor. All potential serious breaches must be reported to the sponsor immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the patients of the study or the scientific value of the study. Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
11.8 Records	New Section in Amendment 05	11.8.1 Records Retention The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact the sponsor prior to destroying any records associated with the study. The sponsor will notify the investigator when the study records are no longer needed. If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Notice of such transfer will be given in writing to the sponsor. 11.8.2 Case Report Forms An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study. The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs. The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections. Each individual electronically signing electronic CRFs must meet training requirements and must only access the electronic data capture tool using their unique user account. User accounts are not to be shared or reassigned to other individuals.

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
12.1 Executive Committee (EC)	The EC will be composed of approximately eleven individuals consisting of nine senior independent academic representatives who are experts in their field and two representatives from the Alliance. The Committee will be co-chaired by Professors Robert Califf (cardiologist) and Rury Holman (endocrinologist). The other academic members will comprise four further diabetologists and three further cardiologists. Geographical balance will be sought. Decision making will be by consensus. An EC charter will delineate operating procedures. The Executive Committee is the main decision-making body for EQW and is charged with the overall scientific, professional, and operational conduct of the trial.	The EC will be composed of senior independent academic representatives who are experts in their field and representatives from the sponsor. The Committee will be co-chaired by Professors Robert Califf (cardiologist) and Rury Holman (endocrinologist). An EC charter will outline the committee membership and structure and delineate operating procedures. The Executive Committee is the main decision-making body for the EXSCEL trial and is charged with the overall scientific, professional, and operational conduct of the trial.
12.3 Data Safety Monitoring Board (DSMB)	DTU will transfer pre-agreed masked datasets to the Independent Statistician who will then prepare unmasked confidential reports for the DSMB, using treatment codes provided in advance by the Sponsor. In addition, the DSMB will evaluate interim analyses of the data every six months (or on an ad hoc basis if needed) to determine if it believes either the trial should be terminated early because the exenatide arm (with respect to the placebo arm) demonstrates (a) clear inferiority, i.e., it is not in patient's best interest to continue taking blinded therapy; or (b) clear superiority, i.e., it is not in patient's best interest to continue taking blinded placebo.	DTU will transfer pre-agreed masked datasets to the Independent Statistician who will then prepare unmasked confidential reports for the DSMB, using treatment codes provided in advance by the IVRS vendor. In addition, the DSMB will evaluate two interim analyses after approximately one-third and two-thirds of the total targeted number of primary composite CV events (see Sec 9.10 for details).
13 Disclosure of Data, Publications, and Clinical Study Report	Following submission for publication of the main trial results, a copy of the database will be transferred to the Sponsor. New addition in Amendment 05:	~~Following submission for publication of the main trial results, a copy of the database will be transferred to the Sponsor.~~ In addition, a Clinical Study Report (CSR) will be prepared for regulatory purposes. The Signatory Investigator responsible for signing the CSR will be selected by the Sponsor in conjunction with the Executive Committee.
Appendix 1: Clinical Events List	List re-organized from: I. Primary or Secondary Trial Endpoints A. Obvious Trial Endpoints B. Cardiovascular Events of Interest II. Expected Events and Diabetic Complications	I. Obvious Trial Endpoints II. Cardiovascular Events of Interest III. Expected Events and Diabetic Complications

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
Appendix 1: Clinical Events List (Obvious Trial Endpoints)	Death • Cardiovascular (CV) Death (i.e., fatal myocardial infarction [MI]/cerebrovascular accident [CVA]/ congestive heart failure [CHF]/arrhythmia, cardiac arrest, death following CV intervention)	Death • Cardiovascular (CV) Death (i.e., fatal myocardial infarction [MI] /cerebrovascular accident [CVA] / congestive heart failure [CHF] / arrhythmia, cardiac arrest, death following CV intervention) • Non-CV Death
Appendix 1: Clinical Events List (Expected Events and Diabetic Complications)	G. Renal Failure • Chronic renal failure, requiring peritoneal hemodialysis, including creation of fistula or other vascular access for hemodialysis	G. Renal Failure • Chronic renal failure, requiring peritoneal ***or*** hemodialysis, including creation of fistula or other vascular access for hemodialysis
Appendix 2: Trial Plan	New addition in Amendment 05	Added "Post-Treatment Follow-up Contact"
Appendix 2: Trial Plan	Blood sample (serum and plasma) and urine sample for archive - specimens obtained at baseline (prior to drug exposure), annually and trial/early termination.	Blood sample (serum and plasma) and urine sample for archive - specimens obtained at baseline (prior to drug exposure), Year 1 and at the Trial Termination visit.
Appendix 2: Trial Plan	EQ-5D Completion listed for "Drug Termination Visit"	EQ-5D Completion removed from "Drug Termination Visit" consistent with Section 6.10
Appendix 6	None	Added Protocol Amendment 04 Summary of Changes

Main Statistical Analysis Plan for the EXenatide Study of Cardiovascular Event Lowering (EXSCEL)

Clinical Study Protocol BCB109

A RANDOMIZED, PLACEBO CONTROLLED CLINICAL TRIAL TO EVALUATE CARDIOVASCULAR OUTCOMES AFTER TREATMENT WITH EXENATIDE ONCE WEEKLY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Revision History

Version	Date	Author(s)	Summary of Changes/Comments
1.0	13 May 2010	Emanuela Pozzi Rury Holman Stuart Pocock	First version

Trial SAP Approval

Signature of Approval for Main Statistical Analysis Plan

Statistics & Modelling Group, DTU — **Emanuela Pozzi**

Signature _____ Date 3.10.13

DTU — **Rury Holman**

Signature _____ Date 8 OCT 2013

DCRI — **Robert Califf**

Signature _____ Date 8 October 2013

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1. Introduction

This document describes the Statistical Analysis Plan (SAP) for the Exenatide Study of Cardiovascular Event Lowering (EXSCEL). It details the statistical methods to be used and outlines the planned analyses for the main study. Any substantive deviations from this SAP will need to be justified and agreed by the Executive Committee prior to database lock.

1.1 Study Design

EXSCEL is a placebo-controlled, double-blind trial that seeks to characterize the effects of exenatide once-weekly (EQW, Bydureon®) treatment on cardiovascular-related outcomes in patients with type 2 diabetes when added to their existing therapy for glycemic control in a standard care setting. The trial population is described in section 5 of the main study protocol (EXSCEL Clinical Study Protocol BCB109).

1.2 Primary Objective

The primary objective of EXSCEL is to evaluate the effect of EQW on major cardiovascular (CV) events, as captured by the primary composi`te cardiovascular outcome of cardiovascular-related death, nonfatal myocardial infarction (MI), or nonfatal stroke.

1.2.1 Primary hypothesis

EQW, when used in addition to usual care, is superior to usual care without EQW with regard to the risk of developing a confirmed component of the primary composite cardiovascular outcome.

1.2.2 Subordinate hypothesis

EQW, when used in addition to usual care, is non-inferior to usual care without EQW with regard to the risk of developing a confirmed component of the primary composite cardiovascular outcome.

1.2.1 Sample Size and Power

A sample size of 9,500 patients, randomized 1:1 to the two treatment arms, is required to give 90% power for EXSCEL assuming a:

- 15% relative risk decrease in the EQW group,
  i.e. a true hazard ratio of 0.85 relative to the placebo group
- 3.8% annual primary composite cardiovascular outcome rate for the population to be enrolled.
- 3 year planned accrual period
- 4 year minimum treatment period
- 1% annual lost-to-follow up rate
- 0.05 two-sided alpha

For an exponential maximum likelihood test of equality of survival curves, a total of 1591 composite cardiovascular events were calculated to be required using nQuery.

1.2 Secondary Objectives

These are as defined in the section 2.2 of the EXSCEL Clinical Study Protocol (BCB109), namely:

- Time to All-cause mortality
- Time to Each of the three components of the primary composite cardiovascular outcome
- Time to Hospitalization for acute coronary syndrome (ACS)
- Time to Hospitalization for heart failure (CHF)

1.3 Exploratory Objectives

These are as defined in the section 2.3 of the EXSCEL Clinical Study Protocol (BCB109), namely:

- Time to Revascularization procedures. These will include:
  - percutaneous coronary intervention with or without stenting
  - coronary artery bypass grafting,
  - revascularization and/or stenting for peripheral arterial disease
  - carotid endarterectomy, or
  - carotid stenting.
- Time to initiation of first co-interventional agent
  i.e. next AHA or chronic insulin therapy
- Number of episodes of severe hypoglycemia
- Absolute values at study end and changes from baseline for each participant in markers of cardiovascular risk including:
  - HbA1c
  - Body weight
  - Blood pressure
  - Lipid profile
- Quality of life assessed by the EQ-5D (EuroQol 5 Dimension) questionnaire.
- Medical resource use and total direct medical costs.
- Incremental cost-effectiveness analysis of EQW as part of usual care compared with usual care without EQW.

1.4 Analysis Sets

1.4.1 Intention to Treat Population (ITT)

This is as defined in section 9.8.1 of the EXSCEL Clinical Study Protocol (BCB109).

The *Intention To Treat* (ITT) population consists of all randomized patients. Evaluation will include all events which have occurred from randomization to the date of the final post-study telephone contact, regardless of the time interval between patient discontinuation of study drug and final contact. Patients who do not have any events during the study will be censored at the date of their final post-study telephone contact. Every effort will be made to collect CV events to study termination even in those who have discontinued the study. For the ITT population, any patient found to

have taken a study medication for the entire duration of the study that is different from that to which he/she was randomized will be counted in the treatment group of the drug to which he/she was randomized.

1.4.2 Per Protocol Population (PP)

This is as defined in section 9.8.2 of the EXSCEL Clinical Study Protocol (BCB109).

The *Per-Protocol* (PP) population consists of all randomized patients who have taken at least one dose of study medication and will include in their analysis all data collected prior to any major protocol violations such as:

- Initiation of an open-label prohibited medication *i.e.* a GLP-1 receptor agonist. Evaluation will include all data up to the day of the initiation of the prohibited medication.
- Permanent discontinuation from study medication. Evaluation will include events which occurred from randomization to 90 days after the last dose of study medication.
- Taking incorrect study medication for more than three months of the main protocol document (EXSCEL Clinical Study Protocol BCB109).

All such protocol violations will be identified prior to unmasking of the data. Events that occurred after protocol violation will be excluded from the analysis. If a patient is found to have taken a study medication for the entire duration of the study that is different from that to which he/she was randomized then the patient is counted in the treatment group of the drug he/she actually received. Patients who do not have any events during the study will be censored 90 days after the last dose of study medication.

1.4.3 Safety Population (SP)

This is as defined in section 9.8.3 of the EXSCEL Clinical Study Protocol (BCB109).

The *Safety Population* (SP) consists of all randomized patients who received at least one dose of study therapy; in addition, if a patient is found to have taken a study therapy for the entire duration of the study, different from that to which he/she was randomized, then the patient is counted in the treatment group of the drug he/she actually received. Serious AEs and AEs leading to discontinuation of study medication, any of which occurred within 90 days after the last dose of study medication, will be collected. For continuous safety parameters, at least one post-randomization measurement is required for inclusion in the analysis. To assess change from baseline, a baseline measurement is also required.

2 Statistical Methodology

Statistical methodologies for the main EXSCEL analyses are described below unless specified otherwise. Statistical tests will be two sided apart from the subordinate hypothesis assessment of non-inferiority for the primary cardiovascular composite outcome, which will be one-sided. Estimated confidence intervals for hazard ratios will be adjusted appropriately for any interim analyses that have been performed.

Two unmasked interim analyses are planned that will be performed by the independent Data Safety Monitoring Board (DSMB) with appropriate alpha allowance for them when the primary analysis is performed.

Statistical programs for tables, listings, figures and statistical analyses will be developed during the trial. Masked analyses will be conducted prior to the end of the trial using dummy treatment assignments to help test the statistical programs in preparation for the final analyses.

Analyses will be performed using the latest version of SAS and the SAS programs will be validated by a peer reviewer.

The six main statistical analyses planned are:

2.1 Demographics and Baseline Characteristics

Demographic characteristics *e.g.* gender, age, ethnicity, body weight, will be summarized for each treatment group. In addition, duration of diabetes, alcohol intake, smoking status, cardiovascular medical history, baseline laboratory results and medication history will be summarized by treatment group.

2.2 Primary Efficacy Outcome Analysis

This analysis relates to the primary cardiovascular composite outcome.

2.2.1. Assessing the Primary Hypothesis

The primary hypothesis is one of superiority, that is the risk of developing component events in the primary composite cardiovascular outcome in patients treated with EQW in addition to usual care, is less than in usual care without EQW. The primary analysis will be based on the time to first confirmed primary composite cardiovascular outcomes.

If this hypothesis is not met, the subordinate non-inferiority hypothesis will be tested. In this analysis, EQW added to usual care will be declared as non-inferior to usual care without EQW if the upper bound of the one-sided adjusted confidence interval (97.51%) for the hazard ratio is below the margin of 1.30.

Both superiority and non-inferiority analyses will use the ITT population. Missing data will not be imputed.

The primary hypothesis will be assessed using a Log rank test stratified for prior cardiovascular event at randomization (Yes/No), followed by a Cox proportional hazards model with treatment group as an explanatory factor. The hazard ratio for the between-treatment difference in time to the first primary composite cardiovascular outcome and its two-sided adjusted 95.02% confidence interval will be calculated. A second Cox model, with treatment group as an explanatory factor, will be fitted that also includes prior cardiovascular event at randomization (Yes/No), region and type of site (Cardiovascular Yes/No) as stratification factors. The validity of the proportional hazard assumption underlying the Cox survival analysis will be examined for both Cox models using standard graphical methods.

Kaplan-Meier plots by treatment group of the cumulative incidence of the primary composite cardiovascular outcome will be produced, as well as hazard plots and failure (1-Survival) plots. The median follow-up and person-years of follow up, for the whole study and by treatment group, will be calculated.

2.2.2. Examination of the Sensitivity of the Primary Composite Cardiovascular Outcome to the Analysis Population and Assumptions.

The analyses outlined in the section 2.2.1 will be repeated for the PP population as a sensitivity analysis for robust interpretation. Additional sensitivity analyses to explore the evidence for 'country' level heterogeneity in relation to the overall event rate will be performed with the 'country' level effect considered as a 'random' effect in time-to-event analyses. If there is a substantive difference in inference between the primary analysis and sensitivity analyses, the inference based on primary analysis will be reported. However, further exploratory analyses will be conducted to understand the reason(s) for any differences seen.

2.3 Secondary Efficacy Outcome Analyses

This section outlines the Statistical analytic strategy relating to secondary efficacy endpoints. Formal testing for superiority for these outcomes will only be undertaken if the primary hypothesis or the subordinate hypothesis for the primary efficacy outcome is met.

The following time to event endpoints will be analysed individually in the ITT population using the statistical methods described in section 2.2.1 above. A Hochberg approach will be used to adjust the level for statistical significance to allow for multiple testing.

2.3.1 Time to All-cause mortality

Defined as time from randomization to death from any cause

2.3.2 Time to the each component event of the primary composite cardiovascular outcome

Defined as time from randomization to:
- cardiovascular-related death
- first nonfatal myocardial infarction
- first nonfatal stroke

2.3.3 Time to hospitalization for acute coronary syndrome

Defined as time from randomization to a confirmed hospital admission for:
- unstable angina
- ST-elevation myocardial infarction or
- non-ST-elevation myocardial infarction

2.3.4 Time to hospitalization for heart failure

Defined as time from randomization to hospital admission for congestive heart failure requiring treatment with intravenous diuretics, inotropes, or vasodilator therapy.

Sensitivity analyses for these secondary efficacy outcomes will be performed in the PP population using the statistical methods described in section 2.2.2 above.

2.4 Exploratory Analyses

This section relates to Statistical analytic strategy relating to exploratory analyses of efficacy endpoints, quality of life and health economics endpoints. These analyses will use the ITT population.

2.4.1 Time to revascularization procedure

Defined as the time from randomization to the first cardiovascular or peripheral revascularization procedure. These include:

- Percutaneous coronary intervention with or without stenting
- Coronary artery bypass grafting
- Revascularization and/or stenting for peripheral arterial disease
- Carotid endarterectomy or
- Carotid stenting.

2.4.2 Time to initiation of the first co-interventional agent

Defined as the time from randomization to:

- Additional AHA therapy
- Chronic insulin therapy

The time to event analyses for 2.4.1 and 2.4.2 will be performed by the methods described in section 2.2, including the sensitivity analyses.

2.4.3 Number of episodes of severe hypoglycemia requiring medical assistance

The annual frequency and patient-specific rates of self-reported severe hypoglycemic events by treatment group will be reported. The number of these events (patient level count data) will be compared between treatment groups using appropriate generalized linear regression model (Negative Binomial model). If the number of 'zeros' in the count data is more than 5% of the total, then a *zero-inflated* Negative Binomial regression model will be used.

The treatment group, prior diabetes pharmacotherapy at randomization and region will be incorporated as covariates in the model. The regression coefficients, robust standard errors, 95% confidence intervals and p values associated with all covariates will be reported. The ITT population will be used for this analysis.

The PP population will be used for this analysis.

2.4.4 Absolute values and changes from baseline in:

- HbA_{1c}
- Body weight
- Blood pressure
- Lipid profile

Absolute and change from baseline values will be presented in graphical format and analysed using generalized linear mixed modelling (GLMM) to ascertain the significance of difference in the average levels of the study variable by treatment group, having modelled the changing correlation patterns over time as unstructured. If the study variable is positively skewed, the Gamma distribution will be assumed with identity link and unstructured correlation structure. In case of non-positive skewness, the Box-Cox Transformation will be considered to achieve approximate normality. If

the exponential transformation family is used, the estimated transformation parameter will be reported. In case the approximate normality is observed in the distributions of the study variables (using the density plots from initial exploratory analyses), the Gaussian model with identity link will be assumed.

Missing data will be imputed with a method appropriate for the type of missing data pattern. Either a parametric regression method that assumes multivariate normality or a non-parametric method that uses propensity scores under the assumption of non-normality will be used for data with monotone missing patterns, *i.e.* observation is missing at time point t and at all subsequent time points. The Bayesian Markov Chain Monte Carlo (MCMC) method that assumes multivariate normality will be used for data with an arbitrary missing data pattern.

If deemed appropriate last observation carried forward (LOCF) and/or the best or worst case imputation, assigning the worst possible value of the outcome to drop-outs for negative reason (treatment failure) and the best possible value to positive drop-outs (treatment success) can be performed to assess a lower bound of efficacy for robust interpretation.

Imputations will be performed using the SAS Proc MI procedure.

2.4.5 Quality of Life and Health Economic Analysis

A separate Health Economic SAP describes the following analyses:

- Quality of life assessed by the EQ-5D (EuroQol 5 Dimension) questionnaire.
- Medical resource use and total direct medical costs.
- Incremental cost-effectiveness analysis of exenatide once weekly as part of usual care compared with usual care without exenatide.

2.5 Subgroup Analyses

This section outlines the Statistical analytic strategy for a set of pre-specified subgroup analyses of the primary cardiovascular composite outcome. These analyses will use the ITT population.

Subgroup analyses for the primary composite cardiovascular outcome will be performed on the ITT population in order to explore whether the treatment effects on the risk of developing cardiovascular events are consistent across subgroups. Cox proportional hazards model with treatment group as an explanatory factor will be used with the subgroups divided by categories or by the Protocol-specified clinically-relevant cut points for continuous variables.

The pre-specified subgroups are:

- Class of AHA therapy at entry (mono or combination)
- Ethnicity/race (Black, Caucasian, Asian, Other)
- Region (North/South America or Canada, Europe or South Africa, ROW)
- Gender (Male, Female)
- Age (<65 or ≥65)
- Baseline HbA_{1c} (<8.0% or ≥8/0%)

- Baseline BMI (<30 or ≥30 kg/m^2)
- Duration of diabetes (<5 years or ≥5 years)
- Baseline eGFR
- History of previous cardiovascular event (e.g., previous MI or stroke)

For each subgroup analysis, hazard ratios, 95% CIs and appropriate summary statistics for each treatment group will be provided with the hazard ratios examined for interaction (heterogeneity) effects.

Forest plots will be drawn with estimated hazard ratios, 95% confidence intervals and p values adjusted for possible heterogeneity, as appropriate. Interclass correlation coefficients will be computed where appropriate.

For continuous measures, subgroup analyses will also be performed by tertiles of the data.

2.6 Gate-keeping Procedure

The gate-keeping procedure listed below will be followed for the primary efficacy analysis in the ITT population. An α=0.0498 will be used for the final analysis to maintain a family-wise error rate of α=0.05. This allows for α=0.0001 and α=0.001 to be spent for the planned first and second interim efficacy analyses respectively that will be performed by the DSMB.

2.6.1 Testing the superiority hypothesis

If the two-sided 95.02% confidence interval for the primary outcome hazard ratio is entirely below 1.0, superiority on the primary outcome will be claimed.

In this event, each secondary efficacy outcome will be tested and superiority claimed where the Hochberg-adjusted two-sided 1-α confidence interval is entirely below 1.0. For outcomes where superiority is claimed, the PP population will be used to assess sensitivity.

For each secondary efficacy outcome where superiority is not claimed, the subordinate non-inferiority hypothesis will be tested. Non-inferiority will be claimed if the Hochberg-adjusted two-sided 1-α confidence interval is entirely below 1.3. For outcomes where non-inferiority is claimed, the PP population will be used to assess sensitivity.

2.6.2 Testing the non-inferiority hypothesis

If the superiority hypothesis is not met, the subordinate non-inferiority hypothesis will be tested.

If the one-sided 97.51% confidence interval for the primary outcome hazard ratio is entirely below 1.30, non-inferiority on the primary outcome will be claimed.

In this event, each secondary efficacy outcome will be tested and superiority claimed where the Hochberg-adjusted two-sided 1-α confidence interval is entirely below 1.0. For outcomes where superiority is claimed, the PP population will be used to assess sensitivity.

For each secondary efficacy outcome where superiority is not claimed, the subordinate non-inferiority hypothesis will be tested. Non-inferiority will be claimed if the Hochberg-adjusted two-sided 1-α confidence interval is entirely below 1.3. For

outcomes where non-inferiority is claimed, the PP population will be used to assess sensitivity.

2.6.3 Testing pre-specified exploratory analyses and subgroup analyses

The pre-specified exploratory analyses and subgroup analyses will be performed at α=0.05 without adjustment for multiplicity.

2.7 Safety Data Analysis and Adverse Event Reporting

This section relates to Statistical analytic strategy for the analyses of serious adverse events and adverse events.

Safety parameters will be summarized and presented in tables for the safety population. Safety Data Analyses will use Safety Population (as described in section 1.4.3). ITT population will be used for sensitivity analyses.

2.7.1 Serious Adverse Events

Serious adverse events (SAEs) will be coded using the most recent MedDRA dictionary. SAE high level and preferred terms will be tabulated by treatment group, with totals for each term. Counting will be done by patient and by event. Between treatment group comparisons will be performed using the 95% confidence intervals along with the significance levels. The Miettinen & Nurminen approach[1] will be followed for safety data analysis and reporting, as appropriate.

2.7.2 Pre-specified Safety Variables

Visit-based Box and Whisker plots by treatment group will be produced for safety variables. Supplementary analyses will only be performed where these summaries suggest that there may be clinically significant differences.

References

1. Miettinen OS, Nurminen M. Comparative analysis of two rates. *Statistics in Medicine* 1985;4:213-226

Statistical Analysis Plan

Study Code	D5551C00003(BCB109)
Edition Number	4.0
Date	23 February 2017

EXSCEL

A Randomized, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes after Treatment with Exenatide once Weekly in Patients with Type 2 Diabetes Mellitus

Statistical Analysis Plan
Study Code D5551C00003(BCB109)
Edition Number 4
February 23rd 2017

A Randomized, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes after Treatment with Exenatide once Weekly in Patients with Type 2 Diabetes Mellitus

24 MAR 2017

Rury Holman, MD
Executive Committee Co-Chair,
Diabetes Trials Unit, Oxford, UK

Date

A Randomized, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes after Treatment with Exenatide once Weekly in Patients with Type 2 Diabetes Mellitus

03-24-17

Adrian Hernandez, MD
Executive Committee Co-Chair,
Duke Clinical Research Institute (DCRI),
Durham, NC, USA

Date

A Randomized, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes after Treatment with Exenatide once Weekly in Patients with Type 2 Diabetes Mellitus

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03/14/2017
Date

A Randomized, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes after Treatment with Exenatide once Weekly in Patients with Type 2 Diabetes Mellitus

15 Mar 2017

Jasmine Choi,
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Date

15 Mar 2017

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Biometrics and Information Sciences
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Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
BMI	Body mass index
CV	Cardiovascular
DPP-IV	Dipeptidyl peptidase-IV
eCRF	Electronic case report form
EQ-5D	EuroQol-5D (health status questionnaire)
GLP-1	Glucagon-like peptide-1
HbA1c	Glycated hemoglobin A1c
HDL	High-density lipoprotein
HR	Hazard ratio
ITT	Intent-to-treat
LDL	Low-density lipoprotein cholesterol
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
SAE	Serious adverse event
SAP	Statistical analysis plan

AMENDMENT HISTORY

Date	Brief description of change
13 Oct. 2010	Initial Approved SAP'
19 Feb. 2015 The protocol was amended on 25 Oct 2013 on the following, so was the SAP accordingly. 09 March 2016 Due to stand-alone protocol amendment	▪ During second half of 2013, blinded review of the primary endpoint event rate, it was discovered that the observed event rate is lower than expected. That led to change in study assumptions. The sample size was increased from 9,500 to 14,000. The number of primary events were reduced to 1360 to detect 15% RRR with 85% power. ▪ Intention to treat analysis, the definition of primary end point is further clarified in that it will not include events after Executive committee cutoff date to close the study nor it will include events observed during the 10 week post study period. ▪ At the request of DSMB, on treatment analysis has been added. ▪ The primary analysis will include adjudicated events through the Trial Termination Visit (rather than just the Cut-Off Date) ▪ Clinical Events will continue to be collected and managed as they have been throughout the entire study (refer to Protocol Section 10.3.1 and Protocol Appendix 1). ▪ Clarify that if the study terminates early for superiority, the key secondary endpoints will be tested at the same significance level as the primary endpoint in the interim analysis using the hierarchical test strategy. ▪ Clarify sensitivity analysis #3 in section 4.5.1.4. ▪ Clarify censoring schemes in Section 4.1.2.1. ▪ Update to region and race definitions (including the addition of Section 5.6) ▪ Remove analysis of hypoglycaemia from efficacy, and clarify hypoglycaemia assessments fall under safety endpoints ▪ Updated section 4.6.3 to add information about additional analysis of calcitonin elevations. ▪ Minor administrative/wording changes to Sections 2.2, 4.4.3, 4.5.3, and 5.5. ▪ Removal of the table of potentially clinical significant vital signs, as vital signs are not collected in a rigorous manner and because this study is focused on outcomes making "potentially clinically significant" changes less relevant.

Date	Brief description of change
23 Feb 2017	▪ Section 1.1.2. Added detail on the components of the primary endpoint. ▪ Section 4.5.1. Inclusion of hazard ratio and confidence intervals for treatment effect on each of the components (non-fatal MI, non-fatal Stroke, CV death) of the primary composite endpoint. ▪ Section 2.1.3. Clarified definition of 'as treated'. ▪ Section 2.2. Defined early discontinuation of study drug. ▪ Section 3.1. Positively adjudicated strokes classified as subdural hematomas are excluded from the definition of stroke in the analysis. ▪ Section 3.1.1. Definition of fatal/non-fatal events was updated to include a 30 day window between the date of the event and the date of the death due to the event. ▪ Section 4.1.2. Clarification of censoring dates. ▪ Section 4.1.2.2. Added detail to description of tipping point analysis. ▪ Section 4.3.2. Updated race definition. ▪ Section 4.4.3. Updated definitions of baseline and new concomitant medications. ▪ Section 4.5.2.3. Added exploratory analysis of recurrent MACE events. ▪ Section 4.5.4. Removed language that quality of life data would be summarized descriptively for the CSR (instead, will be independently analysed and reported). ▪ Section 6. Added changes of analysis from protocol. ▪ Section 4.5.2.1. Added analysis on the homogeneity of the effect of treatment on fatal vs nonfatal MI's and on fatal vs nonfatal strokes.

1. STUDY DETAILS

1.1 Study Objectives

1.1.1 Primary Objective

The primary objective will be to evaluate the effect of EQW, used in addition to the current usual care for glycemic control, on major CV outcomes as measured by the primary CV composite endpoint of CV-related death, nonfatal myocardial infarction (MI), or nonfatal stroke when administered to patients with type 2 diabetes.

Safety hypothesis: EQW, when used in addition to usual care, is non-inferior to usual care without EQW with regard to the risk of developing a confirmed event in the primary CV composite endpoint.

If the objective for safety is met, the following efficacy objective will be considered

Efficacy hypothesis: EQW, when used in addition to usual care, is superior to usual care without EQW with regard to the risk of developing a confirmed event in the primary CV composite endpoint.

1.1.2 Secondary Objectives

The secondary objectives are to evaluate the effect of EQW treatment used in addition to the current usual care for glycemic control on:

1. All cause mortality
2. Each of the components of the primary composite CV endpoint combining fatal and nonfatal events:
   a) CV death
   b) Fatal or nonfatal MI
   c) Fatal or nonfatal stroke
3. Hospitalization for acute coronary syndrome (ACS)
4. Hospitalization for congestive heart failure (CHF)

1.1.3 Additional Objectives

Additional objectives of EXSCEL are to evaluate the effect of EQW treatment used in addition to the current usual care for glycemic control on:

1. Revascularization procedures. This will include percutaneous coronary intervention (PCI) with or without stenting, coronary artery bypass grafting, revascularization and/or stenting for peripheral arterial disease, carotid endarterectomy, or carotid stenting
2. Time to initiation of first co-interventional agent (i.e., next antihyperglycemic agent [AHA] or chronic insulin therapy)
3. Number of episodes of severe hypoglycemia

4. Absolute values of and changes in markers of cardiovascular risk including: HbA1c, body weight, blood pressure, lipid profile
5. Quality of life assessed by the EQ-5D (EuroQol 5 Dimension) questionnaire
6. Medical resource use and total direct medical costs
7. Incremental cost-effectiveness analysis of EQW as part of usual care compared with usual care without EQW

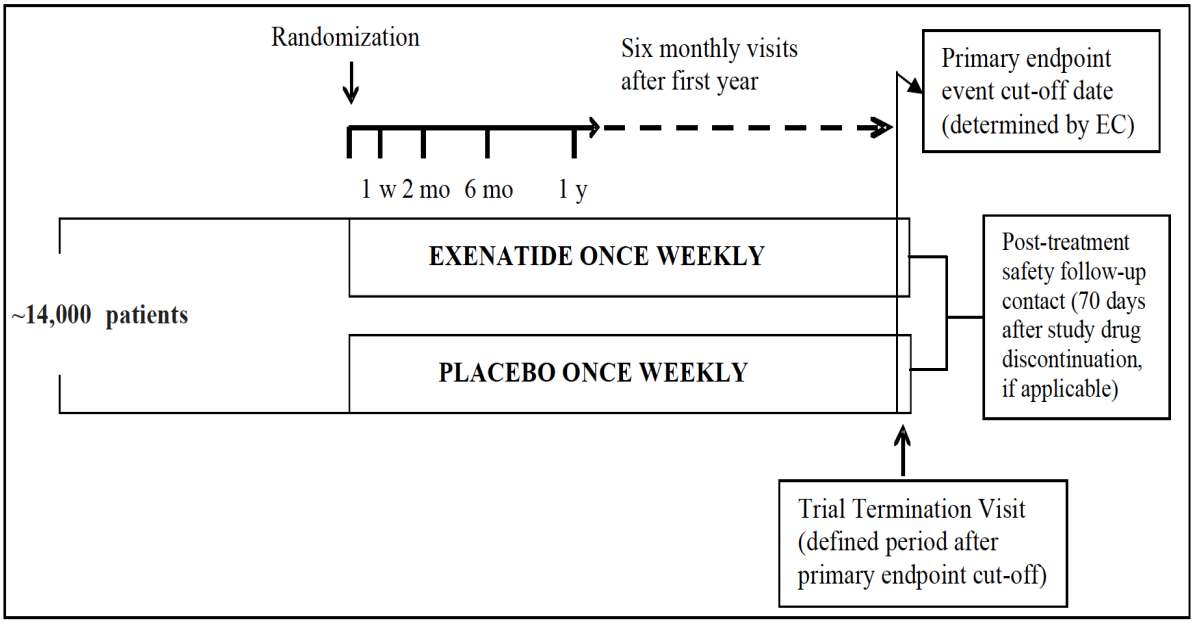
1.2 Study Design

EXSCEL is a multinational, placebo-controlled, double-blind, randomized, parallel-group pragmatic clinical trial. Eligible patients will have type 2 diabetes with an HbA1c ≥6.5% and ≤10.0 % on up to three (i.e., 0-3) oral antihyperglycemic agents (AHAs) or insulin either alone or in combination with up to 2 (i.e., 0-2) oral AHAs. Patients enrolled will be at a wide range of CV risk with approximately 70% having had a prior CV event.

Approximately 14,000 patients meeting enrollment criteria will be recruited in to the trial over approximately a five year period, randomly allocated to treatment with either exenatide once weekly (EQW) 2 mg or matching placebo subcutaneous injections once weekly in a 1:1 ratio, and followed until the requisite number of primary endpoint events have been reported. The trial is planned to continue until a minimum of 1360 patients with positively adjudicated primary endpoint events have been accrued, or until the independent Data Safety Monitoring Board (DSMB) advises otherwise. The EXSCEL Executive Committee will monitor the accrual of the aggregate number of adjudicated primary endpoint events and will determine the primary endpoint event cutoff date (i.e., the date at which the anticipated number of events is expected to have accrued); Based on the primary endpoint event cut-off date, a window of time for conduct of the Trial Termination Visit will be established; all patients will be expected to have follow-up until the Trial Termination Visit.

Patients will be enrolled in the Americas (North/South America), Europe, South Africa and Asia/Australasia. Trial follow-up will consist of a blend of trial visits, laboratory review and phone calls during the double-blind placebo-controlled treatment period. Given that this population will be at elevated CV risk, it is anticipated that patients will see their usual care provider at least twice per year for routine care. There is no requirement to achieve glycemic equipoise between randomized groups but all patients during the double-blind treatment period will have their AHA regimens adjusted as deemed necessary by their usual care provider with the addition or substitution of other AHAs, including insulin, but excluding GLP-1 receptor agonists, to achieve appropriate individualized glycemic goals in line with national guidelines.

Figure 1.1 Illustrates the flow of participants in the EXSCEL trial



1.3 Number of Patients

Sample size calculations

The primary safety/efficacy endpoint is the time from randomization to the first confirmed CV event defined as a CV-related death, nonfatal MI or nonfatal stroke.

The primary safety hypothesis of non-inferiority of EQW to placebo is:

H_0: HR [EQW:placebo] $\geq$1.3 versus H_1: HR [EQW:placebo] <1.3

In order to test the above hypothesis with 90% power and 1-sided α=0.025, a total number of 611 patients with composite CV events are required assuming a risk reduction of 0% on EQW compared with placebo.

The primary efficacy hypothesis of superiority of EQW to placebo is:

H_0: HR [EQW:placebo] $\geq$1 versus H_1: HR [EQW:placebo] <1In order to test the above hypothesis with 85% power and 2-sided α=0.05, a total number of 1360 patients with composite CV events are required assuming a risk reduction of 15% on EQW compared with placebo. With 1360 events, the power will be much larger than 90% to assess the primary safety objective of non-inferiority of EQW compared with placebo.

In addition, with the following assumptions made for this study,

- An annual composite cardiovascular primary endpoint event rate estimated to be around 2.2% per year for the population to be enrolled
- A planned accrual period of about 5 years
- An estimated annual lost-to-follow up rate of 1%
- An anticipated treatment discontinuation rate of 5% per year.

It is expected that a total of 14,000 patients need to be randomized in a 1:1 ratio into EQW and placebo to achieve the targeted 1360 patients with confirmed composite CV events.

2. ANALYSIS SETS

2.1 Definition of Analysis Sets

2.1.1 Intent-To-Treat (ITT) Population

The Intent-To-Treat (ITT) Population will consist of all patients consented and randomized in the study without a major GCP violation. For all analyses using the ITT population, patients will be analyzed **As Randomized**.

2.1.2 Per-Protocol Population

Per-Protocol Population is a subset of the ITT Population excluding data from patients with major protocol deviations (Section 2.2) expected to affect the primary efficacy endpoint. For any analysis utilizing the per-protocol population, patients will be analyzed **As Randomized**.

2.1.3 Safety Population

The Safety Population will consist of all patients in the ITT Population who took at least one dose of study medication. When summarizing data using this population, patients will be analyzed **As Treated**. If a patient receives any exenatide study drug, then the patient will be counted in the exenatide arm, regardless of the amount of medication received; otherwise the patient will be counted in the placebo arm.

2.2 Protocol Deviations

All important protocol deviations will be summarized by treatment group. At the end of the study, any major protocol deviations that are thought to potentially affect the analysis will be reviewed and finalized by the team in a blinded manner, prior to data base lock. Major protocol deviations include, but are not limited to the following:

1. Patient randomized but not dosed will be excluded from the per protocol population.
2. If percent of injection missed > 50% (as assessed by calculation of patients who report temporary discontinuation of study drug; see Section 4.4.2) the patient will be excluded from the per protocol population.
3. Violations of selected inclusion/exclusion criteria at enrolment that would exclude a patient from the per protocol population:

a. Patient has a diagnosis of type 1 diabetes mellitus.
b. Patient does not have diagnosis of type 2 diabetes mellitus.

4. Received incorrect treatment for >6 months; the data collected up to the start of incorrect treatment will be included in the per-protocol population (i.e. data collected after incorrect treatment will be excluded)
5. Early discontinuation from study medication; the data collected up to 70 days after the last dose of study medication or the trial termination visit date (whichever occurs first) will be included in the per-protocol population. Early discontinuation from study medication is defined as a last dose date of study medication that is more than 21 days prior to the end of study date.
6. Initiation of a prohibited medication (an open-label approved or investigational GLP-1 receptor agonist, or another investigational drug or device); the data collected up to the initiation of the prohibited medication will be included in the per-protocol population.

3. STUDY ENDPOINTS

3.1 Primary Safety and All Efficacy Endpoints

Relevant suspected safety events and efficacy endpoints will be adjudicated by the Clinical Events Committee (CEC). The definition of confirmed ssafety events and efficacy endpoints including CV-related death, stroke and myocardial infarction (MI) can be found in the CEC charter.

Confirmed, positively adjudicated hemorrhagic strokes, classified as subdural hematomas will be excluded from any analyses of adjudicated stroke events.

Clinical endpoints occurring through the Trial Termination Visit will be adjudicated and will be included in the primary analysis. Site-reported clinical events occurring after the Trial Termination Visit will not be adjudicated and will not be part of the primary analysis.

3.1.1 Primary Safety/Efficacy Endpoint

The primary safety/efficacy endpoint is time from randomization to the onset of the first occurrence of any confirmed event in the primary composite CV endpoint (CV-related death, nonfatal MI, nonfatal stroke).

Where fatal/non-fatal events are defined as follows:

If there is an event of MI and there is a death due to MI and the date of the MI is within 30 days of the death, then the MI is fatal; if the MI is greater than 30 days prior to the death then the MI is non-fatal; if the cause of death is not MI then the MI is non-fatal

If there are multiple MI's and there is a death due to MI, then the MI closest and within 30 days prior to the death is a fatal MI; all others are non-fatal;

Similar logic is used for stroke events.

3.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are the time from randomization to first occurrence of confirmed:

- all-cause mortality (defined as death due to any cause)
- CV-related death
- fatal or nonfatal MI (MI)
- fatal or nonfatal stroke (stroke)
- hospitalization for acute coronary syndrome
- hospitalization for heart failure

Hospitalization for acute coronary syndrome is defined as a confirmed myocardial infarction or hospital admission for unstable angina. Myocardial infarction includes ST-elevation myocardial infarction, non-ST-elevation myocardial infarction or ST-elevation unknown.

Hospitalization for congestive heart failure is defined as a confirmed hospital admission for congestive heart failure requiring treatment with increased oral or intravenous diuretics, inotropes, or vasodilator therapy.

3.1.3 Additional Efficacy Endpoints

- Time to composite of CV-related death or hospitalization for congestive heart failure, defined as time from randomization to time of first CV-related death or hospitalization for congestive heart failure, in overall and in patients with prior history of CHF at baseline.
- Time to revascularization procedure, defined as time from randomization to time of first cardiovascular or peripheral revascularization procedure. This will include percutaneous coronary intervention with or without stenting, coronary artery bypass grafting, revascularization and/or stenting for peripheral arterial disease, carotid endarterectomy, or carotid stenting.
- Time to initiation of first co-interventional agent, defined as the time from randomization to the start date of one or both of the below agents
  - Additional AHA
  - Chronic insulin therapy (only applies to patients not on chronic insulin therapy at randomization)

  Chronic insulin therapy is defined as a continuous period of insulin use of more than 6 months.

- Absolute values and change from baseline in HbA1c, body weight, blood pressure, heart rate and lipid profile (HDL, LDL, triglycerides, total cholesterol) at the protocol defined measurement time points (see Appendix).
- Quality of life assessed by the EQ-5D (EuroQol 5 Dimension) questionnaire. Mobility, self-care, usual activities, pain and discomfort, and anxiety and depression dimensions will be converted into health state utilities using the United Kingdom tariff for all patients. This analysis will described in a separate analysis plan document.
- Medical resource use and total direct medical costs. This analysis will described in a separate analysis plan document.
- Incremental cost-effectiveness analysis of EQW as part of usual care compared with usual care without EQW. This analysis will described in a separate analysis plan document.

3.2 Other Safety Endpoints

Other safety endpoints include selected adverse events (AEs), serious adverse events (SAEs), and certain laboratory parameters (serum creatinine and calcitonin; see Section 4.6.3) and vital signs (see Section 4.6.4). Adverse events will be monitored over the course of the trial, starting from the time of randomization and through the duration of the patient's participation, including the 70 day post treatment follow-up period. Adverse events reported by the patient will be evaluated by the investigator to determine if a given event meets the criteria for a serious event. An adverse event that does not meet the definition of a serious event will be considered non-serious and will not be collected, with the exception of potential clinical events (non-serious AEs) and expected events of diabetic complication (for details see protocol Section 10.3).

4. ANALYSIS METHODS

4.1 General Principles

In addition to specific analyses and presentations that are detailed in the following sections, results will be summarized for continuous measures using descriptive statistics, including the number of patients, mean, standard deviation, median and range as appropriate. For natural logarithm transformed data, geometric mean, standard error of the geometric mean will also be provided. For categorical variables counts and percentage per treatment group will be presented.

For all time-to event analyses, the treatment groups will be analyzed using a Cox proportional hazards model that includes treatment as an explanatory factor unless specified otherwise. Prior CV event group at randomization from the IVRS randomization strata (prior CV event or no prior CV event, refer to "Prior CV event at randomization based on IVRS" in short) will be included as a stratification factor. The Efron method[1] will be used for handling ties. P-value

and confidence intervals for the HR will be based on the Wald statistic. In addition, the summary tables of these analyses will include the number of patients with the event and Kaplan-Meier estimates of the event rate per treatment group presented annually through the last time point where the 90th percentile of events are collected. Kaplan-Meier failure rates along with respective 95% CI will also be calculated and plotted by treatment group and prior CV risk at randomization based on IVRS, with number of patients at risk indicated below the plot at specific times. The median and total person-years of follow-up for the entire study will also be reported.

An on-treatment analysis using the ITT population will be performed for the primary and some secondary endpoints as sensitivity analyses. This analysis will include those events that occurred from randomization through the last dose of study medication or the Trial Termination Visit, whichever occurs first. The patients will be analyzed according to the treatment group to which they were randomized. An on-treatment censoring scheme, as described later in the text, will also be applied for analysis for on-treatment + n days, where n=7, 30, and 70.

For all time to event analysis of composite endpoints including mortality, if the death occurred after 6 months from the last visit where all components of the endpoint could be assessed, the death will not be counted towards any composite endpoint where death is a component. Instead, such patients will be censored in accordance with the relevant censoring scheme. For analysis of mortality as an endpoint, such deaths will be counted as events. Unless otherwise specified all hypothesis testing will be performed using two-sided tests at the 0.05 level of significance. Statistical analyses will be performed using Version 9.2 (or newer) of SAS® on Unix operating system.

Selected analyses described here will be summarized separately for the US and the China population respectively.

4.1.1 Control of Type I Error

Type I error will be controlled at a one-sided 0.025 level for multiplicity across primary and secondary objectives and in consideration of planned interim analyses. The alpha of 0.02495 represents the final one-sided significance level to be used when the study has been completed in entirety. At an interim analysis, testing for superiority of primary efficacy endpoint will occur, and the significance level for superiority will be replaced by one-sided 0.00005 at the first and one-sided 0.0005 at the second interim (see Section 4.7). Statistical testing will proceed sequentially and statistical significance will be assessed in the following hierarchical order. When a test is found to be statistically significant, testing will proceed to the next test. If a test is not statistically significant, the subsequent one will not be assessed for statistical significance although nominal p-values will be provided.

Hierarchical Testing Order:

1. Non-inferiority test for the primary composite CV endpoint (alpha= 0.02495 1-sided)
2. Superiority test for the primary composite CV endpoint (alpha= 0.02495 1-sided)
3. Superiority test for secondary efficacy endpoint of all-cause death (alpha= 0.02495 1-sided)
4. Superiority test for secondary efficacy endpoints: CV-related death, MI, and stroke (alpha= 0.02495 1-side): The hypothesis for these three secondary efficacy endpoints (null hypothesis is denoted as $H_{0[41]}$, $H_{0[42]}$, $H_{0[43]}$,) will be tested at one-sided 0.02495 level by using the Hochberg procedure[2], which proceeds as follows:
   - *Ordering the raw p-values (one-sided) such that* $p_{(1)} \leq p_{(2)} \leq p_{(3)}$
   - *Step 1. If* $p_{(3)} < 0.02495$, *reject* $H_{0[4i]}$, $i = 1,2,3$ *and stop; otherwise go to Step 2.*
   - *Step 2. If* $p_{(2)} < 0.02495/2$, *reject* $H_{0[4i]}$, $i = 1,2$ *and stop; otherwise go to Step 3.*
   - *Step 3. If* $p_{(1)} < 0.02495/3$ *reject* $H_{0[4i]}$, $i = 1$.
5. If superiority tests for all three secondary efficacy endpoints in number 4 are met, proceed with superiority test for secondary endpoints: hospitalization for acute coronary syndrome and hospitalization for heart failure. The hypothesis for these two secondary efficacy endpoints (null hypothesis is denoted as $H_{0[51]}$, $H_{0[52]}$,) will be tested at one-sided 0.02495 level by using the same Hochberg procedure as described above.

Non-inferiority will be tested only at the completion of the study. Secondary endpoints will only be tested once, at the completion of the trial or if the decision is made to terminate the trial early. If the study terminates early for superiority, the key secondary endpoints of CV death, MI, stroke and all-cause mortality will be tested at the same significance level as the primary endpoint in the interim analysis using the hierarchical test strategy. Additional efficacy endpoints will be tested at the 2-sided 0.05 level.

4.1.2 Censoring

4.1.2.1 Censoring Scheme

Primary Censoring Scheme: in time-to-event analyses in the ITT population, patients will be censored at the earliest of: 1) date of last contact where all elements of the endpoint could be assessed, and 2) the right censoring date. The conclusions regarding non-inferiority or superiority will be based on the analyses using this censoring scheme. Patients without any assessment of the endpoint will be censored at randomization.

On-treatment Censoring Scheme: in the on-treatment time-to-event analyses, patients will be censored at the earliest of: 1) date of last contact where all elements of the endpoint could be

assessed, and 2) the date of last dose of study medication, and 3) the right censoring date. Patients who never start the study drug will be censored at randomization.

On-treatment + n days Censoring Scheme (where n=7, 30, and 70): patients will be censored at the earliest of: 1) date of last contact where all elements of the endpoint could be assessed, 2) the date of last dose of study medication + n days, and 3) the right censoring date. Patients who never start the study drug will be censored at randomization.

Cut-off Date Censoring Scheme: patients will be censored at the earliest of: 1) date of last contact where all elements of the endpoint could be assessed, and 2) the primary endpoint cut off date. The primary endpoint cut off date will be determined by the Executive Committee as the date when the sites will start bringing patients back for the Trial Termination visit. Patients without any assessment of the endpoint will be censored at randomization.

Right censoring date is defined as the last known alive date as collected at the trial termination visit (TTV form) except for deceased patients where it is the adjudicated date of the death.

4.1.2.2 Assumption on Non-informative Censoring

The time to event analysis (Cox regression) relies on the assumption of non-informative censoring. To examine this assumption, variables that may be related to censoring, for example, the most frequent major protocol deviation, certain SAEs, will be explored. Rates per 100 patient-years will be calculated per treatment group and compared between patients censored early without complete follow-up, and those with complete follow-up.

To assess possible effects of informative censoring on the primary efficacy endpoint, sensitivity analyses will be done as follows. First, the tipping point analysis will be performed where in patients who prematurely discontinued the study without having a primary endpoint event prior to discontinuation, events will be imputed during their missing follow up time (i.e. time from censoring to trial termination visit) under various scenarios for the hazard rates for non-completers in each arm. For each scenario, 2000 imputations will be performed and the results will be combined across 2000 combined datasets (actual events in completers + imputed events in non-completers) using SAS PROC MIANALYZE. Specifically, log-hazard ratio estimate of treatment effect will be calculated as an average and its associated variance will be obtained using Rubin's[8] (1987) formula, which combines within-imputation and between-imputation variances. Hazard ratios, Wald's 95% CIs and Wald's test p-values will also be calculated. The goal of this analysis is to find scenarios where the primary analysis results will be “tipped”, i.e. the conclusion will change.

4.2 Study Conduct

Major protocol deviations will be identified for all patients who are randomized (see Section 2.2).

4.3 Study Population

4.3.1 Patient Disposition

The number of patients included in each study population (i.e., Intent-to-Treat, Per-Protocol and Safety) will be summarized by treatment group. The number and percentage of patients who completed and patients who discontinued from treatment and who withdrew from study will be presented for each treatment group and overall for the ITT Population. Reasons for discontinuation from treatment and discontinuation from the study will be summarized (number and percentage) overall and by treatment group for the ITT Population.

4.3.2 Demographics and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group for the ITT Population, Per Protocol Population and Safety Population.

The following demographics and baseline characteristics will be summarized:

- Prior CV event at randomization based on IVRS (yes, no)
- Prior CV event at randomization based on CRF (yes, no)
- Geographic region: North America, Latin America, Europe and Asia Pacific
- Country
- Age: calculated as ((date of randomization- date of birth) +1)/365.25
- Age group (<65, >=65 years, >=75 years)
- Gender
- Race:
    - Indian (American) or Alaska Native
    - Asian: Asian (Oriental), Asian (Other)
    - Black
    - Native Hawaiian or Other Pacific Islander, includes Maori (New Zealand) and Aboriginal (Australian)
    - White: Caucasian or White
    - Hispanic
- Ethnicity: Latino, non-Latino
- Weight
- Height
- BMI
- BMI group: <30, >=30 kg/m^2
- Baseline antihyperglycemic agents therapy
    - None

  - Oral agent use (oral defined as all but insulin or pramlinitide; including "other")
    - Oral agent monotherapy
    - Oral agent dual combo therapy
    - >/= 3 oral agents
  - Insulin use
    - Insulin alone
    - Insulin + 1 oral agent
    - Insulin + >1 oral agent
  - DPP-4i use
- Baseline laboratory results HbA1c
- HbA1c group: <8.0%, >=8.0%
- Duration of diabetes: calculated as (year of randomization – year of diagnosis) +1
- Duration of diabetes group: <5, 5-14, >=15 years
- eGFR: according to the Modification of Diet in Renal Disease (MDRD) formula3
- eGFR groups (ml/min/1.73m2):
  - <60, >=60
  - Stage 1: 90+, Stage 2: 60-89, Stage 3: 30-59, Stage 3a: 45-59, Stage 3b: 30-44, Stage 4: 15-29, Stage 5: <15

Differences in the countries that have historically comprised Eastern vs. Western Europe will also be explored. Medical complications at baseline (amputation, foot ulcer, retinopathy, blindness, albuminuria and diabetic neuropathy) and other medical history (coronary artery stenosis >=50% by coronary catheterization, MI etc.) will also be summarized by treatment group.

4.4 Extent of Exposure

4.4.1 Study Medication

Exposure to study medication for the ITT and Safety Population during the study period will be summarized in terms of treatment duration, which is calculated as the number of days from the date of first medication taken to the date of last dose taken, inclusively ((date of last dose taken – date of first medication taken)+7). This duration will not be adjusted for any period the patient may have been off of study drug temporarily. Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented by treatment group.

4.4.2 Measurement of Treatment Compliance

Number of patients who had more than 4 consecutive missing doses and percent of injections missed will be summarized by treatment group (Data for patients with less than 4 missing dose is not collected in CRF given the long half-life of the study drug).

Percent of injections missed are not directly recorded, as compliance is not recorded in the study database, but will be calculated for those patients who have recorded temporary discontinuation periods by:

(1- (total number of known missed injections for temporary discontinuation periods / number of planned injections based on first and last dose date))*100%

Kaplan Meier estimates of time to permanent study drug discontinuation will be summarized by treatment.

Treatment compliance will also be summarized in terms of percent of time on study drug, which is calculated as actual time on study drug (not adjusting for temporary discontinuations) divided by the study duration, defined as time to last known alive date if patient is alive or at withdrawn consent status, study cut-off date if patient is lost to follow up, and death date if status is deceased.

4.4.3 Concomitant Medication

A baseline concomitant medication is defined as a medication which was reported to have been taken on the concomitant medication eCRF form at the Screening/Randomization visit. A baseline diabetes medication is a diabetes medication that is reported to have been taken on the medical history eCRF form. A new diabetes/concomitant medication is defined as no indication of usage at baseline as well as indication of usage during at least one post-randomization visit.

Patients taking baseline diabetes/concomitant medications will be summarized by treatment group in the ITT and Safety populations. Similar summaries will be presented for patients taking new diabetes/concomitant medications and for patients taking a diabetes/concomitant medication at any visit (i.e. at baseline or at any time during a post-randomization visit).

4.5 Primary Safety and All Efficacy

All confirmed efficacy events will be listed, indicating the patient id, randomized treatment group, age, gender, race and day of event relative to start of dosing. The time of death and cause of death will also be included in the listing of deaths.

4.5.1 Analysis of the Primary Safety/Efficacy Endpoint

The primary safety/efficacy endpoint is defined as the time from randomization to the onset of any event in the primary composite CV endpoint (CV-related death, nonfatal MI, nonfatal stroke).

In the unlikely event that two or more confirmed endpoints occur on the same day, the following hierarchy will be used to ascribe the primary component of the composite:

- Nonfatal Myocardial infarction
- Nonfatal Stroke
- CV-related Death

The contribution of each component of the primary composite safety/efficacy endpoint to the overall treatment effect will be examined.

Event rates of the primary composite CV endpoint will be estimated and Kaplan-Meier curves will be plotted for the time from randomization to first occurrence of the primary composite CV endpoint, by treatment group and prior CV risk at randomization based on IVRS.

Homogeneity of the effect of treatment on the components of the primary safety/efficacy CV composite endpoint will be assessed using the method proposed by Lunn and McNeil[9] (1995). Briefly, this method requires augmenting the analysis dataset by including one observation per component of the CV composite per subject, with an additional variable indicating the type of the potential event (CV-related death, nonfatal MI, nonfatal stroke). If a patient experienced an event which counted as the first instance of the CV composite endpoint, the event status for that event will be one and it will be zero for the other two types of events, which will be censored at the time the first event occurred. If a patient did not have CV composite endpoint, event status will be zero for all three component types of events. For example, if a patient had nonfatal MI on day 270 which counted as his first occurrence of the CV composite, he would have three observations in the analysis dataset: 1) type=nonfatal MI, status=1, time=270; 2) type=nonfatal stroke, status=0, time=270; 3) type=CV death, status=0, time=270. The augmented dataset will be analyzed using Cox regression with (time, status) as response variables and event type, treatment and treatment by event type interaction as covariates. To account for the use of multiple observations per subject in the analysis, Lin-Wei robust sandwich variance[3] will be used. The test of treatment by event type interaction will be the test of homogeneity of treatment effect on the components of the CV composite endpoint. Hazard ratios and 95% CIs for treatment effect on each component of the primary endpoint will be produced.

4.5.1.1 Primary Safety Analysis: Non-inferiority of EQW versus Placebo

To determine whether EQW is non-inferior to placebo, a non-inferiority margin of 1.30 in terms of hazard ratio with respect to developing the primary composite CV endpoint will be used.

The primary safety hypothesis (H_1) is defined as:

H_0: HR $\geq$ 1.3 *vs.* H_1: HR < 1.3

The hypothesis of non-inferiority will be tested at a one-sided significance level of 0.02495 in the ITT population using a Cox Proportional Hazards model which includes treatment as explanatory factor with prior CV event at randomization based on IVRS as a stratification factor. The two-sided 95% confidence interval for the hazard ratio of EQW to placebo will be estimated. If the upper limit of the two-sided confidence interval for the estimated HR for the stratified Cox model is below the non-inferiority margin of 1.30 then non-inferiority of the

primary composite CV endpoint in patients treated with EQW in addition to usual care compared to that of patients treated with usual care alone will be declared.

4.5.1.2 Primary Efficacy Analysis: Superiority of EQW versus Placebo

If the non-inferiority hypothesis is met, the hypothesis of superiority of EQW, when used in addition to usual care versus usual care without EQW with regard to the risk of developing the primary composite CV endpoint will be tested at a one-sided significance level of 0.02495 (i.e. two-sided 0.0499).

The efficacy hypothesis (H_1) is defined as:

$$H_0: HR \geq 1 \textit{ vs. } H_1: HR < 1$$

The Intention to Treat (ITT) population will be used to evaluate the primary efficacy hypothesis. The p-value will be estimated using the same Cox Proportional Hazards model as in the non-inferiority analysis . The estimated HR and two-sided 95% confidence interval for the hazard ratio of EQW to placebo will also be presented.

The above primary safety and efficacy analyses will use the Primary Censoring Scheme (see Section 4.1.2.1).

4.5.1.3 Assessment of Model Assumption

The assumption of proportional hazards for the factor for treatment group will be assessed visually using log-cumulative hazard plots for each stratum, and with models which assess the treatment effect in categorized time intervals (< 1 year, 1- <2 years, 2-<3 years, >=3 years), or time-dependent covariates in the model. The effect of any departures from proportional hazards will be discussed as part of the presentation of results of the analyses. If there is evidence of non-proportionality appropriate further analyses using Lin-Wei information sandwich[3] may be conducted.

4.5.1.4 Sensitivity Analyses of the Primary Efficacy Endpoint

It is expected that complete information on the components of the primary composite endpoint (and as much as possible of the eCRF data for patients contacted by telephone) will be obtained for all patients including those who prematurely discontinue investigational product, unless they refuse any form of follow-up and withdraw consent or where final status could not be determined.

For the primary efficacy endpoint, the following sensitivity analyses will also be performed:

1. Analyze the data in ITT population using Primary Censoring Scheme (see Section 4.1.2.1) and using a Cox proportional hazards model that includes treatment as an explanatory factor and prior CV risk group at randomization based on CRF data as stratification variable.

2. On-treatment analysis in the ITT population using On-treatment and On-treatment + n days Censoring Schemes (see Section 4.1.2.1) and using the same Cox Proportional Hazards model as in the primary safety and efficacy analysis.
3. Analyze the data in Per-Protocol population using the same Cox Proportional Hazards model as in the primary safety and efficacy analysis. Patients with protocol violations will be analyzed as indicated in the Per-Protocol section while others will be analyzed using Primary Censoring Scheme (see Section 4.1.2.1).
4. Analyze the data in ITT population using Cut-off Date Censoring Scheme (see Section 4.1.2.1) and using the same Cox Proportional Hazards model as in the primary safety and efficacy analysis.

In case of a difference in inference between the primary analysis and the sensitivity analyses, further exploratory analyses will be conducted to understand the reasons for a possible difference. Models with additional variables will be considered as appropriate. The site-reported primary efficacy endpoint, regardless of the status of adjudication, will be summarized descriptively.

4.5.1.5 Planned Subgroup Analyses

Subgroup analyses for the primary CV composite endpoint will be performed on the ITT population in order to explore whether the treatment effect on the risk of developing CV events is consistent across subgroups.

Subgroup analyses to evaluate variation in treatment effect will be performed on the basis of tests for interaction using the Cox proportional hazards model stratified by prior CV event at randomization based on IVRS (not applicable for the first subgroup listed) with terms for treatment group, the subgroup variable and treatment by subgroup variable interaction. P-values for the interaction with treatment for each of these subgroup variables will be provided and p-value of <0.1 will be considered as significant interaction. However, it is recognized that testing many subgroups can yield spurious false positive outcomes so that any significant interaction will be further examined to better understand its nature. If some subgroups have very few patients with events, they may be excluded from the interaction test.

Additionally, treatment effects within each subgroup will be examined separately using Cox proportional hazards models stratified by prior CV event at randomization based on IVRS (not applicable for the first subgroup listed) with terms for treatment group. Event rates by treatment and HRs with 95% confidence intervals will be reported for each subgroup. Forest plots will be generated displaying the estimated hazard ratios and 95% confidence intervals for each subgroup will be presented.

The following subgroups determined at baseline will be examined:

- Prior CV event at randomization based on IVRS: yes, no
- History of congestive heart failure: yes, no

- Geographic region:North America, Latin America, Europe and Asia Pacific
- Age groups: <65, >=65 years; <75, >=75 years
- Gender
- Race: Indian (American) or Alaska Native, Asian: Asian (Oriental), Asian (Other), Black, Native Hawaiian or Other Pacific Islander, includes Maori (New Zealand) and Aboriginal (Australian), White: Caucasian or White, Hispanic
- BMI group: <30, >=30 kg/m^2
- Baseline antihyperglycemic oral agent therapy (oral defined as all except insulin or pramlinitide; including "other"): oral agent vs. no oral agent
- Baseline Insulin use: Insulin use vs. no insulin use
- Baseline DPP-4i use: DPP-4i use vs. no DPP-4i use
- HbA1c group: <8.0%, >=8.0%
- Duration of diabetes group: <5, 5-14, >=15 years
- eGFR groups (ml/min/1.73m2):
  - <60, >=60
  - Stage 1: 90+, Stage 2: 60-89, Stage 3: 30-59, Stage 3a: 45-59, Stage 3b: 30-44, Stage 4: 15-29, Stage 5: <15

(see Section 4.3.2for subgroup definitions)

4.5.2 Analyses of the Secondary Endpoints

4.5.2.1 Main Analyses

The secondary efficacy endpoints will be analyzed similarly to the primary efficacy analysis. For each of the secondary efficacy endpoints listed in Section 3.1.2 the p-value and two-sided 95% confidence interval for the hazard ratio of EQW to placebo will be estimated using a Cox Proportional Hazards model which includes treatment as explanatory factor and prior CV event at randomization based on IVRS as a stratification factor.

Homogeneity of the effect of treatment on fatal vs nonfatal MI and on fatal vs nonfatal stroke will be assessed using the method proposed by Lunn and McNeil[9] (1995).

Following the sequential testing strategy outlined in Section 4.1.1, if superiority for the primary efficacy endpoint is demonstrated at the one-sided 0.02495 (i.e. two-sided 0.0499) significance level then superiority of EQW relative to placebo for all-cause death will be tested at the one-sided 0.02495 significance level and so on.

Event rates will be estimated and Kaplan-Meier curves will be plotted for the time from randomization to first occurrence of each secondary efficacy endpoint, by treatment group and prior CV risk at randomization based on IVRS.

4.5.2.2 Sensitivity Analyses

An on-treatment analysis using the ITT population using On-treatment and On-treatment + n days Censoring Schemes will be performed for all cause death as a sensitivity analysis. The site-reported all cause death, regardless of the status of adjudication, will be summarized descriptively.

4.5.2.3 Exploratory Analyses

As a patient can have recurrent events, there will be three additional separate analysis; 1) time to all MI events (fatal and nonfatal), 2) time to all stroke events (fatal and nonfatal), and 3) time to all MI, stroke and CV death combined. These analysis will be performed using the Andersen-Gill[5], modified Cox regression approach, for EQW versus Placebo.

4.5.3 Analysis of Additional Efficacy Endpoints

All time to event additional efficacy endpoints (congestive heart failure, revascularization procedure, and initiation of first co-interventional agent) will be analyzed using the same approach as in the primary efficacy analysis based on the ITT population.

Change from baseline in HbA1c, body weight, blood pressure and lipid profile on ITT population will be analyzed by mixed models for repeated measures (MMRM). The model will include change from baseline of the measure of interest as the dependent variable, baseline value of the measure of interest, time, prior CV event at randomization based on IVRS, treatment group, time by treatment interaction and baseline value by time interaction as fixed factors, and patient random effect. We will evaluate the linearity assumption for time and time by treatment interaction effects. In case the linearity assumptions are violated, piecewise-linear or higher order polynomial terms for time may be included in the model. To model the covariance structure, the within patients unstructured covariance structure will be used. The MIXED model is computationally intensive, if the algorithm does not converge, the Toeplitz, first-order autoregressive or compound symmetric covariance structure will be used. The model will be used to derive a least squares estimate of the treatment difference with 95% confidence interval and corresponding two-sided nominal p-value. Further, two-sided 95% confidence intervals for the mean change within each treatment group will be calculated. Missing data will not be imputed. This model will be used to assess the time points at 1, 2 and 3 years although descriptive summaries at all visits will also be presented.

Triglycerides data will be analyzed after the natural logarithmic transformation. The LS mean and the corresponding 95% CI will be calculated at the log scale, and the geometric mean ratio and the corresponding 95% CI will be calculated by taking the anti-log of the corresponding values within each treatment group and for treatment comparisons.

Note that a baseline assessment and at least one post-randomization measurement is required for inclusion in this analysis.

4.5.4 Analysis of quality of life (QoL), Costs and Cost Effectiveness

Analyses evaluating quality of life, medical resource use, total direct medical costs and the cost-effectiveness of EQW in addition to usual care compared with usual care without EQW, will be described in a separate SAP. These analyses will meet objectives 5, 6 and 7 as described in Section 1.1.3, and will be reported independently from the Clinical Study Report.

4.5.5 Genetic and Biomarker Samples

As part of this study, pharmacogenomic, proteomic, and metabolomic analyses may be performed on samples from patients who have given appropriate consent. These analyses, if performed, will be described separately.

4.6 Other Safety

Primary safety analyses are described in Section 4.5.1.1. This section describes analyses for the other safety endpoints. Other safety endpoints include selected AEs (see Section 3.2), SAEs, selected laboratory parameters and vital signs.

Adverse events will be coded using MedDRA, Version 17.0 or newer.

All safety observations will be listed regardless of when it occurred and whether the patient was taking blinded study drug.

All adverse events will be summarized for the Safety Population during the treatment period (from start of study drug to study drug end), after treatment (after study drug discontinuation to end of study) as well as overall (throughout the study period). Other safety endpoints (e.g. labs, vitals) will also be summarized as indicated in the specific sections below.

4.6.1 Serious Adverse Events

The number and percentage of patients reporting SAEs in each treatment group will be tabulated by system organ class (SOC) and preferred term (PT); and by SOC, PT, and severity. If more than one event occurs with the same PT for the same patient, the patient will be counted only once for that PT using the most severe occurrence for the summarization by severity.

The incidence of most frequent SAEs and SAEs leading to temporary or permanent discontinuation of study medication will be summarized by PT and treatment group, sorted in decreasing frequency for the EQW treatment group. In addition, the incidence of fatal SAEs (i.e. events that caused death) will be summarized separately by PT and treatment group. Also, the incidence of "related" AEs will be summarized in a similar manner.

SAEs will also be presented by SOC, PT and treatment group in subgroups of patients defined by baseline DPP-IV therapy (DPP-IV inhibitors vs non- DPP-IV inhibitors), baseline renal function, age and prior CV event (yes vs no).

Selected SAEs will be listed, such as those leading to treatment discontinuation or those associated with an overdose, indicating the patient ID, treatment group, age, gender, race, day of onset relative to first dose date, resolution date, relationship, severity, action taken and outcome.

In addition, adjudicated all-cause death will be summarized descriptively for the Safety population.

4.6.2 Other Adverse Events

Diabetic complications and expected events collected in the study will be summarized by treatment. Summaries ofneoplasia, pancreatitis, and severe hypoglycemia will be presented separately as well.

All reported severe hypoglycemic events, adjudicated ventricular fibrillation/tachycardia, adjudicated acute pancreatitis and adjudicated charter-defined malignancies will be summarized by treatment. The number and incidence rate per 100 patient-years of these events by treatment groups will be reported. The numerator is the number of events; the denominator is the overall total exposure (person-years) within the period specified calculated from start of event counting period up to the end of event counting period regardless if the patient had events or not. The resulting incidence rate is multiplied by 100 to express the rate per 100 person-years. For severe hypoglycemia events, the incidence rate will be presented per person-years by treatment group for the entire study and additionally within the following sub-groups: patients who were on insulin and/or a sulfonylureas during the study vs. those that were not. Additionally, the number of severe hypoglycemia events will be compared between treatment groups using a negative binomial regression if there are sufficient events in both treatment groups. Kaplan Meier estimates of time to first incidence of: severe hypoglycemic events, confirmed acute pancreatitis and charter-defined malignancies will be summarized by treatment.

Analysis of severe hypoglycemic events will also be generated in the ITT population.

4.6.3 Clinical Safety Laboratory endpoints

Calcitonin concentrations and serum creatinine were measured periodically in this trial. Descriptive statistics for above laboratory values and eGFR and changes from baseline at each assessment time point, and the maximum and minimum values will be presented by treatment group.

In addition, for patients with a screening calcitonin >40ng/L or a follow-up calcitonin ≥ 50ng/L, data was collected to elicit the degree of safety workup undertaken following the

notification of an abnormal calcitonin value. This data will be summarized descriptively and also listed.

Potentially clinically significant (PCS) values of the lab parameters of interest are listed in Table 4.6.3.1. The number and percentage of patients with post-baseline PCS values will be tabulated by treatment group. The percentages are to be calculated relative to the number of patients with baseline and at least one post-baseline assessment. The numerator is the total number of patients with at least one post-baseline PCS value. A listing of patients with post-baseline PCS values will also be provided.

Table 4.6.3.1 Criteria for Potentially Clinically Significant Laboratory Values

Laboratory Parameter	Flag	Observed Value
Calcitonin	High	>= 50 ng/L
eGFR	Low	< 30 mL/Min/1.73m^2

In addition to calcitonin and creatinine, additional labs were collected periodically when available (eg, HbA1c, lipids [HDL, LDL, TC, and TG], hemoglobin, Hs-CRP, RDW (red cell distribution width), BNP, Urine albumin/creatinine ratio). Descriptive statistics for these additional laboratory values and changes from baseline at each assessment time point will be presented by treatment group.

4.6.4 Vital Signs

Descriptive statistics for vital signs (e.g., systolic and diastolic blood pressure, heart rate and body weight) and their changes from baseline at each visit, to the maximum and minimum values will be presented by treatment group.

4.7 Interim Analysis

Two formal interim analyses were planned after approximately 453 and 906 primary composite CV events are adjudicated, corresponding to one-third and two-thirds, respectively, of the target 1360 primary composite events.

To adjust the multiplicity for the interim analysis, the Haybittle-Peto[i] spending function will be used. The study termination guideline for overwhelming superiority will be two-sided p-value < 0.0001 (i.e. <0.00005 one-sided) for the first interim analysis and two-sided p-value <0.001 (i.e. <0.0005 one-sided) for the second interim analysis. To control the Type 1 error rate at 0.05, a significance level of 0.0499 (two-sided) will be used for the final analysis.

At an interim analysis, only superiority test of primary efficacy endpoint will occur. The hypothesis will be tested at one-sided 0.00005 at the first interim (and at one-sided 0.0005 at

the second interim) in the ITT population using a Cox Proportional Hazards model which includes treatment as explanatory factor with prior CV risk at randomization based on IVRS as a stratification factor.

If the stopping boundary for efficacy is met at either of the interim analyses, the DSMB may recommend terminating the study earlier than planned. The DSMB may, however, also advise terminating the study early for safety or ethical reasons.

The interim analyses will be performed by an independent statistical group. Further details regarding interim analyses, including details on interim assessments of safety can be found in the DSMB Charter.

5. CONVENTIONS

5.1 Baseline Measurements

Unless specified otherwise, a baseline value is the last assessment taken prior to or at randomization. When there is a missing baseline assessment it will not be imputed, thus, patients are excluded from any changes from baseline analysis for which they have a missing baseline value.

5.2 Multiple Measurements

For tabulations of changes from baseline or shift analyses, if multiple measurements are obtained within the same nominal visit, then the measurement obtained on the day closest to the target day for that nominal visit will be used; in the case of a tie, the measurement obtained on the earlier day will be used in the analyses; in the case of multi measurement at same day and time, the worst value will be used.

5.3 Counting Rules for Adverse Events

5.3.1 At Patient Level

Where a patient has the same AEs (SAEs), based on PT, reported multiple times in a single analysis period, the patient will only be counted once at the PT level in adverse event frequency tables.

Where a patient has multiple AEs (SAEs) within the same SOC in a single analysis period, the patient will only be counted once at the SOC level in adverse event frequency tables.

When a patient has the same AEs (SAEs), based on PT, reported multiple times in a single analysis period, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

- Relationship to study medication
- Intensity of event

- Onset date and time

1. When assessing relationship to study medication, relationship will be categorized into two categories - related and unrelated ("definitely related to study drug", "probably related to study drug", and "possibly related to study drug" will be categorized into "related" while "probably not related to study drug" and "definitely not related to study drug" will be categorized into "unrelated") . Related events will take precedence over unrelated events in determining the event to include in summary tables.
2. More intense events will take precedence over less intense events in determining the event to include in summary tables.
3. Earlier onset date-time events will take precedence over late onset date-time events in determining the onset to include in summary tables.

When reporting adverse events by intensity, in addition to providing a summary table based on the event selection criteria detailed above, summary tables will also be provided based on the most intense event during the analysis period - independent of relationship to study medication. For these tables, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

- Intensity of event
- Onset date and time

5.3.2 At Event Level

At event level, each unique AE record will be counted. Unique AE record can be obtained by collapsing all AE records following a standard algorithm described below. This algorithm is not applicable to hypoglycemic events. In addition to frequency summary, exposure adjusted summary will also be provided where the overall exposure of a patient is calculated from first dose day to the last day of treatment regardless of whether a patient has had an event or not.

To ensure that multiple events for the same patient are counted accurately in the summaries, for each patient and PT, AE records will be collapsed into a single record (unique AE) when:

1. Multiple AE records have the same onset date,
2. The onset date of an event record is either the same day or 1 day later than the resolution date of a preceding event record (contiguous events),
3. The onset date of an event record is after the onset date and prior to or on the resolution date of a preceding event record (overlapping events).

The unique AE record will contain the earliest onset date, latest resolution date (if available), highest intensity, highest relationship in the following order (highest to lowest: definitely related to study drug, probably related, possibly related, probably not related, definitely not related), and highest action taken in the following order (highest to lowest: drug discontinued,

drug interrupted, none). In addition, the unique AE record will be classified as a SAE if at least 1 AE record was classified as a SAE and also the unique AE record will be classified as requiring treatment if at least 1 AE record required treatment.

5.4 Missing Date of Study Medication

Imputations associated with missing date of study medication will be described in a separate document.

5.5 Missing Dates

Imputations associated with missing dates, such as dates of birth and death will be described in a separate document.

5.6 Allocation of Countries to Regions

North America: Canada, US

Latin America: Argentina, Brazil, Chile, Columbia, Mexico

Asia Pacific: Australia, China, Hong Kong, Malaysia, New Zealand, Philippines, South Korea, Taiwan, Thailand

Europe:

Western: Austria, Belgium, Germany, United Kingdom, Spain, Italy, Netherlands, South Africa, Israel

Eastern: Bulgaria, Czech Republic, Hungary, Latvia, Lithuania, Poland, Romania, Russian Federation, Slovakia, Ukraine

6. CHANGES OF ANALYSIS FROM PROTOCOL

1. When summarizing data using the Safety population, patients will be analyzed As Treated. If a patient receives any exenatide study drug, then the patient will be counted in the Exenatide arm, regardless of the amount of medication received; otherwise the patient will be counted in the placebo arm. Protocol indicated: ‘if a patient is found to have taken a study therapy for the entire duration of the study, different from that to which he/she was randomized, then the patient is counted in the treatment group of the drug he/she actually received‘.
2. Protocol deviation of ’Received incorrect treatment for >3 months’ in the protocol was changed to ’Received incorrect treatment for >6 months’ in this SAP, because visits occurred every 6 months and is when an error in treatment would most likely be identified.

3. Patients are censored as described in Section 4.1.2.1. Protocol indicates 'patients who do not have any events during the study will be censored at the Trial Termination Visit date', and Section 4.1.2.1 provided more specific details and explanation.
4. Section 9.11 of the protocol had the following sentence added as a minor clarification in Amendment 6: *For the main clinical study report (CSR), the quality of life data will be summarized descriptively for baseline and changes from baseline by treatment*. In fact that will not be done, as the data is complex and not suited for simple descriptive analyses. This data will be prepared independently from the main CSR, as stated in previous sections of the SAP and protocol.

7. CONTENT OF REPORTS

The results of this study will be presented in a standard Clinical Study Report (CSR).

8. REFERENCES

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[4] Levy AS, Coresh J, Greene T, Stevens, LA, Zhang YL, Hendriksen S, et al. Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145(4):247-54.

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[8] Rubin, D. B. (1987), Multiple Imputation for Nonresponse in Surveys, New York: John Wiley & Sons.

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9. APPENDIX

APPENDIX 1: Trial Plan (Protocol BCB109)

		Treatment Initiation		Follow-up [4]		Drug or Study Termination		
Evaluation	Screening Day -1	Randomization Day 0 Visit 1 [1]	Week 1 and Month 2 Visit 2 and 3	Semi-Annual	Annual	Drug Termination [5]	Trial Termination [8]	Post-Treatment Follow-up Contact [9]
Informed Consent/HIPAA [2] and Stored Blood Sample Authorization	X							
Medical History	X							
Physical Examination	X							
Height	X							
Blood Pressure, Heart Rate and Body Weight	X	X		X	X	X	X	
Calcitonin Blood Sample		X			X		X	
Collect and review available information including most recent HbA_{1c}, serum creatinine and lipid profile	X [6]			X	X	X	X	
Randomization		X						
If consent obtained, collect blood sample for genetic and genomic analysis		X [7]						
If consent obtained, blood sample (serum and plasma) and urine sample for archive		X			Year 1 only		X	
Drug Dispensation		X		X	X			
Used/Unused Vial Assessment				X	X	X	X	
Clinical and SAE Event Assessment		X	X	X	X	X	X	X
Conmed Assessment	X	X	X	X	X	X	X	
Confirm competency			X					

		Treatment Initiation		Follow-up [4]		Drug or Study Termination		
Evaluation	Screening Day -1	Randomization Day 0 Visit 1 [1]	Week 1 and Month 2 Visit 2 and 3	Semi-Annual	Annual	Drug Termination [5]	Trial Termination [8]	Post-Treatment Follow-up Contact [9]
with injections [3]								
EQ-5D Completion		X		Month 6 only	X	X	X	

[1] Wherever possible the screening and randomization visit should be combined.
[2] Informed Consent Form and if applicable, authorization to use and disclose protected health information.
[3] Patients will return approximately 1 week (±3 days) as well as 2 months (± 2 weeks) after Day 0 to perform a self-injection under the observation of the clinical site to confirm competency with injection. An additional visit can be considered at ~1 month if the patient is not able to adequately inject themselves.

[4] Semi-annual (±1 month) and Annual Follow-up (±1 month) Visits will occur in reference to Visit 1 Day 0 for the duration of participation in the trial.

[5] Patients who terminate study medication are required to have a Drug Termination Visit as part of their next scheduled study visit (unless a separate drug termination visit at that point is deemed necessary by the investigator). Patients will continue to be observed following the Drug Termination visit according to their planned visit schedule for the remainder of the trial. All procedures for remaining Semi-annual and Annual Visits are to be followed with the exception of Drug Dispensation.

[6] It is recommended that serum creatinine value draw dates be within 3 months of randomization but up to 12 months is acceptable (however, if > 6 months old and value is between 30-40mL/min/1.73m^2 it is recommended that a new serum creatinine value is obtained as part of usual care).

[7] Blood sample for genetic and genomic analysis may be collected at any time during the trial after consent is obtained.

[8] For patients who have been discontinued from trial medication for more than 70 days as of the Trial Termination Visit, the Trial Termination Visit will be the final study follow-up.

[9] Patients will be contacted by telephone to check for any clinical events, serious adverse experiences and hospitalizations that occurred within 70 days after the administration of the last dose of trial medication. (see Section 10.3.1).

SUMMARY OF SAP AMENDMENTS

Date	Brief description of change
13 Oct. 2010	Initial Approved SAP'
19 Feb. 2015 The protocol was amended on 25 Oct 2013 on the following, so was the SAP accordingly.	During second half of 2013, blinded review of the primary endpoint event rate, it was discovered that the observed event rate is lower than expected. That led to change in study assumptions. The sample size was increased from 9,500 to 14,000. The number of primary events were reduced to 1360 to detect 15% RRR with 85% power.
	Intention to treat analysis, the definition of primary end point is further clarified in that it will not include events after Executive committee cutoff date to close the study nor it will include events observed during the 10 week post study period.
	At the request of DSMB, on treatment analysis has been added.
09 March 2016 Due to stand-alone protocol amendment	The primary analysis will include adjudicated events through the Trial Termination Visit (rather than just the Cut-Off Date)
	Clinical Events will continue to be collected and managed as they have been throughout the entire study (refer to Protocol Section 10.3.1 and Protocol Appendix 1).
	Clarify that if the study terminates early for superiority, the key secondary endpoints will be tested at the same significance level as the primary endpoint in the interim analysis using the hierarchical test strategy.
	Clarify sensitivity analysis #3 in section 4.5.1.4.
	Clarify censoring schemes in Section 4.1.2.1.
	Update to region and race definitions (including the addition of Section 5.6)
	Remove analysis of hypoglycaemia from efficacy, and clarify hypoglycaemia assessments fall under safety endpoints
	Updated section 4.6.3 to add information about additional analysis of calcitonin elevations.
	Minor administrative/wording changes to Sections 2.2, 4.4.3, 4.5.3, and 5.5.
	Removal of the table of potentially clinical significant vital signs, as vital signs are not collected in a rigorous manner and because this study is

	focused on outcomes making "potentially clinically significant" changes less relevant.
23 Feb 2017	Section 1.1.2. Added detail on the components of the primary endpoint.
	Section 4.5.1. Inclusion of hazard ratio and confidence intervals for treatment effect on each of the components (non-fatal MI, non-fatal Stroke, CV death) of the primary composite endpoint.
	Section 2.1.3. Clarified definition of 'as treated'.
	Section 2.2. Defined early discontinuation of study drug.
	Section 3.1. Positively adjudicated strokes classified as subdural hematomas are excluded from the definition of stroke in the analysis.
	Section 3.1.1. Definition of fatal/non-fatal events was updated to include a 30 day window between the date of the event and the date of the death due to the event.
	Section 4.1.2. Clarification of censoring dates.
	Section 4.1.2.2. Added detail to description of tipping point analysis.
	Section 4.3.2. Updated race definition.
	Section 4.4.3. Updated definitions of baseline and new concomitant medications.
	Section 4.5.2.3. Added exploratory analysis of recurrent MACE events.
	Section 4.5.4. Removed language that quality of life data would be summarized descriptively for the CSR (instead, will be independently analysed and reported).
	Section 6. Added changes of analysis from protocol.
	Section 4.5.2.1. Added analysis on the homogeneity of the effect of treatment on fatal vs nonfatal MI's and on fatal vs nonfatal strokes.