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Supplementary appendix

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Supplementary Appendix for the Study of Diabetic Nephropathy with Atrasentan (SONAR) trial

This appendix has been provided by the authors to give readers additional information about the SONAR trial.

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Section 1: Committees Leadership and Investigators

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Taiwan	Kuang Tien General Hospital, Taichung	Shih-Ting Tseng

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Section 2: Supplementary Methods – Definitions Adverse Events of Interest

Of the 684 PT search terms that comprised AESI, 132 event terms were reported during the SONAR study. Some terms may be counted in more than one event category. The reported terms are listed below.

Event	MedDRAa terms
Hypervolemia or fluid retention	Oedema Peripheral, Weight Increased, Dyspnoea, Cardiac Failure Congestive, Cardiac Failure, Fluid Overload, Brain Natriuretic Peptide Increased, Dyspnoea Exertional, Peripheral Swelling, Pulmonary Oedema, Cardiac Failure Chronic, Fluid Retention, Oedema, Acute Pulmonary Oedema, Cardiac Failure Acute, Left Ventricular Failure, Cardiomegaly, Diastolic Dysfunction, Pulmonary Congestion, Cardiogenic Shock, Orthopnoea, Cardiorenal Syndrome, Left Ventricular Dysfunction, Acute Left Ventricular Failure, Chronic Left Ventricular Failure, Low Cardiac Output Syndrome, N-Terminal Prohormone Brain Natriuretic Peptide Increased, Nocturnal Dyspnoea, Normochromic Normocytic Anaemia, Ventricular Failure , Weight Fluctuation , Abnormal Weight Gain, Brain Natriuretic Peptide Abnormal, Cardiopulmonary Failure , Systolic Dysfunction
Cardiac Failure	Cardiac Failure Congestive, Cardiac Failure, Pulmonary Oedema, Cardiac Failure Chronic, Acute Pulmonary Oedema, Cardiac Failure Acute, Left Ventricular Failure, Cardiogenic Shock, Cardiorenal Syndrome, Acute Left Ventricular Failure, Chronic Left Ventricular Failure, Low Cardiac Output Syndrome, Ventricular Failure, Cardiopulmonary Failure
Anemia	Anaemia, Nephrogenic Anaemia, Iron Deficiency Anaemia, Haemoglobin Decreased, Haematocrit Decreased, Haemorrhagic Anaemia, Normocytic Anaemia, Anaemia Macrocytic, Anaemia Of Chronic Disease, Microcytic Anaemia, Anaemia Of Malignant Disease, Autoimmune Haemolytic Anaemia, Normochromic Normocytic Anaemia, Hypochromic Anaemia
Vasodilation	Hypotension, Dizziness, Syncope, Hypovolaemia, Presyncope, Orthostatic Hypotension, Blood Pressure Decreased, Septic Shock, Blood Pressure Inadequately Controlled, Cardio-Respiratory Arrest, Cardiogenic Shock, Dizziness Postural, Hypovolaemic Shock, Orthostatic Intolerance, Anaphylactic Shock, Systemic Inflammatory Response Syndrome, Coronary Artery Insufficiency, Ischaemic Enteritis, Toxic Shock Syndrome
Cardiac Toxicitiy	Atrial Fibrillation, Acute Myocardial Infarction, Coronary Artery Disease, Angina Pectoris, Myocardial Ischaemia, Myocardial Infarction, Arrhythmia, Angina Unstable, Atrial Flutter, Atrioventricular Block Complete, Arteriosclerosis Coronary Artery, Atrioventricular Block First Degree, Bundle Branch Block Left, Coronary Artery Stenosis, Supraventricular Tachycardia, Troponin Increased, Acute Coronary Syndrome, Atrioventricular Block Second Degree, Sinus Tachycardia, Atrioventricular Block, Bundle

	Branch Block Right, Ventricular Extrasystoles, Ventricular Tachycardia, Coronary Artery Occlusion, Sinus Arrest, Sinus Node Dysfunction, Supraventricular Extrasystoles, Adams-Stokes Syndrome, Arrhythmia Supraventricular, Atrial Tachycardia, Bradyarrhythmia, Bundle Branch Block Bilateral, Cardiac Hypertrophy, Cardiomyopathy, Defect Conduction Intraventricular, Hypertrophic Cardiomyopathy, Ischaemic Cardiomyopathy, Sinoatrial Block, Sinus Bradycardia, Subendocardial Ischaemia, Troponin I Increased, Ventricular Fibrillation, Coronary Artery Insufficiency, Coronary Artery Thrombosis, Extrasystoles, Hypertensive Cardiomyopathy, Prinzmetal Angina, Silent Myocardial Infarction, Sinus Arrhythmia, Sudden Cardiac Death

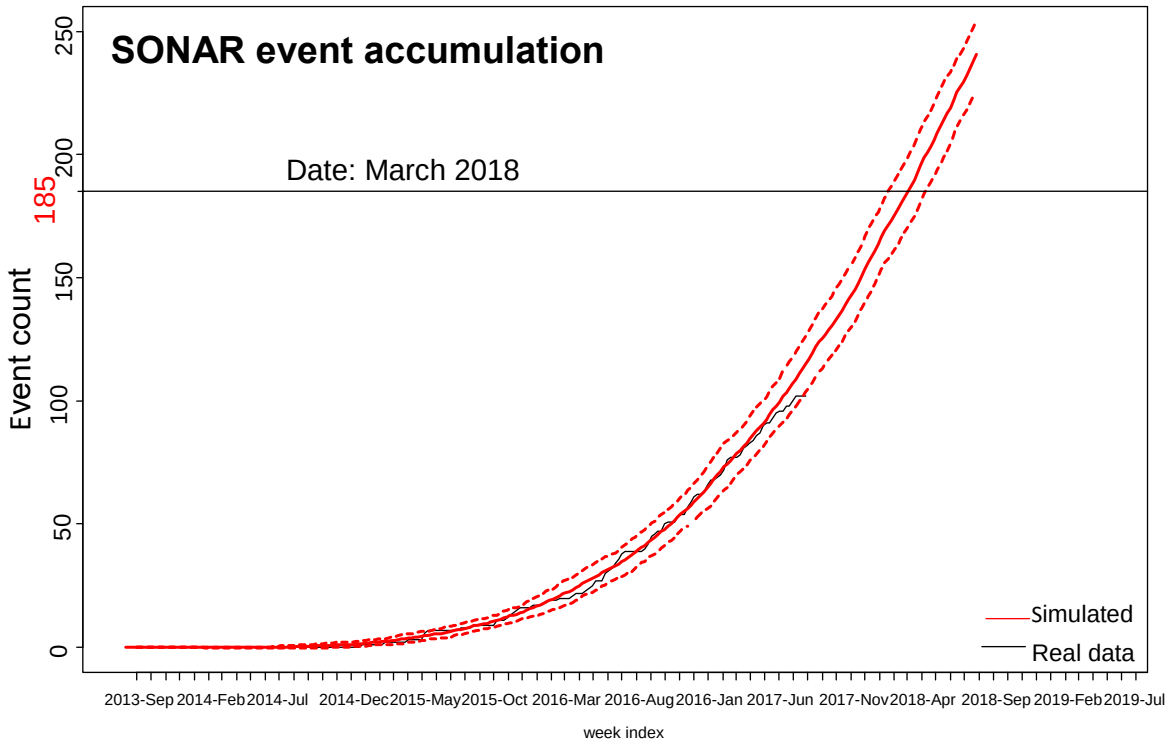
Section 3: Supplementary Methods – Statistical Methods

The trial was originally designed to continue until 425 primary renal events would have occurred which would have provided 90% power to detect a hazard ratio of 0.73 assuming a 6% event rate for the primary outcome at an alpha level of 0.05. During the course of the study, after all patients had completed the enrichment period and were randomized into the double blind treatment period it became clear that the primary event rate was lower than originally expected. Due to the persistently lower than expected renal event rate that yielded less than one-third the originally planned number of primary renal events (425) following four years of study conduct, the sponsor chose to discontinue SONAR. This decision was made after considering how the above characteristics may have impacted factors such as, the sponsor's ability to test the original hypothesis given the additional discontinuation of study drug and loss to follow-up expected in future years, as well as the possiblity that SONAR had selected a cohort at appreciably lower risk for renal events than originally planned.

At the time the decision was made to discontinue ongoing follow-up 121 events were collected. Extrapolations of the event accumulation indicated that by the time all patients would have completed their close-out visit, which was expected to occur in March 2018, 185 primary renal events would have occurred. A total of 185 events provided 90% power to detect a hazard ratio of 0.62 and 80% power to detect a hazard ratio of 0.66 at an alpha level of 0.05. At completion of the trial 184 events had occurred which provided 80% power to detect a hazard ratio of 0.65.

The low event rate in the responder group and the relatively fast event accrual after the decision to stop the trial are interesting also in relation to the new design of this trial, and will be further analyzed in future reports

Supplement Figure: SONAR event rate modelling performed in November 2017 at the time the decision was made to stop the trial.



Section 4: Study eligiblity criteria

Inclusion Criteria

Screening period

- Age 18 to 85 years at the first screening visit
- Completion of a written informed consent form before any study-related procedures
- Type 2 diabetes (including patients with latent autoimmune diabetes or insulin-treated patients without a history of diabetic ketoacidosis who also have a negative antiglutamic acid decarboxylase test *and* an elevated post-prandial serum C-peptide level) and receiving ≥1 antihyperglyemic medication and a renal angiotensin system (RAS) inhibitor (eg, angiotensin-converting enzyme inhibitor [ACEi], angiotensin II receptor blocker [ARB]) for ≥4 weeks before the second screening visit

Run-in period

- Screening laboratory values
    - Estimated glomerular filtration rate (eGFR) ≥25 to ≤75 mL/min/1.73 m^2 (this criterion applied only until approximately 300 patients with eGFR >60 mL/min/1.73 m^2 had been enrolled) and urinary albumin:creatinine ratio ≥300 to <5000 mg/g
    - Serum albumin concentration ≥2.5 g/dL
    - Brain natriuretic peptide (BNP) concentration ≤200 pg/mL
    - Serum potassium concentration ≥3.5 mEq/L
    - Systolic blood pressure (SBP) ≥110 to ≤180 mmHg at any time during the screening period
- maximum tolerated labeled daily dose (MTLDD)
    - If receiving a diuretic at screening, went directly to the last visit of the run-in period
    - If not receiving a diuretic at screening (unless medically contraindicated), started a diuretic and participated in the run-in period for ≥2 weeks

Enrichment period

- At the last visit of the run-in period
    - If receiving a diuretic at screening, had received a RAS inhibitor at the MTLDD for the 4 weeks before the enrichment period, with no dose adjustments
    - If not receiving a diuretic at screening (unless medically contraindicated), had received a RAS inhibitor at the MTLDD for the 4 weeks before the enrichment period and participated in the run-in period for ≥2 weeks

Double-blind treatment period

- At the last visit of the enrichment period

    - Received a RAS inhibitor at the MTLDD for the previous 6 weeks of the enrichment period, with no dose adjustments
    - Received a diuretic (unless medically contraindicated or clinically intolerable in the investigator's judgment [because of hypotension or hypokalemia])
    - No weight change ≥3 kg from the beginning of the enrichment period *and* absolute serum BNP concentration ≥300 pg/mL at the last enrichment visit
    - No increase >0.5 mg/L in serum creatinine concentration *and* >20% increase in serum creatinine concentration from the beginning of the enrichment period
- Male patients had to be surgically sterile or using ≥2 specified methods of contraception (list follows) from initial administration of study drug through 90 days after the last dose, unless the patient's partner(s) was postmenopausal or surgically sterile
    - Partner(s) using intrauterine device
    - Partner(s) using hormonal contraceptives (delivered orally, vaginally, parenterally, or transdermally)
    - Patient, partner(s), or both using barrier method (condoms, contraceptive sponge, diaphragm, or vaginal ring with spermicidal jellies or creams)
    - Total abstinence from sexual intercourse as the preferred lifestyle of the patient; periodic abstinence was unacceptable
- Male patients had to agree to not donate sperm from initial administration of study drug through 90 days after the last dose

Exclusion Criteria

Run-in period

- History of severe peripheral edema or facial edema requiring diuretics unrelated to trauma or a history of myxedema in the 4 weeks before the first screening visit
- History of pulmonary hypertension, pulmonary fibrosis, or any lung disease requiring oxygen therapy (eg, chronic obstructive pulmonary disease, emphysema)
- Documented diagnosis of heart failure, previous hospitalization for heart failure, or current constellation of symptoms (dyspnea on exertion, pedal edema, orthopnea, paroxysmal nocturnal dyspnea) felt to be compatible with heart failure, that was not explained by other causes, and for which there was a change in medication or other management directed at heart failure
- Known non-diabetic kidney disease (other than kidney stones)
- Liver enzymes (serum alanine aminotransaminase, serum aspartate aminotransaminase, or both) elevated to >3 × the upper limit of normal
- Hemoglobin concentration <9 g/dL
- Sensitivity to loop diuretics
- History of an allergic reaction or significant sensitivity to atrasentan (or its excipients) or similar compounds
- History of chronic gastrointestinal disease that, in the investigator's opinion, may cause significant gastrointestinal malabsorption

- History of secondary hypertension (ie, hemodynamically significant renal artery stenosis, primary aldosteronism, or pheochromocytoma)
- Significant comorbidities (eg, advanced malignancy, advanced liver disease) with a life expectancy <1 year
- Clinically significant cerebrovascular disease or coronary artery disease within 3 months before the first screening visit, defined as 1 of the following:
    - Hospitalization because of myocardial infarction or unstable angina
    - New-onset angina with positive functional study or coronary angiogram revealing stenosis
    - Coronary revascularization procedure
    - Transient ischemic attack or stroke
- Receipt of any investigational drug, including atrasentan, within 3 months before the first screening visit
- Receiving dialysis treatments or expected to receive dialysis or renal transplant within 6 months of screening
- Currently receiving rosiglitazone, moxonidine, aldosterone blockers, aliskiren, or a combination of ACEi and ARB
- Patient was a premenopausal woman defined (for study purposes) as any woman with menses in the past 2 years. For women who were <50 years old, serum follicle-stimulating hormone (FSH) concentration must have been >35 IU/L. Women who were surgically sterile or had a history of hysterectomy must also have had FSH >35 IU/L
- High risk for QT/QTc prolongation such as a family history of long QT syndrome, defined as QTc prolongation exceeding 450 ms in men or 460 ms in women
- Type 1 diabetes
- Clinically unstable regarding general, metabolic, or cardiovascular health, as determined by the investigator

Section 5: Study Endpoint and Event Definitions

Doubling of Serum Creatinine

Doubling of serum creatinine is an important component of the primary endpoint. To adjudicate this endpoint, baseline serum creatinine will be defined as the last non-missing measurement prior to or pre-dose on the first day of atrasentan administration at the beginning of the enrichment period. If more than one measurement is taken on the same day, then the average of the measurements will be used to calculate baseline serum creatinine. This will be designated as the "reference value" for determination of doubling of serum creatinine.

For purposes of defining doubling of serum creatinine, all creatinine measurements will be evaluated in mg/dL units. Subsequent serum creatinine values will be compared to the baseline serum creatinine to determine whether a doubling of the creatinine value has occurred.

All creatinine comparisons will occur automatically through the Central Laboratory. Once a doubling of serum creatinine has been recorded, the subject will return to the site sometime between 30 and 40 days from the last visit to have blood sampling for a confirmatory serum creatinine measurement.

The date of initial doubling will be defined as day one for purposes of counting days to confirmation. If, for practical reasons, the participant has returned for the confirmation visit prior to 30 days, and no subsequent confirmatory visit is available, the event will be assembled and sent to the adjudicators, who will have discretion to adjudicate with the available data on a case by case basis.

The confirmatory doubling of serum creatinine will be flagged by the Central Laboratory and marked as confirmed if the repeat creatinine continues to show at least a doubling from the baseline value. Confirmed doubling of serum creatinine will be adjudicated positively if the process is deemed irreversible in the judgment of the adjudicator.

Date of event will be the date on which the creatinine first doubled. If the subject starts chronic renal replacement therapy (RRT) prior to the 30-day confirmation, doubling of serum creatinine will be considered to be confirmed if the subject is still receiving chronic RRT on Day 30.

The endpoint of doubling of serum creatinine is intended to be based on laboratory values measured via the study Central Laboratory. However, in instances where Central Laboratory values are unavailable, the adjudicators will have discretion to determine whether adequate evidence of endpoint determination has been achieved. Reasons for failure to document doubling of serum creatinine include death, renal transplantation, trial terminated, subject could not be contacted, or other reasons.

End-Stage Renal Disease (ESRD)

At this time there are no universally accepted guidelines that define the onset of end-stage renal disease (ESRD). Therefore, the definitions outlined below will serve to identify and establish events as ESRD.

As chronic kidney disease (CKD) progresses to ESRD, subjects frequently present with a characteristic constellation of symptoms. These are due to worsening uremia. Once this constellation develops, RRT, whether it be renal transplantation, peritoneal dialysis, or hemodialysis, is necessary to reverse the symptoms of chronic uremia and prolong life.

The diagnosis of ESRD is possible if the subject has an eGFR < 15 mL/min/1.73 m^2 (confirmed at 90 days), undergoes kidney transplantation, or is initiated on chronic dialysis.

eGFR < 15 mL/min/1.73 m^2

ESRD will be diagnosed when there is an eGFR < 15 mL/min/1.73 m^2 that is confirmed approximately 90 days later or otherwise judged to be sustained by the adjudicators in individual cases. Confirmatory values within the intended study visit window will be acceptable for purposes of adjudication.

If the subject is known to have chronic progression and has eGFR < 15 mL/min/1.73 m^2 confirmed at > 30 days but < 90 days, or even < 30 days and is not known to recover, the definition of ESRD may be considered met. Reasons for failure to document eGFR < 15 mL/min/1.73 m^2 at ≥ 90 days include death, renal transplantation, trial terminated, subject could not be contacted, or other reasons.

If the subject starts chronic RRT before the planned 90 day confirmation, eGFR < 15 mL/min/1.73 m^2 will be confirmed if the subject is still receiving chronic RRT on Day 90 (or earlier for reasons including death, futility, renal transplantation, trial terminated, subject could not be contacted, or other reasons).

Confirmed eGFR < 15 mL/min/1.73 m^2 will be adjudicated positively if the process is deemed irreversible. Date of event will be the date on which the first eGFR < 15 mL/min/1.73 m^2 occurred.

The endpoint of ESRD as defined by eGFR < 15 mL/min/1.73 m^2 is intended to be based on laboratory values measured via the study central laboratory. However, in instances where Central Laboratory values are unavailable, the adjudicators will have discretion to determine whether adequate evidence of endpoint determination has been achieved.

Kidney Transplantation

Kidney transplantation is considered definitive RRT and is prescribed when irreversible CKD has progressed to a degree that uremic symptoms are anticipated or have already occurred. Death during the surgical placement of the kidney or shortly thereafter will still be considered kidney transplantation.

Chronic Dialysis

ESRD will be diagnosed if chronic dialysis is performed on a continuous, regular basis, and the subject is not subsequently known to recover (see below for details). Chronicity will be confirmed 90 days after initiation of dialysis. In cases where a 90 day confirmation is not available, the case will be adjudicated according to the definitions below.

Establishing Chronicity of Dialysis

Chronic Dialysis 90-Day Confirmation

The subject will be contacted at 90 days after the start of dialysis to document whether he or she continues on dialysis.

Chronic Dialysis 30-Day but Not 90-Day Confirmation

If the subject is known to have chronic progression and receives dialysis for > 30 days but < 90 days and is not known to recover, the definition of ESRD will be considered met. The lack of information of chronicity beyond 30 days may occur due to several reasons that will be documented. These include death, futility, subject declined dialysis, renal transplantation, trial terminated, subject could not be contacted, or other reasons.

Chronic Dialysis for Less Than 30 Days

If a subject with chronic progression initiates chronic dialysis but is unable to continue dialysis for even 30 days due to death, futility, subject declined dialysis, renal transplantation, trial terminated, subject could not be contacted, or other reasons, the subject will be considered to have reached the ESRD endpoint. The reason for failure to continue chronic dialysis for 30 days will be clearly documented by the adjudicators.

Date of event will be the date on which dialysis was initiated.

Definition of ESRD in the Setting of Severe Acute Kidney Injury

The intent of this trial is to identify the ability of atrasentan to delay progression of chronic kidney disease. However, it is recognized that sometimes it can be challenging to distinguish between chronic progression and cases of severe AKI requiring acute RRT. If a subject develops an episode of AKI secondary to another severe, acute illness (e.g., MI, Cardiogenic Shock, Sepsis, etc.) and requires acute RRT, such events will be adjudicated as ESRD if the subject has a continuous requirement for acute and/or chronic RRT for > 30 days and is not subsequently known to recover. Analogous to the cases presenting with chronic progression, confirmation at 90 days will be obtained if possible.

Given the complexity of acute or chronic kidney failure, the adjudication committee will have the option of adjudicating cases with death before 30 days based upon consideration of multiple risk factors (e.g., level of eGFR at the time of the event, progression of CKD prior to the event, severity of the acute insult, etc.) to determine if such cases should be adjudicated as ESRD. The adjudication committee will clearly document the rationale for adjudicating an event as ESRD or not ESRD when it occurs in the context of severe AKI. If such an event is not coded as ESRD, it will still be captured as an AKI event in the e-Clinical voting forms.

Date of ESRD Event

If an event is classified as ESRD, the initial date of the confirmed eGFR < 15 mL/min/1.73m^2, the date when dialysis was initiated, or the date of renal transplant will be the date of the event.

Renal Death

Subjects with CKD may die prior to initiating RRT. This may occur when the subject refuses RRT because they believe their current quality of life, with their expected lifespan, outweighs the quality and quantity of life following RRT. It may also occur when both the clinician and the subject consider RRT futile and believe that the subject's current quality of life, with their expected lifespan, outweighs the quality and quantity of life following RRT.

Such events will be classified as renal death when the subject dies following refusal of dialysis and no other cause of death is adjudicated.

The diagnosis of renal death is not intended for subjects in whom dialysis is not offered or withdrawn because of advanced cancer, severe sepsis, advanced HF, or terminal organ failure. Renal death is intended for those events in which dialysis is deliberately withheld due to advanced age of the subject, lack of availability of dialysis, or the wishes of the subject not to be dialyzed. When a more specific cause of death is adjudicated, such as sepsis, pneumonia, or trauma, such more specific causes will be designated as the primary cause of death.

Non-Fatal Cardiovascular Endpoints

Non-fatal cardiovascular endpoints include the secondary endpoints of MI and stroke, and the safety outcome of special interest, heart failure.

Non-Fatal MI

The expert consensus document on the third universal definition of MI for arriving at a diagnosis of MI will be followed. Acute MI will be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions, any of the following criteria will be sufficient to diagnose MI.

Spontaneous MI (Type 1)

Spontaneous MI is related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The subject may have underlying severe coronary artery disease (CAD) but on occasion, non-obstructive or no CAD.

Spontaneous MI is classified as an event when a subject demonstrates rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

1. Symptoms of ischemia.
2. New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB).
3. Development of pathological Q waves in the ECG.
4. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
5. Identification of an intracoronary thrombus by angiography or autopsy.

If cTn is not available then serial measurements of creatine kinase-MB would be sufficient – at least one value should show a rise above the local upper reference limit.

The following EKG findings will be considered significant manifestations of acute myocardial ischemia in the absence of LBBB or LVH:

New ST elevation at the J point in two contiguous leads with the cutpoints: ≥ 0.1 mV in all leads other than leads V2 – V3, where the following cutpoints apply: ≥ 0.2 mV in men ≥ 40 years; ≥ 0.25 mV in men < 40 years; or ≥ 0.15 mV in women.

ST depression and T wave changes.

New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads and/or T inversion ≥ 0.1 mV in two contiguous leads with prominent R wave or R/S ratio > 1.

"Demand" Related MI (Type 2)

Type 2 MI is classified as an event when a subject satisfies the diagnostic criteria of a Type 1 MI; however, the infarction is the result of a supply/demand inequity. Type 2 MI occurs in instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g., coronary endothelial dysfunction, coronary artery spasm,

coronary embolism, tachy-/brady-arrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH.

Cardiac Death Due to MI (MI Type 3)

Type 3 MI is classified as an event when a subject presents symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurs before cardiac biomarkers can be obtained, or before cardiac biomarker values would be increased. In these instances, the event will be adjudicated as a cardiovascular death due to MI per Section 0.

MI Related to Percutaneous Coronary Intervention (PCI) (MI Type 4a)

Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values $\geq 5 \times 99^{th}$ percentile URL in subjects with normal baseline values ($< 99^{th}$ percentile URL) or a rise of cTn values $\geq$ 20% if the baseline values are elevated and are stable or falling. In addition, the following findings may be considered:

1. Symptoms suggestive of myocardial ischemia, or
2. New ischemic ECG changes or new LBBB, or
3. Angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or
4. Imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality

MI Related to Stent Thrombosis (MI Type 4b)

Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99^{th} percentile URL.

MI Related to Coronary Artery Bypass Grafting (CABG) (MI Type 5)

Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values $\geq 10 \times 99^{th}$ percentile URL in subjects with normal baseline cTn values ($< 99^{th}$ percentile URL). In addition, the following may be considered:

1. New pathological Q waves or new LBBB, or
2. Angiographic documented new graft or new native coronary artery occlusion, or
3. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Non-Fatal HF

Hospitalization for HF

Hospitalization for HF is classified as an event if it meets all of the following criteria:

1. The subject is admitted to the hospital with clinical signs and symptoms consistent with HF.
2. The subject's length of stay in hospital is at least 24 hours (or includes a change in calendar date if the hospital admission and discharge times are unavailable).
3. The subject exhibits at least one of the following new or worsening symptoms:

Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)
Decreased exercise tolerance
Fatigue

Other symptoms of worsened end-organ perfusion or volume overload (e.g., confusion)

4. At least two (2) physical exam findings OR one (1) physical finding and at least one (1) diagnostic criterion are noted.
    a. Physical examination findings:

Peripheral edema
Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
Pulmonary rales/crackles/crepitations
Increased jugular venous pressure and/or hepatojugular reflux
S_3 gallop
Clinically significant or rapid weight gain thought to be related to fluid retention

    b. Diagnostic criteria:
        i. Increased B-type natriuretic peptide (BNP)/N-terminal pro-BNP (NT-proBNP) concentrations consistent with decompensation of HF (such as BNP > 500 pg/mL or NT-proBNP > 2,000 pg/mL). In subjects with chronically elevated natriuretic peptides, a significant increase should be noted as above baseline.
        ii. Radiological evidence consistent with pulmonary congestion
        iii. Clinically significant elevation of left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiography demonstrating E/e > 15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral (TCI) OR right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) > 18 mmHg, central venous pressure > 12 mmHg, or cardiac index < 2.2 L/min/m^2.

The subject received treatment specifically for HF, including at least one (1) of the following:

a. New or increased oral diuretic therapy
b. Intravenous diuretic, inotrope or vasodilator therapy
c. Mechanical or surgical intervention, including:
    i. Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device)
    ii. Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis)

In addition to the above, the HF subtype according to left ventricular systolic function will be assessed as relatively preserved, significantly reduced, or unknown. It is acknowledged that there is controversy regarding ejection fraction cutpoints, mode of assessment, and how recently assessments were made. In addition, clinically available left ventricular systolic function data are likely to be variable in quality since it is not a primary focus of the trial. However, given the potential importance of this distinction, adjudicators will assign HF subtype according to left ventricular systolic function, based on the available data and their best judgement. If a specific left ventricular ejection fraction is provided in the medical record, then < 45% will be designated as significantly reduced, and ≥ 45% will be designated as relatively preserved. If an ejection fraction range is provided in the report (such as 45% – 50%, for example), then the lowest ejection fraction in the range provided will be used as the ejection fraction for this designation.

If the EAC positively adjudicates the event, the date of hospitalization will be considered the date of the event.

What is Not Being Captured as Heart Failure?

If the subject is admitted to the hospital with another condition and develops HF during the course of hospitalization, then the diagnosis of HF as an event is NOT made. However, in certain instances the admitting diagnosis may be a condition that is often confused with HF such as pneumonia, COPD exacerbation, or pulmonary embolism. The diagnosis of HF as an event may be made by the EAC in these instances if the requisite criteria are met.

Hospitalized HF Equivalent

Subjects who require treatment for acute HF but do not require hospitalization will be designated as having a hospitalized HF equivalent. This is defined as someone who is treated in the emergency room, urgent care center, observation unit, or hospital, a diuretic dose is given intravenously to ameliorate the symptoms of HF, the intended effect is observed, and the subject is discharged after less than 24 hours.

Non-Fatal Stroke

For the diagnosis of stroke, the following 3 criteria should be fulfilled:

1. Rapid onset* of a focal/global neurological deficit with at least one of the following:
    a. Change in level of consciousness
    b. Hemiplegia
    c. Hemiparesis
    d. Numbness or sensory loss affecting one side of the body
    e. Dysphasia/Aphasia
    f. Hemianopsia (loss of half of the field of vision of one or both eyes)
    g. Complete/partial loss of vision of one eye
    h. Other new neurological sign(s)/symptom(s) consistent with stroke
2. Duration of a focal/global neurological deficit either
    a. $\geq$ 24 hours, or
    b. < 24 hours, if
        i. A therapeutic intervention resolves the symptoms (e.g., thrombolytic drug administration, intracranial angioplasty), (or)
        ii. Brain imaging documents a new hemorrhage or infarct, (or)
        iii. The neurological deficit results in death

No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion)

In the absence of confirmation via items 1, 2, and 3 above, a stroke may still be adjudicated using additional evidence including at least one of the following:

a. Neurology or neurosurgical specialist
b. Brain imaging procedure (at least one of the following):
    i. CT scan
    ii. MRI scan
    iii. Cerebral vessel angiography
    iv. Lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage)

* If the mode of onset is uncertain, a diagnosis of stroke may be made provided that there is no plausible non-stroke cause for the clinical presentation.

If the acute focal signs represent a worsening of a previous deficit, the worsening signs must have either persisted for more than 1 week, or persisted for more than 24 hours and be accompanied by an appropriate new CT or MRI finding.

Strokes will be classified as ischemic, hemorrhagic, or unknown.

For events adjudicated as non-fatal stroke, the date of first medical contact will be considered the date of the event.

Fatalities

All fatal events will be evaluated to determine the cause of death. The cause of death will be classified as cardiovascular death, presumed cardiovascular death, death due to other cause (non-cardiovascular), or death due to unknown cause. A fatality will only be considered death due to other cause (non-cardiovascular) if the cause of death is clear, unambiguous, and well-documented. Cardiovascular death will be further adjudicated as due to MI/ischemic heart disease, HF, stroke, cardiogenic shock, or other known cardiovascular causes (including arrhythmia, pulmonary embolism, abdominal aortic aneurysm rupture, thoracic aortic aneurysm rupture, or other causes). The date of death will be considered the date of the event.

Cardiovascular Death

The cause of death will be determined as the primary condition that caused the death, not the immediate mode of death.

The following definitions will be used for the adjudication of fatal cases.

Fatal MI/Ischemic Heart Disease

Fatal MI/Ischemic Heart Disease is classified as an event when a subject meets one of the following criteria:

1. Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
2. Death occurring as a direct cause or complication after a documented MI.
3. Death as a direct complication resulting from a procedure to treat an MI or its complication (e.g., PCI, CABG).
4. Death as a direct complication resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina), including cardiac catheterization or angioplasty, or stent deployment.
5. Death due to a MI that occurs as a direct consequence of a cardiovascular investigation/procedure/operation.

Fatal HF

Fatal HF is classified as an event if it meets the following criteria:

1. Death
2. No evidence of acute MI
3. No evidence of an arrhythmia
4. The subject exhibited at least one of the following new or worsening symptoms:
   a. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)
   b. Decreased exercise tolerance
   c. Fatigue
   d. Other symptoms of worsened end-organ perfusion or volume overload (e.g., confusion)
5. At least two (2) physical exam findings OR one (1) physical finding and at least one (1) diagnostic criterion are noted:
   a. Physical examination findings:
      i. Peripheral edema
      ii. Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
      iii. Pulmonary rales/crackles/crepitations
      iv. Increased jugular venous pressure and/or hepatojugular reflux
      v. S_3 gallop
      vi. Clinically significant or rapid weight gain thought to be related to fluid retention
   b. Diagnostic criteria:
      i. Increased B-type natriuretic peptide (BNP)/N-terminal pro-BNP (NT-proBNP) concentrations consistent with decompensation of HF (such as BNP > 500pg/mL or NT-proBNP > 2,000 pg/mL). In subjects with chronically elevated natriuretic peptides, a signification increase should be noted as above baseline.
      ii. Radiological evidence of pulmonary congestion
      iii. Clinically significant elevation of left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiography demonstrating E/e > 15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral (TCI) OR right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mmHg, central venous pressure ≥ 12 mmHg, or cardiac index < 2.2 L/min/m^2.

The subject received treatment specifically for HF, including at least one (1) of the following:
   a. Intravenous diuretic, inotrope or vasodilator therapy
   b. Mechanical or surgical intervention including:
      i. Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device)
      ii. Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis)

Cardiogenic Shock

Death due to cardiogenic shock is classified as an event if it meets all of the following criteria:
1. Death
2. No evidence of acute MI

3. No evidence of an arrhythmia
4. Systolic blood pressure (SBP) < 90 mmHg for more than 1 hour*
5. The subject is unresponsive to fluid resuscitation and/or heart rate correction
6. One of the following signs of hypoperfusion is present:
   a. Cool, clammy skin
   b. Oliguria (urine output < 30 mL/hour)
   c. Altered sensorium
   d. Cardiac index < 2.2 L/min/m^2

* SBP may be ≥ 90 mmHg for a time period of less than 1 hour if the blood pressure measurement or the time period is influenced by the presence of positive inotropic or vasopressor agents alone and/or with mechanical support.

Cardiovascular Death (Other Known Cardiovascular Cause)

Death due to a cardiovascular cause not included in the endpoint definitions for fatal MI, fatal stroke, fatal HF or cardiogenic shock will be adjudicated as a cardiovascular death, other known cause. Examples of CV deaths from other known CV causes include death attributed to an arrhythmia, pulmonary embolism, abdominal aortic aneurysm rupture, or thoracic aneurysm rupture.

Fatal Stroke

A fatal stroke is classified as an event that meets the following criteria:

1. Death occurs no more than 30 days following a stroke
2. The death is either a direct consequence of the stroke or a complication of the stroke

Presumed Cardiovascular Death

Deaths in which the participant has documented preceding signs, symptoms, or history consistent with a cardiovascular etiology but do not meet all the criteria for death due to MI/ischemic heart disease, HF, cardiogenic shock, or other specific cardiovascular cause may be considered, based on the adjudicators' best judgement, to be presumed cardiovascular death. Examples that may be considered presumed cardiac death are:

Subject has known history of severe chronic heart disease (CHD) and/or recent severe cardiovascular disease event (such as MI) and is found dead with no other explanation.

Subject did not have history of CHD, but manifested typical symptoms in the days or hours prior to death (complaining of chest pain, shortness of breath; took a spouse's nitroglycerin pills; had an ER visit for such symptoms) and was found dead with no other explanation.

Subject complained of palpitations and fast heart rate, and died suddenly.

Subject had history of known large uncorrected thoracic or abdominal aortic aneurysm and had chest or abdominal pain shortly before death.

Subject had history of thromboembolism or pulmonary embolism, or a typical scenario such as a long car ride and complained of symptoms such as unilateral leg pain, chest pain, shortness of breath, and died shortly after.

The above examples suggest at least moderate likelihood that the death was due to MI, arrhythmia, pulmonary embolism, abdominal aortic aneurysm rupture, or thoracic aneurysm rupture. The signs, symptoms, history, and other features that led the adjudicator to presume that a cardiovascular cause of death was likely will be clearly and amply documented as a narrative in the adjudicator comments section of the voting form.

Presumed Sudden Cardiac Death

Presumed sudden cardiac death is defined as: Unwitnessed death in a participant seen alive and clinically stable ≤ 24 hours prior to being found dead without evidence supporting a specific non-cardiovascular cause of death or a specific alternate cardiovascular cause of death.

Death Due to Other Non-Cardiovascular Cause

Death will be considered to be due to other cause when a clear etiology can be identified that is not cardiovascular. Examples of this include malignancy, accidental/trauma, pulmonary causes, gastrointestinal causes, hepatobiliary causes, pancreatic causes, renal, infection, non-infectious, hemorrhagic, suicide, drug overdose, non-cardiovascular system organ failure, and non-cardiovascular surgery.

Death Due to Unknown Cause

Death will be considered to be due to an unknown cause when there is death without a clearly defined etiology, and when criteria for the above specific causes are not met, including for Presumed Sudden Cardiac Death. This includes subjects found dead at home without a clear cause and no preceding signs or symptoms, and subjects who were previously clinically stable and die without any evidence or information of a specific cause of death.

Section 6 Supplementary Results

Supplement table 1: Baseline characteristics of non-responders

Variable*	**Atrasentan (N=509)**	**Placebo (N=511)**
Age, years	63.8 (9.1)	63.6 (8.9)
Female sex, *n* (%)	127 (25.0)	136 (26.6)
Race, *n* (%)		
White	313 (61.5)	300 (58.7)
Black	36 (7.1)	39 (7.6)
Asian	143 (28.1)	154 (30.1)
Other	17(3.3)	18 (3.5)
Weight, kg	87.5 (20.4)	86.3 (19.2)
BMI, kg/m^2	31.1 (5.8)	30.7 (5.9)
Duration of diabetes, years	15.6 (8.4)	16.1 (8.7)
Current Smoker, n (%)	97 (19.1)	92 (18.0)
Retinopathy, n (%)	146 (28.7)	146 (28.6)
Blood Pressure		
Systolic, mm Hg	136.4 (14.9)	135.5 (16.5)
Diastolic, mm Hg	75.0 (10.2)	74.7 (9.4)
Serum creatinine, µmol/L	154.6 (45.7)	156.4 (45.6)
eGFR, $ml/min/1.73m^2$	42.2 (14.3)	41.4 (13.4)
Cholesterol, mmol/L		
Total	4.6 (1.2)	4.6 (1.3)
LDL	2.8 (1.1)	2.8 (1.0)
HDL	1.1 (0.4)	1.1 (0.3)
HbA1c, %	7.8 (1.5)	7.9 (1.6)
Serum albumin, g/L	38.7 (3.8)	38.5 (3.8)
Hemoglobin, g/L	129.9 (18.3)	128.2 (17.1)
B-type Natriuretic Peptide, pg/mL	47.0 [27 – 81]	44.0 [25-86]
Serum potassium, mmol/l	4.5 (0.5)	4.5 (0.6)
UACR, mg/g	920 [501-1877]	920 [459-1854]
Prior Medication		
ACE-inhibitor, *n* (%)	172 (33.8)	186 (36.4)
Angiotensin Receptor Blocker, *n* (%)	340 (66.8)	340 (66.5)
Beta blocker, *n* (%)	203 (39.9)	198 (38.7)
Calcium channel blocker, *n* (%)	287 (56.4)	295 (57.7)
Diuretic, *n* (%)		
Loop	230 (45.2)	247 (48.3)
Thiazide	153 (30.1)	127 (24.9)
Other**	55 (10.8)	56 (11.0)
Statin, *n* (%)	374 (73.5)	374 (73.2)
Glucose-lowering therapies, n (%)		

Insulin	326 (64.0)	331 (64.8)
Metformin	179 (35.2)	175 (34.2)
Sulphonylurea Derivatives	120 (23.6)	159 (31.1)
DPP4-inhibitor	105 (20.6)	111 (21.7)
GLP-1 Receptor Agonist	22 (4.3)	27 (5.3)
SGLT-2 inhibitor	6 (1.2)	5 (1.0)
Antithrombotic agent, n (%)†	307 (60.3)	273 (53.4)

* Continuous variables are given as mean (SD) except BNP and UACR which are presented as median (25th to 75th Percentile).

** Other include chlorthalidone, indapamide, mefruside, metolazone, tripamide and xipamide

† Antithrombotic agents include anticoagulants and antiplatelets.

Supplement table 2: Secondary endpoints and annual rate of eGFR change in non-responders

	Atrasentan (N=509)	**Placebo (N=511)**	**Hazard Ratio (95% CI)**	**P-value**
	No. of patients (%)	*No. of patients (%)*		
Secondary Outcomes				
Time to a 50% eGFR reduction	66 (13.0)	77 (15.1)	0.81 (0.58 – 1.13)	0.205
Time to cardio-renal composite endpoint	104 (20.4)	116 (22.7)	0.83 (0.63 – 1.08)	0.160
Time to the CV composite endpoint: CV death, nonfatal myocardial infarction or nonfatal stroke	34 (6.7)	37 (7.2)	0.93 (0.58 – 1.48)	0.750
eGFR change				
eGFR change during the trial (ml/min/1.73m^2/year)	-4.1 (-4.6 - -3.6)	-4.6 (-5.1 - -4.0)		0.210

The annual mean rate of change (95%CI) are reported for eGFR change

Supplement table 3: Adverse events during the double blind treatment period in "non-resopnders"

	Atrasentan (N=508)	**Placebo (N=510)**	**P-value ǂ**
Any Serious Adverse Events, n† (%)	206 (40.6)	196 (38.4)	0.521
Any Adverse events leading to discontinuation	73 (14.4)	78 (15.3)	0.724
Treatment Emerging Adverse events of interest – n patients (%)‡			
Hypervolemia or fluid retention	206 (40.6)	173 (33.9)	0.032
Cardiac Failure*	34 (6.7)	16 (3.1)	0.009
Anemia	88 (17.3)	57 (11.2)	0.005
Vasodilation	42 (8.3)	56 (11.0)	0.167
Cardiac Toxicity	68 (13.4)	60 (11.8)	0.451
Serious Adverse events in >1% in either group – n patients (%)			
Acute kidney injury	22 (4.3)	8 (1.6)	0.010
Pneumonia	22 (4.3)	19 (3.7)	0.637
Congestive Cardiac Failure	14 (2.8)	7 (1.4)	0.129
Acute Myocardial Infarction	13 (2.6)	7 (1.4)	0.184
Coronary artery disease	11 (2.2)	2 (0.4)	0.012
Anemia	11 (2.2)	1 (0.2)	0.003
Hypoglycemia	8 (1.6)	4 (0.8)	0.263
Cardiac failure	6 (1.2)	3 (0.6)	0.341
Atrial Fibrillation	6 (1.2)	3 (0.6)	0.341
Urinary tract infection	5 (1.0)	5 (1.0)	1.000
Cerebral accident	9 (1.8)	6 (1.2)	0.450
Acute respiratory failure	6 (1.2)	1 (0.2)	0.069

Data are derived from the safety population including 508 patients in the atrasentan and 510 patients in the placebo group

† Number of patients with at least one serious adverse event

ǂ P values calculated from Fisher Exact Test.

‡ Detailed definitions of treatment emerging adverse events of interest are provided in supplementary appendix 2

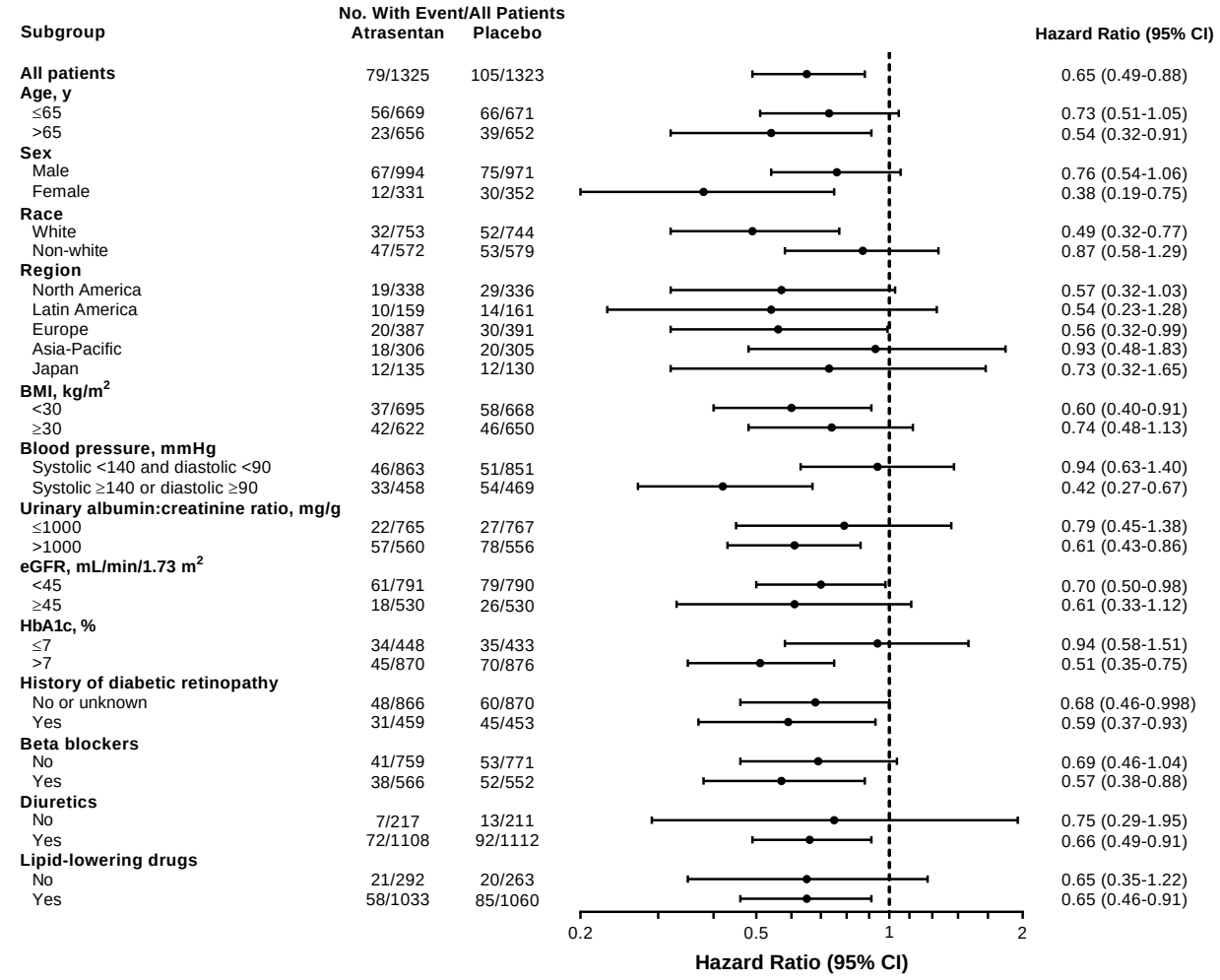
*Cardiac Failure events included all investigator reported treatment emerging adverse events.

Supplement table 4: Treatment emergent adverse events in “responders” and “non-responders”. Events with frequency >5% are reported.

	Reponders		**Non-Responders**	
	Atrasentan (N=1321)	**Placebo (N=1320)**	**Atrasentan (N=508)**	**Placebo (N=510)**
Any adverse event, n(%)	1113 (84.3)	1119 (84.8)	439 (86.4)	442 (86.7)
Oedema Peripheral	385 (29.1)	344 (26.1)	155 (30.5)	142 (27.8)
Anaemia	174 (13.2)	97 (7.3)	69 (13.6)	41 (8.0)
Nasopharyngitis	134 (10.1)	120 (9.1)	46 (9.1)	50 (9.8)
Hypertension	111 (8.4)	151 (11.4)	56 (11.0)	76 (14.9)
Hyperkalemia	105 (7.9)	101 (7.7)	43 (8.5)	58 (11.4)
Hypoglycaemia	98 (7.4)	88 (6.7)	38 (7.5)	44 (8.6)
Urinary Tract Infection	75 (5.7)	74 (5.6)	39 (7.7)	31 (6.1)
Upper Respiratory Tract Infection	73 (5.5)	83 (6.3)	35 (6.9)	32 (6.3)
Diarrhoea	75 (5.7)	78 (5.9)	28 (5.5)	28 (5.5)
Pneumonia	69 (5.2)	40 (3.0)	34 (6.7)	26 (5.1)
Hyperuricaemia	80 (6.1)	73 (5.5)	21 (4.1)	33 (6.5)
Acute Kidney Injury	61 (4.6)	57 (4.3)	37 (7.3)	14 (2.7)
Back pain	73 (5.5)	102 (7.7)	17 (3.3)	27 (5.3)
Blood Creatinine Increased	42 (3.2)	54 (4.1)	37 (7.3)	37 (7.3)

Data are derived from the safety population including 1321 patients in the atrasentan and 1320 patients in the placebo responder stratum and 508 patients in the atrasentan and 510 patients in the placebo non-responder stratum

Figure S1: Effects of atrasentan on the primary renal outcome in pre-specified participant subgroups



BMI=body mass index; eGFR=estimated glomerular filtration rate; HbA1c=glycated haemoglobin A1C.