Supplementary Appendix

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

Supplement to: 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

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Inclusion and Exclusion Criteria

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 HbA1c 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 time of enrolment.

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 (≥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 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 enrolment

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 of (≥2 episodes) of severe hypoglycemia within 12 months of enrolment
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 <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 <30mL/min/1.73m^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 >40ng/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.

Clinical Event Definitions

Excerpt from Clinical Events Classification Committee Charter, version 6.0

6.0 Endpoint Definitions

6.1 Stroke

Stroke is defined as the rapid onset of a new persistent neurologic deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent non-vascular cause (e.g., trauma, tumor, or infection). Available neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. Strokes will be classified as ischemic, hemorrhagic, or unknown. Confirmed hemorrhagic strokes classified as subdural hematoma will be excluded from any analyses of adjudicated stroke events.

A. For the diagnosis of stroke, the following 4 criteria should be fulfilled:

1. Rapid onset* of a focal/global neurological deficit with at least one of the following:

- Change in level of consciousness
- Hemiplegia
- Hemiparesis
- Numbness or sensory loss affecting one side of the body
- Dysphasia/Aphasia
- Hemianopsia (loss of half of the field of vision of one or both eyes)
- Amaurosis fugax (transient complete/partial loss of vision of one eye)
- Other new neurological sign(s)/symptom(s) consistent with stroke

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

2. Duration of a focal/global neurological deficit ≥ 24 hours

OR < 24 hours if

i. This is because of at least one of the following therapeutic interventions:

a. Pharmacologic (i.e., thrombolytic drug administration)

b. Non-pharmacologic (i.e.,neurointerventional procedure (e.g. intracranial angioplasty))

or

ii. Available brain imaging clearly documents a new hemorrhage or infarct

or

iii. The neurological deficit results in death

1. No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, other metabolic abnormality, peripheral lesion, or drug side effect)

2. Confirmation of the diagnosis by 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

c. Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)

d. Other compelling evidence of stroke

B. If the acute focal signs represent a worsening of a previous deficit, these signs must have either

1. Persisted for more than one week, or
2. Persisted for more than 24 hours and were accompanied by an appropriate new CT or MRI finding

C. Strokes may be sub-classified as follows:

1. Ischemic (Non-hemorrhagic): a stroke caused by an arterial obstruction due to either a thrombotic (e.g., large vessel disease/atherosclerotic or small vessel disease/lacunar) or embolic etiology. Ischemic strokes which cannot clearly be attributed to either a thrombotic or embolic etiology should be designated as Uncertain.

2. Hemorrhagic: a stroke due to a hemorrhage in the brain as documented by neuroimaging or autopsy. This category will include strokes due to primary intracerebral hemorrhage (intraparenchymal or intraventricular), ischemic strokes with hemorrhagic transformation (i.e., no evidence of hemorrhage on an initial imaging study but appearance on a subsequent scan), subdural hematoma,* and primary subarachnoid hemorrhage.
***All subdural hematomas that develop during the clinical trial should be recorded and classified as either traumatic versus non-traumatic.**

3. Unknown: the stroke type could not be determined by imaging or other means (e.g., lumbar puncture, neurosurgery, or autopsy) or no imaging was performed.

6.2 Myocardial Infarction

A. Criteria for Acute Myocardial Infarction

The term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any one of the four following criteria meets the diagnosis for acute myocardial infarction.

1. Spontaneous MI

- Detection of rise and/or fall of cardiac biomarkers (CK-MB or troponin) with at least one value above the 99th percentile of the upper reference limit (URL)* together with evidence of myocardial ischemia with at least one of the following:
  - Symptoms of ischemia
  - ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)]**
  - Development of pathological Q waves ***
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

*For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the upper reference limit (URL) from the respective laboratory performing the assay is not available,

then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL. Laboratories can also report both the 99th percentile of the upper reference limit and the MI decision limit. Reference limits from the laboratory performing the assay are preferred over the manufacturer's listed reference limits in an assay's instructions for use. CK may be used in the absence of CK-MB.

**ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)):

- ST elevation

New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.

- ST depression and T-wave changes

New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥ 0.1 mV in two contiguous leads.

The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

***Definition of a pathological Q-wave

- Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
- Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF)[a]

[a]The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

2. Percutaneous Coronary Intervention-Related Myocardial Infarction

For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL* within 48 hours of the procedure are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 x 99th percentile URL* (Troponin or CK-MB > 3 x 99th percentile URL*) are consistent with PCI-related myocardial infarction. MB is the preferred biomarker.

If the cardiac biomarker is elevated prior to PCI, a ≥ 50% increase of the value in the second cardiac biomarker sample within 48 hours of the PCI (and Troponin or CK-MB > 3x 99th percentile URL*) and documentation that cardiac biomarker values were decreasing (two samples at least 3 hours apart) prior to the suspected recurrent MI is also consistent with PCI-related myocardial infarction.

Symptoms of cardiac ischemia are not required.

3. Coronary Artery Bypass Grafting-Related Myocardial Infarction

For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevation of cardiac biomarkers above the 99th percentile URL within 72 hours of the procedure is indicative of peri-procedural myocardial necrosis. By convention, an increase of biomarkers greater than 5 x 99th percentile URL (Troponin or CK-MB > 5 x 99th percentile URL) plus

- Either new pathological Q waves in at least 2 contiguous leads that persist through 30 days or new persistent non-rate related LBBB

OR

- Angiographically documented new graft or native coronary artery occlusion or other complication in the operating room resulting in loss of myocardium

OR

- Imaging evidence of new loss of viable myocardium

is consistent with CABG-related myocardial infarction. MB is the preferred biomarker. If the cardiac biomarker is elevated prior to CABG, a ≥ 50% increase of the value in the second cardiac biomarker sample within 72 hours of CABG (and Troponin or CK-MB > 5 x 99th percentile URL) and documentation that cardiac biomarker values were decreasing (two samples at least 3 hours apart) prior to the suspected recurrent MI plus any of the three bullets above is consistent with a peri-procedural myocardial infarction after CABG.

Symptoms of cardiac ischemia are not required.

4. Pathological findings of an acute myocardial infarction

B. Criteria for Prior Myocardial Infarction

No evidence of acute myocardial infarction

AND any one of the following criteria:

- Appearance of new pathological Q waves with or without symptoms
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
- Pathological findings of a healed or healing myocardial infarction

ECG Changes associated with prior myocardial infarction:

- Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
- Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF)[a]
- R-wave ≥ 0.04 seconds in V1-V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect

[a]The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

C. Criteria for Reinfarction

In patients where recurrent myocardial infarction is suspected from clinical signs or symptoms following the initial infarction, recurrent infarction should be diagnosed if there is a ≥ 20% increase of the value between a measurement (cardiac biomarker) made at the time of the initial presentation and a further sample taken 3-6 hours later. This value should also exceed the 99th percentile URL.*

If cardiac biomarkers are elevated prior to the suspected new MI, there must be decreasing cardiac biomarker values on two samples at least 3 hours apart prior to the suspected new MI in combination with other criteria for re-infarction (ECG, imaging).

If biomarkers are increasing or peak is not reached, then a definite diagnosis of recurrent MI is generally not possible.

Clinical Classification of Different Types of Myocardial Infarction

- **Type 1**

Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection

- **Type 2**

Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension

- **Type 3**

Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

- **Type 4a**

Myocardial infarction associated with PCI

- **Type 4b**

Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy

- **Type 5**

Myocardial infarction associated with CABG

For each myocardial infarction (MI) identified by the CEC, the type of MI may also be described as:

- ST-Elevation MI (STEMI) Also categorize as:
  - Q-wave

    - Non-Q-wave
    - Unknown (no ECG or ECG not interpretable)
- Non-ST-Elevation MI (NSTEMI) Also categorize as:
    - Q-wave
    - Non-Q-wave
    - Unknown (no ECG or ECG not interpretable)
- Unknown (no ECG or ECG not interpretable)

6.3 Unstable Angina Requiring Hospitalization

Unstable angina requiring hospitalization is defined as:

1. Symptoms of myocardial ischemia at rest (chest pain or equivalent) or an accelerating pattern of angina with frequent episodes associated with progressively decreased exercise capacity

AND

2. Prompting an unscheduled visit to a healthcare facility and hospitalization (does not include chest pain observation units) within 24 hours of the most recent symptoms

AND

3. At least one of the following:

- New or worsening ST or T wave changes on resting ECG

ST elevation

New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.

ST depression and T-wave changes

New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥ 0.1 mV in two contiguous leads.

- Definite evidence of myocardial ischemia on myocardial scintigraphy (clear reversible perfusion defect), stress echocardiography (reversible wall motion abnormality), or MRI (myocardial perfusion deficit under pharmacologic stress) that is believed to be responsible for the myocardial ischemic symptoms/signs
- Angiographic evidence of ≥ 70% lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs
- Need for coronary revascularization procedure (PCI or CABG) during the same hospital stay. This criteria would be fulfilled if the admission for myocardial ischemia led to transfer to another institution for the revascularization procedure without interceding home discharge

AND

4. No evidence of acute myocardial infarction

6.4 Death

All deaths will be considered cardiovascular unless an unequivocal non-cardiovascular cause of death can be established.

A. <u>Cardiovascular death includes</u>:

Sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, death due to stroke, and death due to other cardiovascular causes, as follows:

1. **Sudden Cardiac Death:** refers to death that occurs unexpectedly and includes the following deaths:
   - Witnessed and instantaneous without new or worsening symptoms
   - Witnessed within 60 minutes of the onset of new or worsening cardiac symptoms
   - Witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
   - Subjects unsuccessfully resuscitated from cardiac arrest
   - Subjects successfully resuscitated from cardiac arrest but who die without identification of a non-cardiac etiology (Post-Cardiac Arrest Syndrome)
   - Unwitnessed death or other causes of death (information regarding the patient's clinical status preceding death should be provided, if available)

2. **Death due to Acute Myocardial Infarction:** refers to an acute myocardial infarction (MI) leading inexorably to death, generally within 30 days. Death due to known sequelae of MI including mechanical complications, arrhythmia, and/or pump failure, as well as death resulting from a procedure to treat myocardial ischemia or to treat a complication resulting from myocardial infarction should be considered death due to acute MI. The acute myocardial infarction should be verified either by the diagnostic criteria outlined for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus, and there should be no conclusive evidence of another cause of death.

   If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and ECG evidence.

   Death due to a myocardial infarction that occurs as a direct consequence of a cardiovascular investigation/procedure/operation should be classified as death due to other cardiovascular cause.

3. **Death due to Heart Failure or Cardiogenic Shock:** refers to death occurring in the context of clinically worsening symptoms and/or signs of heart failure (See CHF definition) without evidence of another cause of death.

Death due to heart failure or cardiogenic shock should include sudden death occurring during an admission for worsening heart failure as well as death from progressive heart failure or cardiogenic shock following implantation of a mechanical assist device.

New or worsening signs and/or symptoms of congestive heart failure (CHF) include any of the following:

a. New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure
b. Heart failure symptoms or signs requiring continuous intravenous therapy or chronic oxygen administration for hypoxia due to pulmonary edema
c. Confinement to bed predominantly due to heart failure symptoms
d. Pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an acute myocardial infarction, worsening renal function, or as the consequence of an arrhythmia occurring in the absence of worsening heart failure
e. Cardiogenic shock not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure.

Cardiogenic shock is defined as systolic blood pressure (SBP) < 90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

- Cool, clammy skin *or*
- Oliguria (urine output < 30 mL/hour) *or*
- Altered sensorium *or*
- Cardiac index < 2.2 L/min/m^2

Cardiogenic shock can also be defined if SBP < 90 mm Hg and increases to ≥ 90 mm Hg in less than 1 hour with positive inotropic or vasopressor agents alone and/or with mechanical support.

4. **Death due to Cerebrovascular Event:** (intracranial hemorrhage or non-hemorrhagic stroke): refers to a cerebrovascular event or a complication of a cerebrovascular event that leads inexorably to death, generally within 30 days after the suspected event. These deaths may be based on clinical signs and symptoms as well as neuroimaging and/or autopsy. There should be no conclusive evidence of another cause of death.

5. **Death due to Other Cardiovascular Causes:** refers to death due to a cardiovascular cause not included in the above categories (e.g. dysrhythmia, pulmonary embolism, cardiovascular intervention, aortic aneurysm rupture, or peripheral arterial disease). Mortal complications of cardiac surgery or non-surgical revascularization, even if "non-cardiovascular" in nature, should be classified as cardiovascular deaths.

B. Non-cardiovascular death:

Non-cardiovascular death is defined as any death not covered by cardiac death or vascular death. Categories include:

- Pulmonary causes
- Renal causes
- Gastrointestinal causes
- Infection (includes sepsis)
- Non-infectious (e.g., systemic inflammatory response syndrome (SIRS))
- Malignancy (i.e., new malignancy, worsening of prior malignancy)
- Accidental/Trauma
- Hemorrhage, not intracranial
- Suicide
- Non-cardiovascular system organ failure (e.g., hepatic failure)
- Non-cardiovascular surgery
- Other non-cardiovascular

C. Undetermined Cause of Death:

Undetermined cause of death refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause.

6.5 Congestive Heart Failure Requiring Hospitalization

Congestive heart failure requiring hospitalization is defined as an event that meets **ALL** of the following criteria (1-5):

1. The patient is admitted to the hospital with a primary diagnosis of heart failure (HF)

2. The patient's length of stay in the hospital extends for at least 24 hours or a change in calendar date if the hospital admission and discharge times are unavailable.

3. The patient exhibits documented new or worsening symptoms due to HF on presentation, including **at least ONE** of the following:
   a. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea, nocturnal cough in supine position, tachypnea)
   b. Decreased exercise tolerance
   c. Fatigue
   d. Worsened end-organ perfusion
      (worsening cerebral, renal, liver, abdominal or gastrointestinal, peripheral circulatory function as manifested by symptoms such as dizziness, lightheadedness, syncope, confusion, altered mental status, restlessness, decline in cognitive state, nausea, vomiting, abdominal

pain, abdominal fullness, abdominal discomfort or abdominal tenderness, cold clammy extremities, discoloration of extremities or lips, jaundice, pain in extremities, reduced urine output, darkening of urine color, chest pain, palpitations)

e. Volume overload
(swelling of lower extremities, swelling or indentation of pressure marks in areas of fluid accumulation such as legs, ankles, lower back; increase in abdominal girth, right-sided abdominal fullness, discomfort or tenderness, increase in body weight, oozing and development of skin breakdown in lower extremities)

4. The patient exhibits objective evidence of new or worsening HF, consisting of **at least TWO** physical examination findings **OR** **ONE** physical examination finding and **at least ONE** laboratory criterion.

Physical examination findings considered to be due to HF, include new or worsened:

a. Peripheral edema (swelling or pitting indentation when pressed in feet, ankles, legs, thighs, upper extremities, scrotal, pre-sacral area, or abdominal wall)
b. Increasing abdominal distention or ascites (in the absence of primary hepatic disease.
c. Pulmonary rales/crackles/crepitations
d. Increased jugular venous pressure and/or hepatojugular reflux
e. S3 gallop
f. Clinically significant or rapid weight gain thought to be related to fluid retention (usually more than 3-4 lbs in 3-4 days)

Laboratory Evidence of HF: Laboratory evidence of new or worsening HF should be obtained within 24 hours of presentation. Laboratory criteria include new or worsened:

a. Increased B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) concentrations.
b. Radiological evidence of pulmonary congestion.
c. Non-invasive diagnostic evidence of HF (echocardiography, cardiac MRI, Cardiac PET scan, nuclear imaging).
d. Invasive diagnostic evidence of HF.

5. Initiation or intensification of HF treatment, including at least **ONE** of the following:

a. Augmentation in oral diuretic therapy
b. Intravenous diuretic, or intravenous vasoactive therapy
c. Mechanical or surgical intervention, including mechanical circulatory support or mechanical fluid removal.

6.6 Ventricular Tachycardia/Ventricular Fibrillation requiring Intervention

Ventricular Tachycardia/Ventricular Fibrillation requiring intervention is defined as:

Sustained Ventricular Tachycardia (VT)

Sustained Ventricular Tachycardia (VT) is defined as a wide complex tachycardia of ventricular origin:

Lasting > 30 seconds and requiring intervention such as a new medication or medication change directed to VT

OR

Requiring external cardioversion or ICD/AICD therapy (anti-tachycardic pacing or electrical cardioversion)

OR

Resulting in significant hemodynamic compromise

OR

Requiring hospitalization

Ventricular Fibrillation (VF)

Ventricular Fibrillation (VF) is defined as irregular undulations of varying contour and amplitude on ECG with absence of distinct QRS complexes and requiring intervention such as a new medication or medication change directed to VF or associated with external cardioversion or ICD/AICD therapy (anti-tachycardic pacing or electrical cardioversion) or hemodynamic compromise.

6.7 Pancreatitis

Pancreatitis is defined as:

Symptoms of abdominal pain **OR** vomiting

AND

Objective evidence of pancreatic inflammation:

Elevated pancreatic enzymes, defined by:

- Amylase OR Lipase > 3x the upper limit normal.
- Amylase OR Lipase > 2x the upper limit normal. (In patients with chronic pancreatitis)

OR

Evidence of pancreatitis documented by imaging:

Abdominal CT, MRI or ultrasound showing focal, diffuse and inhomogeneous gland enlargement

Confirmed acute pancreatitis will be graded as *mild or severe*.

To confirm <u>severe pancreatitis</u>, the following criteria must be present:

1. Evidence of organ failure (at least one of the following)
    a. Shock: systolic BP < 90 mm Hg
    b. Pulmonary insufficiency: Pa02 < 60 mm Hg
    c. Renal failure: serum creatinine > 2 mg/dl after rehydration
    d. Gastrointestinal bleeding: > 500 ml/24 hours

OR

2. Local complications demonstrated on abdominal CT, MRI, or ultrasound (at least one of the following)
    a. Pancreatic necrosis (note: hemorrhagic pancreatitis is a pathologic term often used synonymously with pancreatic necrosis)
    b. Pancreatic abscess
    c. (Acute) Pancreatic pseudocyst

Confirmed cases of acute pancreatitis not meeting criteria for severe pancreatitis will be classified as mild pancreatitis.

6.8 Neoplasms

The following definitions will be utilized by the CEC for purposes of adjudication neoplasms:

Has a malignancy occurred? The CEC will answer yes to this question if the subject has either evidence of a new malignancy or the first recurrence (during the study period) of a previous cancer.

New malignancies:

1. New primary cancer in patients with or without pre-existing cancer, or
2. New metastatic cancer in patients without previous diagnosis of cancer, or
3. New metastatic cancer of a clearly distinct histology from any pre-existing cancer

Recurrence of previous cancer:

1. Evidence of first recurrence of a pre-existing cancer during the study period (histological, imaging, or clinical)

AND

2. History of this pre-existing cancer at the time of randomization (i.e. diagnosis of original cancer predates randomization)

AND

3. No evidence to indicate based on histological type or clinical picture that this is a different cancer.

Non-malignant neoplasms which are reported should be classified as benign neoplasms.

Progression of prior malignancy - does not meet EXSCEL definition of malignancy

Date of Initial Detections: This will be the date of initial detection by a treating physician, when the patient demonstrated either clinical symptoms or diagnostic testing results (for example, imaging, laboratory) with evidence of neoplasm that allows for a probable clinical diagnosis. Whichever date can be confirmed to occur first will be used.

Date of histological diagnosis: This will be the date that the diagnosis of Neoplasm was documented by histological and/or cytological evidence.

Status of Disease:

1. No evidence of disease: A patient who after treatment has normal tumor markers and no evidence of disease on physical exam or imaging studies.
2. Active disease: A patient who has evidence of disease and has either had a new and/or change in treatment since their previous evaluation or could be eligible for a new and/or change in treatment but either refused or did not receive the therapy for another clinical reason (e.g. terminal disease for which alteration in treatment would not be expected to meaningfully prolong life expectancy).
3. Stable/Inactive disease: A patient that has evidence of disease, but is not progressing, and has had no new and/or change in treatment since their previous evaluation
4. Cannot be determined: Is used to describe cases for which there is not enough information to indicate a classification.

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Figure S1: EXSCEL Study Design

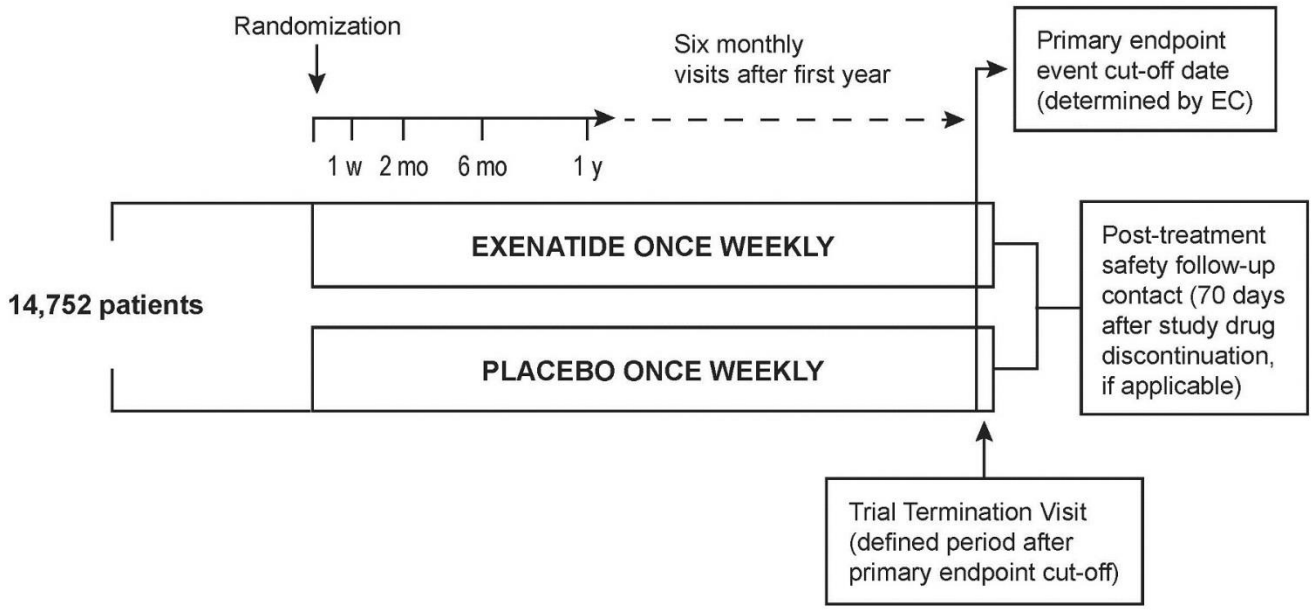
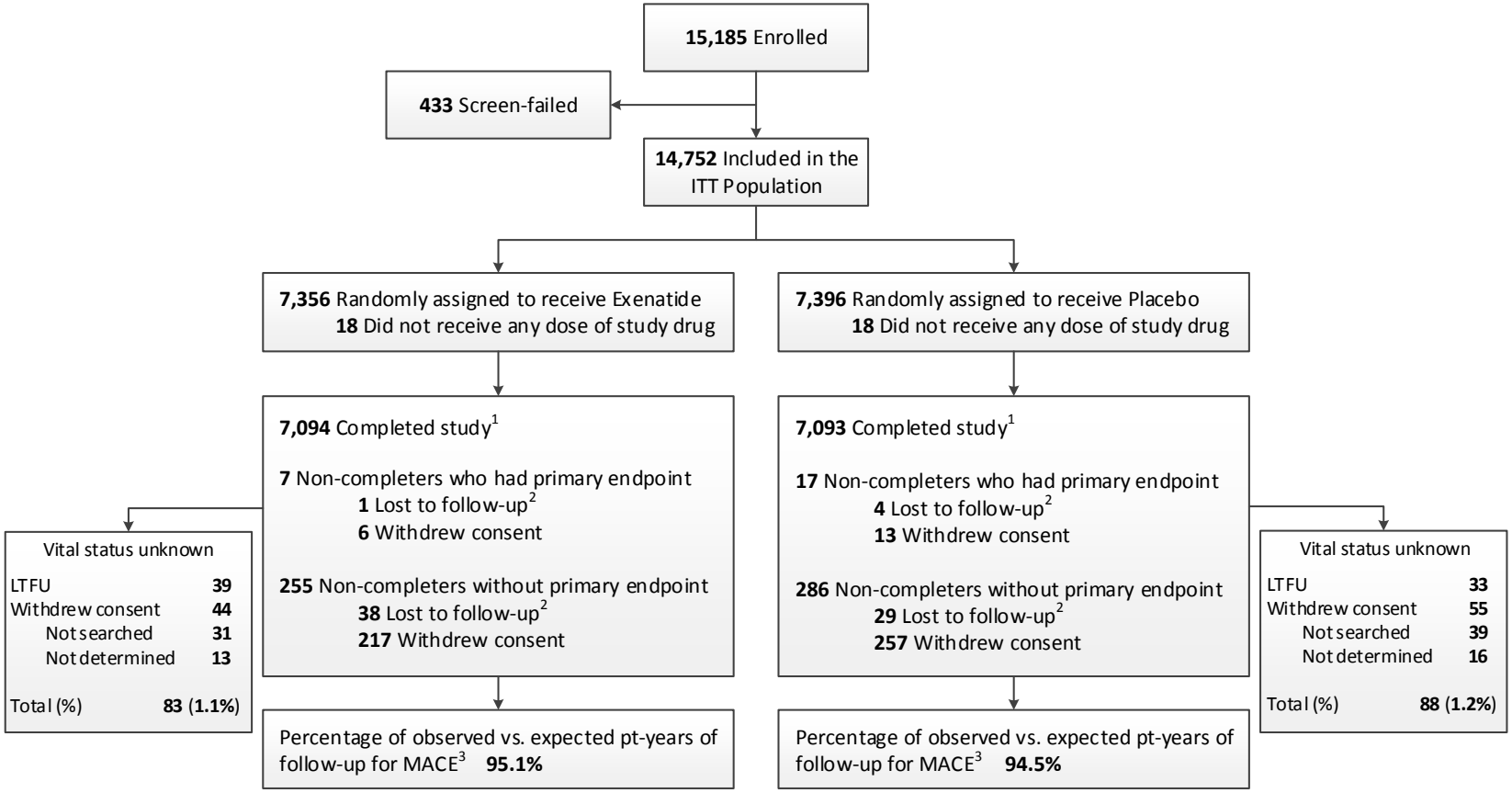


Figure S2: Enrollment, Follow-up, and Vital Status



[1] Subjects were counted as completers if they had vital status assessed as alive or deceased at the trial termination visit and had not withdrawn consent.

[2] Subjects were counted as lost to follow-up if they were lost and their vital status could not be determined at the trial termination visit.

[3] Time from randomization to the time of first MACE event or the time when censored for MACE according to the primary censoring scheme for event-free subjects, divided by the time from randomization to the time of first MACE event or the expected follow-up time for event-free subjects as follows: vital status date at the trial termination visit for subjects counted as completers assessed as alive, the date of death for subjects counted as completers assessed as deceased, and December 5, 2016 (the cut-off date) for subjects who were counted as lost to follow-up or withdrew consent.

Table S1: Baseline Characteristics of the Trial Participants by Treatment Assignment (Intention-to-Treat Population)*

Characteristic	Exenatide N=7356	Placebo N=7396
Age at randomization (years)	62.0 (56.0, 68.0)	62.0 (56.0, 68.0)
Min, Max	21.0, 92.0	24.0, 90.0
<65 years	4392 / 7356 (59.7)	4421 / 7396 (59.8)
≥65 years	2964 / 7356 (40.3)	2975 / 7396 (40.2)
≥75 years	609 / 7356 (8.3)	641 / 7396 (8.7)
Female	2794 / 7356 (38.0)	2809 / 7396 (38.0)
Ethnicity		
Hispanic or Latino	1506 / 7355 (20.5)	1520 / 7395 (20.6)
Not Hispanic or Latino	5849 / 7355 (79.5)	5875 / 7395 (79.4)
Race		
White	5554 / 7354 (75.5)	5621 / 7393 (76.0)
Black	442 / 7354 (6.0)	436 / 7393 (5.9)
Asian	725 / 7354 (9.9)	727 / 7393 (9.8)
Indian (American) or Alaska Native	38 / 7354 (0.5)	35 / 7393 (0.5)
Native Hawaiian or Other Pacific Islander	18 / 7354 (0.2)	17 / 7393 (0.2)
Hispanic	577 / 7354 (7.8)	557 / 7393 (7.5)
Region		
Europe	3389 / 7356 (46.1)	3399 / 7396 (46.0)
North America	1834 / 7356 (24.9)	1874 / 7396 (25.3)
Latin America	1364 / 7356 (18.5)	1363 / 7396 (18.4)
Asia Pacific	769 / 7356 (10.5)	760 / 7396 (10.3)
European subcategories		
Western Europe	1374 / 7356 (18.7)	1399 / 7396 (18.9)
Eastern Europe	2015 / 7356 (27.4)	2000 / 7396 (27.0)
Diabetes duration (years)	12.0 (7.0, 17.0)	12.0 (7.0, 18.0)
<5 years	1032 / 7331 (14.1)	980 / 7368 (13.3)

≥5 – <15 years	3612 / 7331 (49.3)	3654 / 7368 (49.6)
≥15 years	2687 / 7331 (36.7)	2734 / 7368 (37.1)
Prior CV event at randomization†	5394 / 7356 (73.3)	5388 / 7396 (72.9)
History of cardiovascular disease		
Coronary artery disease	3898 / 7356 (53.0)	3896 / 7396 (52.7)
Cerebrovascular disease	1233 / 7354 (16.8)	1276 / 7396 (17.3)
Peripheral arterial disease	1400 / 7355 (19.0)	1400 / 7396 (18.9)
History of congestive heart failure	1161 / 7355 (15.8)	1228 / 7396 (16.6)
HbA1c (%)	8.0 (7.3, 8.9)	8.0 (7.3, 8.9)
Min, Max	5.9, 12.0	5.6, 12.7
<8%	3546 / 7313 (48.5)	3625 / 7362 (49.2)
≥8%	3767 / 7313 (51.5)	3737 / 7362 (50.8)
eGFR via MDRD (mL/min/1.73m^2)	76.6 (61.3, 92.0)	76.0 (61.0, 92.0)
>90	2127 / 7334 (29.0)	2141 / 7371 (29.0)
60-89	3642 / 7334 (49.7)	3604 / 7371 (48.9)
30-59	1557 / 7334 (21.2)	1620 / 7371 (22.0)
<30	8 / 7334 (0.1)	6 / 7371 (0.1)
Body mass index (kg/m^2)	31.8 (28.2, 36.2)	31.7 (28.2, 36.1)
<30	2659 / 7287 (36.5)	2704 / 7315 (37.0)
≥30	4628 / 7287 (63.5)	4611 / 7315 (63.0)
Cigarette smoking status		
Current	864 / 7353 (11.8)	857 / 7392 (11.6)
Former	2902 / 7353 (39.5)	2889 / 7392 (39.1)
Never	3587 / 7353 (48.8)	3646 / 7392 (49.3)
Antihyperglycemic Medication Usage		
None	107 / 7356 (1.5)	121 / 7396 (1.6)
Oral agents use	6213 / 7356 (84.5)	6278 / 7396 (84.9)
Monotherapy	3070 / 7356 (41.7)	3165 / 7396 (42.8)
Dual therapy	2469 / 7356 (33.6)	2452 / 7396 (33.2)
≥3 oral agents	674 / 7356 (9.2)	661 / 7396 (8.9)
Biguanides	5618 / 7356 (76.4)	5677 / 7396 (76.8)
Sulfonylurea	2697 / 7356 (36.7)	2704 / 7396 (36.6)
Thiazolidinedione	292 / 7356 (4.0)	287 / 7396 (3.9)

Insulin	3397 / 7356 (46.2)	3439 / 7396 (46.5)
Insulin alone	1036 / 7356 (14.1)	997 / 7396 (13.5)
Insulin plus 1 oral agent	1742 / 7356 (23.7)	1795 / 7396 (24.3)
Insulin plus >1 oral agent	619 / 7356 (8.4)	647 / 7396 (8.7)
Pramlintide	1 / 7356 (<0.1)	2 / 7396 (<0.1)
Non-sulfonylurea secretagogues	97 / 7356 (1.3)	105 / 7396 (1.4)
Alpha-glucosidase inhibitors	150 / 7356 (2.0)	150 / 7396 (2.0)
GLP-1 receptor agonist (other than study drug)	0 / 7356 (0.0)	2 / 7396 (<0.1)
Exenatide	0 / 7356 (0.0)	0 / 7356 (0.0)
Exenatide LAR	0 / 7356 (0.0)	0 / 7356 (0.0)
Liraglutide	0 / 7356 (0.0)	2 / 7396 (<0.1)
Other GLP-1 receptor agonist	0 / 7356 (0.0)	0 / 7356 (0.0)
DPP-4 inhibitor therapy	1118 / 7356 (15.2)	1085 / 7396 (14.7)
Sitagliptin	758 / 7354 (10.3)	725 / 7396 (9.8)
Vildagliptin	201 / 7354 (2.7)	193 / 7396 (2.6)
Allogliptin	0 / 7354 (0.0)	3 / 7396 (<0.1)
Saxagliptin	106 / 7354 (1.4)	101 / 7396 (1.4)
Linagliptin	51 / 7354 (0.7)	63 / 7396 (0.9)
SGLT-2 inhibitors‡	49 / 4250 (1.2)	28 / 4290 (0.7)
Dapagliflozin‡	39 / 4250 (0.9)	19 / 4290 (0.4)
Other SGLT-2 inhibitor	10 / 4250 (0.2)	9 / 4290 (0.2)
Other antihyperglycemic agents, not listed	25 / 4209 (0.6)	33 / 4257 (0.8)
Cardiovascular Medication Usage		
Antihypertensive, antianginal, and other cardiovascular medications	6627 / 7356 (90.1)	6696 / 7396 (90.5)
ACE inhibitor	3535 / 7356 (48.1)	3647 / 7396 (49.3)
Angiotensin receptor blockers	2334 / 7356 (31.7)	2272 / 7396 (30.7)
Diuretic	3216 / 7356 (43.7)	3227 / 7396 (43.6)
Thiazide	1968 / 7356 (26.8)	1932 / 7396 (26.1)
Beta blockers	4082 / 7356 (55.5)	4129 / 7396 (55.8)
Aldosterone antagonists (e.g. spironolactone)	456 / 7356 (6.2)	456 / 7396 (6.2)
Hydralazine	64 / 7356 (0.9)	59 / 7396 (0.8)

Calcium channel blockers	2380 / 7356 (32.4)	2330 / 7396 (31.5)
Alpha 1 blockers	560 / 7356 (7.6)	529 / 7396 (7.2)
Nitrates	1003 / 7356 (13.6)	972 / 7396 (13.1)
Renin inhibitor (e.g. aliskerin)	34 / 7356 (0.5)	37 / 7396 (0.5)
Other antihypertensive	432 / 7356 (5.9)	473 / 7396 (6.4)
Ranolazine	35 / 7356 (0.5)	38 / 7396 (0.5)
Digoxin/digitalis glycoside	173 / 7356 (2.4)	184 / 7396 (2.5)
Antithrombotic and anticoagulant medications	5442 / 7349 (74.1)	5393 / 7384 (73.0)
Aspirin	4713 / 7356 (64.1)	4667 / 7396 (63.1)
Low molecular weight heparin	16 / 7356 (0.2)	10 / 7396 (0.1)
Vitamin K antagonist (e.g. warfarin/coumarol)	414 / 7356 (5.6)	377 / 7396 (5.1)
Factor Xa inhibitor	35 / 7356 (0.5)	49 / 7396 (0.7)
Direct thrombin inhibitors	45 / 7348 (0.6)	39 / 7374 (0.5)
Other anti-platelet agents	261 / 7356 (3.5)	303 / 7396 (4.1)
Clopidogrel/ticlopidine	1255 / 7356 (17.1)	1269 / 7396 (17.2)
Lipid-lowering medications‡	5734 / 7356 (77.9)	5636 / 7396 (76.2)
Statin‡	5465 / 7356 (74.3)	5380 / 7396 (72.7)
Ezetimibe	347 / 7356 (4.7)	364 / 7396 (4.9)
Fibrate	650 / 7356 (8.8)	641 / 7396 (8.7)
Niacin‡	113 / 7356 (1.5)	151 / 7396 (2.0)
Other Medication Usage		
Hormone replacement therapy	300 / 7356 (4.1)	258 / 7396 (3.5)
Chronic non-steroidal anti-inflammatory drugs	320 / 7356 (4.4)	324 / 7396 (4.4)
Chronic COX2 inhibitors	45 / 7356 (0.6)	45 / 7396 (0.6)
Fish oil	498 / 7356 (6.8)	492 / 7396 (6.7)
Proton pump inhibitors	1428 / 7356 (19.4)	1427 / 7396 (19.3)

* Results are median (Q1, Q3) or n/N (%), except where indicated.

† Prior CV event at randomization based on IVRS.

‡ Statistically significant differences: Compared with placebo, there was higher use in the exenatide group of SGLT-2 inhibitors (P = 0.01), dapagliflozin (P = 0.008), lipid-lowering medications (P = 0.01), and statins (P= 0.03). There was higher use of niacin (P = 0.02) in the placebo group. There were no other statistically significant differences by treatment assignment.

Table S2: Reasons for Premature Permanent Discontinuation of Study Drug*

	Exenatide N=7356	Placebo N=7396
Premature, permanent discontinuation of treatment	3164 (43.0%)	3343 (45.2%)
Patient decision	2231 (30.3%)	2369 (32.0%)
Did not want to give injections	766 (10.4%)	968 (13.1%)
Study drug injection site reactions	249 (3.4%)	134 (1.8%)
GI side effects such as nausea, vomiting, diarrhea	333 (4.5%)	109 (1.5%)
Travel to clinic difficult	209 (2.8%)	245 (3.3%)
Follow-up period too long	14 (0.2%)	23 (0.3%)
Other patient decision	447 (6.1%)	601 (8.1%)
No reason given	213 (2.9%)	289 (3.9%)
Physician / investigator decision	183 (2.5%)	188 (2.5%)
SAE	109 (1.5%)	100 (1.4%)
eGFR <30 mL/min/1.73m^2	80 (1.1%)	95 (1.3%)
Patient died	228 (3.1%)	255 (3.4%)
Other reason	195 (2.7%)	174 (2.4%)

* Permanent discontinuation of treatment as reported by sites.

Change in Physiological and Biochemical Parameters Over Time (Intention-to-Treat Populations)

Data are shown as mean values.

Figure S3: LDL cholesterol

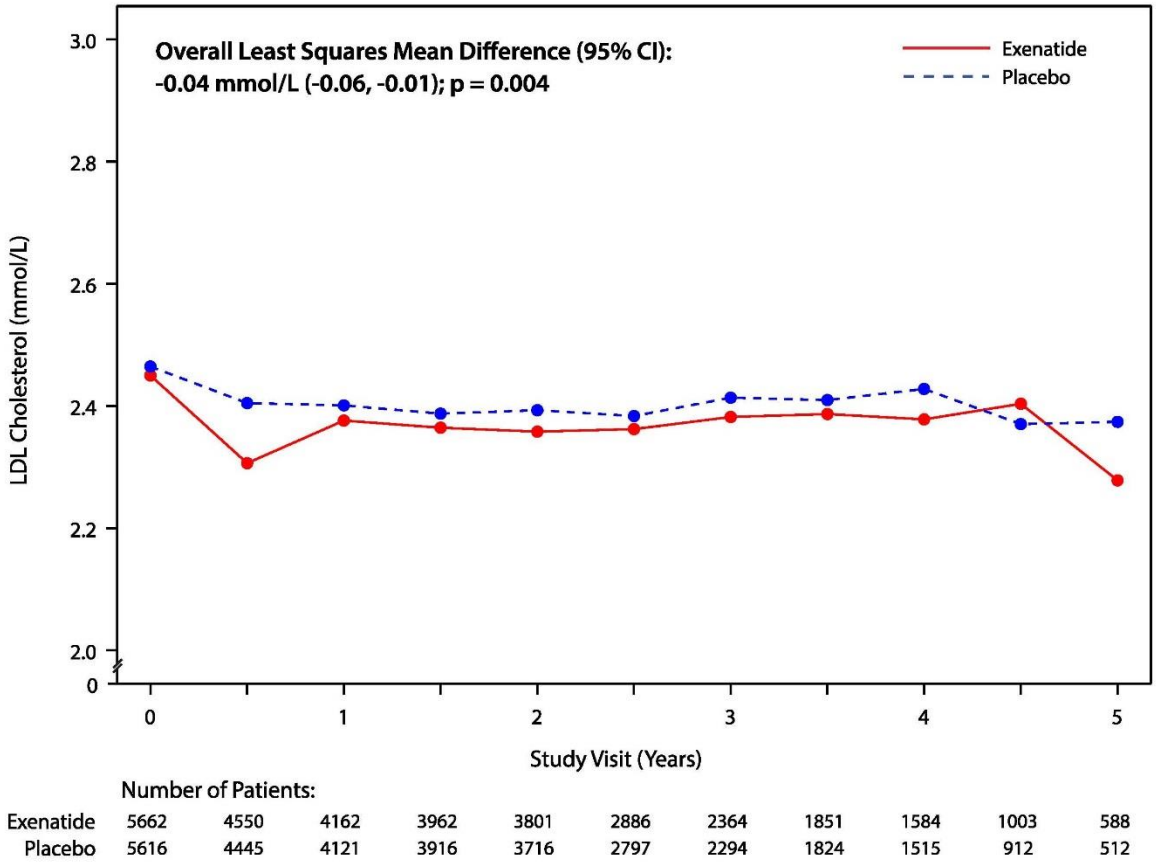


Figure S4: Triglycerides

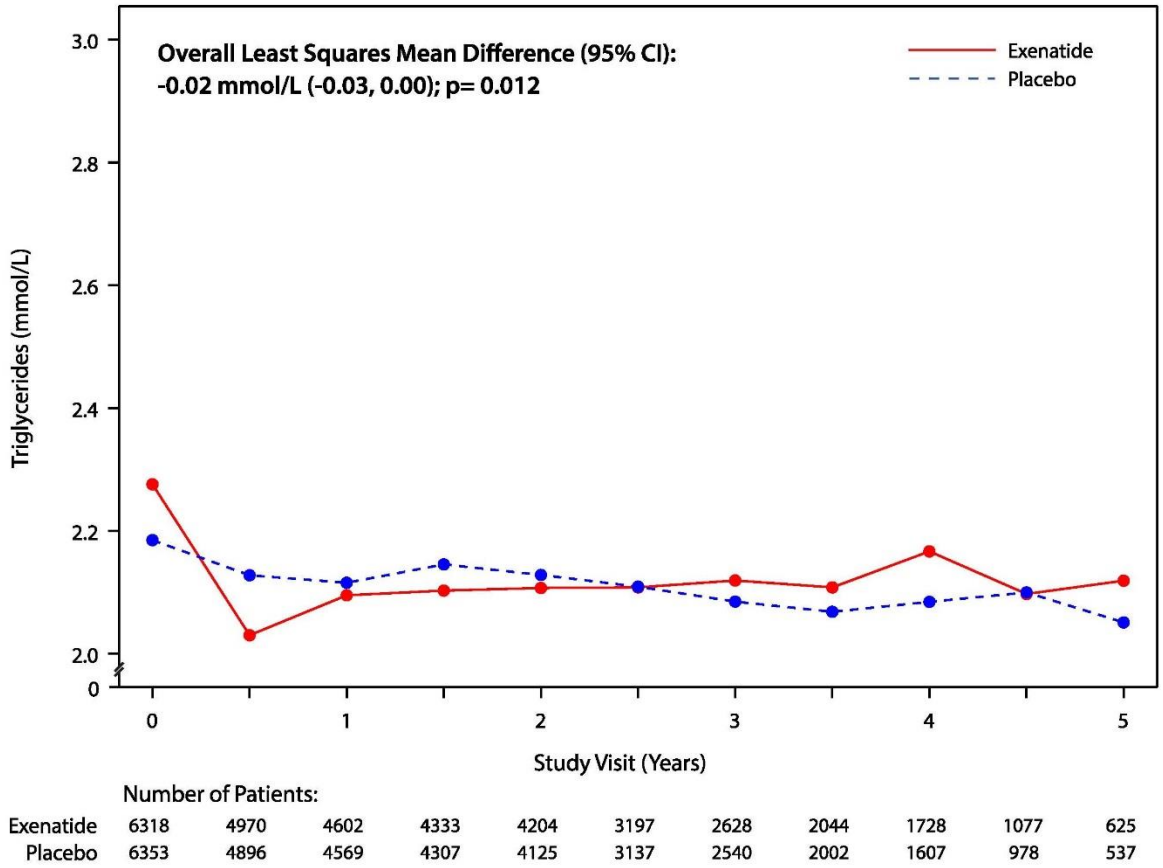


Figure S5: Diastolic blood pressure

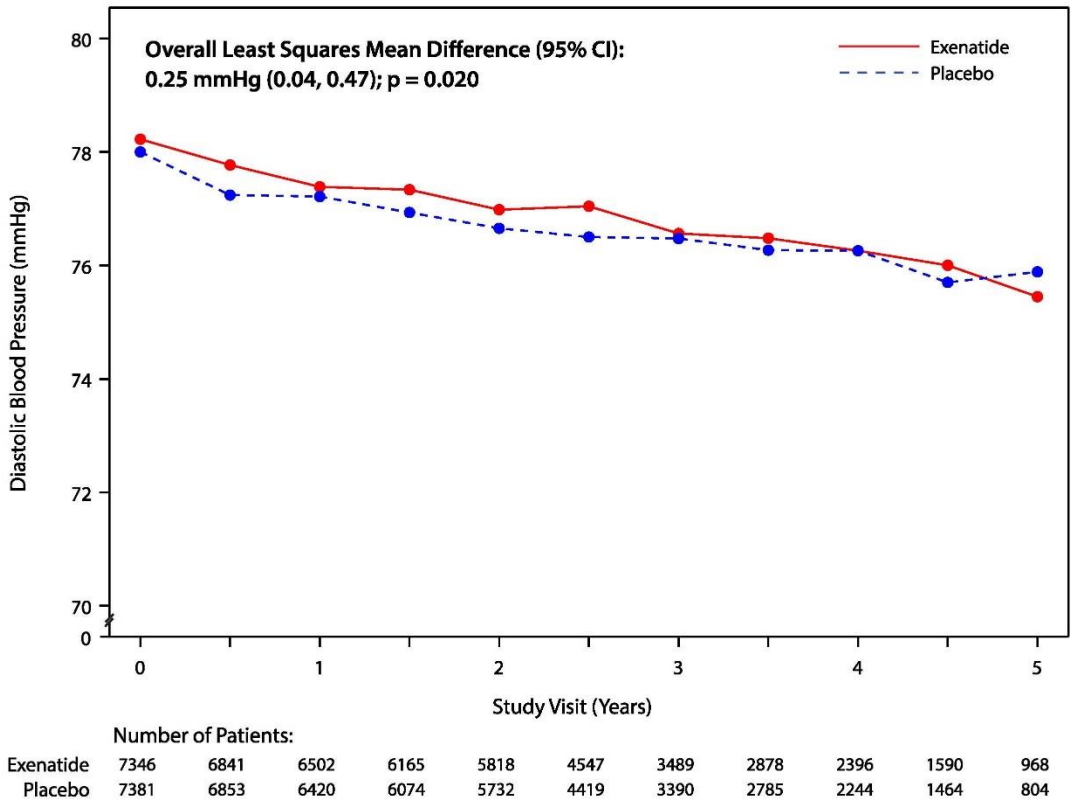
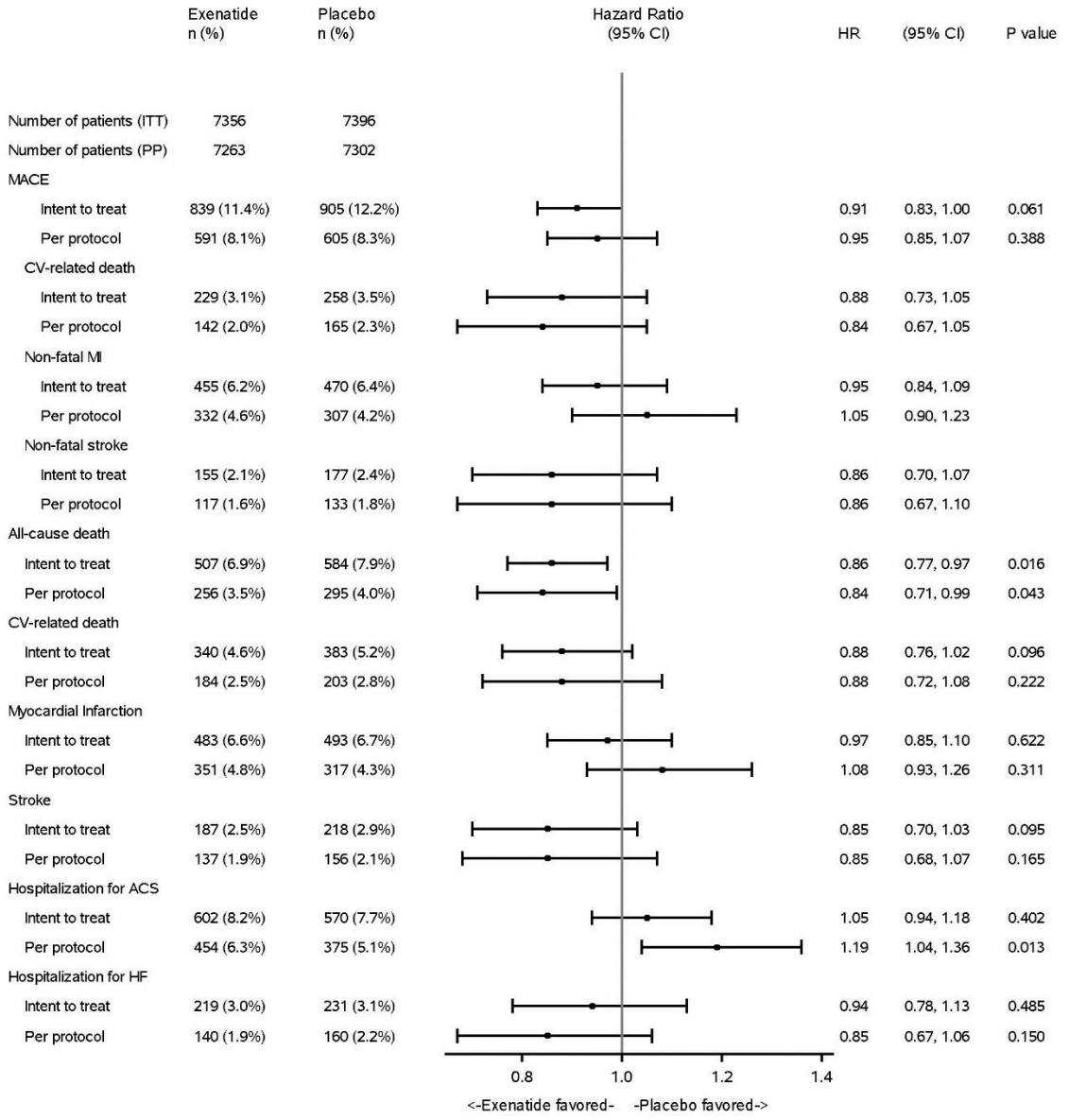


Figure S6: Forest Plot of Primary and Secondary Endpoints (Intention-to-Treat and Per-Protocol Populations)



MACE is defined as a composite of CV-related death, non-fatal MI or non-fatal stroke. CV-related death includes unknown cause deaths. Myocardial infarction includes fatal and non-fatal events. Stroke includes fatal and non-fatal events. ACS refers to acute coronary syndrome. HF refers to heart failure.

Hazard ratio (active/placebo) and CI are based on Cox proportional hazards regression model, stratified by prior CV event, with treatment group only as explanatory variable.

Table S3: Rates of the Components of the Primary Composite Cardiovascular Outcome*

Intention-to-treat analysis	**Exenatide (N=7356)**		**Placebo (N=7396)**		**Hazard Ratio†** **(95% CI)**	**P value**
Outcome	*No. (%)*	*First event rate per 100 patient-yr*	*No. (%)*	*First event rate per 100 patient-yr*		
Primary composite outcome	839 (11.4)	3.7	905 (12.2)	4.0	0.91 (0.83, 1.00)	<.001‡ (non-inferiority) 0.061‡ (superiority)
Components						
Cardiovascular death§	229 (3.1)	-	258 (3.5)	-	0.88 (0.73, 1.05)	0.628¶ (homogeneity among components)
Non-fatal myocardial infarction	455 (6.2)	-	470 (6.4)	-	0.95 (0.84, 1.09)	
Non-fatal stroke	155 (2.1)	-	177 (2.4)	-	0.86 (0.70, 1.07)	

*The primary composite outcome is the time to the first occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke.

† Hazard ratio (active/placebo) and CI for the primary composite outcome are based on Cox proportional hazards regression model, stratified by prior cardiovascular event, with treatment group only as explanatory variable.

‡ P values based on the Wald statistic. P value for non-inferiority of exenatide versus placebo by a non-inferiority hazard ratio upper 95% CI margin of 1.30.

§ Cardiovascular death includes death of unknown cause.

¶ Hazard ratio (active/placebo), CI, and P value are computed using Lunn-McNeil competing risk model. P value is from the test of equality of the treatment effect on components of the primary cardiovascular composite outcome, also based on Lunn-McNeil competing risk model.

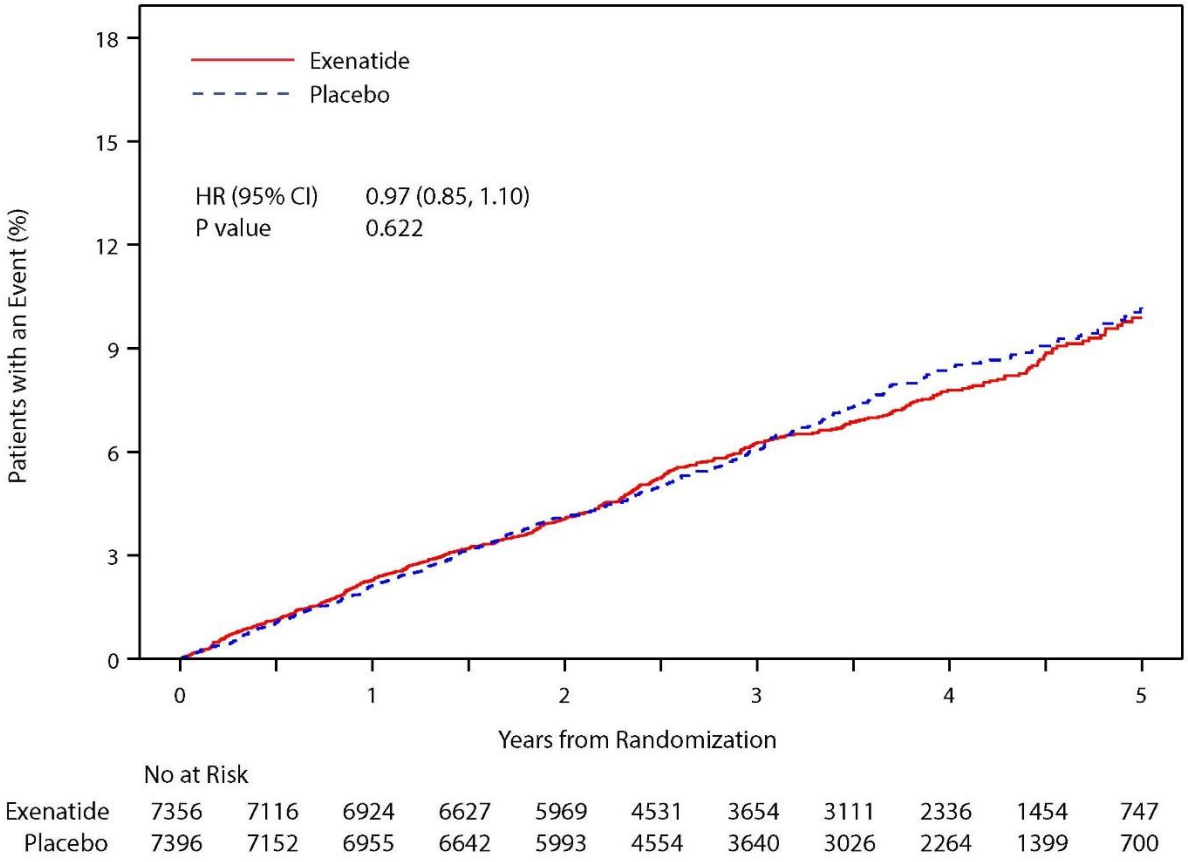
Table S4: All-cause Mortality: Modalities of Death (Intention-to-Treat Population)*

	Exenatide N=7356	Placebo N=7396
Number of all-cause mortality events	**507 (100%)**	**584 (100%)**
Cardiovascular death	**230 (45.4%)**	**241 (41.3%)**
Sudden cardiac death	122 (24.1%)	128 (21.9%)
Acute myocardial infarction	28 (5.5%)	15 (2.6%)
Heart failure or cardiogenic shock	42 (8.3%)	46 (7.9%)
Cardiovascular procedure	4 (0.8%)	8 (1.4%)
Stroke	33 (6.5%)	34 (5.8%)
Other cardiovascular causes	1 (0.2%)	10 (1.7%)
Non-cardiovascular death	**167 (32.9%)**	**201 (34.4%)**
Pulmonary	8 (1.6%)	14 (2.4%)
Renal	5 (1.0%)	5 (0.9%)
Gastrointestinal	2 (0.4%)	6 (1.0%)
Infection	56 (11.0%)	65 (11.1%)
Non-infectious	0 (0.0%)	1 (0.2%)
Malignancy	68 (13.4%)	78 (13.4%)
Accidental/trauma	13 (2.6%)	13 (2.2%)
Hemorrhage, not intracranial	3 (0.6%)	4 (0.7%)
Suicide	0 (0.0%)	1 (0.2%)
Non-cardiovascular system organ failure	4 (0.8%)	4 (0.7%)
Non-cardiovascular surgery	3 (0.6%)	4 (0.7%)
Pancreatitis	0 (0.0%)	2 (0.3%)
Other non-cardiovascular	5 (1.0%)	4 (0.7%)
Unknown†	**110 (21.7%)**	**142 (24.3%)**

* Percentages calculated out of all mortality events within treatment arm.

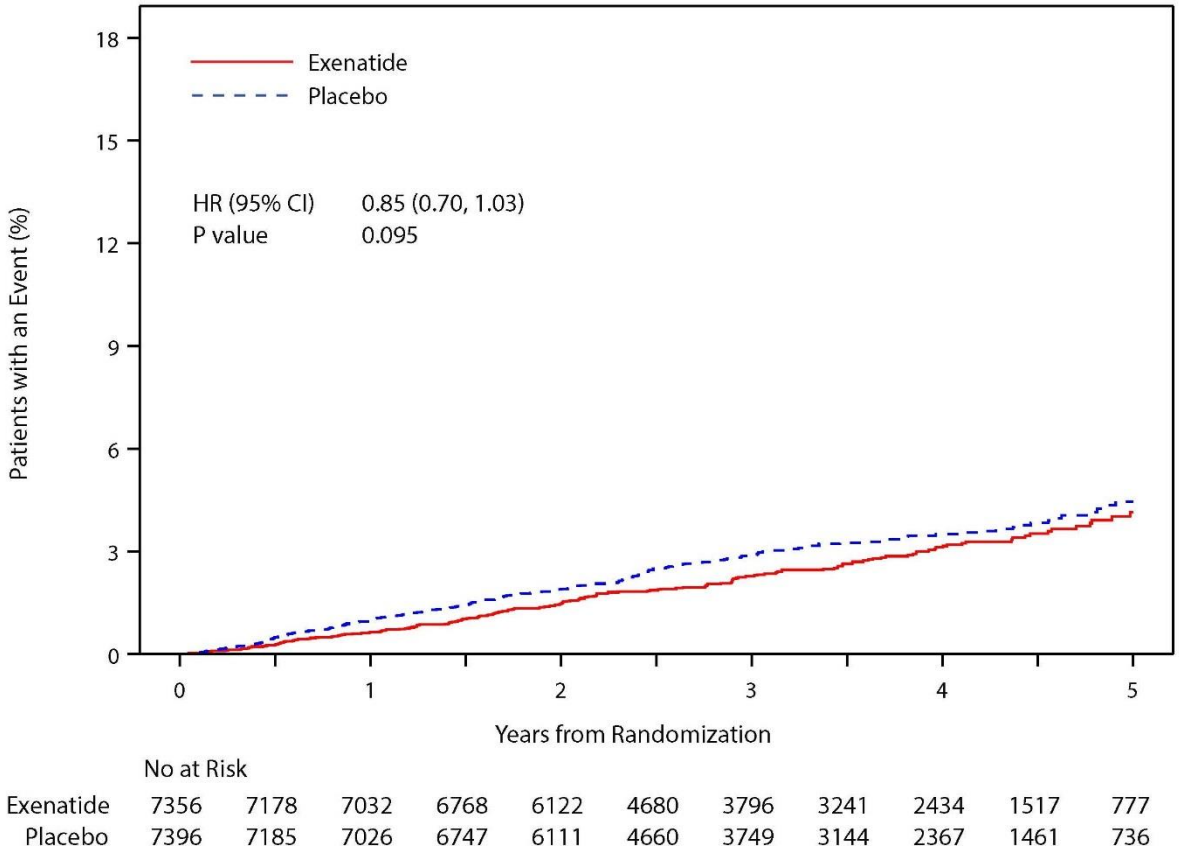
† These are the deaths that could not be classified as either cardiovascular or non-cardiovascular by the Clinical Events Classification Committee. Unknown deaths are counted with cardiovascular deaths for any analyses that includes cardiovascular deaths.

Figure S7: Time to First Adjudicated Myocardial Infarction [Fatal and Non-Fatal] (Intention-to-Treat Population)



No at Risk											
Exenatide	7356	7116	6924	6627	5969	4531	3654	3111	2336	1454	747
Placebo	7396	7152	6955	6642	5993	4554	3640	3026	2264	1399	700

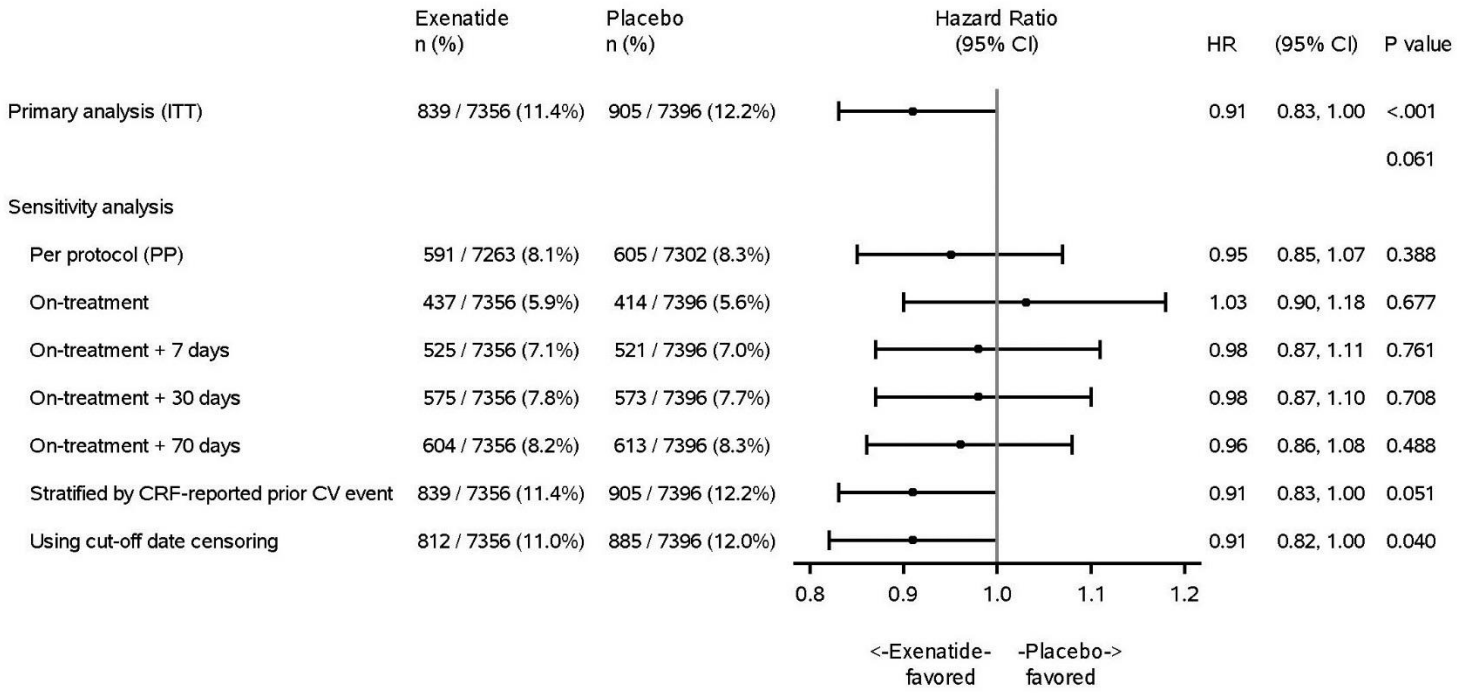
Figure S8: Time to First Adjudicated Stroke [Fatal and Non-Fatal] (Intention-to-Treat Population)



No at Risk

Exenatide	7356	7178	7032	6768	6122	4680	3796	3241	2434	1517	777
Placebo	7396	7185	7026	6747	6111	4660	3749	3144	2367	1461	736

Figure S9: Prespecified Sensitivity Analyses for the Primary Efficacy Endpoint



P values for non-inferiority (upper) and superiority (lower) are provided for the primary analysis.

In time-to-event analyses in the Intention-to-Treat population, patients are 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. Patients without any assessment of the endpoint were censored at randomization.

Data analyzed in the Intention-to-Treat population using primary censoring scheme 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. Patients without any assessment of the endpoint were censored at randomization.

Data analyzed in the Intention-to-Treat population using cut-off date censoring scheme, where patients 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 (5 December 2016), using the same Cox Proportional Hazards model as in the primary safety and efficacy analysis. Patients without any assessment of the endpoint were censored at randomization. Events that occurred after study closeout are not included in the Primary Outcome analysis.

On treatment analysis in the Intention-to-Treat population using On-treatment and On-treatment + n days censoring schemes, and using the same Cox Proportional Hazards model as in the primary safety and efficacy analysis. Patients 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, where n = 7, 30 and 70 days, and 3) the last censoring date. Patients who never started the study drug were censored at randomization.

In time-to-event analyses in the Per Protocol population, patients are censored at the earliest of: 1) date of last contact where all elements of the endpoint could be assessed, 2) the right censoring date and 3) major protocol violation censoring date.

Table S5: New Antihyperglycemic Medication Usage During Follow-Up (Intention-to-Treat Population)*

	Exenatide N=7356	Placebo N=7396
Biguanides	356 / 7337 (4.9)	450 / 7385 (6.1)
Sulfonylurea	508 / 7337 (6.9)	652 / 7385 (8.8)
Thiazolidinedione	146 / 7337 (2.0)	173 / 7385 (2.3)
Insulin	692 / 7337 (9.4)	1021 / 7385 (13.8)
Pramlintide	7 / 7337 (0.1)	6 / 7385 (0.1)
Non-sulfonylurea secretagogues	52 / 7337 (0.7)	74 / 7385 (1.0)
Alpha-glucosidase inhibitors	50 / 7337 (0.7)	68 / 7385 (0.9)
GLP-1 receptor agonists (other than study drug)	182 / 7337 (2.5)	265 / 7385 (3.6)
Exenatide	14 / 7337 (0.2)	43 / 7385 (0.6)
Exenatide LAR	44 / 7337 (0.6)	61 / 7385 (0.8)
Liraglutide	98 / 7337 (1.3)	147 / 7385 (2.0)
Other GLP-1 receptor agonists	55 / 7337 (0.7)	65 / 7385 (0.9)
DPP-4 inhibitor therapy	549 / 7337 (7.5)	782 / 7385 (10.6)
Sitagliptin	368 / 7326 (5.0)	512 / 7375 (6.9)
Vildagliptin	115 / 7326 (1.6)	160 / 7374 (2.2)
Allogliptin	37 / 7327 (0.5)	45 / 7375 (0.6)
Saxagliptin	79 / 7326 (1.1)	118 / 7375 (1.6)
Linagliptin	147 / 7329 (2.0)	181 / 7375 (2.5)
SGLT-2 inhibitors†	274 / 4237 (6.5)	401 / 4820 (9.4)
Dapagliflozin	132 / 4236 (3.1)	179 / 4280 (4.2)
Other SGLT-2 inhibitor	160 / 4237 (3.8)	241 / 4280 (5.6)
Other antihyperglycemic agents, not listed	31 / 4196 (0.7)	33 / 4247 (0.8)

*Subjects are considered to have taken a new antihyperglycemic medication if there is no indication of usage at baseline visit as well as indication of usage during at least one post-randomization analysis visit. Subclasses of medication are not mutually exclusive. Results are n/N (%). Denominator consists of subjects whose indication of usage for the class of medication was available at baseline and during at least one post-randomization visit. The denominator for the subclass of medications consists of subjects for whom the following information was available at baseline and during at least one post-randomization visit: the class of medication was not taken or the class of medication was taken and the information regarding which subclass of medication was available.
† Information regarding SGLT-2 inhibitor usage and 'other antihyperglycemic agent' usage was added to the eCRF on 9 May 2013.

Table S6: New Concomitant Medication (Cardiovascular and Other) Usage During Follow-Up (Intention-to-Treat Population)*

	Exenatide N=7356	Placebo N=7396
Antihypertensive, antianginal, and other cardiovascular medications		
ACE inhibitor	732 / 7337 (10.0)	711 / 7384 (9.6)
Angiotensin receptor blockers	897 / 7337 (12.2)	996 / 7384 (13.5)
Diuretic	1018 / 7337 (13.9)	1099 / 7384 (14.9)
Thiazide	1039 / 7337 (14.2)	1094 / 7384 (14.8)
Beta blockers	746 / 7337 (10.2)	747 / 7384 (10.1)
Aldosterone antagonists (e.g. spironolactone)	405 / 7337 (5.5)	457 / 7384 (6.2)
Hydralazine	183 / 7337 (2.5)	178 / 7384 (2.4)
Calcium channel blockers	872 / 7337 (11.9)	931 / 7384 (12.6)
Alpha 1 blockers	488 / 7337 (6.7)	502 / 7384 (6.8)
Nitrates	506 / 7337 (6.9)	546 / 7384 (7.4)
Renin inhibitor (e.g. aliskerin)	94 / 7337 (1.3)	83 / 7384 (1.1)
Other antihypertensive	512 / 7337 (7.0)	527 / 7384 (7.1)
Ranolazine	88 / 7337 (1.2)	99 / 7384 (1.3)
Digoxin/digitalis glycoside	137 / 7337 (1.9)	124 / 7384 (1.7)
Antithrombotic and anticoagulant medications		
Aspirin	704 / 7337 (9.6)	707 / 7384 (9.6)
Low molecular weight heparin	137 / 7337 (1.9)	143 / 7384 (1.9)
Vitamin K antagonist (e.g. warfarin/coumarol)	244 / 7337 (3.3)	269 / 7384 (3.6)
Factor Xa inhibitor	267 / 7337 (3.6)	308 / 7384 (4.2)
Direct thrombin inhibitors	132 / 7328 (1.8)	127 / 7362 (1.7)
Other anti-platelet agents	290 / 7337 (4.0)	284 / 7384 (3.8)
Clopidogrel/ticlopidine	609 / 7337 (8.3)	577 / 7384 (7.8)
Lipid-lowering medications		
Statin	764 / 7337 (10.4)	821 / 7384 (11.1)
Ezetimibe	271 / 7337 (3.7)	267 / 7384 (3.6)

Fibrate	362 / 7337 (4.9)	399 / 7384 (5.4)
Niacin	95 / 7337 (1.3)	93 / 7384 (1.3)
Other medications		
Hormone replacement therapy	297 / 7337 (4.0)	266 / 7384 (3.6)
Chronic non-steroidal anti-inflammatory drugs	531 / 7337 (7.2)	502 / 7384 (6.8)
Chronic COX2 inhibitors	153 / 7337 (2.1)	141 / 7384 (1.9)
Fish oil	329 / 7337 (4.5)	306 / 7384 (4.1)
Proton pump inhibitors	1101 / 7337 (15.0)	989 / 7384 (13.4)

*Subjects are considered to have taken a new concomitant medication if there is no indication of usage at baseline visit as well as indication of usage during at least one post-randomization analysis visit. Individual medications are not mutually exclusive. Results are n/N (%). Denominator consists of subjects for whom information regarding usage of medication was available at baseline visit and during at least one post-randomization visit.

Table S7: Post-randomization Diabetes Complications, Expected Events, and Cardiovascular Events of Interest (Intention-to-Treat Population)*

	Exenatide N=7356	Placebo N=7396
Diabetes complications		
Any diabetes complications†	1339 / 7046 (19.0)	1409 / 7090 (19.9)
Number of diabetes complications‡		
None	5707 / 7024 (81.3)	5681 / 7070 (80.4)
1	1047 / 7024 (14.9)	1117 / 7070 (15.8)
2	221 / 7024 (3.1)	198 / 7070 (2.8)
3 or more	49 / 7024 (0.7)	74 / 7070 (1.0)
Amputation (non-traumatic)§	128 / 7344 (1.7)	127 / 7389 (1.7)
Retinopathy§	214 / 7344 (2.9)	238 / 7389 (3.2)
Blindness due to diabetes§	8 / 7344 (0.1)	9 / 7389 (0.1)
Other diabetic eye disease§	201 / 7344 (2.7)	195 / 7389 (2.6)
Albuminuria§	661 / 7022 (9.4)	727 / 7069 (10.3)
Microalbuminuria	504 / 7022 (7.2)	530 / 7069 (7.5)
Macroalbuminuria	154 / 7022 (2.2)	196 / 7069 (2.8)
Diabetic neuropathy§	328 / 7344 (4.5)	320 / 7388 (4.3)
End stage renal failure needing chronic peritoneal/hemodialysis (including creation of fistula or other vascular access for hemodialysis) or renal transplantation§	55 / 7344 (0.7)	65 / 7389 (0.9)
Chronic peritoneal/hemodialysis	25 / 7344 (0.3)	38 / 7389 (0.5)
Renal transplant	0 / 7344 (0.0)	2 / 7389 (<0.1)
Hospitalization due to renal failure	28 / 7344 (0.4)	21 / 7389 (0.3)
Gangrene§	80 / 7344 (1.1)	91 / 7389 (1.2)
Expected events		
Infections	1795 / 7345 (24.4)	1869 / 7389 (25.3)
Metabolic conditions associated with diabetes (including hyperlipidemia/dyslipidemia, hypertension and gout)	288 / 7344 (3.9)	330 / 7389 (4.5)

Gastrointestinal conditions associated with diabetes	437 / 7344 (6.0)	290 / 7389 (3.9)
Hyperglycemia requiring hospitalization	140 / 7344 (1.9)	171 / 7389 (2.3)
Cholecystitis/cholelithiasis	178 / 7345 (2.4)	146 / 7389 (2.0)
Blindness (not due to diabetes)	6 / 7344 (0.1)	6 / 7389 (0.1)
Amputation (traumatic)	2 / 7344 (<0.1)	6 / 7389 (0.1)
Cardiovascular events of interest		
Carotid endarterectomy	31 / 7345 (0.4)	31 / 7390 (0.4)
Carotid angioplasty and/or stenting	22 / 7346 (0.3)	27 / 7390 (0.4)
Renal artery angioplasty and/or stenting	8 / 7345 (0.1)	12 / 7389 (0.2)
Peripheral arterial disease (PAD): ≥50% stenosis of lower extremity artery or ABI <0.9	214 / 7344 (2.9)	243 / 7389 (3.3)
Without revascularization	77 / 7344 (1.0)	86 / 7389 (1.2)
With percutaneous revascularization	93 / 7344 (1.3)	110 / 7389 (1.5)
With surgical revascularization	44 / 7344 (0.6)	47 / 7389 (0.6)
PAD: abdominal aortic aneurysm	18 / 7344 (0.2)	12 / 7389 (0.2)
Without surgical repair	12 / 7344 (0.2)	8 / 7389 (0.1)
With surgical repair	6 / 7344 (0.1)	4 / 7389 (0.1)
Cerebrovascular disease: ≥50% stenosis of carotid artery	111 / 7348 (1.5)	128 / 7390 (1.7)
Without revascularization	73 / 7348 (1.0)	72 / 7390 (1.0)
With percutaneous revascularization	13 / 7348 (0.2)	26 / 7390 (0.4)
With surgical revascularization	25 / 7348 (0.3)	30 / 7390 (0.4)
Percutaneous coronary intervention	450 / 7346 (6.1)	445 / 7390 (6.0)
Reason for PCI		
Stable angina	85 / 7346 (1.2)	77 / 7390 (1.0)
Unstable angina	138 / 7346 (1.9)	122 / 7390 (1.7)
Post myocardial infarction	90 / 7346 (1.2)	113 / 7390 (1.5)
Other	137 / 7346 (1.9)	133 / 7390 (1.8)
Circumstance		
Elective	266 / 7346 (3.6)	253 / 7390 (3.4)
Urgent	184 / 7346 (2.5)	192 / 7390 (2.6)
PCI type		

Balloon only	31 / 7346 (0.4)	39 / 7390 (0.5)
Stent	389 / 7346 (5.3)	370 / 7390 (5.0)
Unknown PCI	30 / 7346 (0.4)	35 / 7390 (0.5)
Coronary artery bypass graft (CABG) surgery	111 / 7347 (1.5)	121 / 7390 (1.6)
Reason for CABG		
Stable angina	23 / 7347 (0.3)	20 / 7390 (0.3)
Unstable angina	33 / 7347 (0.4)	29 / 7390 (0.4)
Post myocardial infarction	28 / 7347 (0.4)	32 / 7390 (0.4)
Other	27 / 7347 (0.4)	40 / 7390 (0.5)
Circumstance		
Elective	67 / 7347 (0.9)	75 / 7390 (1.0)
Urgent	44 / 7347 (0.6)	46 / 7390 (0.6)
Atrial fibrillation or flutter	322 / 7347 (4.4)	350 / 7390 (4.7)
Deep vein thrombosis	42 / 7347 (0.6)	58 / 7390 (0.8)
Pulmonary embolism	34 / 7347 (0.5)	29 / 7390 (0.4)
Shock/hypotension	131 / 7348 (1.8)	145 / 7390 (2.0)
Cardiac catheterization	725 / 7348 (9.9)	750 / 7390 (10.1)
Stress test	626 / 7337 (8.5)	608 / 7370 (8.2)
Ventricular fibrillation/tachycardia¶	41 / 7356 (0.6)	26 / 7396 (0.4)

*Data are n/N (%) and are presented for the 'overall period'; defined as the interval between randomization date, up to and including last known alive date.
† 'Any diabetes complication' is defined as the number of subjects who experienced at least one of the following events: amputation (non-traumatic), retinopathy, blindness due to diabetes, other diabetic eye disease, microalbuminuria, macroalbuminuria, end stage renal failure, diabetic neuropathy or gangrene. Denominator for 'any diabetes complication' consists of subjects who experienced at least one event or answered 'No' to all of the questions that make up the composite of 'any diabetes complication' at least one time post-randomization.
‡ Denominator for the 'number of diabetes complications' consists of those subjects who experienced at least 3 events; otherwise it consists of those who answered all of the questions that make up the composite of 'any diabetes complication' at least one time post-randomization.
§ Component of 'any diabetes complication' row.
¶ Refers to positively adjudicated events of ventricular fibrillation/tachycardia. The time period for the reporting of adjudicated events is from the date of randomization up to and including the trial termination visit or the last event assessed date, whichever is earlier.