Supplementary Online Content

Rosenstock J, Perkovic V, Johansen OE, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. *JAMA*. doi:10.1001/jama.2018.18269

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

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eAppendix 2. Trial Committees and Independent Statistical Center

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Data Monitoring Committee

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Independent Statistical Center

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eAppendix 3. Inclusion Criteria

1) Documented diagnosis of type 2 diabetes before visit 1 (screening).
2) Male or female patients who are drug-naïve or pre-treated with any antidiabetic background therapy, excluding treatment with GLP-1 receptor agonists, DPP-4 inhibitors or SGLT-2 inhibitors if ≥ 7 consecutive days.
3) Stable antidiabetic background medication (unchanged daily dose) for at least 8 weeks prior to randomization. If insulin is part of the background therapy, the average daily insulin dose should not have been changed by more than 10% within the 8 weeks prior to randomization compared with the daily insulin dose at randomization.
4) HbA1c of ≥ 6.5% and ≤ 10.0% at visit 1 (screening).
5) Age ≥ 18 years at visit 1 (screening). *For Japan only: Age ≥ 20 years at Visit 1.*
6) Body Mass Index (BMI) $\leq$ 45 kg/m^2 at visit 1 (screening).
7) Signed and dated written informed consent by date of visit 1 (screening) in accordance with GCP and local legislation prior to any study related procedure.
8) High risk of CV events (I and/or II):

I.		Albuminuria (UACR ≥ 30 mg/g creatinine or ≥ 30 µg/min [microgram albumin per minute] or ≥ 30 mg/24 h [milligram albumin per 24 hours] in two out of three unrelated spot urine or timed samples in the last 24 months prior to randomization)* AND previous macrovascular disease, defined as either one or more:
	a	Confirmed history of MI (> 2 months prior to Visit 1)
	b	Advanced coronary artery disease, defined by any one of the following: - ≥ 50% narrowing of the luminal diameter in 2 or more major coronary arteries by coronary angiography, MRI angiography or CT angiography; *Definition of major coronary arteries: LAD (Left Anterior Descending). CX (Circumflex) or RCA (right coronary artery)* - Left main stem coronary artery with ≥ 50% narrowing of the luminal diameter by coronary angiography, MRI angiography or CT angiography; - Prior percutaneous or surgical revascularization of ≥ 2 major coronary arteries at least 2 months prior to Visit 1 (screening); - The combination of prior percutaneous or surgical revascularization of 1 major coronary artery at least 2 months prior to visit 1 (screening), and ≥ 50% narrowing of the luminal diameter by coronary angiography, MRI angiography or CT angiography of at least 1 additional major coronary artery.

	c	High-risk single-vessel coronary artery disease, defined as the presence of ≥ 50% narrowing of the luminal diameter of one major coronary artery by coronary angiography, MRI angiography or CT angiography in patients not revascularized**:** **AND** at least one of the following: □ A positive non invasive stress-test, confirmed by either: o a positive ECG exercise tolerance test in patients without left bundle branch block, Wolff-Parkinson-White syndrome, left ventricular hypertrophy with repolarization abnormality, or paced ventricular rhythm, atrial fibrillation in case of abnormal ST-T segments; o a positive stress echocardiogram showing induced regional systolic wall motion abnormalities; o a positive nuclear myocardial perfusion imaging stress test showing stress-induced reversible perfusion abnormality; o a positive cardiac stress perfusion MRI showing a stress induced perfusion defect; □ Patient discharged from hospital with a documented diagnosis of unstable angina pectoris between 2 and 12 months prior to visit 1 (screening).
	d	History of ischemic or haemorrhagic stroke (>3 months prior to visit 1)
	e	Presence of carotid artery disease (symptomatic or not) documented by either: o imaging techniques with at least one lesion estimated to be ≥50% narrowing of the luminal diameter; o prior percutaneous or surgical carotid revascularization.
	f	Presence of peripheral artery disease documented by either: o previous limb angioplasty, stenting or bypass surgery; o previous limb or foot amputation due to macrocirculatory insufficiency; o angiographic evidence of peripheral artery stenosis ≥ 50% narrowing of the luminal diameter in at least one limb (definition of peripheral artery: common iliac artery, internal iliac artery, external iliac artery, femoral artery, popliteal artery).
II.		Evidence of impaired renal function with predefined UACR, with or without CV co-morbidities, defined as follows (and/or criteria): □ Impaired renal function (as defined by MDRD formula) with an eGFR:15- **<**45 mL/min/1.73 m^2 at visit 1 (screening) with any UACR. □ Impaired renal function (as defined by MDRD formula) with an eGFR ≥ 45-75 mL/min/1.73 m^2 at visit 1 (screening) with an UACR > 200 mg/g creatinine or > 200 µg/min (microgram albumin per minute) or > 200 mg/24 h [milligram albumin per 24 hours] demonstrated in two out of three unrelated spot urine or timed samples in the last 24 months prior to randomization.

eAppendix 4. Exclusion Criteria

1) Type 1 diabetes mellitus.
2) Treatment (≥ 7 consecutive days) with GLP-1 receptor agonists, other DPP-4 inhibitors or SGLT-2 inhibitors prior to informed consent. Note: This also includes clinical trials where these antidiabetic drugs have been provided to the patient.
3) Active liver disease or impaired hepatic function, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatase (AP) ≥3 x upper limit of normal (ULN) as determined at Visit 1.
4) eGFR <15 ml/min/1.73 m^2 (severe renal impairment or ESRD, MDRD formula), as determined during screening at Visit 1 and/or the need for maintenance dialysis.
5) Any previous (or planned within next 12 months) bariatric surgery (open or laparoscopic) or intervention (gastric sleeve).
6) Pre-planned coronary artery re-vascularisation (PCI, CABG) or any previous PCI and/or CABG ≤ 2 months prior informed consent
7) Known hypersensitivity or allergy to the investigational products or its excipients.
8) Any previous or current alcohol or drug abuse that would interfere with trial participation in the opinion of the investigator.
9) Participation in another trial with an investigational drug ongoing or within 2 months prior to visit 1 (screening)*.
10) Pre-menopausal women (last menstruation $\leq$ 1 year prior to informed consent) who:

    - are nursing or pregnant,

    - or are of child-bearing potential and are not practicing an acceptable method of birth control (acceptable methods of birth control include tubal ligation, transdermal patch, intra uterine devices/systems (IUDs/IUSs), oral, implantable or injectable contraceptives, sexual abstinence (if allowed by local authorities), double barrier method and vasectomised partner) or do not plan to continue using acceptable method of birth control throughout the study and do not agree to submit to periodic pregnancy testing during participation in the trial.
11) Patients considered unreliable by the investigator concerning the requirements for follow-up during the study and/or compliance with study drug administration, have a life expectancy less than 5 years for non-CV causes, or have cancer other than non-melanoma skin cancer within last 3 years, or has any other condition than mentioned which in the opinion of the investigator, would not allow safe participation in the study.
12) Acute coronary syndrome (ACS), diagnosed ≤ 2 months prior to visit 1 (screening).
13) Stroke or TIA ≤ 3 months prior to visit 1 (screening).

eAppendix 5. Definitions of Major Clinical Outcomes

Cardiovascular death

The cause of death was determined by the principal condition that caused the death, not the immediate mode of death. Clinical Events Committee (CEC) members reviewed all available information and used their clinical expertise to adjudicate the cause of death. All deaths not attributed to the categories of CV death and not attributed to a non-CV cause were presumed CV deaths. Death certificates or summary, if possible, were provided for all patients who died, including date and details surrounding death. However, if a death certificate was the only information available for review besides the patient profile in the clinical trial database, the CEC may have decided not to use this information as cause of death if another etiology appeared more plausible. The following definitions were used for the adjudication of fatal cases:

Sudden cardiac death

Death that occurs unexpectedly in a previously stable patient 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 ECG recording or witnessed on a monitor by either a medic or paramedic)
- Subjects unsuccessfully resuscitated from cardiac arrest or successfully resuscitated from cardiac arrest but who die within 24 hours without identification of a non-cardiac etiology
- Unwitnessed death and there is no conclusive evidence of another, non-CV, cause of death (i.e. presumed CV death)

Sudden death due to acute MI (MI type 3)

Sudden death occurring up to 14 days after a documented acute MI (verified either by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombus) and where there is 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 heart failure or cardiogenic shock

Death occurring in the context of clinically worsening symptoms and/or signs of congestive heart failure (CHF) without evidence of another cause of death.

New or worsening signs and/or symptoms of CHF include any of the following:

- 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
- Heart failure symptoms or signs requiring continuous intravenous therapy or oxygen administration
- Confinement to bed predominantly due to heart failure symptoms
- Pulmonary edema sufficient to cause tachypnea and distress 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 not occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening heart failure
  - Cardiogenic shock is defined as SBP <90 mmHg for more 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
    - Oliguria (urine output < 30 mL/hour)
    - Altered sensorium
    - Cardiac index < 2.2 L/min/m^2
  - Cardiogenic shock can also be defined in the presence of SBP ≥90 mmHg or for a time period <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 <1 hour. The outcome of cardiogenic shock will be based

on CEC assessment and must occur after randomization. Episodes of cardiogenic shock occurring before and continuing after randomization will not be part of the study outcome. This category will include sudden death occurring during an admission for worsening heart failure

Death due to stroke, cerebrovascular event

Death occurring up to 30 days after a stroke that is either due to the stroke or caused by complication of the stroke.

Death due to other CV causes

Death must be due to a fully documented CV cause not included in the above categories (e.g. dysrhythmia, pulmonary embolism, or CV intervention). Death due to a MI that occurs as a direct consequence of a CV investigation/procedure/ operation will be classified as death due to other CV cause.

Non-CV death

Non-CV death is defined as any death not covered by cardiac death or vascular death. The CEC will be asked to indicate the most likely cause of non-CV death. Examples of non-CV death are: pulmonary causes, renal causes, gastrointestinal causes, infection (including sepsis), non-infectious (e.g., systemic inflammatory response syndrome (SIRS)), malignancy (i.e., new malignancy, worsening of prior malignancy), hemorrhage (not intracranial), accidental/trauma, suicide, non-CV organ failure (e.g., hepatic failure) or non-CV surgery.

Myocardial infarction (MI) (non-fatal)

The term 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 following criteria A to C meets the diagnosis for myocardial infarction.

Criteria A: Spontaneous MI (type 1)
To identify a type 1 MI, patients should demonstrate spontaneous symptoms of myocardial ischemia unprovoked by supply/demand inequity, together with ≥1 of the following criteria:

- Cardiac biomarker elevation: Troponin is the preferred marker for use to adjudicate the presence of acute myocardial infarction. At least one value should show a rise and/or fall above the lowest cut-point providing 10% imprecision (typically the upper reference limit for the troponin run per standard of clinical care). Creatine kinase-MB is a secondary choice to troponin; a rise of CK-MB above the local upper reference limit would be consistent with myocardial injury

- ECG changes consistent with new ischemic changes

- ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]) or ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy [LVH] and LBBB):
- Development of pathological Q waves in the ECG
    - 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)
- ST elevation: New ST elevation at the J-point in two contiguous leads with the cut-off points: ≥0.2 mV in men 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 T inversion ≥0.1 mV in two contiguous leads with prominent R-wave or R/S ratio >1

- Imaging evidence of new non-viable myocardium or new wall motion abnormality

Criteria B: "Demand" related (type 2) MI

- Patients with type 2 MI should be considered with similar diagnostic criteria as a type 1 MI, however type 2 MI should be considered present when myocardial ischemia and infarction are consequent to supply/demand inequity, rather than a spontaneous plaque rupture and coronary thrombosis.

Criteria C: Percutaneous Coronary Intervention (PCI)-related MI (type 4a/4b)

- For PCI in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL within 24 hours of the procedure are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers >3 x 99th percentile URL (troponin or CK-MB >3 x 99th percentile URL) are consistent with PCI-related MI.
- If the cardiac biomarker is elevated prior to PCI, a ≥20% increase of the value in the second cardiac biomarker sample within 24 hours of PCI and documentation that cardiac biomarker values were decreasing (two samples ≥6 hours apart) prior to the suspected recurrent MI is consistent with PCI-related MI.
- Symptoms of cardiac ischemia are not required.

Criteria D: Coronary Artery Bypass Grafting (CABG)-related MI (type 5)

- For 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 >5 x 99th

percentile URL (troponin or CK-MB >5 x 99th percentile URL) plus at least one of the following

  - New pathological Q waves in at least 2 contiguous leads on the electrocardiogram that persist through 30 days or new LBBB
  - Angiographically documented new graft or native coronary artery occlusion
  - Imaging evidence of new loss of viable myocardium is consistent with CABG-related MI

- If the cardiac biomarker is elevated prior to CABG, a ≥20% increase of the value in the second cardiac biomarker sample within 72 hours of CABG and documentation that cardiac biomarker values were decreasing (two samples ≥6 hours apart) prior to the suspected recurrent MI plus new pathological Q waves in ≥2 contiguous leads on the electrocardiogram or new LBBB, angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium is consistent with a periprocedural MI after CABG. Symptoms of cardiac ischemia are not required.

Clinical classification of acute MI

For every MI identified by the CEC, one of the following will be assigned:

- Type 1: Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
- Type 2: MI 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: MI associated with PCI
- Type 4b: MI associated with stent thrombosis as documented by angiography or at autopsy
- Type 5: MI associated with CABG

Hospitalization for unstable angina

The date of this event is the day of hospitalization of the patient including any overnight stay at an emergency room or chest pain unit. Unstable angina requiring hospitalization is defined as all of the following:

- No elevation in cardiac biomarkers (cardiac biomarkers are negative for myocardial necrosis) according to conventional assays or contemporary sensitive assays
- Clinical presentation: Cardiac symptoms lasting ≥10 minutes and considered to be myocardial ischemia on final diagnosis with one of the following:
  - Rest angina
  - New-onset (<2 months) severe angina (Canadian Cardiovascular Society [CCS] Grading Scale, or CCS classification system, classification severity ≥III)
  - Increasing angina (in intensity, duration, and/or frequency) with an increase in severity of >1 CCS class to CCS class >III

Class	**Description of stage**
Class I	"Ordinary physical activity does not cause . . . angina," such as walking or climbing stairs. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation
Class II	"Slight limitation of ordinary activity." Angina occurs on walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals; in cold, in wind, or under emotional stress; or only during the few hours after awakening. Angina occurs on walking more than 2 blocks on the level and climbing more than 1 flight of ordinary stairs at a normal pace and under normal conditions
Class III	"Marked limitations of ordinary physical activity." Angina occurs on walking 1 to 2 blocks on the level and climbing 1 flight of stairs under normal conditions and at a normal pace
Class IV	"Inability to carry on any physical activity without discomfort—anginal symptoms may be present at rest"

- Requiring an unscheduled visit to a healthcare facility and overnight admission
- At least one of the following:
  - New or worsening ST or T wave changes on ECG. ECG changes should satisfy the following criteria for acute myocardial ischemia in the absence of LVH and LBBB:
    - ST elevation: New transient (known to be <20 minutes) ST elevation at the J-point in two contiguous leads with the cut-off points - ≥0.2 mV in men 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 T inversion ≥0.1 mV in two contiguous leads with prominent R-wave or R/S ratio >1

    – Evidence of ischemia on stress testing with cardiac imaging

    – Evidence of ischemia on stress testing with angiographic evidence of ≥70% lesion and/or thrombus in an epicardial coronary artery or initiation/increased dosing of antianginal therapy

    – Angiographic evidence of ≥70% lesion and/or thrombus in an epicardial coronary artery

Stent thrombosis

Timing

Type		**Timing**
Early stent thrombosis	Acute stent thrombosis	0 to 24 hours after stent implantation
	Subacute stent thrombosis	>24 hours to 30 days after stent implantation
Late stent thrombosis*		>30 days to 1 year after stent implantation
Very late stent thrombosis*		>1 year after stent implantation

Stent thrombosis should be reported as a cumulative value over time and at the various individual time points specified above. Time 0 is defined as the time point after the guiding catheter has been removed and the patient has left the catheterization laboratory

*Includes primary as well as secondary late stent thrombosis; secondary late stent thrombosis is a stent thrombosis after a target lesion revascularization

Definitions of definite, probable, and possible stent thrombosis

Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation:

- Angiographic confirmation of stent thrombosis: The presence of an intracoronary thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of ≥1 of the following criteria within a 48-hour time window:

    – Acute onset of ischemic symptoms at rest

    – New ischemic ECG changes that suggest acute ischemia

  - Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI: troponin or CK-MB >99th percentile of URL, according to conventional assays or contemporary sensitive assays)

  - Non-occlusive thrombus Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream

  - Occlusive thrombus TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch)

NOTE: The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion)

- Pathological confirmation of stent thrombosis Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy

Probable Stent Thrombosis is considered to have occurred after intracoronary stenting in the following cases:

- Any unexplained death within the first 30 days

  - In ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis

- Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

Possible Stent Thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.

Heart Failure (HF) requiring hospitalization

The date of this event is the day of hospitalization of the patient including any overnight stay at an emergency room or chest pain unit. HF requiring hospitalization is defined as an event that meets all of the following criteria:

- Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 12-hour stay (or a date change if the time of admission/discharge is not available)

- Clinical manifestations of heart failure (new or worsening) including at least one of the following:

  - Dyspnea

  - Orthopnea
  - Paroxysmal nocturnal dyspnea
  - Edema
  - Pulmonary basilar crackles
  - Jugular venous distension
  - Third heart sound or gallop rhythm
  - Radiological evidence of worsening heart failure
- Additional/increased therapy: at least one of the following:
  - Initiation of oral diuretic, intravenous diuretic, inotrope, or vasodilator therapy
  - Uptitration of oral diuretic or intravenous therapy, if already on therapy
  - Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of heart failure

Changes in biomarker (e.g., brain natriuretic peptide) consistent with CHF will support this diagnosis.

Coronary revascularization procedure

Either CABG or PCI (e.g., angioplasty, coronary stenting).

- CABG: the successful placement of $\geq$1 conduit with either a proximal and distal anastomosis or a distal anastomosis only
- PCI: Successful balloon inflation with or without stenting and the achievement of a residual stenosis <50%. The balloon inflation and/or stenting could have been preceded by device activation (e.g., angiojet, directional coronary atherectomy, or rotational atherectomy)

In cases where the procedure leads to a MI (type 4a, 4b or 5) the event will be adjudicated as an MI.

Transient Ischemic Attack (TIA)

TIA: a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

Stroke

Stroke: 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 are considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. Strokes are classified as ischemic, hemorrhagic, or unknown.

Diagnosis of stroke.

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

- 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
  - Hemianopia (loss of half of the field of vision of one or both eyes)
  - Other new neurological sign(s)/symptom(s) consistent with stroke

NOTE: 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

- Duration of a focal/global neurological deficit ≥24 hours OR < 24 hours if this is because of at least one of the following therapeutic interventions:
  - Pharmacologic (i.e., thrombolytic drug administration)
  - Non-pharmacologic (i.e., neurointerventional procedure [e.g. intracranial angioplasty])

OR

  - Available brain imaging clearly documents a new hemorrhage or infarct

OR

  - 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)

- Confirmation of the diagnosis by at least one of the following:*
    - Neurology or neurosurgical specialist
    - Brain imaging procedure (at least one of the following):
        - CT scan
        - MRI scan
        - Cerebral vessel angiography
    - Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)

If a stroke is reported but evidence of confirmation of the diagnosis by the methods outlined above is absent, the event will be discussed at a full CEC meeting. In such cases, the event may be adjudicated as a stroke on the basis of the clinical presentation alone, but full CEC consensus is mandatory.

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

- Persisted for more than one week

OR

- Persisted for more than 24 hours and were accompanied by an appropriate new CT or MRI finding

Classification of stroke

Strokes are sub-classified as follows:

- Ischemic (non-hemorrhagic): A stroke caused by an arterial obstruction due to a thrombotic (e.g., large vessel disease/atherosclerotic or small vessel disease/lacunar) or embolic etiology. This category includes ischemic strokes with hemorrhagic transformation (i.e. no evidence of hemorrhage on an initial imaging study but appearance on a subsequent scan)
- Hemorrhagic: A stroke due to a hemorrhage in the brain as documented by neuroimaging or autopsy. This category includes strokes due to primary intracerebral hemorrhage (intraparenchymal or intraventricular) and primary subarachnoid hemorrhage
- Not assessable: The stroke type could not be determined by imaging or other means (e.g., lumbar puncture, neurosurgery, or autopsy) or no imaging was performed

End-stage kidney disease (ESKD)

The following identifies ESKD:

- Transplantation will be classified as ESKD when the patient undergoes kidney transplantation
- Peritoneal dialysis or hemodialysis for at least 30 days and not known to recover at 90 days. At the termination of the trial, 30 days of renal replacement therapy (RRT) without reasonable chance of renal recovery will be taken as evidence of ESKD
- RRT may be indicated for symptomatic uremia (eGFR < 15 + symptoms) or asymptomatic advanced uremia (eGFR < 10) but RRT may not be available or affordable, or the subject may not elect RRT. In such instances ESKD will be diagnosed even without initation of RRT. If these conditions are not met, the treating nephrologist must provide documentation for the need of RRT. If at a visit after 30 days if the condition is documented, ESKD is diagnosed.

The date of onset of ESKD is the date of start RRT if applicable, or when the condition was first documented in the clinical database.

If an event is classified as ESKD by the CEC and subsequently the patient elects to withdraw from RRT without demonstrating recovery in eGFR, or signs and symptoms, the CEC decision should not be rescinded.

When a regular course of RRT has not been documented for 60 days or more, questions may arise regarding the event was acute or chronic in nature. If a subject is unable to continue for 60 or more days after initiating chronic RRT due to receiving a renal transplant or the subject dying the event will be classified as ESKD, and the date when RRT was initiated will be considered the date of the event.

Death from renal failure

The following events will be classified as death from renal failure when they satisfy the following criteria:

- The patient dies,

  AND

- RRT has not been initated (although clinically indicated), e.g.,death due to progressive kidney failure occurs before RRT can be introduced
- RRT has been discontinued due to patient withdrawal:
    - The patient refuses RRT or withdraws from chronic RRT, e.g., the caring physician and the patient (or legal representative) decide to withhold the regular course of chronic RRT

      AND

- There is no other likely cause of death

If RRT is not provided, for instance, due to terminal cancer then the cause of death is cancer and not renal death since the more proximal cause of death is cancer and not withdrawal. Similarly, if someone dies after refusing RRT due to trauma then death from renal failure cannot be diagnosed. If RRT is discontinued due to hemodynamic instability (such as Heart Failure), the the cause of death is cardiovascular and not renal.

Sustained decrease of eGFR of 40% or more

Sustained decrease in eGFR of 40% or higher (i.e., equal to 40% and above but less than 50%) from baseline (Randomization visit) is defined by evidence of at least two or more consecutive laboratory assessments demonstrating the decrease and by decrease of eGFR to below 60 ml/min. The confirmatory sample is expected to be collected within 4-8 weeks from the initial assessment showing decrease of 40%. However, if the only confirmatory assessment is outside of the window, it will be accepted by the CEC and used for decision making.

CEC will only adjudicate positively cases with no confirmatory assessment when:

- Decrease happened at trial end

OR

- Due to patient's death after the initial decrease

Sustained decrease of eGFR of 50% or more

Sustained decrease in eGFR of 50% or higher (i.e., equal to 50% and above) from baseline (Randomization visit) is defined by evidence of at least two or more consecutive laboratory assessments demonstrating the decrease and by decrease of eGFR to below 60 ml/min. The confirmatory sample is expected to be collected within 4-8 weeks from the initial assessment showing decrease of 50%. However, if the only confirmatory assessment is outside of the window, it will be accepted by the CEC and used for decision making.

CEC will only adjudicate positively cases with no confirmatory assessment when:

- Decrease happened at trial end

OR

- Due to patient's death after the initial decrease

Albuminuria progression

Albumniuria progression is defined as change from normoalbuminuria to either microalbuminuria (UACR ≥ 30 mg/g and ≤ 300 mg/g) or clinical proteinuria (macroalbuminuria, UACR > 300 mg/g) or from microalbuminuria (UACR ≥ 30 mg/g and ≤ 300 mg/g) to clinical proteinuria (macroalbuminuria, UACR > 300 mg/g).

Retinal laser coagulation

The following MedDRA preferred terms will be considered: “retinal laser coagulation”, “eye laser surgery”, “laser therapy”, “phototherapy” and “photocoagulation” with a concomitant indication for use “therapy of diabetic retinopathy”.

Intra-vitreal injections of an anti-VEGF therapy

The following treatments will be considered: ”Lucentis, ranibizumab compound (WhoDrug preferred term=”RANIBIZUMAB”)”, “Eylea, aflibercept compound (WhoDrug preferred term =”AFLIBERCEPT”)”, “Avastin, bevacizumab compound (WhoDrug preferred term =”BEVACIZUMAB”)” with a concomitant indication for use ”therapy of diabetic retinopathy”

Therapy of diabetic retinopathy

The criterion ‘therapy of diabetic retinopathy’ is fulfilled if the indication for use of retinal laser coagulation or Intra-vitreal injections of an anti-VEGF therapy is an adverse event or medical history with preferred code ”10012689” (with corresponding preferred term ”Diabetic retinopathy”) (MedDRA version 20.1). In addition, the criterion is fulfilled in case of an ongoing baseline condition or reported adverse event of “Diabetic retinopathy” at the start date of the corresponding therapy (except indication for use clearly indicates different underlying disease based on blinded medical review).

eAppendix 6. Description of Superiority Tests of 3-Point MACE and the Secondary Kidney Outcome and Their Sensitivity Analyses and Subgroup Analyses

Superiority tests of 3-point MACE and the key secondary kidney outcome.

Superiority tests of (a) 3-point MACE and (b) the key secondary kidney outcome. Both superiority hypotheses were to be tested separately, at the initial alpha-levels of 0.2*alpha for the primary outcome and 0.8*alpha for the key secondary kidney outcome, respectively.

Sensitivity analyses of 3-point MACE and the key secondary kidney outcome

For the primary and key secondary outcome sensitivity analyses were conducted on the per-protocol set (i.e. excluding patients with important protocol violations), the on-treatment set (i.e. patients with a minimum treatment duration of 30 days, OS) and the treated set with censoring at day 0 (TS+0) and day 30 (TS+30) after last dose of study drug, respectively.

Subgroup analyses of 3-point MACE and the key secondary kidney outcome

Prespecified subgroup analyses were performed in 33 subgroups by baseline age, gender, race, ethnicity, region, glycated hemoglobin, body mass index, blood pressure control, estimated glomerular filtration rate according to the Modification of Diet in Renal Disease equation, urine albumin-to-creatinine ratio, cardiovascular risk factors, risk for kidney disease, history of heart failure, duration of type 2 diabetes, use of glucose-lowering medication, use of lipidlowering drugs, use of anti-hypertensive therapy, and use of antiplatelet drugs.

Analysis of Continuous parameters

Continuous parameters were analysed using mixed-effect models for repeated measures including randomized treatment, region, week, treatment by week interaction, and linear covariates of baseline measurement and baseline by week interaction in the model. An unstructured variance-covariance matrix was specified for the within-subject covariance between weeks. In case of non-convergence, the AR(1) covariance structure was applied. All measurements (independent of discontinuation of medication) are considered.

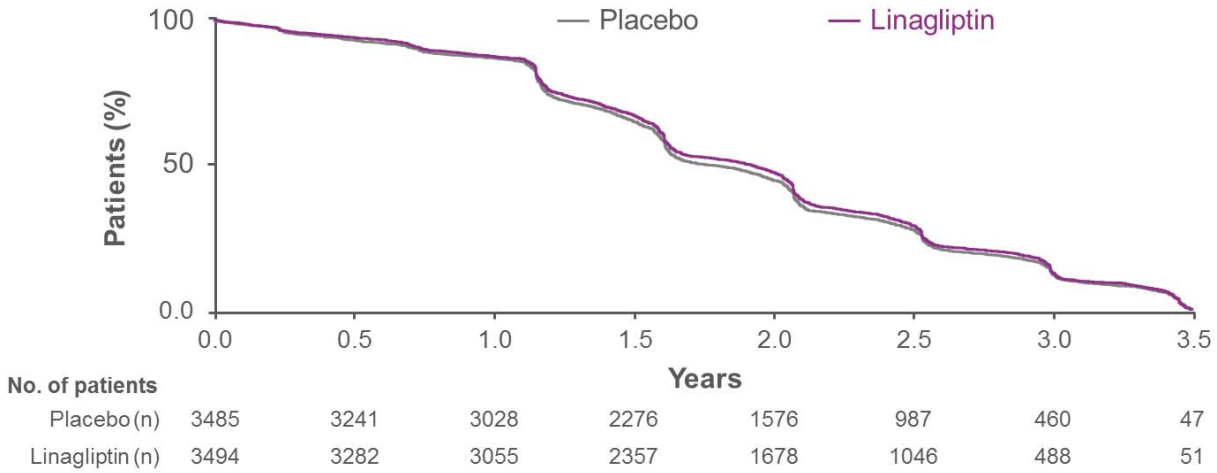
eAppendix 7. Observation and On-Treatment Observation Times

eTable 1. Observation and treatment times (years) by randomized treatment groups.

	Placebo (N = 3485)	Linagliptin (N = 3494)
Observation – years		
Median (25th – 75th quartile)	2.2 (1.6–3.0)	2.2 (1.6–3.0)
Mean	2.2	2.2
Cumulative time in study, patient-years	7781.6	7829.1
Treatment – years		
Median (25th – 75th quartile)*	1.8 (1.2–2.5)	1.9 (1.2–2.6)
Mean	1.9	1.9
Cumulative time under treatment, patient years	6585.9	6766.2

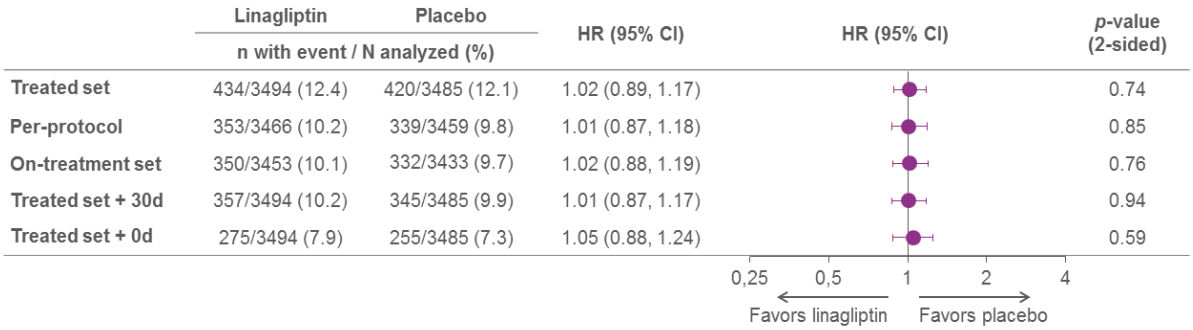
*: 4.0% of patients in the placebo group and 3.8% in the linagliptin group had < 3 months exposure; 46.2% in the placebo group and 49.0% in the linagliptin had ≥ 2 years treatment exposure

eFigure 1. Percentage of patients exposed to trial medication over time by treatment groups



eAppendix 8. Sensitivity and Subgroup Analyses of the Primary Outcome

eFigure 2. Sensitivity analyses of the primary outcome (3-point MACE)



eTable 2. Analyses for the primary outcome (3-point MACE) by pre-specified baseline characteristics.

	Patients with event/ patients analyzed		Hazard ratio	(95% CI)	p-for interaction
	Linagliptin	Placebo			
All patients	434/3493	420/3485	1.02	0.89, 1.17	
Age[a]					
<65 years	154/1467	140/1501	1.11	0.89, 1.40	0.35
≥65 years	280/2027	280/1984	0.97	0.82, 1.15	
Sex					
Male	282/2148	276/2242	1.06	0.90, 1.25	0.50
Female	152/1346	144/1243	0.96	0.77, 1.21	
Race					
White	340/2827	341/2769	0.97	0.83, 1.13	0.24
Asian	40/307	40/333	1.09	0.70, 1.70	
Black/African-American	31/194	27/217	1.30	0.78, 2.18	
Other	23/166	12/166	1.86	0.93, 3.75	
Ethnicity					
Hispanic/Latino	143/1227	130/1274	1.13	0.89, 1.43	0.31
Not Hispanic/Latino	291/2267	290/2211	0.97	0.83, 1.14	
Region[b]					
Europe + South Africa	182/1473	196/1461	0.92	0.75, 1.12	0.33
North America	91/593	72/587	1.25	0.92, 1.71	
Latin America	132/1156	119/1154	1.10	0.86, 1.40	
Asia	29/272	33/283	0.90	0.55, 1.48	
Glycated hemoglobin					
<8.0%	229/1915	243/1855	0.90	0.75, 1.08	0.04
≥8.0%	205/1579	177/1630	1.20	0.98, 1.46	
Body mass index					
<30 kg/m^2	191/1516	189/1517	0.98	0.80, 1.20	0.55
≥30 kg/m^2	243/1978	230/1965	1.06	0.89, 1.27	
Blood pressure control[c]					
SBP ≥140 mmHg or DBP ≥90 mmHg	249/1800	231/1834	1.11	0.93, 1.33	0.21
SBP <140 mmHg and DBP <90 mmHg	185/1694	189/1651	0.93	0.76, 1.14	

	Patients with event/ patients analyzed		Hazard ratio	(95% CI)	p-for interaction
	Linagliptin	Placebo			
All patients	434/3493	420/3485	1.02	0.89, 1.17	
Estimated glomerular filtration rate[d]					
≥60 mL/min/1.73m^2	103/1294	110/1337	0.96	0.73, 1.25	0.84
≥45 to <60 mL/min/1.73m^2	81/690	69/658	1.12	0.81, 1.54	
≥30 to <45 mL/min/1.73m^2	149/994	133/944	1.07	0.84, 1.35	
<30 mL/min/1.73m^2	101/516	108/546	0.97	0.74, 1.27	
Urine albumin-to-creatinine ratio					
<30 mg/g	67/696	60/696	1.10	0.78, 1.56	0.70
30 to 300 mg/g	158/1463	160/1431	0.95	0.77, 1.19	
>300 mg/g	208/1333	199/1357	1.06	0.88, 1.29	
Metformin					
No	242/1613	230/1558	1.02	0.85, 1.22	0.99
Yes	192/1881	190/1927	1.02	0.83, 1.25	
Metformin-dose					
≤1500 mg	81/787	80/792	1.02	0.75, 1.39	0.99
>1500 mg	111/1094	110/1135	1.02	0.78, 1.33	
Not on metformin	242/1613	230/1558	1.02	0.85, 1.22	
Sulfonylurea					
No	315/2392	314/2345	0.98	0.84, 1.14	0.31
Yes	119/1102	106/1140	1.15	0.88, 1.49	
Insulin					
No	139/1487	159/1542	0.88	0.70, 1.11	0.13
Yes	295/2007	261/1943	1.10	0.93, 1.30	
Lipidlowering drugs					
No	95/871	99/839	0.90	0.68, 1.20	0.33
Yes	339/2623	321/2646	1.06	0.91, 1.24	
Angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers					
No	89/634	101/687	0.93	0.70, 1.23	0.43
Yes	345/2860	319/2798	1.06	0.91, 1.23	
Calcium channel blockers (CCB)					
No	239/2061	256/2039	0.91	0.76, 1.08	0.04
Yes	195/1433	164/1446	1.21	0.98, 1.49	
Beta blockers					
No	134/1414	152/1412	0.87	0.69, 1.09	0.08
Yes	300/2080	268/2073	1.11	0.95, 1.31	
Diuretics					
No	159/1602	134/1549	1.15	0.92, 1.45	0.22
Yes	275/1892	286/1936	0.97	0.82, 1.14	

	Patients with event/ patients analyzed		Hazard ratio	(95% CI)	p-for interaction
	Linagliptin	**Placebo**			
All patients	434/3493	420/3485	1.02	0.89, 1.17	
Antiplatelet drugs					
No	125/1102	115/1084	1.10	0.85, 1.42	0.50
Yes	309/2392	305/2401	0.99	0.85, 1.16	
History of heart failure					
No	275/2542	269/2564	1.02	0.86, 1.21	0.96
Yes	159/952	151/921	1.01	0.81, 1.27	
Duration of type 2 diabetes					
≤ 5 years	45/521	47/553	0.98	0.65, 1.48	0.98
>5 to <10 years	73/696	71/688	1.01	0.73, 1.40	
≥10 years	316/2277	302/2244	1.03	0.88, 1.20	
CKD prognosis by KDIGO[e]					
Low	11/232	11/252	1.13	0.49, 2.60	0.87
Medium	61/766	68/795	0.89	0.63, 1.26	
High	111/995	96/905	1.05	0.80, 1.38	
Very high	250/1499	245/1533	1.04	0.87, 1.24	
Cardiorenal risk by combinations of macrovascular disease, albuminuria and eGFR[f]					
Cat A	117/1361	120/1367	0.97	0.75, 1.25	0.57
Cat B	86/394	75/345	0.92	0.67, 1.25	
Cat C	33/253	44/270	0.76	0.49, 1.20	
Cat D	163/1153	147/1156	1.12	0.89, 1.40	
Cat E	32/309	30/303	1.13	0.68, 1.85	
Cardiorenal risk					
Albuminuria and previous macrovascular disease without established renal disease	117/1361	120/1367	0.97	0.75, 1.25	0.34
Established renal disease (eGFR 15 - <45 mL/min/1.73 m^2 with any UACR mg/g or eGFR ≥45-75 mL/min/ 1.73 m2 with an UACR >200 mg/g) without previous macrovascular and albuminuria disease	195/1462	177/1459	1.12	0.91, 1.37	
Albuminuria and previous macrovascular disease plus established renal disease (eGFR 45-75 mL/min/1.73 m^2 with an UACR >200 mg/g or eGFR 15 - <45 mL/min/1.73 m^2 with any UACR mg/g)	119/647	119/615	0.88	0.69, 1.14	

	Patients with event/ patients analyzed		Hazard ratio	(95% CI)	p-for interaction
	Linagliptin	Placebo			
All patients	434/3493	420/3485	1.02	0.89, 1.17	
Established renal disease[g]					
Yes	314/2109	296/2074	1.04	0.89, 1.22	0.68
No	120/1385	124/1411	0.98	0.76, 1.25	
Established macrovascular disease and albuminuria					
Yes	236/2008	239/1982	0.94	0.79, 1.13	0.19
No	198/1486	181/1503	1.13	0.92, 1.38	
Prevalent kidney disease (eGFR< 60 mL/min/1.73m² or macroalbuminuria UACR >300 mg/g)					
Yes	374/2606	348/2541	1.04	0.90, 1.21	0.37
No	60/887	72/944	0.88	0.62, 1.24	

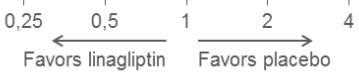
Cox regression analysis in patients treated with ≥1 dose of study drug. Subgroup factors were pre-specified for the primary outcome. For the test of homogeneity of the treatment group difference among subgroups (test for group by covariate interaction) no adjustment for multiple tests were performed.

[a:] consistent results in the additional prespecifed age subgroups <65, 65-75 and ≥ 75 years (p-for interaction 0.09), [b:] an additional prespecifed regional subgroup analyses (Japan, non-Japan) involved too few events to be analysed, [c:] consistent results in the additional prespecifed BP subgroups: SBP < 140 and >= 140 mmHg (p-for interaction 0.22) and < 160 and >= 160 (p-for interaction 0.79) mmHg, [d:] consistent results in the additional prespecifed eGFR subgroups < 60 and >= 60 ml/min/1.73m2 (p-for interaction 0.62), [e:] Per 2012 KDIGO criteria; Low risk defined as eGFR ≥60 ml/min/1.73m^2 and UACR <30 mg/g, Moderately increased risk defined as eGFR 45–59 ml/min/1.73m^2 and UACR <30 mg/g, or eGFR ≥60 ml/min/1.73m^2 and UACR 30–300 mg/g, High risk defined as eGFR 30–44 ml/min/1.73m^2 and UACR <30 mg/g, eGFR 45–59 ml/min/1.73m^2 and UACR 30–300 mg/g, or eGFR ≥60 and UACR >300 mg/g, Very high risk defined as eGFR <30 ml/min/1.73m^2 with any UACR, eGFR 30–44 and UACR 30–300 mg/g, or eGFR 45–59 ml/min/1.73m^2 and UACR >300 mg/g, [f:] A) albuminuria and previous macrovascular disease without evidence of impaired renal function, B) albuminuria and previous macrovascular disease plus renal impairment (eGFR 15-<45 mL/min/1.73 m^2 with any UACR mg/g), C) albuminuria and previous macrovascular disease plus renal impairment (eGFR ≥45-75 mL/min/1.73 m^2 with an UACR >200 mg/g), D) impaired renal function (eGFR 15-<45 mL/min/1.73 m^2 with any UACR), E) impaired Renal function (eGFR ≥45-75 mL/min/1.73 m^2 with an UACR >200 mg/g), [g:]patients in the "yes" category fulfils any one of the categories: albuminuria and previous macrovascular disease plus renal impairment (eGFR 15 – <45mL/min/1.73m^2 with any UACR), albuminuria and previous macrovascular disease plus renal impairment (eGFR 45-75 mL/min/1.73 m^2 with an UACR >200 mg/g), impaired renal function (eGFR 15- <45 mL/min/1.73 m^2 with any UACR mg/g), impaired renal function (eGFR 45-75 mL/min/1.73 m^2 with UACR >200 mg/g).

eAppendix 9. Sensitivity and Subgroup Analyses of the Secondary Outcome

eFigure 3 Sensitivity analyses of the secondary kidney composite endpoint

	Linagliptin	Placebo	HR (95% CI)	HR (95% CI)	*p*-value (2-sided)
	n with event / N analyzed (%)				
Treated set	327/3494 (9.4)	306/3485 (8.8)	1.04 (0.89, 1.22)		0.62
Per-protocol	295/3466 (8.5)	271/3459 (7.8)	1.05 (0.89, 1.24)		0.55
On-treatment set	299/3453 (8.7)	271/3433 (7.9)	1.06 (0.90, 1.25)		0.47
Treated set + 30d	299/3494 (8.6)	272/3485 (7.8)	1.06 (0.90, 1.25)		0.49
Treated set + 0d	257/3494 (7.4)	233/3485 (6.7)	1.06 (0.89, 1.27)		0.49



eTable 3 Subgroup analyses for the secondary kidney outcome by pre-specified baseline characteristics.

	Patients with event/ patients analyzed		Hazard ratio	(95% CI)	p-for interaction
	Linagliptin	Placebo			
All patients	327/3493	306/3485	1.04	0.89, 1.22	
Age[a]					
<65 years	180/1467	173/1501	1.05	0.85, 1.29	0.98
≥65 years	147/2027	133/1984	1.05	0.83, 1.33	
Sex					
Male	210/2148	189/2242	1.12	0.92, 1.36	0.23
Female	117/1346	117/1243	0.92	0.71, 1.19	
Race					
White	237/2827	220/2769	1.03	0.86, 1.24	0.72
Asian	32/307	37/333	0.90	0.56, 1.44	
Black/African-American	35/194	30/217	1.31	0.80, 2.13	
Other	23/166	19/166	1.16	0.63, 2.14	
Ethnicity					
Hispanic/Latino	156/1227	142/1274	1.10	0.88, 1.38	0.52
Not Hispanic/Latino	171/2267	164/2211	0.99	0.80, 1.23	
Region[b]					
Europe + South Africa	98/1473	98/1461	0.96	0.72, 1.27	0.82
North America	51/593	43/587	1.19	0.79, 1.78	
Latin America	149/1156	134/1154	1.07	0.85, 1.36	
Asia	29/272	31/283	0.96	0.58, 1.59	
Glycated hemoglobin*					
<8.0%	186/1915	158/1855	1.13	0.91, 1.40	0.26
≥8.0%	141/1579	148/1630	0.94	0.75, 1.19	
Body mass index					
<30 kg/m^2	162/1516	135/1517	1.14	0.91, 1.43	0.27
≥30 kg/m^2	165/1978	171/1965	0.96	0.77, 1.19	
Blood pressure control[c]					
SBP ≥140 mmHg or DBP ≥90 mmHg	222/1800	205/1834	1.08	0.89, 1.31	0.60
SBP <140 mmHg and DBP <90 mmHg	105/1694	101/1651	0.99	0.75, 1.30	

	Patients with event/ patients analyzed		Hazard ratio	(95% CI)	p-for interaction
	Linagliptin	Placebo			
All patients	434/3493	420/3485	1.02	0.89, 1.17	
Estimated glomerular filtration rate[d]					
≥60 mL/min/1.73m^2	54/1294	38/1337	1.46	0.97, 2.21	0.36
≥45 to <60 mL/min/1.73m^2	51/690	49/658	0.94	0.64, 1.39	
≥30 to <45 mL/min/1.73m^2	89/994	86/944	0.95	0.70, 1.27	
<30 mL/min/1.73m^2	133/516	133/546	1.05	0.82, 1.33	
Urine albumin-to-creatinine ratio					
<30 mg/g	22/696	16/696	1.46	0.77, 2.79	0.24
30 to 300 mg/g	53/1463	38/1431	1.30	0.86, 1.98	
>300 mg/g	252/1333	251/1357	0.97	0.81, 1.15	
Metformin					
No	212/1613	203/1558	0.99	0.82, 1.20	0.51
Yes	115/1881	103/1927	1.11	0.85, 1.44	
Metformin-dose					
≤1500 mg	53/787	39/792	1.29	0.85, 1.95	0.51
>1500 mg	62/1094	64/1135	0.99	0.70, 1.40	
Not on metformin	212/1613	203/1558	0.99	0.82, 1.20	
Sulfonylurea					
No	252/2392	220/2345	1.10	0.92, 1.32	0.21
Yes	75/1102	86/1140	0.87	0.64, 1.19	
Insulin					
No	101/1487	94/1542	1.08	0.82, 1.43	0.69
Yes	226/2007	212/1943	1.01	0.84, 1.22	
Lipidlowering drugs					
No	101/871	82/839	1.13	0.85, 1.52	0.48
Yes	226/2623	224/2646	1.00	0.83, 1.20	
Angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers					
No	62/634	69/687	0.96	0.68, 1.36	0.61
Yes	265/2860	237/2798	1.07	0.89, 1.27	
Calcium channel blockers (CCB)					
No	155/2061	147/2039	1.03	0.82, 1.29	0.87
Yes	172/2860	159/2798	1.05	0.85, 1.31	
Beta blockers					
No	161/1414	142/1412	1.14	0.91, 1.42	0.30
Yes	166/2080	164/2073	0.97	0.78, 1.20	

	Patients with event/ patients analyzed		Hazard ratio	(95% CI)	p-for interaction
	Linagliptin	Placebo			
All patients	434/3493	420/3485	1.02	0.89, 1.17	
Diuretics					
No	129/1602	117/1549	1.06	0.82, 1.36	0.91
Yes	198/1892	189/1936	1.04	0.85, 1.26	
Antiplatelet drugs					
No	131/1102	102/1084	1.25	0.97, 1.62	0.08
Yes	196/2392	204/2401	0.94	0.77, 1.14	
History of heart failure					
No	252/2542	230/2564	1.07	0.90, 1.28	0.52
Yes	75/952	76/921	0.95	0.69, 1.31	
Duration of type 2 diabetes					
$\leq$ 5 years	41/521	22/553	1.97	1.17, 3.30	0.04
>5 to <10 years	56/699	55/688	0.94	0.65, 1.37	
$\geq$10 years	230/2277	229/2244	0.97	0.81, 1.17	
CKD prognosis by KDIGO[e]					
Low	8/232	2/252	NC*	NC*	NC*
Medium	14/766	17/795	NC*	NC*	
High	57/995	37/905	NC*	NC*	
Very high	248/1499	250/1533	NC*	NC*	
Cardiorenal risk by combinations of macrovascular disease, albuminuria and eGFR[f]					
Cat A	38/1361	31/1367	1.22	0.76, 1.96	0.44
Cat B	51/394	50/345	0.79	0.53, 1.16	
Cat C	23/253	15/270	1.53	0.80, 2.94	
Cat D	180/1153	176/1156	1.01	0.82, 1.24	
Cat E	35/309	33/303	1.04	0.64, 1.67	
Cardiorenal risk					
Albuminuria and previous macrovascular disease without established renal disease	38/1361	31/1367	1.22	0.76, 1.95	0.75
Established renal disease (eGFR 15 - <45 mL/min/1.73 m^2 with any UACR mg/g or eGFR ≥45-75 mL/min/ 1.73 m2 with an UACR >200 mg/g) without previous macrovascular and albuminuria disease	215/1462	209/1459	1.01	0.84, 1.23	
Albuminuria and previous macrovascular disease plus established renal disease (eGFR 45-75 mL/min/1.73 m^2 with an UACR >200 mg/g or eGFR 15 - <45 mL/min/1.73 m^2 with any UACR mg/g)	74/647	65/615	0.99	0.71, 1.38	

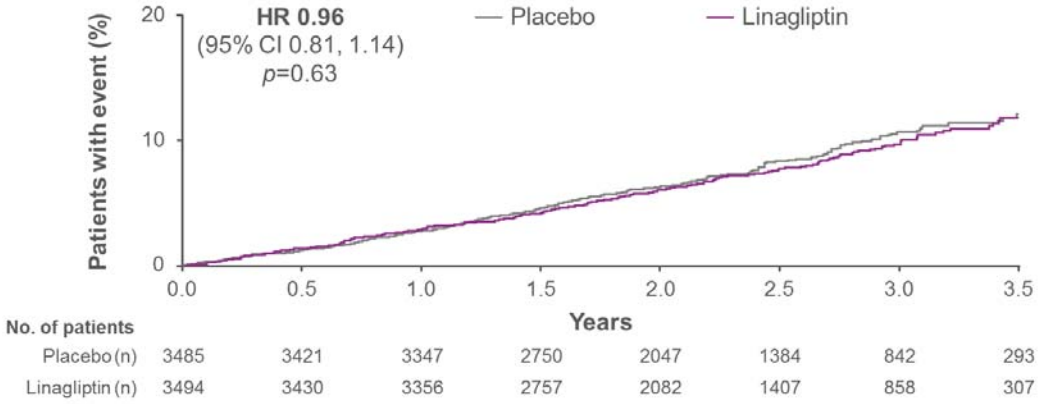
	Patients with event/ patients analyzed		Hazard ratio	(95% CI)	p-for interaction
	Linagliptin	Placebo			
All patients	434/3493	420/3485	1.02	0.89, 1.17	
Established renal disease[g]					
Yes	289/2109	274/2074	1.00	0.85, 1.18	0.48
No	38/1385	32/1411	1.20	0.75, 1.91	
Established macrovascular disease and albuminuria					
Yes	112/2008	96/1982	1.11	0.85, 1.46	0.63
No	215/1486	210/1503	1.03	0.85, 1.24	
Prevalent kidney disease (eGFR< 60 mL/min/1.73m² or macroalbuminuria UACR >300 mg/g)					
Yes	308/2606	291/2541	0.99	0.85, 1.17	0.38
No	19/887	15/944	1.36	0.69, 2.67	

Cox regression analysis in patients treated with ≥1 dose of study drug. Subgroup factors were pre-specified for the key secondary kidney outcome. For the test of homogeneity of the treatment group difference among subgroups (test for group by covariate interaction) no adjustment for multiple tests were performed.*: NC – not calculated owing to few events in some subgroups (<14).

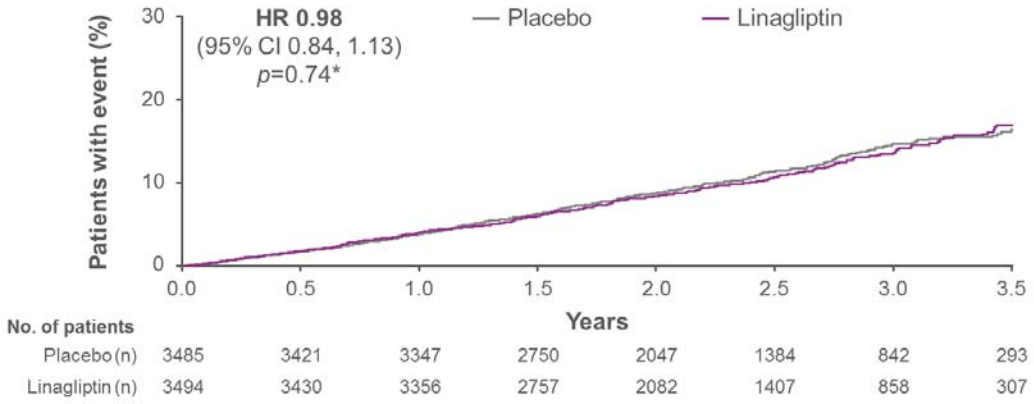
[a:] consistent results in the additional prespecifed age subgroups <65, 65-75 and ≥ 75 years (p-for interaction 1.00), [b:] an additional prespecifed regional subgroup analyses (Japan, non-Japan) involved too few events to be analysed, [c:] consistent results in the additional prespecifed BP subgroups: SBP < 140 and >= 140 mmHg (p-for interaction 0.37) and < 160 and >= 160 (p-for interaction 0.81) mmHg, [d:] consistent results in the additional prespecifed eGFR subgroups < 60 and >= 60 ml/min/1.73m2 (p-for interaction 0.06), [e:] Per 2012 KDIGO criteria; Low risk defined as eGFR ≥60 ml/min/1.73m^2 and UACR <30 mg/g, Moderately increased risk defined as eGFR 45–59 ml/min/1.73m^2 and UACR <30 mg/g, or eGFR ≥60 ml/min/1.73m^2 and UACR 30–300 mg/g, High risk defined as eGFR 30–44 ml/min/1.73m^2 and UACR <30 mg/g, eGFR 45–59 ml/min/1.73m^2 and UACR 30–300 mg/g, or eGFR ≥60 and UACR >300 mg/g, Very high risk defined as eGFR <30 ml/min/1.73m^2 with any UACR, eGFR 30–44 and UACR 30–300 mg/g, or eGFR 45–59 ml/min/1.73m^2 and UACR >300 mg/g, [f:] A) albuminuria and previous macrovascular disease without evidence of impaired renal function, B) albuminuria and previous macrovascular disease plus renal impairment (eGFR 15-<45 mL/min/1.73 m^2 with any UACR mg/g), C) albuminuria and previous macrovascular disease plus renal impairment (eGFR ≥45-75 mL/min/1.73 m^2 with an UACR >200 mg/g), D) impaired renal function (eGFR 15-<45 mL/min/1.73 m^2 with any UACR), E) impaired Renal function (eGFR ≥45-75 mL/min/1.73 m^2 with an UACR >200 mg/g), [g:]patients in the "yes" category fulfils any one of the categories: albuminuria and previous macrovascular disease plus renal impairment (eGFR 15 – <45mL/min/1.73m^2 with any UACR), albuminuria and previous macrovascular disease plus renal impairment (eGFR 45-75 mL/min/1.73 m^2 with an UACR >200 mg/g), impaired renal function (eGFR 15- <45 mL/min/1.73 m^2 with any UACR mg/g), impaired renal function (eGFR 45-75 mL/min/1.73 m^2 with UACR >200 mg/g).

eAppendix 10. Exploratory CV Analyses

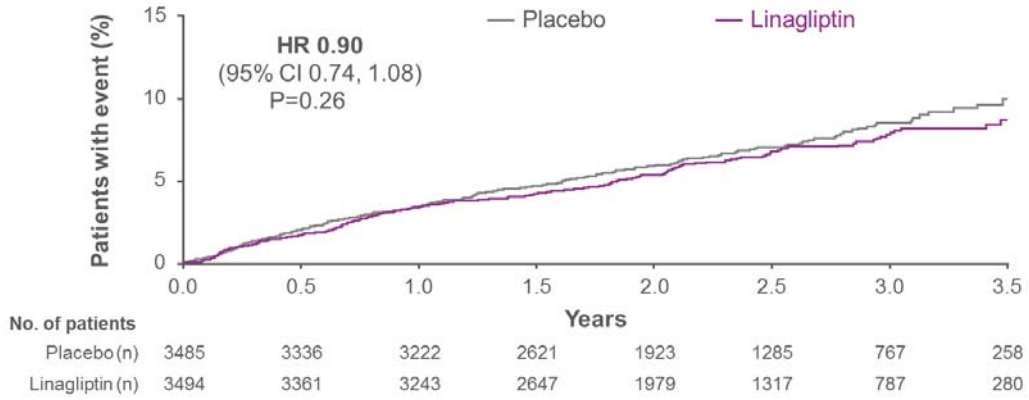
eFigure 4. Time to First occurrence of CV Death. Median (1st, 3rd quartile) time in study (years): Linagliptin 2.2 (1.6, 3.0) and Placebo 2.2 (1.6, 3.0).



eFigure 5. Time to First Occurrence of All-cause Death. Median (1st, 3rd quartile) time in study (years): Linagliptin 2.2 (1.6, 3.0) and Placebo 2.2 (1.6, 3.0).

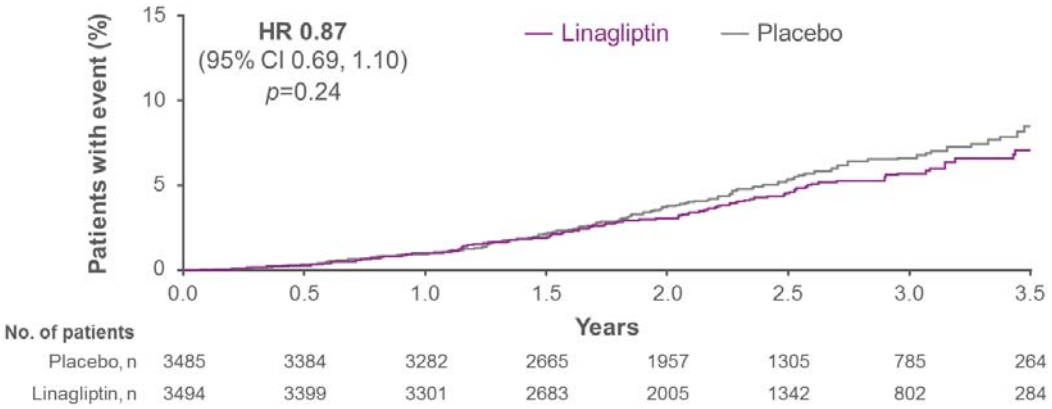


eFigure 6. Time to First Occurrence of Hospitalization for Heart Failure. Median (1st, 3rd quartile) time in study (years): Linagliptin 2.2 (1.6, 3.0) and Placebo 2.2 (1.6, 3.0).

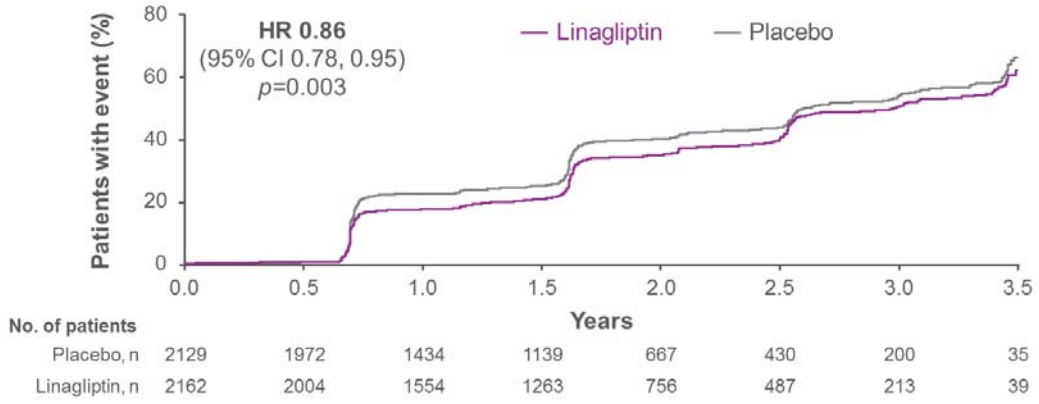


eAppendix 11. Exploratory Kidney and Microvascular Analyses

eFigure 7. Time to First Occurrence of renal death or sustained end stage kidney disease. Median (1st, 3rd quartile) time in study (years): Linagliptin 2.2 (1.6, 3.0) and Placebo 2.2 (1.6, 3.0).

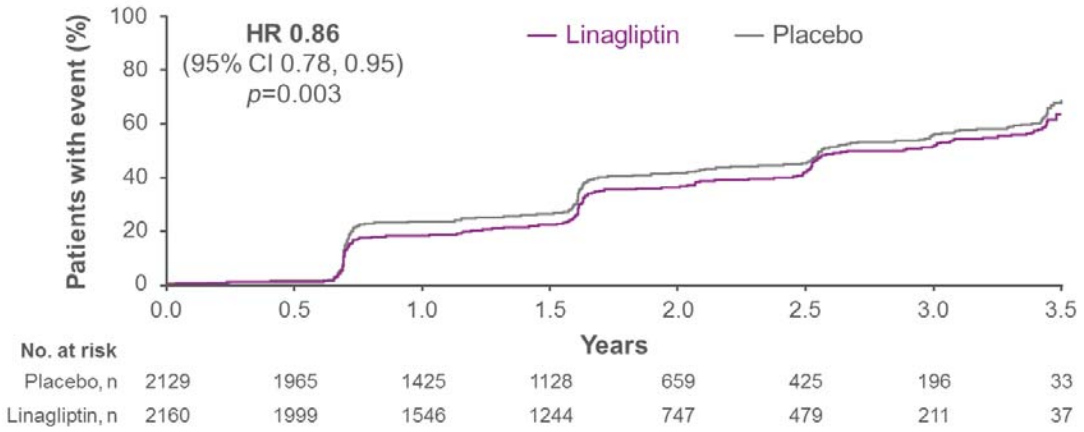


eFigure 8. Time to First Occurrence of Albuminuria Progression. Median (1st, 3rd quartile) time in study (years): Linagliptin 2.2 (1.6, 3.0) and Placebo 2.2 (1.6, 3.0).



eFigure 9. Time to First Occurrence of Composite Microvascular Endpoint*. Median (1st, 3rd quartile) time in study (years): Linagliptin 2.2 (1.6, 3.0) and Placebo 2.2 (1.6, 3.0).

*Sustained ESKD, sustained decrease of ≥50% in eGFR, death from renal failure, albuminuria progression, retinal photocoagulation or intavitreal injection of an anti-vascular endothelial growth factor (VEGF) therapy for diabetic retinopathy, vitreous haemorrhage or diabetes-related blindness. Treated set, Kaplan-Meier estimate. Hazard ratio and 95% CI based on Cox regression model with terms for treatment group and region. 2-sided *p*-value



eTable 4. Distribution of events contributing to the composite microvascular outcome

	Linagliptin (n=3494) (%)	Placebo (n=3485) (%)
Number with events	785 (22.5)	843 (24.2)
Kidney components		
Patients with renal death	0	0
Patients with sustained ESKD	10 (0.3)	8 (0.2)
Patients with sustained >50% eGFR decrease	21 (0.6)	14 (0.4)
Patients with albuminuria progression	745 (21.3)	810 (23.2)
Ocular components		
Patients with retinal laser coagulation or anti-VEGF injection for diabetic retinopathy	8 (0.2)	9 (0.3)
Patients with vitreous haemorrhage	4 (0.1)	5 (0.1)
Patients with diabetes related blindness	0	0

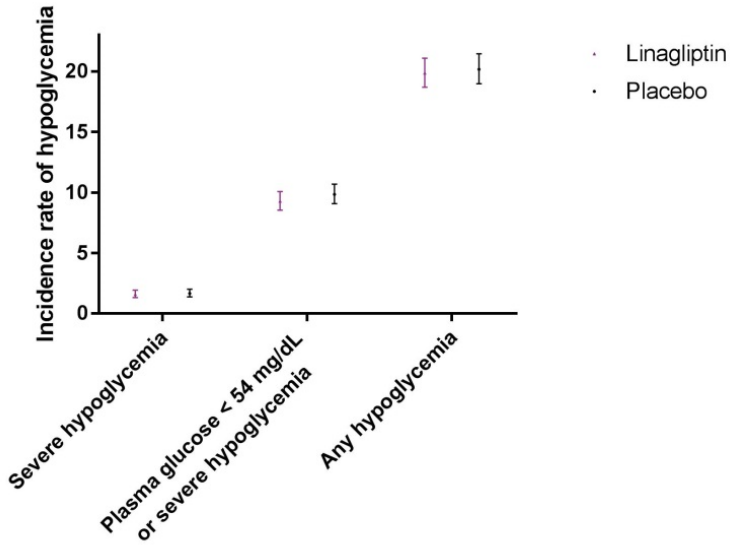
eTable 5. Distribution of events contributing to the composite ocular outcome

	Linagliptin (n=3494) (%)	**Placebo (n=3485) (%)**
Number with events	36 (1.0)	49 (1.4)
Patients with retinal laser coagulation	7 (0.2)	11 (0.3)
Patients with anti-VEGF injection for diabetic retinopathy	10 (0.3)	11 (0.3)
Patients with vitreous haemorrhage	18 (0.5)	27 (0.8)
Patients with diabetes related blindness	2 (0.1)	2 (0.1)

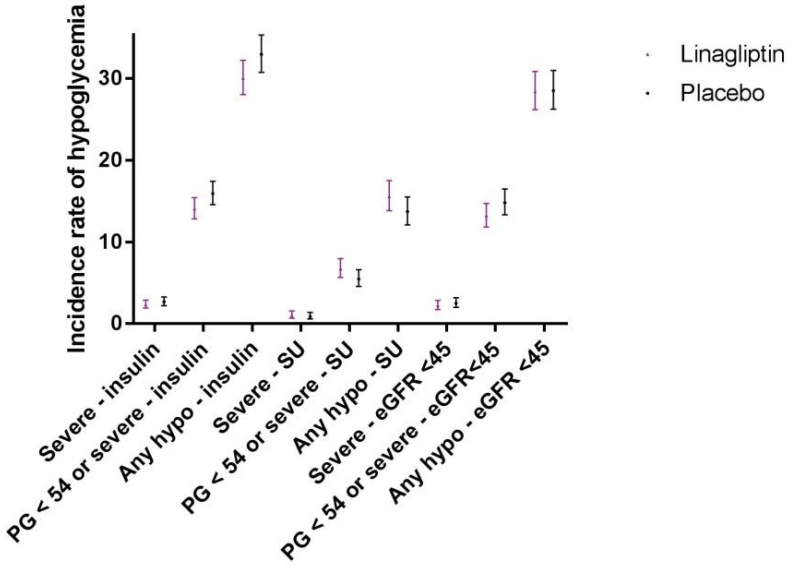
eAppendix 12. Hypoglycemia Incidence Rates Overall and in Subgroups at Elevated Hypoglycaemia Risk

Shown are incidence rates (95% confidence intervals) of any investigator reported hypoglycemic event, investigator reported hypoglycemic event with plasma glucose <54 mg/dl or severe event, or severe hypoglycemic events. Severe events defined as events requiring assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions

eFigure 10. Hypoglycemia (investigator reported) incidence rate (95% CI) in the overall population by severity and treatment group.



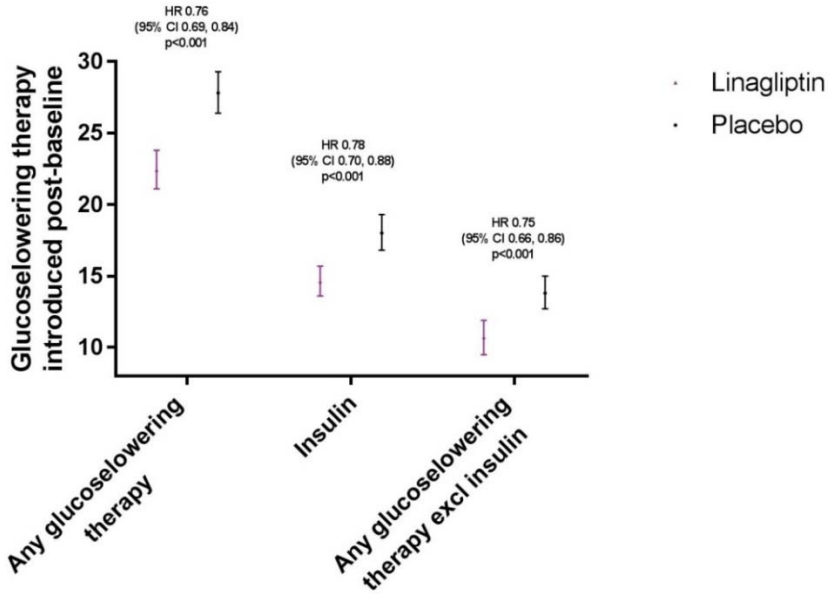
eFigure 11. Hypoglycemia (investigator reported) incidence rate (95% CI) in subgroups at elevated hypoglycemia risk by severity and treatment group.



eAppendix 13. Post-baseline Introduction of New Glucose-Lowering and CV Therapies

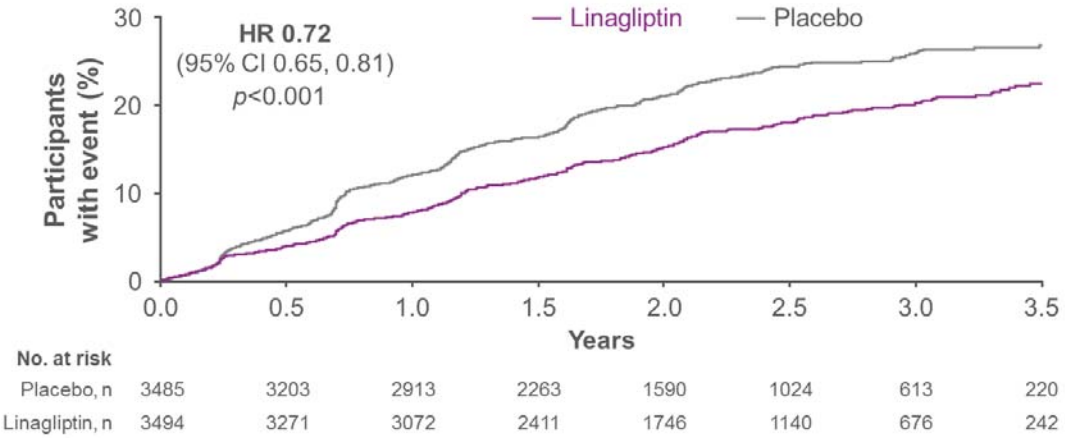
eFigure 12. New introduction of glucoselowering therapies post-baseline by treatment groups.

Shown are percentage (95% confidence interval) of patients with glucose-lowering medication initiated after first trial administration and without previous (either ongoing or discontinued) prescription of the same preferred name according to standardized drug groupings. Dose increases are not considered. Hazard ratios (HR) for time to first initiation of the corresponding antidiabetic medication are based on a Cox regression model,



eFigure 13. Initiation or dose increase of insulin by treatment groups. Median (1st, 3rd quartile) time in study (years): Linagliptin 2.2 (1.6, 3.0) and Placebo 2.2 (1.6, 3.0).

Kaplan-Meier estimates and HR (95% confidence interval) for time to initiation or dose increase of insulin. Initiation of insulin was considered if continuous period of insulin ≥ 3 months. Insulin dose increase was defined as an increase for at least 3 months of >50%; >30%; >20% for patients with baseline daily insulin dose of ≤10 units; >10 and ≤20 units; > 20 units, respectively.



eTable 6. Post-baseline introduction of new glucoselowering therapies according to standardized drug groupings by treatment groups.

Shown are percentage (95% confidence interval) of patients with glucose-lowering medication initiated after first trial administration and without previous (either ongoing or discontinued) prescription of the same preferred name according to standardized drug groupings. Dose increases are not considered

	Linagliptin (N = 3494)	Placebo (N = 3485)
	no. (% [95% CI])	
α-glucosidase inhibitors	24 (0.7 [0.5, 1.0])	32 (0.9 [0.7, 1.3])
DPP-4 inhibitors	64 (1.8 [1.4, 2.3])	83 (2.4 [1.9, 2.9])
GLP-1 receptor agonists	14 (0.4 [0.2, 0.7])	23 (0.7 [0.4, 1.0])
Insulins	509 (14.6 [13.4, 15.8])	628 (18.0 [16.8, 19.3])
Meglitinides	13 (0.4 [0.2, 0.6])	28 (0.8 [0.6, 1.2])
Metformin	100 (2.9 [2.4, 3.5])	127 (3.6 [3.1, 4.3])
SGLT-2 inhibitors	25 (0.7 [0.5, 1.1])	29 (0.8 [0.6, 1.2])
Sulfonylurea	158 (4.5 [3.9, 5.3])	220 (6.3 [5.6, 7.2])
Thiazolidinedione	23 (0.7 [0.4, 1.0])	28 (0.8 [0.6, 1.2])
Other therapies	10 (0.3 [0.2, 0.5])	8 (0.2 [0.1, 0.5])

eTable 7. Post-baseline introduction of cardiovascular therapies according to standardized drug groupings by treatment groups.

	Linagliptin (N = 3494)	Placebo (N = 3485)
	no. (%)	
Anti-hypertensive therapy	1188 (34.0)	1231 (35.3)
ACEi/ARB	496 (14.2)	521 (14.9)
ACE inhibitors	256 (7.3)	239 (6.9)
ARB	291 (8.3)	319 (9.2)
Renin inhibitors	2 (0.1)	0 (0.0)
Diuretics	634 (18.1)	657 (18.9)
Loop or high ceiling diuretics	382 (10.9)	381 (10.9)
Mineralacorticoid receptor antagonists	151 (4.3)	131 (3.8)
Other diuretics	267 (7.6)	275 (7.9)
Beta blockers	360 (10.3)	381 (10.9)
Calcium channel blockers	434 (12.4)	392 (11.2)
Other	271 (7.8)	284 (8.1)
Lipid-lowering drugs	499 (14.3)	499 (14.3)
Statins	395 (11.3)	393 (11.3)
Fibrates	82 (2.3)	87 (2.5)
Ezetimibe	37 (1.1)	29 (0.8)
Niacin	3 (0.1)	2 (0.1)
Other	39 (1.1)	39 (1.1)

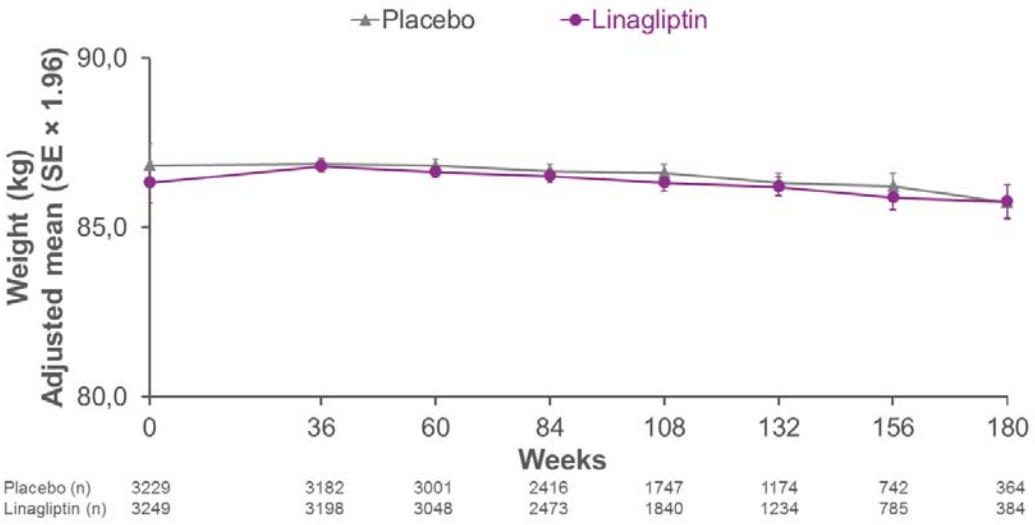
	Linagliptin (N = 3494)	Placebo (N = 3485)
	no. (%)	
Acetylsalicylic acid (ASA)	170 (4.9)	164 (4.7)
Other platelet inhibitors and antithrombotic agents	393 (11.2)	406 (11.6)
Platelet inhibitors excluding ASA and heparin	234 (6.7)	262 (7.5)
Clopidogrel	151 (4.3)	177 (5.1)
Dipyridamole	4 (0.1)	4 (0.1)
Other	95 (2.7)	104 (3.0)
Vitamin K antagonists	77 (2.2)	71 (2.0)
Direct factor Xa inhibitors	74 (2.1)	77 (2.2)
Direct thrombin inhibitors	13 (0.4)	13 (0.4)

Data are from patients treated with ≥1 dose of study drug. ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker

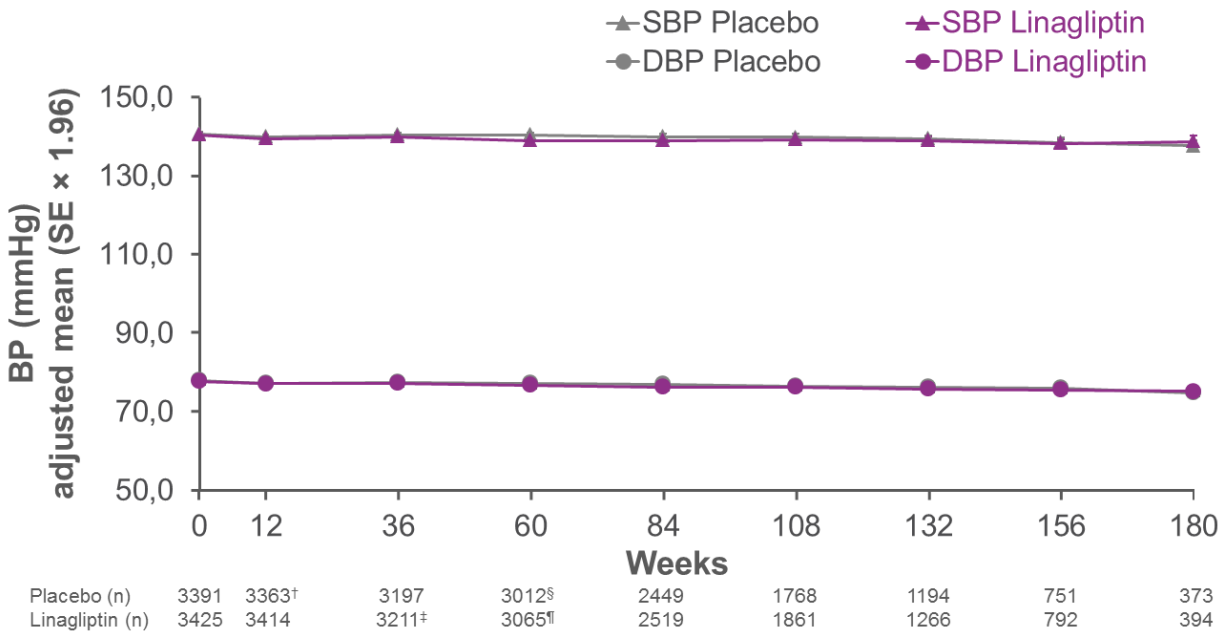
eAppendix 14. Exploratory CV and Renal Risk Factor Analysis

Continuous variables were analysed using mixed-effect model for repeated measures with randomized treatment, region, week, treatment by week interaction, and linear covariates of baseline measurement and baseline by week interaction as factors. An unstructured variance-covariance matrix was specified for the within-subject covariance between weeks. In case of non-convergence, an autoregressive(1) covariance matrix was applied.

eFigure 14. Weight over time by treatment groups. Median (1st, 3rd quartile) time in study (years): Linagliptin 2.2 (1.6, 3.0) and Placebo 2.2 (1.6, 3.0).

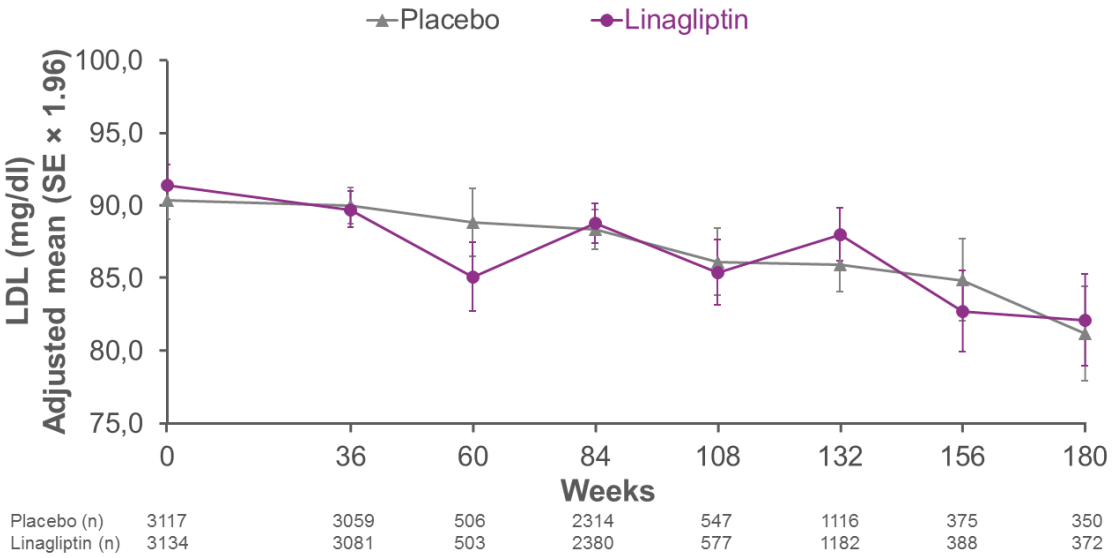


eFigure 15 Blood pressure over time by treatment groups. Median (1st, 3rd quartile) time in study (years): Linagliptin 2.2 (1.6, 3.0) and Placebo 2.2 (1.6, 3.0). (†n=3362 for DBP; ‡n=3210 for DBP; §n=3011 for DBP; ¶n=3064 for DBP)



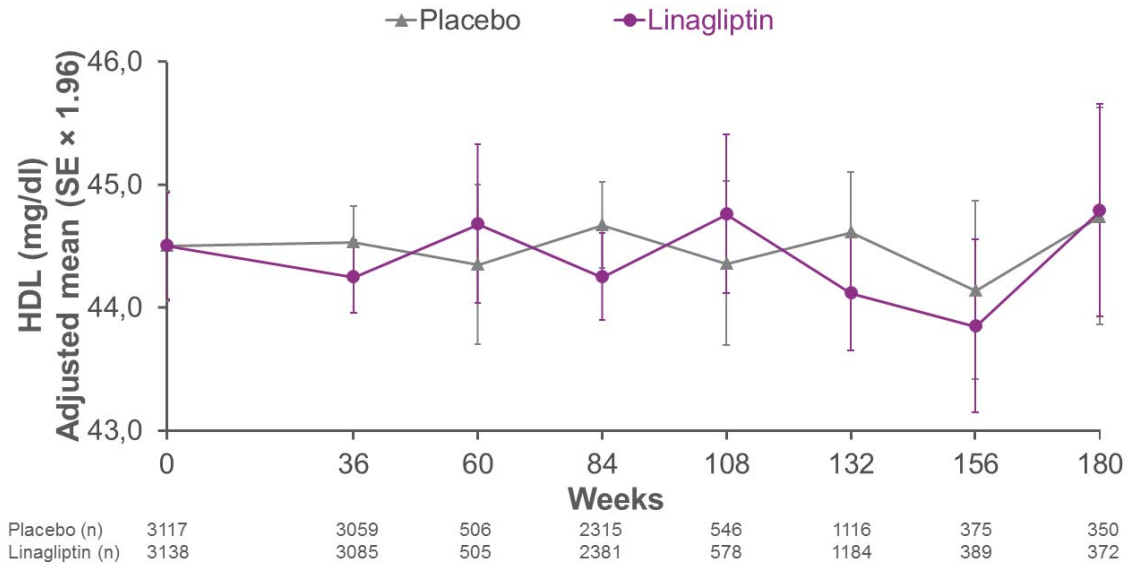
eFigure 16. Low density lipoprotein cholesterol over time by treatment groups. Median (1st, 3rd quartile) time in study (years): Linagliptin 2.2 (1.6, 3.0) and Placebo 2.2 (1.6, 3.0).

Conversion factor: 1 mg/dL = 0.02586 mmol/L



eFigure 17. High density lipoprotein cholesterol over time by treatment groups. Median (1st, 3rd quartile) time in study (years): Linagliptin 2.2 (1.6, 3.0) and Placebo 2.2 (1.6, 3.0).

Conversion factor: 1 mg/dL = 0.02586 mmol/L



eAppendix 15. Endpoints prespecified in the statistical analysis plans of CARMELINA

Primary endpoint

The primary endpoint is time to the first occurrence of any of the following by adjudication confirmed components of the primary composite endpoint (3-point major adverse cardiovascular events (MACE)): CV death, non-fatal MI or non-fatal stroke.

Key secondary endpoint

The key secondary endpoint is time to the first occurrence of any of the following by adjudication confirmed components: renal death, sustained end stage renal disease (ESRD) or sustained decrease of 40% or more in eGFR from baseline. This endpoint will also be further referred to as composite renal endpoint 1.

Tertiary endpoints:

Endpoints analyzed as time to event endpoints:

- CV death, non-fatal MI, non-fatal stroke or hospitalisation for unstable angina pectoris (4-point MACE)
- CV death
- Fatal or non-fatal MI
- Fatal MI
- Non-fatal MI
- Fatal or non-fatal stroke
- Fatal stroke
- Non-fatal stroke
- Hospitalisation for unstable angina pectoris
- Stent thrombosis
- Transient ischemic attack (TIA)
- All-cause mortality
- Coronary revascularization procedures (CABG or PCI)
- Occurrence of and time to first occurrence of any of the following components of overall mortality, non-fatal MI, non-fatal stroke

- Occurrence of and time to first occurrence of any of the following components of overall mortality, non-fatal MI, non-fatal stroke, hospitalization for unstable angina pectoris
- Occurrence of and time to first occurrence of any of the following components of overall mortality, non-fatal MI, non-fatal stroke, hospitalization for unstable angina pectoris and hospitalisation for heart failure
- Occurrence of and time to first occurrence of the composite cerebrovascular endpoint defined as stroke (fatal or non-fatal) or TIA
- Occurrence of and time to first occurrence of any adjudicated cardiovascular endpoint or all-cause mortality (all-cause mortality, MI (fatal or non-fatal), stroke (fatal or non-fatal), TIA, hospitalisation for unstable angina, hospitalisation for heart failure, stent thrombosis, coronary revascularization procedures (CABG or PCI)).
- Hospitalisation for peripheral revascularization
- Hospitalisation for heart failure
- CV death or hospitalisation for heart failure
- Occurrence of and time to first occurrence of any of the following components of CV death, non-fatal MI, non-fatal stroke and hospitalisation for heart failure
- occurrence of and time to first occurrence of any of the following components of CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina pectoris and hospitalisation for heart failure
- Composite renal endpoint 2 (renal death, sustained ESRD or sustained decrease of 50% or more in eGFR from baseline)
- Composite renal endpoint 3 (renal death, sustained ESRD or sustained decrease of 30% or more in eGFR (MDRD) from baseline accompanied by eGFR (MDRD) <60 ml/min/m2)
- Sustained decrease of 30% or more in eGFR (MDRD) from baseline accompanied by eGFR (MDRD) <60 ml/min/m^2
- Composite renal endpoint 4 with all-cause mortality, defined as any of the following components:
  - Sustained* macroalbuminuria
  - Sustained decrease of 40% or more in eGFR from baseline
  - Sustained ESRD
  - All-cause mortality

- Composite renal endpoint 5, defined as any of the following components:
  - Sustained* macroalbuminuria
  - Sustained decrease of 40% or more in eGFR from baseline
  - Sustained ESRD
  - Renal death
  - CV death
- Composite renal endpoint 6, defined as any of the following components:
  - Sustained decrease of 40% or more in eGFR from baseline
  - Sustained ESRD
  - All-cause mortality
- Composite renal endpoint 7, defined as any of the following components:
  - Sustained decrease of 40% or more in eGFR from baseline
  - Sustained ESRD
  - Renal death
  - CV death
- Composite renal endpoint 8, defined as any of the following components:
  - Sustained* macroalbuminuria
  - Sustained decrease of 50% or more in eGFR from baseline
  - Sustained ESRD
  - All-cause mortality
- Composite renal endpoint 9, defined as any of the following components:
  - Sustained* macroalbuminuria
  - Sustained decrease of 50% or more in eGFR from baseline
  - Sustained ESRD
  - Renal death
  - CV death
- Composite renal endpoint 10, defined as any of the following components:
  - Sustained decrease of 50% or more in eGFR from baseline
  - Sustained ESRD
  - All-cause mortality
- Composite renal endpoint 11, defined as any of the following components:
  - Sustained decrease of 50% or more in eGFR from baseline
  - Sustained ESRD
  - Renal death
  - CV death

- Composite renal endpoint 12, defined as any of the following components:
  - Sustained* eGFR (MDRD) <15 ml/min/m2
  - Sustained ESRD
  - Renal death
- Composite renal endpoint 13, defined as any of the following components:
  - sustained* eGFR (MDRD) <15 ml/min/m2
  - Sustained ESRD
  - Renal death
  - CV death
- Composite renal endpoint 14, defined as any of the following components:
  - Sustained* eGFR (MDRD) <10 ml/min/m2
  - Sustained ESRD
  - Renal death
- Renal composite outcome 15, defined as any of the following components:
  - Sustained* eGFR (MDRD) <10 ml/min/m2
  - sustained ESRD
  - Renal death
  - CV death
- Renal composite outcome 16, defined as any of the following components:
  - Sustained decrease of 40% or more in eGFR from baseline
  - Sustained* eGFR (MDRD) <10 ml/min/m2
  - sustained ESRD
  - Renal death
  - CV death
- Composite renal endpoint 17, defined as any of the following components:
  - Sustained* increase of serum creatinine ≥ 2-fold from baseline, accompanied by an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73m2 (MDRD)
  - Sustained ESRD
  - Renal death
- Composite renal endpoint 18, defined as any of the following components:
  - Sustained* increase of serum creatinine ≥ 2-fold from baseline, accompanied by an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73m2 (MDRD)
  - Sustained ESRD
  - Renal death

- CV death

- Sustained decrease of 50% or more in eGFR from baseline
- Sustained decrease of 40% or more in eGFR from baseline
- Sustained ESRD or renal death
- Renal death
- Renal death, sustained ESRD or CV death
- New incidence of macroalbuminuria defined as Urinary Albumin-to-Creatinine Ratio (UACR)>300mg/g at any post baseline measurement
- Sustained* progression of albuminuria (defined as change from normalbuminuria at baseline to micro- or macroalbuminuria or as change from microalbuminuria to macroalbuminuria).
- Onset of sustained macroalbuminuria, defined as UACR > 300 mg/g in patients with normo- or microalbuminuria at baseline
- Onset of sustained microalbuminuria, defined as UACR ≥ 30 mg/g.
- Sustained* regression to normalbuminuria defined as UACR < 30 mg/g in patients with micro- or macroalbuminuria at baseline (improvement)
- Sustained* regression to normo- or microalbuminuria in patients with macroalbuminuria at baseline (improvement)
- Sustained UACR reduction of ≥ 30 % from baseline.
- Onset of renal impairment, defined as sustained eGFR (MDRD) < 60 mL/min/1.73m2 in patients with eGFR ≥ 60 mL/min/1.73m2 at baseline
- Onset of overt CKD, defined as sustained* eGFR (MDRD) < 60 mL/min/1.73m2 or onset of sustained* macroalbuminuria (UACR > 300mg/g) in patients with eGFR ≥ 60 mL/min/1.73m2 and normo- or microalbuminuria at baseline
- Sustained increase of serum creatinine ≥ 2-fold from baseline, accompanied by an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73m2 (MDRD).
- Composite diabetic retinopathy endpoint 1 defined as use of retinal laser coagulation therapy or treatment with intravitreal injection(s) of an anti-vascular endothelial growth factor (VEGF) therapy for diabetic retinopathy
- Composite diabetic retinopathy endpoint 2 defined as use of retinal laser coagulation therapy or treatment with intravitreal injection(s) of an anti-VEGF therapy for diabetic retinopathy or vitreous haemorrhage or diabetes-related-blindness
- Silent MI

- Composite microvascular outcome 1 (renal death, sustained ESRD, sustained 50% decrease or more in eGFR from baseline, albuminuria progression, use of retinal photocoagulation or intravitreal injection(s) of an anti-VEGF therapy for diabetic retinopathy or vitreous haemorrhage or blindness)
- Composite microvascular outcome 2 (renal death, sustained ESRD, sustained 40% decrease or more in eGFR from baseline, albuminuria progression, use of retinal photocoagulation or intravitreal injection(s) of an anti-VEGF therapy for diabetic retinopathy or vitreous haemorrhage or blindness).
- Composite microvascular outcome 3 (renal death, sustained ESRD, sustained 30% decrease or more in eGFR from baseline accompanied by eGFR (MDRD) <60 ml/min/m2, albuminuria progression, use of retinal photocoagulation or intravitreal injection(s) of an anti-VEGF therapy for diabetic retinopathy or vitreous haemorrhage or blindness).
- Albuminuria progression (defined as change from normoalbuminuria to micro- or macroalbuminuria or as change from microalbuminuria to macroalbuminuria from baseline to any measurement post-baseline)
- Heart failure adverse events (based on narrow SMQ 20000004 ‘cardiac failure’)
- Hospitalisation for heart failure or all-cause mortality By adjudication confirmed events will be used for hospitalisation for heart failure.
- Occurrence of and time to first occurrence of 3P-MACE after severe hypoglycaemia or hypoglycaemia with plasma glucose <54 mg/dL
- Occurrence of and time to first occurrence of all-cause mortality after severe hypoglycaemia or hypoglycaemia with plasma glucose <54 mg/dL
- Occurrence of and time to first severe hypoglycaemia or hypoglycaemia with plasma glucose <54 mg/dL reported as adverse event

Endpoints not analyzed as time to event endpoints:

- Transition in albuminuria class
- Transition of eGFR (CKD-EPI) and eGFR (MDRD) categories
- Urine albumin creatinine ratio (UACR) change from baseline over time
- eGFR (MDRD and CKD-EPI) change from baseline over time
- eGFR (MDRD and CKD-EPI) slope from baseline to last value on-treatment
- eGFR (MDRD and CKD-EPI) slope from baseline to last value collected during follow-up visit

- eGFR (MDRD and CKD-EPI) slope from last value on-treatment to follow-up value
- Number of events of hospitalisation for heart failure
- Number of events of hospitalisation for heart failure or CV death
- Number of events of MI (fatal or non-fatal MI)
- Number of events of stroke (fatal or non-fatal stroke)

Other endpoints are:

- HbA1c (%) change from baseline over time
- Fasting plasma glucose (FPG) (mg/dL) change from baseline over time
- Proportion of patients who at the study end visit achieve glycaemic control (HbA1c ≤ 7.0%) without need for additional antidiabetic medication or increase in antidiabetic background medication therapy (between baseline and study end visit).
- This endpoint will be analysed on all patients in the treated set and in addition on patients with HbA1c > 7.0% at baseline.
- Proportion of patients with HbA1c ≤ 7.0% over time and at the study end visit
- This endpoint will be analysed on all patients in the treated set and in addition on patients with HbA1c > 7.0% at baseline.
- Proportion of patients initiated on insulin after baseline
  This endpoint will be analysed on all patients in the treated set and in addition on patients without insulin (basal insulin or mixed insulin) use at baseline.
- Time (days) to initiation of insulin (among patients not on insulin at baseline).
- Time to initiation of long-term use of insulin or long-term dose increase in insulin, where long-term is defined as a continuous period of insulin use of more than 3 months
- Change from baseline over time in total daily dose of insulin
- Weight (kg) change from baseline over time
- Proportion of patients with ≤ 2% weight gain at the study end visit
- Incidence of fast decline in eGFR, defined as annual loss in eGFR (MDRD) ≥ 5mL/min/year.
- Descriptive statistics for mRS
- Recurrent hypoglycaemia adverse events (based on narrow SMQ hypoglycaemia)
- Recurrent events of severe hypoglycaemia or hypoglycaemia with plasma glucose <54 mg/dL

Other safety endpoints include:

- Adverse events (including AEs of special interest, hypoglycaemic events and changes from baseline in ECG and physical examination documented as adverse events)
- Change from baseline in safety laboratory parameters. See TSAP Section 7.8.2.
- Additional safety endpoints (see TSAP Section 7.8)
- Vital signs
- Electrocardiogram (ECG).
- Cognitive function endpoints