



## Trial Statistical Analysis Plan

### for Final Analysis

<b>BI Trial No.:</b>	1218.22
<b>Title:</b>	A multicenter, international, randomized, parallel group, double-blind, placebo-controlled Cardiovascular Safety & Renal Microvascular outcome study with Linagliptin, 5 mg once daily in patients with type 2 diabetes mellitus at high vascular risk. <b>CARMELINA.</b> Including Protocol Amendment 2 1218.22 [C02155180-06].
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<b>Date of statistical analysis plan:</b>	18 DEC 2017
<b>Version:</b>	Revised
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## **2. LIST OF ABBREVIATIONS**

Include a list of all abbreviations used in the TSAP

Term	Definition / description
ALT	Alanine Transaminase (SGPT)
AP	Alkaline Phosphatase
ARB	Angiotensin Receptor Blocker
ASA	Acetylsalicylic Acid
AST	Aspartate Transaminase (SGOT)
ATC	Anatomical-Therapeutic-Chemical
BMI	Body Mass Index (weight in kg divided by height in meters squared)
bpm	Beat per minute
CABG	Coronary Artery Bypass Graft
CEC	Clinical Event Committee
CI	Confidence Interval
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRA	Clinical Research Associate
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Cardiovascular
DBL	Data Base Lock
DBP	Diastolic Blood Pressure
DPP-4	Dipeptidyl-peptidase 4
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular filtration Rate
EMA	European Medicines Agency
EOT	End Of Treatment
EPO	Erythropoietin

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Term	Definition / description
ESRD	End Stage Renal Disease
FPG	Fasting Plasma Glucose
GLP-1	Glucagon-like Peptide 1
HbA <sub>1c</sub>	Glycosylated Haemoglobin
HR	Hazard Ratio
IC	Informed Consent
ICH	International Conference on Harmonisation
IQR	Interquartile Range
IRT	Interactive Response Technology
ISF	Investigator Site File
ITT	Intent To Treat
KDIGO	Kidney Disease Improving Global Outcomes
KM	Kaplan-Meier
LTFU	Lost To Follow Up
MACE	Major Adverse Cardiovascular Events
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MMRM	Mixed Model Repeated Measures
OC	Observed Case
OR	Odds Ratio
OS	On-Treatment Set
PCI	Percutaneous Coronary Intervention
PPS	Per Protocol Set
PT	Preferred Term
pt-yrs	Patient-years
PV	Protocol Violation
Q1	Lower quartile
Q3	Upper quartile

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Term	Definition / description
RS	Randomized Set
REML	Restricted Maximum Likelihood
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SCR	Screened Set
SD	Standard Deviation
SDG	Standardized Drug Grouping
SGLT	Sodium Glucose Linked Transporter
SMQ	Standardized MedDRA Query
SOC	System Organ Class
T2DM	Type 2 Diabetes Mellitus
TEAE	Treatment Emergent Adverse Events
TIA	Transient Ischemic Attack
TNM	Tumor Node Metastasis
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
UACR	Urine Albumin Creatinine Ratio
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
WHO-DD	World Health Organization Drug Dictionary

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### **3. INTRODUCTION**

As per ICH E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This Trial Statistical Analysis Plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the trial, e.g., on trial objectives, trial design and population, treatments, definition of measurements and variables, planning of sample size, randomisation.

This TSAP will be used for the final analysis only.

**CTP:** *The primary objective is to demonstrate non-inferiority (by means of comparing the upper limit of a two-sided 95% confidence interval (CI) with the non-inferiority margin of 1.3) of treatment with linagliptin in comparison to placebo (as add-on therapy on top of standard of care) with respect to time to first occurrence of any of the adjudicated components of the primary cardiovascular (CV) composite endpoint (i.e. CV death, non-fatal stroke or non-fatal myocardial infarction (MI)) in patients with type 2 diabetes mellitus (T2DM).*

*If non-inferiority has been demonstrated, then the primary CV composite endpoint will be tested for superiority and the other objective, to assess the impact of treatment with respect to the composite renal endpoint (i.e. renal death, sustained end-stage renal disease (ESRD), sustained decrease in estimated glomerular filtration rate (eGFR)  $\geq$  40% from baseline), will be investigated separately with a test on superiority.*

SAS<sup>®</sup> Version 9.4 (or later version) will be used for all analyses.

#### 4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The revisions of the protocol, up to including version 3.0 dated 22 November 2016 (document number C02155180-06) were taken into account.

Following changes as compared to the last protocol version 3.0 apply:

1. The tertiary endpoint of time to first occurrence of sustained ESRD (based on by adjudication confirmed events) will not be analysed as separate endpoint, but as the time to the first event of the composite of sustained ESRD or renal death (based on by adjudication confirmed events).  
The rationale is that events of ESRD may not be confirmed by the adjudication committee as a separate endpoint if timely related with a confirmed renal death.
2. The time to first occurrence of sustained decrease of 50% or more in eGFR from baseline (based on by adjudication confirmed events) and the time to first sustained decrease of 40% or more in eGFR from baseline (based on by adjudication confirmed events) will not be analysed as separate endpoints.  
The rationale is that these events may not be confirmed by the adjudication committee as a separate endpoint if timely related with a confirmed event of ESRD or renal death.

The following changes were made based on an FDA Advice Letter dated August 14, 2017 regarding the first signed version of this Trial Statistical Analysis (SAP) dated May 5, 2017. These revisions were accepted by the FDA on November 09, 2017.

1. Study populations ([Section 6.3](#)) and censoring methods ([Section 6.8.3](#)) were separated and described separately to add clarity on the planned analyses. [Sections 6.2](#), [7.4.3](#), [7.4.4](#), and [7.6.1](#) were updated accordingly.
2. The censoring rules in [Section 6.8.3](#) were clarified and dates not expected to occur after the date of trial completion (e.g. laboratory sampling or ECG measurements) are not taken into account for censoring.
3. As requested by FDA, the 'TS+0' censoring approach was added as an additional sensitivity analysis for the treated set in [Section 6.8.3](#). [Sections 7.4.3](#), [7.4.4](#) and [7.6.1](#) were updated accordingly to reflect this additional sensitivity analysis.

In addition, the following minor changes have been made compared to the first signed TSAP version.

1. Minor changes in the definition of geographical regions were made to align with BI standards and remove countries not recruiting patients (see [Sections 6.4](#), [9.1](#) and [9.2](#)).
2. The comment on iPv criterion C3.1 (Non-compliance with criteria for removal from the trial) was modified since treatment should also be discontinued due to other criteria mentioned in the CTP. This change in [Section 6.2](#) does not alter the analysis sets since a violation of criterion C3.1 does not result in an exclusion from the TS/PPS.

## **5. ENDPOINTS**

The trial is set up with prospective centralized blinded adjudication of cardiovascular, cerebrovascular and renal trigger events. The prospectively defined adjudication process will assess cardiac, neurological, vascular and renal events through independent, blinded, external Clinical Event Committees (CEC).

Additionally, two separate independent, blinded, external committees were set up for adjudication of pancreatic events and assessment of oncological events, respectively.

Definitions of endpoints to be adjudicated and details on the composition of the committees, their procedures and interactions for all events (cardiovascular, cerebrovascular, renal, pancreatic and oncological events) are provided in the CEC charter.

Throughout the SAP the term ‘adjudicated’ means ‘by adjudication confirmed’. The analyses of primary and key secondary endpoint are based on adjudicated events.

### **5.1 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.

This endpoint will also be further referred to as time to 3-point MACE, or shortly 3P-MACE.

### **5.2 SECONDARY ENDPOINTS**

#### **5.2.1 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.

#### **5.2.2 Secondary endpoint**

Not applicable as no secondary endpoint other than the key secondary endpoint is defined for this study.

### **5.3 FURTHER ENDPOINTS**

For definition of “baseline”, refer to [Section 6.7.1](#).

#### **5.3.1 Tertiary endpoints**

Tertiary endpoints are the occurrence of and time to first occurrence of:

- CV death, non-fatal MI, non-fatal stroke or hospitalisation for unstable angina pectoris (4-point MACE)  
By adjudication confirmed events will be used.
- CV death  
By adjudication confirmed events will be used.
- Fatal or non-fatal MI  
By adjudication confirmed events will be used.
- Fatal MI  
By adjudication confirmed events will be used.
- Non-fatal MI  
By adjudication confirmed events will be used.
- Fatal or non-fatal stroke  
By adjudication confirmed events will be used.
- Fatal stroke  
By adjudication confirmed events will be used.
- Non-fatal stroke  
By adjudication confirmed events will be used.
- Hospitalisation for unstable angina pectoris  
By adjudication confirmed events will be used.
- Stent thrombosis  
By adjudication confirmed events will be used.
- Transient ischemic attack (TIA)  
By adjudication confirmed events will be used.
- All-cause mortality  
Data as reported in the eCRF will be used, defined as the occurrence of death and time to death.
- Coronary revascularization procedures (CABG or PCI)  
By adjudication confirmed events will be used.
- Hospitalisation for peripheral revascularization  
The eCRF data will be used: identified using terms from CV outcome page “Condition leading to peripheral revascularization procedure” with SAE criterion “requires hospitalisation” or “prolongs hospitalisation”.
- Hospitalisation for heart failure  
By adjudication confirmed events will be used.

- CV death or hospitalisation for heart failure  
By adjudication confirmed events will be used.
- Composite renal endpoint 2 (renal death, sustained ESRD or sustained decrease of 50% or more in eGFR from baseline)  
By adjudication confirmed events will be used.
- 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/m<sup>2</sup>)

By adjudication confirmed events will be used for renal death and sustained ESRD. The derivation of sustained decrease of 30% or more from baseline in eGFR (MDRD) accompanied by eGFR (MDRD) <60 ml/min/m<sup>2</sup> will be based upon the central laboratory data available for eGFR (MDRD).

- Sustained decrease of 30% or more in eGFR (MDRD) from baseline accompanied by eGFR (MDRD) <60 ml/min/m<sup>2</sup>

The central laboratory data eGFR (MDRD) will be used for the calculations. To be consistent with the criteria as defined for the adjudication of sustained decrease of 40% or more in eGFR (MDRD) from baseline and the sustained decrease of 50% or more in eGFR (MDRD) from baseline, the additional cut-off of eGFR (MDRD) <60 ml/min/m<sup>2</sup> is used.

Sustained decrease of 30% or more in eGFR (MDRD) from baseline is defined by at least two or more consecutive laboratory assessments demonstrating the decrease accompanied by eGFR (MDRD) <60 ml/min/m<sup>2</sup> within the same sample.

The consecutive confirmatory assessment must be performed at least 28 days after the initial 30% drop from baseline accompanied by eGFR (MDRD) <60 ml/min/m<sup>2</sup> (i.e. assessments performed less than 28 days after the initial drop will not qualify for a sustained event).

For a patient with no confirmatory assessment, the patient will still be considered with a sustained event when:

- decrease happened at trial end or
- due to patient's death after the initial decrease

Hereby trial end refers to the trial end of each individual patient.

- Sustained ESRD or renal death  
By adjudication confirmed events will be used.
- Renal death  
By adjudication confirmed events will be used.
- Renal death, sustained ESRD or CV death  
By adjudication confirmed events will be used.
- New incidence of macroalbuminuria defined as Urinary Albumin-to-Creatinine Ratio (UACR)>300mg/g at any post baseline measurement



Only patients without macroalbuminuria at baseline will be considered at risk for this endpoint in the analysis.

The central laboratory data will be used.

- 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

Definitions for AEs and concomitant therapies used to identify this endpoint will be specified in a separated document and stored in Clinical Trial Master File (CTMF).

- 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

Definitions for AEs and concomitant therapies used to identify this endpoint will be specified in a separated document. The terms used to define diabetes-related blindness include the preferred term “blindness”.

- Silent MI

Silent MI is an investigator reported endpoint, and is a trigger term for central adjudication for cardiovascular events. Any investigator reported silent MI that is adjudicated and confirmed as being an MI by the CEC will be counted as MI. Silent MI is not an outcome of adjudication.

Silent MI is defined as any adverse event reported as “silent MI” by the investigator, either coded as preferred term “Silent myocardial infarction” or via the eCRF tick box “silent MI” or both. Only events that are no trigger events for an adjudicated confirmed MI as determined by the CEC are considered 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)
  - By adjudication confirmed events will be used as source for:
    - renal death
    - sustained ESRD
    - sustained 50% decrease or more in eGFR from baseline
  - eCRF data and central laboratory data will be used as source for
    - 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)
    - use of retinal photocoagulation or intravitreal injection(s) of an anti-VEGF therapy for diabetic retinopathy
    - vitreous haemorrhage,
    - blindness.

Definitions for AEs and concomitant therapies used to identify components of this endpoint will be specified in a separated document and stored in CTMF.

- 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).
  - By adjudication confirmed events will be used as source for:
    - renal death
    - sustained ESRD
    - sustained 40% decrease or more in eGFR from baseline
  - eCRF data and central laboratory data will be used as source for
    - albuminuria progression
    - use of retinal photocoagulation or intravitreal injection(s) of an anti-VEGF therapy for diabetic retinopathy
    - vitreous haemorrhage,
    - blindness.

Definitions for AEs and concomitant therapies used to identify components of this endpoint will be specified in a separated document and stored in CTMF.

- Composite microvascular outcome 3 (renal death, sustained ESRD, sustained 30% decrease or more in eGFR from baseline accompanied by eGFR (MDRD) <60 ml/min/m<sup>2</sup>, albuminuria progression, use of retinal photocoagulation or intravitreal injection(s) of an anti-VEGF therapy for diabetic retinopathy or vitreous haemorrhage or blindness).
  - By adjudication confirmed events will be used as source for:
    - renal death
    - sustained ESRD
  - eCRF data and central laboratory data will be used as source for
    - sustained 30% decrease or more in eGFR from baseline accompanied by eGFR (MDRD) <60 ml/min/m<sup>2</sup>
    - albuminuria progression
    - use of retinal photocoagulation or intravitreal injection(s) of an anti-VEGF therapy for diabetic retinopathy
    - vitreous haemorrhage,
    - blindness.

Definitions for AEs and concomitant therapies used to identify this endpoint will be specified in a separated document and stored in CTMF.

- 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.

General note:

If a patient has been adjudicated to have a confirmed sustained decrease of 50% or more in eGFR from baseline, then the patient is also considered with an event in the analysis of sustained decrease of 40% or more in eGFR from baseline.

If a patient has an initial drop of 50% or more without a confirmatory sample, but at the next scheduled visit the eGFR shows a drop of 40% or more, in that case, the first drop of 50% or more will be used for the analysis of a drop of 40% or more.

For definition of “baseline”, refer to [Section 6.7.1](#). See [Tables 6.7.2: 1](#) and [6.7.3: 1](#) for further details.

Tertiary endpoints not analysed as time-to-event endpoints:

- Transition in albuminuria class  
The central laboratory data will be used for the calculations.
- Transition of eGFR (CKD-EPI) and eGFR (MDRD) categories  
The central laboratory data will be used for the calculations. Refer to [Section 7.6.5](#) for further details.
- Urine albumin creatinine ratio (UACR) change from baseline over time  
The central laboratory data will be used for the calculations.
- eGFR (MDRD and CKD-EPI) change from baseline over time  
The central laboratory data will be used for the calculations.
- 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  
By adjudication confirmed events will be used.
- Number of events of hospitalisation for heart failure or CV death  
By adjudication confirmed events will be used.
- Number of events of MI (fatal or non-fatal MI)  
By adjudication confirmed events will be used.

- Number of events of stroke (fatal or non-fatal stroke)  
By adjudication confirmed events will be used.

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  $\leq 7.0\%$ ) 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.

For the purpose of the analysis of this endpoint, the need for additional antidiabetic medication or increase in antidiabetic background medication therapy is defined as follows:

- A new introduction of antidiabetic treatment (except only fast-acting insulin) for  $> 7$  days or
- A dose increase of antidiabetic background medication other than insulin for  $> 7$  days.
- For patients with a baseline daily basal insulin dose  $\leq 10$  units as indicated on CRF page, any increase of basal insulin  $> 50\%$  from baseline for  $> 7$  days duration
- For patients with a baseline daily basal insulin dose  $> 10$  and  $\leq 20$  units, any increase of basal insulin  $> 30\%$  from baseline for  $> 7$  days duration
- For patients with a baseline daily basal insulin dose  $> 20$  units, any increase of basal insulin  $> 20\%$  from baseline for  $> 7$  days duration

In general “Baseline” for this comparison is the date one day prior to first study drug administration, please refer to baseline basal insulin dose in [Section 6.7.1](#).

In general, any therapy with the start date equal to the date of first trial drug intake is considered as being taken after first trial drug intake.

- Proportion of patients with HbA1c  $\leq 7.0\%$  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. Only the initiation of basal insulin or mixed insulin is considered.
- Time (days) to initiation of insulin (among patients not on insulin at baseline)  
Only the initiation of basal insulin or mixed insulin is considered.

- 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, where dose increase is defined as:
  - For patients with a baseline daily basal insulin dose  $\leq 10$  units as indicated on CRF page, any increase of basal insulin  $>50\%$  from baseline for  $> 3$  months duration
  - For patients with a baseline daily basal insulin dose  $>10$  and  $\leq 20$  units, any increase of basal insulin  $>30\%$  from baseline for  $> 3$  months duration
  - For patients with a baseline daily basal insulin dose  $> 20$  units, any increase of basal insulin  $>20\%$  from baseline for  $> 3$  months duration

Only the initiation of basal insulin or mixed insulin is considered.

- Proportion of patients treated with insulin as antidiabetic background therapy at baseline and selected visits during the study and study end visit  
Only the initiation of basal insulin or mixed insulin is considered.

- Change from baseline over time in total daily dose of insulin

This endpoint will be analysed descriptively on all patients in the treated set with insulin use at baseline who have at least one post-baseline measurement for the daily dose of insulin.

The total daily dose of insulin is derived based on the dose of basal insulin (alone or as part of mixed insulin) and the dose of bolus insulin as part of mixed insulin.

- Weight (kg) change from baseline over time
- Proportion of patients with  $\leq 2\%$  weight gain at the study end visit

In the above definition, weight gain is based on the percentage change from baseline at the study end visit.

In all those endpoints “study end visit” refers to the last documented study visit per patient, irrespective of whether this visit was performed before or after start of study close-out phase.

### **5.3.2 Other safety endpoints**

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). See [Section 7.8.1](#).
- Change from baseline in safety laboratory parameters. See [Section 7.8.2](#).
- Vital signs. See [Section 7.8.3](#).
- Electrocardiogram (ECG). See [Section 7.8.4](#).

## 5.4 OTHER VARIABLES

### 5.4.1 Modified Rankin Scale (MRS)

Data for assessment of modified rankin scale (MRS) will be displayed in patient listings only.

### 5.4.2 Cognitive function

The details on the analysis of cognitive functioning are specified in a separate Statistical Analysis Plan. The results will be reported separately from the Clinical Trial Report.

### 5.4.3 Demographic and other baseline characteristics

Data will be used as collected in the eCRF. In addition, the following variables need to be derived. The sources of information for the derivation of the endpoints are the eCRF and the central laboratory data.

#### Time since diabetes mellitus type 2 was first diagnosed (years):

Defined as [date of informed consent - date of first diagnosis + 1] / 365.25 (Refer to [Section 6.6](#) for handling of missing data).

#### Baseline Body Mass Index (BMI) (kg/m<sup>2</sup>):

Defined as weight [kg] / (height [m])<sup>2</sup>.

#### Age (years) at date of study entry:

Defined as (consent date – birth date) / 365.25 (Refer to [Section 6.6](#) for handling of missing information).

For displays of baseline characteristics, the following categories will be derived in addition to the subgroup categories described in [Section 6.4](#), which are also part of the tables of baseline characteristics:

- Age (years): < 65, ≥ 65 to < 75, ≥ 75 to < 80, ≥ 80
- HbA1c (%): < 7, ≥ 7 to < 8, ≥ 8 to < 9, ≥ 9
- eGFR (MDRD and CKD-EPI) (mL/min/1.73 m<sup>2</sup>): < 15, ≥ 15 to < 30, ≥ 30 to < 45, ≥ 45 to < 60, ≥ 60 to < 90, ≥ 90
- FPG (mg/dL): < 126, ≥ 126 to < 140, ≥ 140 to < 200, ≥ 200
- BMI (kg/m<sup>2</sup>): <25, ≥25 to <30, ≥30 to <35, ≥35
- SBP (mmHg) <130, ≥130 to <140, ≥140 to <160, ≥160
- DBP (mmHg): <80, ≥80 to <90, ≥90 to <100, ≥100
- SBP <140 and DBP <90, SBP ≥140 or DBP ≥90
- SBP <160 and DBP <100, SBP ≥160 or DBP ≥100

- Time since diabetes mellitus type 2 was first diagnosed (years):  $\leq 1$ ,  $> 1$  to  $\leq 5$ ,  $> 5$  to  $\leq 10$ ,  $> 10$  to  $\leq 15$ ,  $> 15$

The following variables will be derived from the concomitant therapy eCRF data. Selection on ATC3 and Standardized Drug Grouping (SDG) will be used for the classification and will be described in a separated document and stored in CTMF.

- Antihypertensives at baseline (yes/no)
- Calcium channel blockers at baseline (yes/no)

In addition further therapies may be added.

In addition, all subgroup categories defined in [Table 6.4: 1](#) that are not already mentioned above will be described at baseline. For smoking status and race, all categories collected in the eCRF will be displayed.

## 6. GENERAL ANALYSIS DEFINITIONS

### 6.1 TREATMENTS

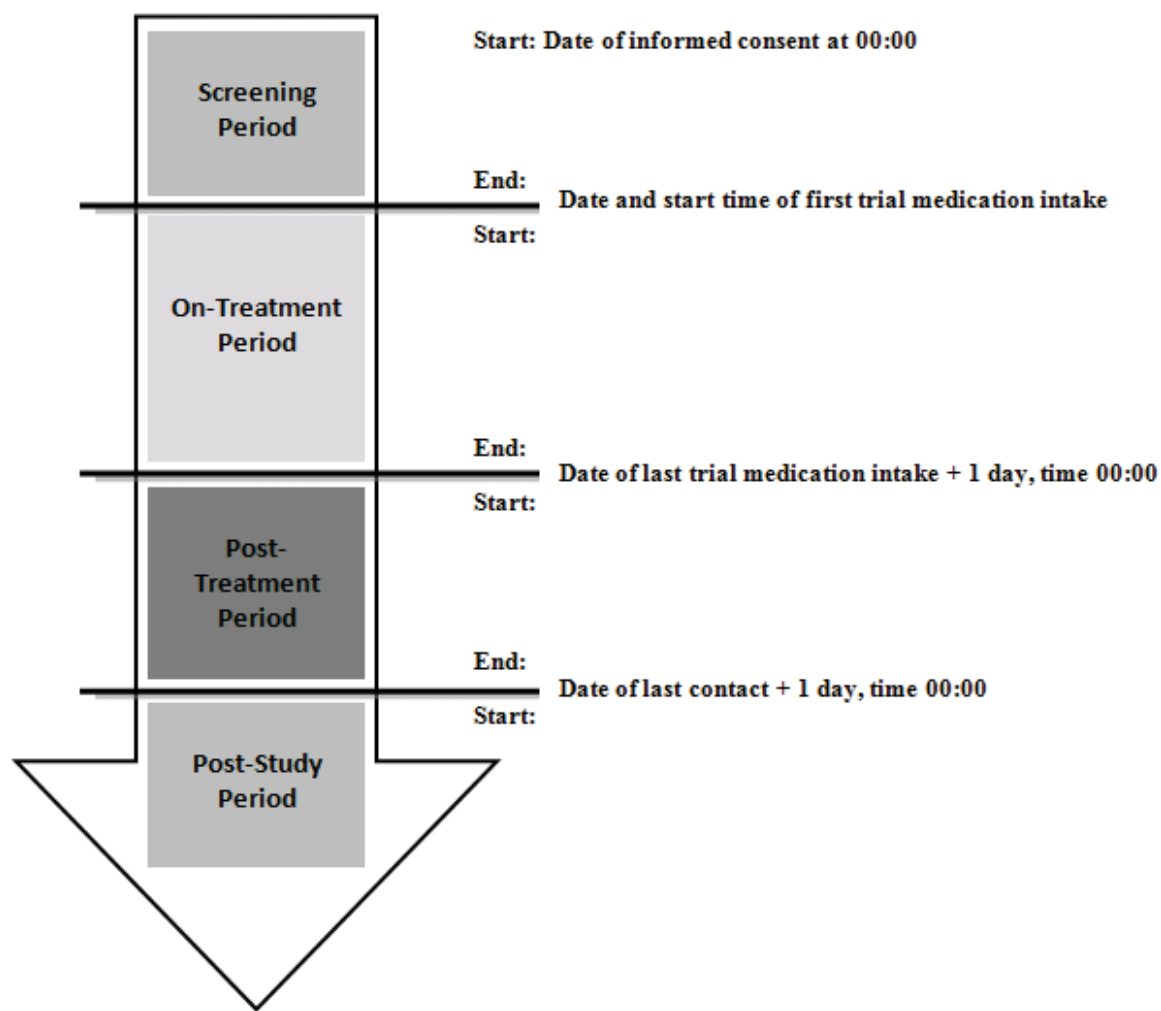
The following treatments are investigated in this trial:

Table 6.1: 1 Treatments and labels used in the analysis

Treatment		Short label
A	Linagliptin 5 mg	Lina
B	Placebo	Placebo

Study intervals are defined in the following figure:

Figure 6.1: 1 Study intervals



Refer to [Section 6.6](#), in case of missing information in eCRF.



During the study treatment phase, patients are allowed to go off trial medication and subsequently re-start trial medication. This may not happen or may happen repeatedly for a given patient, as this trial is expected to go on for a number of years. This is reflected by the off-treatment phase.

For specific safety and efficacy parameters, the duration of the on-treatment phase is given in [Section 6.7.2](#) and [Section 7.8.1.1](#).

Patients will be analysed as randomized for all analyses (safety and efficacy).

## **6.2 IMPORTANT PROTOCOL VIOLATIONS**

Data discrepancies and deviations from the CTP will be identified for all patients randomized and/or treated.

A protocol violation (PV) is defined as important, if it affects the rights or safety of the trial patients or if it can potentially influence the primary endpoint for the respective patients in a way that is neither negligible nor in accordance with the trial objectives.

The category of important PVs, which can potentially influence the primary or key secondary outcome measures, forms the basis for the decision of whether a patient belongs to a patient analysis set.

The following table displays the categories considered to be important protocol violations. If the data indicate further important PVs, this table will be supplemented accordingly, with the latest modification made prior to database lock.

The important PVs will be described in the Clinical Trial Report (CTR). A listing of patients who had the medication code broken will be provided.

A table showing the number of patients and frequency with violation of in- or exclusion criteria will be provided.

Table 6.2: 1 Important Protocol Violations

Category / Code	Description	Comment/Example	Affects rights (R)/ safety (S) or primary/ key secondary outcome (E)	Excluded from
<b>A</b>	<b>Entrance Criteria Not Met</b>			
<b>A.1</b>	<b>Inclusion criteria violated</b>			
A1.1	No type 2 diabetes	Inclusion criterion IN1 ticked "No"	E	PPS
<b>A.2</b>	<b>Exclusion criteria violated</b>			
A.2.1	Type I diabetes	Exclusion criterion EX1 ticked "Yes"	E	PPS
A.2.2	Severe renal impairment (eGFR < 15 ml/min/1.73 m <sup>2</sup> ) or ESRD at Visit 1 and/or the need for maintenance dialysis	Exclusion criterion EX4 ticked "Yes" Or eGFR < 15 ml/min/1.73 m <sup>2</sup> at visit 1	E	PPS
A.2.3	Pre-planned coronary artery re-vascularisation (PCI, CABG)	Exclusion criterion EX6 ticked "Yes"	E	PPS
A.2.4	Specific exclusion criterion for premenopausal women violated	Exclusion criterion EX10 ticked "Yes"	R/S	None

Table 6.2: 1 Important Protocol Violations (cont.)

Category / Code	Description	Comment/Example	Affects rights (R)/ safety (S) or primary/ key secondary outcome (E)	Excluded from
A.2.5	Patients considered unreliable by the investigator for safe participation in the study	Exclusion criterion EX11 ticked "Yes"	E	PPS
A.2.6	Acute coronary syndrome (ACS), diagnosed $\leq 2$ months prior to Visit 1	Exclusion criterion EX12 ticked "Yes"	E	PPS
A.2.7	Stroke or transient ischemic attack (TIA) $\leq 3$ months prior to Visit 1	Exclusion criterion EX13 ticked "Yes"	E	PPS
<b>B</b>	<b>Informed Consent</b>			
B1	Informed consent not available	Inclusion criterion IN7 ticked "No" Or Date of informed consent missing Or No signature on patient's "Declaration of Informed Consent" (to be identified by CRA)	R/S	All

Table 6.2: 1 Important Protocol Violations (cont.)

<b>Category / Code</b>		<b>Description</b>	<b>Comment/Example</b>	<b>Affects rights (R)/ safety (S) or primary/ key secondary outcome (E)</b>	<b>Excluded from</b>
	B2	Informed consent given too late	Date of informed consent for the study not obtained prior to any study related procedure  Minimum requirement for initial informed consent ≤ date of visit 1/date of any study procedure	R/S	None
<b>C</b>		<b>Trial medication and randomisation</b>			
	<b>C1</b>	<b>Incorrect Trial Medication Taken</b>			
	C1.1	No study medication taken	Patient randomised, but no study medication taken	E	PPS, TS

Table 6.2: 1 Important Protocol Violations (cont.)

Category / Code	Description	Comment/Example	Affects rights (R)/ safety (S) or primary/ key secondary outcome (E)	Excluded from
C1.2	Incorrect trial medication taken	<p>Wrong medication (different medication than the patient was randomised to) taken for more than 20% of the overall treatment duration (between randomisation and first outcome event) of a patient.</p> <p>This is identified by the medication kit number recorded in eCRF as well as the medication kit number as assigned by IRT.</p> <p>Can also be manually identified by investigator or CRA.</p> <p>Can only be finally judged after DBL since unblinding information is required.</p>	E	PPS
<b>C2</b>	<b>Randomisation not followed</b>			
C2.1	Treated before randomisation	<p>Date of randomisation after date of study medication intake at visit 2;            Or            Patient treated according to eCRF, but not randomised according to IRT.</p>	E	PPS
<b>C3</b>	<b>Non-compliance</b>			

Table 6.2: 1 Important Protocol Violations (cont.)

<b>Category / Code</b>	<b>Description</b>	<b>Comment/Example</b>	<b>Affects rights (R)/ safety (S) or primary/ key secondary outcome (E)</b>	<b>Excluded from</b>
C3.1	Non-compliance with criteria for removal from the trial	A missing pregnancy test does not qualify as IPV.	R/S	None
<b>D</b>	<b>Concomitant Medication</b>	Not Applicable		
<b>E</b>	<b>Missing data</b>	Not Applicable		
<b>F</b>	<b>Incorrect timing</b>	Not Applicable		
<b>G</b>	<b>Trial specific protocol violations</b>			
G1.1	Previous participation (randomisation) within this study		E/S/R	PPS
G1.2	Serious non-compliance potentially affecting primary endpoint		E/S/R	PPS*

Note: Missing visits, evaluations, and tests will be considered missing data, not protocol deviations

\*These patients might be kept out of some further patient analysis sets. The details are described in a separate document.

### 6.3 PATIENT SETS ANALYSED

- **Screened Set (SCR):**  
The Screened (Enrolled) Set will include all patients who signed the informed consent.
- **Randomized Set (RS):**  
All screened patients who were randomized, whether treated with trial medication or not.
- **Treated Set (TS):**  
All patients treated with at least one dose of trial medication. If no trial medication is taken at site during the visit, but the medication kit was dispensed to the patient and not all trial medication has been returned, the patient will be included in the TS. The TS is the basis for the primary efficacy and the safety analyses.
- **Per Protocol Set (PPS):**  
All patients included in the TS who have no important PV leading to exclusion from the PPS. It will be used for sensitivity analyses.
- **On-treatment Set (OS):**  
The 'On-treatment' set will include all randomized patients with a minimum treatment duration of 30 days (cumulative). It will be used for sensitivity analysis. The time from last permanent treatment stop (excluding reported treatment gaps) minus first drug intake + 1 day has to be equal or greater than 30 days to qualify a patient to be included in this analysis set.

The following table defines for each planned analysis, which patient set is to be used.

Table 6.3: 1 Table specifying patient sets for analyses

Endpoint	Patient Sets				
	SCR	RS	TS	PPS	OS
Disposition	X				
Patient analysis sets		X			
Demographic/baseline characteristics <sup>^</sup>			X		
Important PVs			X		
Primary/Key secondary endpoint			X	X*	X*
Time to first MI (fatal or non-fatal MI), time to first stroke (fatal or non-fatal stroke), time to CV death, time to first hospitalisation for unstable angina, time to first hospitalisation for heart failure, time to first CV death or hospitalisation for heart failure			X		X*
4P-MACE			X	X*	X*
Tertiary endpoints (not mentioned above)			X		
Other safety endpoints as per <a href="#">Section 5.3.2</a>			X		
Post stroke functional assessment as per <a href="#">Section 5.4.1</a>			X		

\* Sensitivity analysis

<sup>^</sup> Demographic analyses will be repeated on the randomised set for EudraCT purposes.

Note that the number of patients with available data for an endpoint may differ. For details, see [Section 6.6](#).

## 6.4 SUBGROUPS

For all subgroups and category definitions defined in that section, the baseline information will be used.

The primary endpoint, key secondary endpoint, time to first 4P-MACE event, time to CV death, time to first MI (fatal or non-fatal MI), time to first stroke (fatal or non-fatal stroke), time to first hospitalisation for unstable angina, time to first hospitalisation for heart failure and time to first hospitalisation for heart failure or CV death will be explored across the subgroups according to the [Table 6.4: 1](#) below, except for the subgroup CV risk (per highest risk) see below.

The subgroup categories can be pooled, if the number of patients within a category is small. The final decision will be taken before the trial database lock.



For each subgroup, baseline demographics and diabetic variables will be displayed based on the TS. Patients with missing information for a subgroup definition will not be considered in the respective analysis.

All subgroup analyses will be based on the TS. Subgroup analyses are described in [Section 7.4.4](#).

Table 6.4: 1 Subgroups

<b>Variable</b>	<b>Categories</b>
Age (years)	<65 65 to < 75 ≥ 75
	<65 ≥65
Region	<u>Version 1:</u> North America Latin America Europe Asia  <u>Version 2:</u> Japan Non-Japan
Race	Black White Asian Other
Ethnicity	Not Hispanic/Latino Hispanic/Latino
Gender	Male Female
Insulin (basal insulin (alone or as part of mixed insulin) and bolus insulin as part of mixed insulin)	Yes No
Beta blockers at baseline	Yes No

Table 6.4: 1 Subgroups (cont.)

<b>Variable</b>	<b>Categories</b>
Diuretics at baseline	Yes No
Calcium channel blockers	Yes No
Antiplatelets at baseline	Yes No
Any lipid lowering drugs	Yes No
ARB or ACE inhibitor at baseline	Yes No
Metformin at baseline	Yes No
Metformin dose at baseline	≤1500mg >1500mg Not on metformin
SU at baseline	Yes No
Time since diabetes mellitus type 2 was first diagnosed (years)	≤ 5 > 5 to < 10 ≥ 10
History of heart failure  (based on Medical history eCRF page and on narrow MedDRA SMQ "Cardiac failure"; one or both needs to be fulfilled)	Yes No
Baseline HbA1c (%)*	< 8 ≥ 8

Table 6.4: 1 Subgroups (cont.)

Variable	Categories
Baseline eGFR (MDRD) (mL/min/1.73 m <sup>2</sup> )*	<p><u>Version 1</u> &lt;60 ≥60</p> <p><u>Version 2</u> &lt;30 ≥30 to &lt;45 ≥45 to &lt;60 ≥60</p>
Baseline UACR (mg/g)*	<p>&lt;30 ≥30 to ≤300 &gt;300</p>
Prognosis of CKD by eGFR and albuminuria category (according KDIGO, 2012)	<ul style="list-style-type: none"> <li>• Low risk (defined as eGFR ≥60 ml/min/1.73m<sup>2</sup> and UACR &lt;30 mg/g)</li> <li>• Moderately increased risk (defined as eGFR 45–59 ml/min/1.73m<sup>2</sup> and UACR &lt;30 mg/g, or eGFR ≥60 ml/min/1.73m<sup>2</sup> and UACR 30–300 mg/g)</li> <li>• High risk (defined as eGFR 30–44 ml/min/1.73m<sup>2</sup> and UACR &lt;30 mg/g, eGFR 45–59 ml/min/1.73m<sup>2</sup> and UACR 30–300 mg/g, or eGFR ≥60 and UACR &gt;300 mg/g)</li> <li>• Very high risk (defined as eGFR &lt;30 ml/min/1.73m<sup>2</sup> with any UACR, eGFR 30–44 and UACR 30–300 mg/g, or eGFR 45–59 ml/min/1.73m<sup>2</sup> and UACR &gt;300 mg/g)</li> </ul>
Baseline systolic blood pressure (SBP) and baseline diastolic blood pressure (DBP) (mmHg)*	<p><u>Version 1</u> SBP &lt;140 and DBP &lt;90 SBP ≥140 or DBP ≥90</p> <p><u>Version 2</u> SBP ≥140 SBP &lt;140</p> <p><u>Version 3</u> SBP ≥160 SBP &lt;160</p>
Baseline Body Mass Index (BMI) (kg/m <sup>2</sup> )*	<p>&lt;30 ≥30</p>
CV risk (per highest risk) (only for subgroup analysis of primary endpoint)	<p>(a) albuminuria and previous macrovascular disease without evidence of impaired renal function</p> <p>(b) albuminuria and previous macrovascular disease plus renal impairment (eGFR 15–&lt;45 mL/min/1.73 m<sup>2</sup> with any UACR mg/g)</p>

Table 6.4: 1 Subgroups (cont.)

Variable	Categories
and key secondary endpoint)**	(c) albuminuria and previous macrovascular disease plus renal impairment (eGFR $\geq$ 45-75 mL/min/1.73 m <sup>2</sup> with an UACR >200 mg/g) (d) impaired renal function (eGFR 15-<45 mL/min/1.73 m <sup>2</sup> with any UACR mg/g) (e) impaired renal function (eGFR $\geq$ 45-75 mL/min/1.73 m <sup>2</sup> with an UACR >200 mg/g)
CV risk**	<ul style="list-style-type: none"> <li>Established macrovascular disease and albuminuria without established renal disease ((a) from above)</li> <li>Established renal disease without macrovascular and albuminuria disease ((d) and (e) from above)</li> <li>Established macrovascular disease and albuminuria and established renal disease ((b) and (c) from above)</li> </ul>
Established renal disease**	Defined as: patient is in any of the following 4 CV risk categories vs. patient is in none of them (yes/no) <ul style="list-style-type: none"> <li>albuminuria and previous macrovascular disease plus renal impairment (eGFR 15 - &lt;45 mL/min/1.73 m<sup>2</sup> with any UACR mg/g)</li> <li>albuminuria and previous macrovascular disease plus renal impairment (eGFR 45-75 mL/min/1.73 m<sup>2</sup> with an UACR &gt;200 mg/g)</li> <li>impaired renal function (eGFR 15- &lt;45 mL/min/1.73 m<sup>2</sup> with any UACR mg/g)</li> <li>impaired renal function (eGFR 45-75 mL/min/1.73 m<sup>2</sup> with UACR &gt;200 mg/g)</li> </ul>
Established macrovascular disease and albuminuria**	Defined as: patient is in any of the following 3 CV risk categories vs. patient is in none of them (yes/no) <ul style="list-style-type: none"> <li>albuminuria and previous macrovascular disease without evidence of impaired renal function</li> <li>albuminuria and previous macrovascular disease plus renal impairment (eGFR 15 - &lt;45 mL/min/1.73 m<sup>2</sup> with any UACR mg/g)</li> <li>albuminuria and previous macrovascular disease plus renal impairment (eGFR 45-75 mL/min/1.73 m<sup>2</sup> with an UACR &gt;200 mg/g)</li> </ul>
Prevalent kidney disease (eGFR < 60 mL/min/1.73m <sup>2</sup> or macroalbuminuria UACR >300	Yes No

Table 6.4: 1 Subgroups (cont.)

Variable	Categories
mg/g)	

\* For definition of “baseline” refer to [Section 6.7.1](#).

\*\* According to eCRF risk factor groups

^ Patients who could potentially be included in several categories will be assigned to the worse CV risk category. Note that (b) is worse than (d) and (c) is worse than (e).

In addition to the subgroup analyses of the primary endpoint, key secondary endpoint and their individual components defined above, the following subgroup analyses will be provided.

The occurrence and time to first “hospitalisation for heart failure” and “CV death or hospitalisation for heart failure” will be explored across the following subgroups in addition to the subgroups mentioned in [Table 6.4: 1](#) above based on baseline information:

- ACE-inhibitor (yes/no) at baseline
- Loop diuretics at baseline (yes/no)
- Atrial fibrillation (based on MedDRA PTs atrial fibrillation and atrial flutter)
- Ischemic heart disease (based on MedDRA HLTG “Coronary artery disorders” and eCRF entries for “Confirmed history of MI”, “Advanced coronary artery disease”, “High-risk single-vessel coronary artery disease”)

The time to first occurrence of the following tertiary endpoints will be explored by prevalent kidney disease at baseline (eGFR < 60 mL/min/1.73m<sup>2</sup> or macroalbuminuria UACR >300 mg/g) (yes/no):

- Composite renal endpoint 2
- Composite renal endpoint 3
- New incidence of macroalbuminuria

The same subgroups will be explored for the following:

- Transition in albuminuria class (normo-, micro-, macroalbuminuria) from baseline to last value in study
- Transition of eGFR (CKD-EPI) categories from baseline to last value in study
- Transition of eGFR (MDRD) categories from baseline to last value in study
- 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

UACR change from baseline over time will be also explored by baseline UACR (mg/g) categories (< 30, ≥ 30 to ≤ 300, > 300).

Note: subgroup analysis of UACR and eGFR change from baseline is described in [Section 7.6.3](#). Subgroup analysis of eGFR slope is described in [Section 7.6.4](#). Subgroup analysis of transition in albuminuria class and CKD stage is described in [Section 7.6.5](#).

Adverse events (overall summary and frequency by primary SOC and PT, SAEs, fatal SAEs), Hypoglycaemia (based on narrow SMQ), Hypersensitivity reactions, Skin lesions, Hepatic events and Renal adverse events will be displayed descriptively for the following subgroups:

- Age (< 65, ≥ 65 to < 75, ≥ 75 to < 80, ≥ 80 years)
- BMI (kg/m<sup>2</sup>) (<30, ≥30)
- Race (Black, White, Asian, Other)
- Gender
- Renal impairment (yes/no)
- Albuminuria and previous macrovascular disease (yes/no)
- Baseline eGFR (MDRD) (<30, ≥30 to <45, ≥45 to <60, ≥60 mL/min/1.73 m<sup>2</sup>)
- Insulin (basal insulin (alone or as part of mixed insulin) and bolus insulin as part of mixed insulin) (yes/no)
- SU (yes/no)
- Prevalent kidney disease (yes/no)
- Ethnicity (Hispanic/Latino, Not Hispanic/Latino)
- Geographical region (North America, Latin America, Europe, Asia)
- Metformin (yes, no)

Adverse events (overall summary and frequency by primary SOC and PT):

- CYP 3A4 inhibitors use at baseline (yes/no)
- P-gp inhibitors use at baseline (yes/no)

Adjudication results from the pancreatic adjudication will be presented by the following subgroups:

- Age (< 65, ≥ 65 years)
- BMI (kg/m<sup>2</sup>) (<30, ≥30)
- Race (Black, White, Asian, Other)

- Gender
- Baseline eGFR (MDRD) (<60, ≥60 mL/min/1.73 m<sup>2</sup>)
- Insulin (basal insulin (alone or as part of mixed insulin) and bolus insulin as part of mixed insulin) (yes/no)
- Ethnicity (Hispanic/Latino, Not Hispanic/Latino)

In addition, Hypoglycaemia (based on narrow SMQ) will be displayed descriptively for the following subgroup:

- Insulin alone, SU alone, Insulin and SU, Other  
Insulin is defined as basal insulin (alone or as part of mixed insulin) and bolus insulin as part of mixed insulin.

Hypersensitivity:

- ACE-inhibitor (yes/no) at baseline

## **6.5 POOLING OF CENTERS**

As stated in the CTP, no center effect is included into the model, as the center size is usually expected to be rather small. Furthermore, due to the anticipated low event rate a sufficient number of events per center for the analysis of a center effect and a center by treatment interaction are not expected.

Subgroup analyses by region are addressed in [Section 6.4](#).

## **6.6 HANDLING OF MISSING DATA AND OUTLIERS**

Every effort will be made to collect data as complete as possible. The rules given below are the planned methods for imputation depending upon the type of the endpoint.

For each time to event analysis, patients who do not have a particular outcome will be censored (for details, refer to [Section 6.8](#)).

For continuous endpoints of HbA1c, FPG, eGFR, UACR, weight, SBP, DBP, pulse rate, heart rate, waist circumference the following rules will be applied:

### Observed cases - ALL (OC-ALL)

All available data will be considered, including values obtained on-treatment and post-treatment. Missing data will not be replaced.

For continuous endpoint of eGFR over time the following approach will be implemented in addition:

Observed cases on-treatment (OC-OT)

All available data obtained on-treatment will be used. Missing data will not be replaced.

### Partial or missing dates and times

#### *Non-fatal outcome events*

In the unlikely case that only the year is documented, the day and month will be imputed as 01 Jan unless the subsequently derived date is before randomisation; in this case the date of randomisation will be used as start date. If year and month is present the day will be imputed as first of the month unless the subsequently derived date is before randomisation; in this case the date of randomisation will be used.

#### *Adverse event (AE) data*

Beforehand the missing or partially missing date of first drug administration is imputed. For the handling of AE partial and missing dates the following definitions will be used:

First possible = first possible date of an incomplete AE date

- if only month and year are given: day is set to 1
- if only year is given: day is set to 1 and month is set to January

Last possible = last possible date of an incomplete AE date

- if only month and year are given: day is set to the last possible day of the month
- if only year is given: day is set to 31 and month is set to December

The imputation must be performed in the following order:

- 1) Imputation of completely missing AE end dates
- 2) Imputation of missing/partial AE onset dates
- 3) Imputation of partial AE end dates

#### *1) Completely missing AE end dates*

When an AE end date is missing but there is another AE occurrence with the same lowest level term (LLT) and onset date and with an end date, this end date will be used for the imputation.

Otherwise, the imputation rules described in the [Table 6.6: 1](#) are used.



Table 6.6: 1 Algorithm for missing AE end date

Outcome of event	Action
Patient died	Impute all missing AE end dates with date of death
Patient did not die	If follow-up performed, impute missing AE end date for on-going AEs with the latest follow-up date. Otherwise, impute missing AE end date with the date of the last available visit.

2) *Missing/partial AE onset date*

Step 1

For each missing or partial AE onset date, a time-interval (O1 - O2) has to be defined as follows:

If AE onset date is missing then:

O1 = minimum between AE end date and date of informed consent

O2 = minimum between AE end date and date of last visit

If AE onset date is partial:

O1 = minimum between AE end date and First Possible onset date

O2 = minimum between AE end date and Last Possible onset date

For the definition of this time-interval only, partial AE end date must be **initially** imputed as Last Possible end date.

Step 2

Then the AE onset date is imputed according to the rules described in [Table 6.6: 2](#).

Table 6.6: 2 Algorithm for missing or partial AE onset date

Condition	Action
Date of first drug administration > O2	Impute onset date with O2
$O1 \leq$ Date of first drug administration $\leq$ O2	Impute onset date with date of first drug administration
Date of first drug administration < O1	Impute onset date with O1

3) *Partial AE end date*

Step 1

For each partial AE end date, a time-interval (E1- E2) has to be defined as follows:

E1 = maximum between AE onset date and First Possible end date

E2 = maximum between AE onset date and Last Possible end date

Step 2

Then the AE end date is imputed according to the rules described in [Table 6.6: 3](#).

Table 6.6: 3                      Algorithm for partial AE end date

<b>Condition</b>	<b>Action</b>
Date of first drug administration > AE onset date and patient died	Impute end date with minimum (E1, date of death)
Date of first drug administration > AE onset date and patient did not die	Impute end date with minimum (E1, last visit date including follow-up visits)
Date of first drug administration ≤ AE onset date and patient died	Impute end date with minimum (E2, date of death)
Date of first drug administration ≤ AE onset date and patient did not die	Impute end date with minimum (E2, last visit date including follow-up visits)

*Partial or missing information on the date of first administration of trial drug*

If patients have been randomised but not treated, no imputation will be done for the date of first administration of trial drug. Patients are considered randomised but not treated if they have been randomised, no administration has been done during the visits, and the number of kits dispensed equals the number of kits returned.

Otherwise, if the date of first drug administration is missing but the patient was randomised and treated, the date of the first drug administration will be set to the date of kit dispensation.

For partial date of first drug administration, if only the year is present and equal to the year of the randomisation date, the first drug administration will be set to the date of randomisation.

If only the day is missing (month and year present), if randomisation was in the same month and year, then the first drug administration will be set to the date of randomisation. If randomisation was in the month prior to the first drug administration the missing day will be imputed as the first day of the month.

*Missing information on the time of administration of trial drug*

A missing time of first drug administration will be imputed as 12:00 o'clock noon. Missing administration times at on-treatment visits will be imputed by 8:00 o'clock in the morning.

*Partial or missing information on the date of last administration of trial drug*

If this date is partial or missing, the date will be imputed by the date of the respective visit, if available.

If the date is partial with only month and year and the visit date is missing, it should be the last day of this month.

If a patient is lost-to-follow up and no date of last drug administration is reported, the date of last drug administration is set as the date of last contact.

For a patient who dies in the treatment phase, the date of last drug administration is set as the date of death, assuming that the patient took the medication until the date of death.

Rules following this are described in [Section 6.1](#). All other cases need to be assessed by the trial team on an individual basis, trying to use the points above as guidance.

*Partial or missing information on the date of administration of trial drug (excluding first and last administration)*

If any such date is missing, it will be imputed by the respective visit date.

If month and year are available and equal to the visit date, the date is imputed by the day of the respective visit. If month is later than the month of the visit date, the day will be imputed by the 1<sup>st</sup> of the month.

*Missing information on the birth date*

If only the year of birth is known, the day and month of birth will be imputed as 01 January.

*Missing information on concomitant therapy dates*

For incomplete date information always the midpoint of the possible interval will be used.

If only the year is present the day and month will be imputed as 01 July, if year and month is present the day will be imputed as 15. If the year is missing, the date will be considered missing.

If this leads to contradictions for the start or end date of a concomitant therapy (e.g. imputed end date before documented start date) a partial end date will be imputed as the end of the interval or a partial start date will be imputed as the start of the interval in the database to resolve this contradiction.

*Missing date of last contact*

If a patient dies and had not withdrawn consent, the date of last contact will be the date of death. If a patient did not die, the date of last contact will be the latest date of the individual trial completion date, last administration date and the last available measurement/procedure date.

*Missing date of diagnosis of type 2 diabetes*

If the day is missing, but month and year is reported, the day will be imputed as the 15<sup>th</sup>, except if this would result in a date > informed consent date; in this case the day is imputed as the 1<sup>st</sup>.

If the day and month are missing, but year is reported, the missing parts will be imputed as July 1<sup>st</sup>, except if this would result in a date > informed consent date; in this case the day is imputed as January 1<sup>st</sup>.

Laboratory data

Missing safety laboratory data will not be replaced.

Laboratory data outside the limits of quantification

The value outside the limits of quantification is set to the respective limit of quantification.

Biomarker measurements of HbA1c or plasma glucose below the limit of quantification will be imputed by 2/3 times the lower limit of quantification for analysis and derivation of indices. Values above the upper limit of quantification will be replaced by 1.5 times the upper limit of quantification.

In general, imputed dates will not be presented in the listings.

Missing onset time of hypoglycaemia/ missing plasma concentration

If onset times are available for hypoglycaemic events then those events are only considered as on-treatment, if the onset is at or after the time of first drug administration. Missing onset times on the day of first drug administration will be imputed as the time of the start of drug administration and those hypoglycaemias will be counted as on treatment. Missing onset times on other days will be imputed as 0:00.

Imputation of missing or incomplete onset dates:

- A) Hypoglycaemic adverse events: Missing or incomplete AE dates are imputed as defined above.
- B) Hypoglycaemic events, which are reported on the Home Glucose Monitoring eCRF page:
  - If the start date is incomplete with only month and year reported, the date will be imputed by the first day of this month, or respectively the date of study medication start, if this is later and in the same month.
  - If both the start date and start time are missing, the start date and start time will be imputed by the date and time of the first study drug intake to ensure that this event will be counted as on-treatment.

- If only the start date is missing, the start date will be imputed by the date of the first study drug intake.
  - If the start time is < time of first study drug intake the ‘start date of first study drug intake + 1 day’ should be used for imputation to ensure that this event will be counted as on-treatment.
- C) For hypoglycaemic events reported on the Fasting Plasma Glucose eCRF page there is no date to be entered, as the visit date is used, imputation of dates is not applicable.

If a patient has multiple hypoglycaemic episodes and some of them have missing plasma glucose values, those with missing values will be excluded from the derivation of the minimum glucose level (worst episode).

## **6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS**

### **6.7.1 Baseline**

The term "baseline" refers to the last available measurement prior to administration of any randomised trial medication.

The following considerations apply for laboratory measurements, if the time of the sample is missing on the day of first study medication intake:

- a) For FPG: the measurement will not be considered as baseline
- b) For all other lab investigations: The last measurement on this day will still be considered as baseline measurement.

Baseline daily insulin dose is derived from eCRF and is based on the daily basal insulin dose (alone or as part of mixed insulin) and bolus insulin dose, if part of mixed insulin) at day of first study medication intake. Bolus insulin dose, if given alone (i.e. without basal insulin) is not considered.

### **6.7.2 Time windows for assignment to on-treatment phase**

Measurements taken prior to the first intake of randomised trial medication will be considered pre-treatment values.

The date and clock time of the first drug administration will be used to separate pre-treatment from on-treatment values. Measurements taken after the first intake of randomised trial medication will be considered on-treatment values if they have been obtained up to end of the parameter specific follow-up period as defined in [Table 6.7.2: 1](#) and will be assigned to the randomised trial medication for analyses.

Measurements taken after the end of the endpoint specific follow-up period will be considered post-treatment values.

Table 6.7.2: 1 Endpoint specific follow-up period for the assignment to treatment

Endpoint	Last day of assignment to treatment (days after last trial medication stop date)
HbA <sub>1c</sub>	7
FPG	1
Body weight	7
Waist circumference	7
Adverse events	7
All hypoglycaemia	7
Laboratory measurements including eGFR and UACR	7
Vital signs	7
Heart rate based on ECG data	7

For HbA<sub>1c</sub>, for example, assessments performed until the last trial medication stop date +7 days (included) will be considered as on-treatment.

Any measurement obtained in the window of “last day of assignment to treatment” (as defined in [Table 6.7.2:1](#)) + 1 day to “last day of assignment to treatment” + 44 days will be assigned as “Follow-up measurement”, corresponding to planned measurement at 30 days after last study drug stop.

### 6.7.3 Time windows for assignment to visits

Analyses by study visit are performed to assess the effects of treatment over time. Planned measurements are not always taken on the exact day or time as planned in the protocol. To be able to use measurements in analyses over time, time windows are defined to also assign measurements deviating from the planned schedule to a study visit.

Measurements deviating from the planned visit schedule will be allocated to the planned visit on the basis of the actual number of days following first study drug intake (defined as (date of measurement – treatment start date + 1)).

Pre-treatment values will be assigned to a visit according to the nominal visit number as recorded on the eCRF or as provided by e.g. the laboratory.

For the by-visit- presentation, the measurements for all applicable parameters will be assigned to visits based on time windows around the planned visit dates.

Reasons to base the time windows on the actual treatment start date rather than the randomisation date are:

- If first intake of trial medication shows a large delay by e.g. more than one week after the date of randomisation, a measurement taken four weeks after randomisation rather

reflects the drug effect after three weeks than after four weeks and thus may underestimate the treatment effect at this visit.

- With large delays of the introduction of trial medication after the randomisation, the time window for the first on-treatment visit could include times the patient was not yet on trial medication.

The time window for the first visit after randomisation starts on the day after the first intake of trial medication. This maximizes the number of measurements used in by visit analyses and provides consistency with the approach to include patients with a baseline and at least one post-baseline measurement into the analysis.

The midpoint between two post-baseline visits defines the end of a time window, with the midpoint being included in the time window of the preceding visit.

All measurements obtained post-baseline will be assigned to the visits.

In a second approach, for certain parameters (e.g. eGFR) only the measurements obtained after first study drug intake while the patient is on-treatment are assigned to the visits. The end of the time window of the last on-treatment visit (end of treatment (EOT)) and Follow-up (FU) visit is endpoint dependent (see ).

The following table shows the time windows for measurements, which are planned to be assessed at every visit.

Table 6.7.3: 1 Time windows for parameters scheduled for each visit

Visit number	Visit label	Time Window based on planned days on treatment (Inclusive)		
		Exact	Start	End
3	Week 12	85 (±7)	(+)1	169
4	Week 36	253 (±14)	170	337
5	Week 60	421 (±14)	338	505
6	Week 84	589 (±14)	506	XX
X	Week X	XX (±14)	XX	XX
		...		

\*The definition of X is endpoint specific, cf. [Table 6.7.2: 1](#).

Data obtained at the EOT visit will be assigned to a planned week as per the table above but additionally flagged as EOT in order to provide report separately.

Data obtained at the FU visit will be assigned to a planned week number as per the table above (only for the approach where all post-baseline measurements are assigned to planned

weeks, but not in the approach where only on-treatment measurements are assigned to planned weeks), but additionally flagged as FU in order to provide report separately.

If an endpoint is not assessed at every visit, then the time windows will be defined according to the available visits for this endpoint.

For example if UACR is not measured at every visit, the time windows until visit 6 would be as shown in [Table 6.7.3: 2](#). From visit 7 on windows as described above in [Table 6.7.3: 1](#) apply.

Table 6.7.3: 2 Time windows for measurements until visit 6 for UACR

Visit number	Visit label	Time Window based on planned days on treatment (Inclusive)		
		Exact	Start	End
4	Week 36	253 (±14)	(+)1	421
6	Week 84	589 (±14)	422	XX

Only one observation per time window will be selected for analysis at a visit – the value will be selected which is closest to the protocol planned visit day. If there are two observations which have the same difference in days to the planned day or if there are two observations on the same day, the first value will be used.

For OC-OT: If there are multiple values within the time window of the last visit, including a value on the last day of drug intake, the value on the last day of drug intake is used as the value of the last visit.

The same rules will be applied for assignment of insulin dose to visits.

## 6.8 CALCULATION OF TIME TO EVENT

This section describes the calculation of the time to event and the time that patients without an event were in the trial (under risk). See [Section 6.8.3](#) on censoring rules.

Consistent with that approach, the respective time intervals determine the start and end for the derivation of occurrence of a specific event.

For patients with an event, the time to event is calculated as:

$$\langle \text{date of event} \rangle - \langle \text{start date} \rangle + 1$$

For patients without an event, the time at risk is calculated as:

$$\langle \text{date of censoring} \rangle - \langle \text{start date} \rangle + 1$$



### **6.8.1 Start date**

In general, the time to event will be derived from the date of randomisation, e.g. for the primary endpoint, the key secondary endpoint, their individual components, and the tertiary adjudicated endpoints.

For the endpoints of time-to-first-hypoglycemia and time-to-AE analysis, time to first silent MI and laboratory based endpoints (except by adjudication confirmed) the first drug administration date will be considered as the starting point for the analyses. The use of a different start date as compared to efficacy is justified as in general AEs (including hypoglycemia) are analysed based on the concept of treatment-emergent adverse events, refer to [Section 7.8.1.1](#).

For composite endpoints that include component(s) using randomisation date and other component(s) using first drug intake date as start date, the time at risk for the composite will start with date of randomisation. For the individual components, the component specific start date is used.

### **6.8.2 Date of event**

For composite outcomes, e.g. time to first 3P-MACE, the earliest onset date of the corresponding components will be used. For fatal MI and fatal stroke the onset date of the event is used while for other CV deaths, the date of death is used.

The dates determined by the adjudication committee will be used; these can be different from the investigator reported dates. For the endpoints of time to CV death, renal death and time to all-cause mortality and other endpoints only based on a fatal component the respective death date will be used.

The time to the first silent MI is determined by the onset date of the adverse event defined as silent MI by the investigator.

For events with multiple episodes, such as hypoglycemia, the onset date of the first episode will be used. The same applies to time-to-AE analysis.

The time to first occurrence of endpoints based on not by adjudication confirmed laboratory data, e.g. 'time to first new onset of macroalbuminuria' is determined by the date of the first laboratory measurement, in this example UACR measurement, that fulfils this condition.

### **6.8.3 Censoring**

*Primary and tertiary endpoints (except stand-alone endpoints of CV death, all-cause mortality, renal death or other endpoints that consist of only fatal component(s)):*

The underlying principle is that the censoring date should be the date at which the patient was last known to be free of an endpoint event (e.g. free of each component of the 3P-MACE).

Patients without occurrence of a specific endpoint (composite endpoint or individual components) will be considered censored at the individual day of trial completion\*.

- \* This is defined as the latest of the following dates as of
- adverse event/outcome event start dates (if non-fatal event),
  - onset dates of adjudicated (by adjudication confirmed and non-confirmed) events (if non-fatal event),
  - date of trial completion (defined as latest of date of last clinic visit, last telephone contact, date of last contact if lost to follow-up).

For patients who died during the study, the date until which follow-up for non-fatal outcome events was performed will be used for censoring.

Censoring is considered independent from trial drug intake.

*Endpoints of CV or renal death and all-cause mortality and endpoints that consist of only fatal component(s)*

A patient who did not die/died from another event will be censored at the latest date of the dates as described above, and the date of vital status (if alive)/ date last known to be alive (if LTFU)/ date of death (if died from another than event of interest).

*30 days censoring definition will be used for the sensitivity analysis done on PPS, OS and as an additional sensitivity analysis on the TS (TS+30).*

*0 days censoring definition will be used for an additional sensitivity analysis on the TS (TS+0).*

*Generally, the 7 days censoring definition will be used for adverse events incl. hypoglycaemia.*

All of the above mentioned x-day censoring rules will be handled as follows:

Patients who did not experience the event will be censored at the earliest date between the individual day of trial completion (defined above) and x days after last intake of study drug. For this analysis events will be considered that occurred not later than x days after last intake of study drug, or until individual day of trial completion (defined above), whichever is earlier.

*Endpoints based only on laboratory data (by adjudication confirmed or not)*

Patients who already fulfil the respective condition at baseline are generally not considered in the number of patients at risk for this endpoint (see exception for HbA1c analysis below).

If a baseline laboratory measurement is not available for the parameter of interest, it is assumed that the patient did not experience the condition corresponding to the endpoint at baseline and the patient is included in the patients at risk for this endpoint.

Patients without an event and available post-baseline laboratory measurements will be considered censored at the date of last laboratory sampling of the corresponding parameter. Patients with missing baseline laboratory required to derive a change from baseline and patients without laboratory data following the baseline measurement will be censored on the day of randomisation or date of first study drug intake, respectively.

For the endpoint of “Proportion of patients with HbA1c  $\leq$  7.0% at the study end visit” and composite endpoints the analysis will be performed as described above, i.e. on patients with HbA1c  $>$  7.0% at baseline, and in addition on all patients in the treated set.

*Composite endpoints based on laboratory data and adverse events*

Only patients that are included in the analyses for all components of the composite endpoint will be included in the analysis of the composite.

Of those, a patient with at least one event in any of the components of the composite will be considered to have an event and the date of the first event will be used for the composite endpoint.

A patient without an event will be considered censored at the earliest of all censoring dates of the component endpoints.

#### **6.8.4 Definition of lost-to follow-up for vital status**

If a patient could not be followed up at study termination for primary endpoint information or respectively vital status could not be collected, this patient will be considered as Lost-To-Follow-Up (LTFU) for 3P-MACE or respectively as LTFU for vital status. Study termination is defined by the start of the close-out period. The number of patients and frequency will be provided.

Patients with an adjudicated event for the primary endpoint event are not regarded as LTFU for 3P-MACE. Patients who died are not regarded as LTFU for vital status.

The close-out period is defined as the time period communicated to the site to schedule the end of trial visit (EOT).

## **7. PLANNED ANALYSIS**

For End-of-text and appendix tables, the set of summary statistics is: N / Mean / standard deviation (SD) / Min / Q1 (lower quartile) / Median / Q3 (upper quartile) / Max.

Baseline data will be presented overall and per treatment group.

The 1<sup>st</sup> and 99<sup>th</sup> percentiles might be substituted for minimum and maximum in tables with open-ended values to safeguard against implausible extremes.

Geometric means and ranges can be added to the presentation or replace the presentation of mean and standard deviation for parameters which rather follow a log-normal distribution than a normal distribution.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group. The category missing will be displayed only if there are actually missing values. In general, unless otherwise specified, percentages will be based on all patients in the respective patient set, irrespective of whether they have missing values or not.

Statistical parameters will be displayed to a defined number of decimal places as specified in the Global Biostatistics Standard Output Conventions (1), with exception of p-values presentation which will be displayed with 4 decimal places.

A general overview on patient disposition will be provided by treatment group and in total and presented in the clinical trial report by frequency tabulations. This will include the number of patients screened, randomised, screened but not randomised, treated as well as those who did/ did not prematurely discontinue trial medication, did/did not prematurely discontinue from trial by region/country/centre. See also [Table 9.1: 1](#) Table 9.1: 1 for assignment of countries to region. The reason for not randomising screened patients will also be summarized.

In addition, the number of patients who discontinued trial medication due to fatal and non-fatal adverse events will be displayed for public data disclosure on European Union Drug Regulating Authorities Clinical Trials (EudraCT). Additionally, baseline data analyses of screened patients by country and by age groups will be done for EudraCT.

The frequency of patients with important protocol violations as well as the frequency of patients in the different analysis sets will be presented by randomised treatment group.

The number of patients included in each analysis set will be displayed with percentages based on the randomised set.

## 7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive analysis of the following demographic characteristics and variables measured at baseline will be presented by treatment group and in total for the TS. These analyses will be then repeated on the randomised population for disclosure on EudraCT. Tables run on the TS will be repeated by subgroups as defined in [Section 6.4](#) and for specific country analyses.

Tables will display the following variables using the categories defined in [Section 5.4.3](#) and [Section 6.4](#), if applicable.

- Demographics:
  - Gender, age (continuous and categorical), height, weight (continuous and in categories), BMI (continuous and in categories), waist circumference (continuous), race, ethnicity, region, country
  - Smoking history: smoking status (categorical), cigarettes smoked/day (continuous), smoking years (continuous), pack years (continuous)
  - Alcohol history: alcohol status (categorical), alcohol frequency (categorical), total average amount of alcohol consumption per frequency in ml (continuous), total average alcohol volume per frequency in % (continuous)
  - Duration of formal education in years (continuous)
  
- Other baseline information:
  - Time since diabetes mellitus type 2 was first diagnosed (continuous and categorical)
  - HbA<sub>1c</sub> in % (continuous and categorical)
  - FPG in mg/dL (continuous and categorical)
  - Calcium channel blockers (categorical)
  - Beta blockers (categorical)
  - Diuretics (categorical)
  - Loop diuretics (categorical)
  - History of hypertension (categorical)
  - Antihypertensives (categorical)
  - Prior anti-diabetic treatment (categorical)
  - ASA (categorical)
  - Lipid lowering drugs, Statins and/or ezetimibe (categorical)
  - ARB/ACE inhibitor (categorical)
  - Metformin (categorical)
  - Insulin (categorical) (basal insulin, fast-acting, mixed insulin)
  - SU (categorical)
  - Thiazolidinedione (categorical)

Additional classes of baseline medications may be shown.
  
- Renal function at baseline:
  - eGFR (MDRD and CKD-EPI) in mL/min/1.73m<sup>2</sup> (continuous and categorical)
  - UACR in mg/g (continuous and categorical)
  
- CV risk:
  - CV risk categories

- Vital signs at baseline:
  - Systolic blood pressure in mmHg (continuous and categorical)
  - Diastolic blood pressure in mmHg (continuous and categorical)
  - Pulse rate in beats per minute (bpm) (continuous)
  - Heart rate (bpm) (based on ECG data)

## **7.2 CONCOMITANT DISEASES AND MEDICATION**

Descriptive statistics are planned for this section of the report. Data will be presented based on the TS.

### **7.2.1 Relevant medical history/concomitant diseases**

Frequency tabulations of the following diseases present before randomisation will be displayed by treatment group and in total:

- Cardiovascular risk factor categories as reported in the CRF page “Risk Factor Groups”.
- Relevant medical history as reported in the CRF page “Medical History Details”.
- Additional condition/diagnosis by System Organ Class (SOC) and by Preferred Term (PT) or SMQ: The number of patients (including percentages) with at least one concomitant disease at baseline will be presented. Concomitant disease with a preferred term incidence of  $\geq 1\%$  in at least one treatment group will be displayed in frequency tables.
- Cancer history as reported in the CRF page “History of Cancer”:
  - Diagnosis of cancer
  - Tumor-Node-Metastasis (TNM) staging
  - Type of treatment (Chemotherapy/ Radiotherapy/ Surgery/ Other)

Additional condition/diagnosis and cancer history will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock.

### **7.2.2 Concomitant medication**

Medications will be summarised by Anatomical-Therapeutic-Chemical classification level 3 (ATC3).

Overall concomitant medication use (excluding antidiabetic therapy) with an incidence of  $\geq 1\%$  in at least one treatment group per World Health Organization Drug Dictionary (WHO-DD) preferred name will be summarised by Anatomical-Therapeutic-Chemical classification level 3 (ATC3).

Antidiabetic therapies will be presented with categorization into medication category (metformin / insulin / SU / TZD / SGLT-2 / DPP4 inhibitor / GLP1 /others) /monotherapy/ dual therapy etc.

Summaries on the total daily dose of metformin and insulin will be provided at baseline and study end.

Separate summaries of use of anti-hypertensive, anticoagulants, acetylsalicylic acid (ASA) or lipid lowering drugs and subcategories of those, and P-gp or CYP 3A4 inhibitors will be presented.

Separate tables will summarize medications taken at baseline, newly introduced following first study drug intake and concomitant medications (medications taken following first study drug intake, either started before or after first study drug intake).

Change in ARB/ACE inhibitor therapies at any time starting from the date of first intake of trial drug (included) until study end will be presented.

In general, any therapy with the start date equal to the date of first trial drug intake is considered as being taken after first trial drug intake.

For handling of missing or incomplete dates refer to [Section 6.6](#).

### **7.3 TREATMENT COMPLIANCE**

Compliance will be presented descriptively based on the TS.

A table showing the frequency of patients within ('yes') respectively outside ('no') of 80%-120% compliance will be produced, presenting information as per eCRF entry for all visits for each treatment group, as well as for the total of all patients.

The time windows as described in [Section 6.7.3](#) will also be used for compliance, except, that the time window end for the last visit is determined by the last information entered for a patient. This includes, that whenever compliance is documented due to premature treatment discontinuation, the information will be assigned to the respective week. That can result in varying denominators of patients with compliance information over time, as a patient might stop drug permanently and restart again.

Whenever compliance information is given twice or more within one time window, the following rules will be applied:

1. Compliance outside of 80-120% at least once in that window: this information is used and 'no' is displayed
2. Compliance always inside 80-120% in that window: this information is used and 'yes' is displayed

3. Compliance always missing in that window: 'Missing' is displayed
4. Compliance missing at least once in that window: compliance will be based on the available values according to the above rules 1 and 2.

Patients who switched study treatment will be presented in a listing, but that information is not considered in the compliance presentation in the table.

## 7.4 PRIMARY ENDPOINT

### 7.4.1 Primary analysis

The primary analysis on the primary endpoint time to first 3P-MACE (cf. [Section 5.1](#)) will be performed on the TS.

**Section 7.1 of the CTP:** *For the primary objective the upper bound of the two-sided (1-2\*alpha) confidence interval which equals the upper bound of the one-sided (1-alpha) confidence interval will be used to investigate non-inferiority (NI) of linagliptin versus placebo regarding the hazard ratio (HR) of the primary endpoint. The non-inferiority margin is chosen as 1.3. The overall one-sided significance level is 2.5%.*

The allocated trial treatment at randomisation will be used for analysis, and all events which occur until trial end will be taken into account.

The time to the primary endpoint will be derived from the date of randomisation. The censoring rules are described in [Section 6.8.3](#).

Hypotheses tested are described in the Section 7.2 of the CTP.

### Statistical methods

For the primary analysis, a Cox proportional hazard regression model will be performed to compare the effect of linagliptin versus placebo. The model will include randomised treatment and geographical region as factors. Breslow's method will be used for dealing with ties. The SAS PHREG procedure will be used.

The hypothesis of non-inferiority will be tested at the one-sided significance level of  $\alpha_1=2.5\%$ .

The hazard function of an event for patient  $j$  at time  $t$  is assumed to have the form:

$$h_j(t) = \exp(\beta_1 x_{1j} + \beta_2 x_{2j}) h_0(t), j=1, \dots, n,$$

where

- $h_0(t)$  is the non-negative baseline hazard function for a patient with a value of zero for the explanatory value  $x_{1j}$  and  $x_{2j}$
- $\beta_1$  is the (unknown) coefficient of the explanatory variable  $x_1$
- $x_{1j}$  is an indicator variable representing the treatment group for patient  $j=1, \dots, n$



- $\beta_2$  is the (unknown) coefficient of the explanatory variable  $x_2$
- $x_{2j}$  is an indicator variable representing the geographical region for patient  $j=1, \dots, n$

The hazard ratio (HR) for the effect of treatment (linagliptin vs. placebo), adjusted for geographical region, will be presented with the 95% confidence interval, the 99% confidence interval and the p-values based on the Wald Chi-Square statistic: one-sided p-value for the non-inferiority test (NI margin 1.3), the one-sided p-value for the superiority test and the two-sided p-value.

Non-inferiority of the primary endpoint will be investigated by comparing the upper limit of the two sided 95% confidence interval of the hazard ratio with the non-inferiority margin of 1.3: if the upper limit is less than 1.3, non-inferiority has been demonstrated.

In case non-inferiority of the primary endpoint is demonstrated, then superiority of the primary endpoint and superiority of the key secondary endpoint will be investigated:

For the final analysis, the first hypothesis (non-inferiority of the primary endpoint) will be tested at the one-sided alpha-level of 2.5%. In case of significance, the null hypothesis is rejected in a confirmatory sense and the next set of hypotheses (two separate hypothesis tests) will be tested: a) test of the primary endpoint for superiority and b) test of the composite renal endpoint for superiority.

To adjust for multiplicity a sequentially rejective multiple test procedure will be applied (3). Both one-sided hypotheses  $H_0(\text{Sup1})$  and  $H_0(\text{Sup2})$  will be tested separately, at the initial alpha-levels of  $0.2 \cdot \alpha$  for 3-point MACE and  $0.8 \cdot \alpha$  for the composite renal endpoint, respectively. If both null hypotheses cannot be rejected at these initial alpha-levels, the procedure stops and for none of these endpoints superiority can be declared. After having shown superiority for one of these endpoints, the used alpha can be shuffled to the other test: If  $H_0(\text{Sup2})$  is rejected at the alpha-level of  $0.8 \cdot \alpha$ , then  $H_0(\text{Sup1})$  can be tested at the full alpha-level of 2.5% (one-sided). If  $H_0(\text{Sup1})$  is rejected at the alpha-level of  $0.2 \cdot \alpha$ , then  $H_0(\text{Sup2})$  can be tested at the full alpha-level of 2.5% (one-sided).

#### **7.4.2 Secondary analysis**

The Kaplan-Meier (KM) estimates of failure rate per treatment group will be presented graphically. In addition, certain quantiles of the failure times (e.g. 2.5%, 5%, 7.5% and 10% quantiles) will be provided per treatment group. Kaplan-Meier estimates for failure rates at 6 months, 1, 1.5, 2, etc years after randomisation will be presented per treatment group.

The two-sided p-value resulting from the log-rank test will be presented for completeness.

The cumulative incidence function adjusting for the competing risk of non-CV death per the Aalen Johansen estimator will be presented on the TS. In addition a Cox proportional hazards model will be applied to the competing risk, including the effects of the primary model.

Descriptive statistics will display the number of patients at risk, the number of patients with event, the incidence (proportion of patients with event), the time at risk for event and the incidence rate (number of patients with event per 1000 years at risk) per treatment group.

### **7.4.3 Sensitivity analysis**

#### **7.4.3.1 Proportional hazards assumption**

The proportional hazards assumption will be explored by plotting  $\log(-\log(\text{survival function}))$  against the log of time by treatment group and by geographical region and checked for parallelism. The interaction of treatment and geographic region with log of time will be included in the model described above for an exploratory analysis. Further, Schoenfeld residuals will be plotted against time and  $\log(\text{time})$ .

In case the proportionality assumption for the treatment effect does not hold, an attempt will be undertaken to identify groups of patients for which the proportionality assumption holds and a stratified Cox regression and stratified log-rank test will be performed. The HR and corresponding CI will be obtained from the stratified Cox model.

In addition a piecewise Cox model assuming proportional hazards in a series of consecutive time intervals as proposed by Collett (2) will be investigated.

#### **7.4.3.2 General sensitivity analysis**

For the primary endpoint sensitivity analyses will be done on the PPS, OS, and the TS in combination with the 0 days (TS+0) and 30 days censoring (TS+30) definition. For all these analyses the allocated trial treatment at randomisation will be used for treatment assignment.

The sensitivity analyses done on the PPS, OS and TS in combination with the 30 days censoring definition will be performed based on events occurring within the time patients are on-treatment + 30 days after permanent treatment discontinuation or date of the individual day of trial completion, whichever comes first.

The sensitivity analysis done on the TS in combination with the 0 days censoring definition will be based on events occurring within the time patients are on-treatment or date of the individual day of trial completion, whichever comes first.

The same models and testing procedures as the primary analysis (i.e. refer to [Section 7.4.1](#)) will be applied to compare the two treatment groups, including presentation of Kaplan-Meier estimates and the descriptive statistics.

These analyses will be performed as described in [Section 7.4.1](#) with the significance levels as used in the primary analysis.

The following table provides an overview of the planned analyses:

Table 7.4.3.2: 1 Overview of analyses on the primary endpoint

Censoring mechanism	Analysis set		
	TS	PPS	OS
Individual day of trial completion	X (primary analysis)		
0 days censoring	X (TS+0)		
30 days censoring	X (TS+30)	X	X

#### 7.4.3.3 Sensitivity analysis using another model

For the primary endpoint sensitivity analyses will be done on the TS utilizing a Cox proportional hazard regression model with factors for randomised treatment, geographical region, baseline age (cont.), time since diagnosis of T2DM (cont.), HbA1c (cont.), eGFR (MDRD) (cont.), UACR (cont.), SBP (cont.), DBP (cont.), and BMI (cont.) to compare the effect of linagliptin versus placebo.

#### 7.4.4 Subgroup analysis

All subgroup analyses will be performed on the TS with censoring at the individual day of trial completion. See [Section 6.4](#) for details on the list of subgroups.

A Cox proportional hazards model will be fitted including terms for treatment, region, subgroup and subgroup-by-treatment interaction. The p-value for the subgroup-by-treatment interaction, the HR, 95% CI and the corresponding two-sided p-value for the treatment group comparison (linagliptin vs. placebo) for each subgroup category will be obtained from this model.

A forest plot will be used to present graphically the results (HR and 95% CI) across subgroups.

The Kaplan-Meier estimates will be presented graphically for the subgroup categories.

For time-to-event endpoints at minimum 14 patients with events in total over both treatment groups for each subgroup category will be required to conduct a Cox regression analysis. If the affected category is too small (<14 patients with events), a category may be pooled with another category.

#### 7.4.5 Other

Kaplan Meier estimates of time to censoring for 3P-MACE will be used to examine the pattern of censoring in linagliptin versus placebo. In this analysis censoring for 3P-MACE will be the event of interest.

## **7.5 SECONDARY ENDPOINTS**

### **7.5.1 Key secondary endpoint**

#### *Main analysis of key secondary endpoint*

The key secondary endpoint will be analyzed on the TS in the same way as described in [Section 7.4.1](#) and [Section 7.4.2](#) for the primary endpoint.

The hazard ratio (HR) for the effect of treatment (linagliptin vs. placebo), adjusted for geographical region, will be presented with the 95% confidence interval, the 96% confidence interval, and the p-values based on the Wald Chi-Square statistic: the one-sided p-value for the superiority test and the two-sided p-value.

The time to first occurrence will be counted from the date of randomisation. The censoring rules are described in [Section 6.8.3](#).

#### *Sensitivity analysis of key secondary endpoint*

The same approach will be used as for the sensitivity analysis for the primary endpoint. For further details refer to [Section 7.4.3.1](#) and [7.4.3.2](#).

#### *Subgroup analysis of key secondary endpoint*

The same approach will be used as for the subgroup analysis for the primary endpoint. For details on subgroup analysis refer to [Section 7.4.4](#).

#### *Other*

Kaplan Meier estimates of time to censoring for key secondary endpoint will be used to examine the pattern of censoring in linagliptin versus placebo. In this analysis censoring for key secondary endpoint will be the event of interest.

### **7.5.2 Secondary endpoint**

Not applicable as no secondary endpoint apart from the key secondary endpoint is defined for this study.

## **7.6 FURTHER ENDPOINTS**

All further endpoint analyses are of exploratory nature, no correction for multiple hypotheses testing will be made. All statistical tests and confidence intervals are two-sided with a significance level of 5%.

The further efficacy endpoints will be analyzed on the TS.

### **7.6.1 “Time-to-event” endpoints**

For all endpoints that include time-to-event data the same models and testing procedures as the primary analysis (refer to [Section 7.4.1](#)) will be applied to compare the two treatment groups, including presentation of Kaplan-Meier estimates. For analysis of time to first initiation of insulin refer to [Section 7.6.8](#).

In case of a small number of patients with events, the Cox proportional hazards model may not be performed (i.e. <14 patients with events in total for the comparison of the treatment groups), and only incidences and incidence rates will be presented.

For endpoints to be confirmed by adjudication, the cumulative incidence function adjusting for the competing risk of non-CV death or death respectively, per the Aalen Johansen estimator will be presented on the TS. In addition a Cox proportional hazards model will be applied to the competing risk.

Subgroup analysis will follow the same approach as for the primary endpoint. Refer to [Section 6.4](#) for subgroup definitions and for the endpoints to be investigated by subgroups.

For “time to first hospitalization for heart failure” and “time to first CV death or hospitalisation for heart failure” the main analysis and sensitivity analyses on OS, TS+30, TS+0 and subgroup analyses will include the term “history of heart failure” in the Cox regression. Furthermore an additional analysis is performed on the TS using the primary analysis model, i.e. not including this term.

For heart failure adverse events (based on narrow SMQ cardiac failure 20000004) frequencies and incidence rates will be provided. In addition another analysis will be performed on the TS based on events occurring until 7 days after permanent treatment discontinuation or date of individual trial completion, whichever comes first.

For stent thrombosis the number of patients with event and frequency will be provided.

For the time to first 4P-MACE and time to first MI (fatal or non-fatal MI), time to first stroke (fatal or non-fatal stroke), time to CV death, time to first hospitalisation for unstable angina, time to first hospitalisation for heart failure, time to first CV death or hospitalisation for heart failure sensitivity analyses will be performed as defined in [Table 6.3: 1](#) and on the TS in combination with 0 days and 30 days censoring definition. Hereby the same models and testing procedures as for the primary analysis (refer to [Section 7.4.1](#)) will be applied.

Kaplan Meier estimates of time to censoring for all-cause mortality will be used to examine the pattern of censoring in linagliptin versus placebo. In this analysis censoring for all-cause mortality will be the event of interest.

### **7.6.2 Analysis of recurrent events**

Descriptive statistics will display the number of patients at risk for 1<sup>st</sup> event (respectively 2<sup>nd</sup>, 3<sup>rd</sup> etc. event), the number of patients with 1 event (respectively 2, 3 etc. events),  $\geq 2$  events and the incidence (proportion of patients with 1 event (respectively 2, 3 etc. events),  $\geq 2$  events) per treatment group.

### **7.6.3 UACR and eGFR changes from baseline**

Measurements will be assigned to planned weeks as described in [Section 6.7.3](#). The absolute change from baseline will be calculated for each timepoint by subtracting the baseline value from the selected value at the respective time point.

Descriptive statistics will be calculated for the following parameters over time and for their change from baseline:

- UACR
- Log10 (UACR)
- eGFR (MDRD and CKD-EPI)

The time course of mean absolute values for log10 (UACR) and eGFR (MDRD and CKD-EPI) will be presented graphically along with the standard deviation at every visit. The same analyses will be repeated for UACR while presenting gMean and 95% confidence interval.

The change from baseline over time will be evaluated for these endpoints with a restricted maximum likelihood (REML) based mixed model repeated measures (MMRM) approach. This analysis will be performed on OC-ALL data, for eGFR in addition using only data obtained on-treatment (OC-OT). The statistical model will be:

Endpoint as absolute change from baseline where the endpoint is measured =  
overall mean  
+ treatment  
+ region  
+ baseline measurement  
+ week  
+ treatment-by-week interaction  
+ baseline-by-week  
+ random error

“Treatment”, “region”, “week”, “treatment-by-week interaction” are fixed classification effects, and “baseline measurement” and “baseline-by-week interaction” are linear covariates. The adjusted least-squares mean with standard error (SE) per treatment group, the mean difference with SE and 95% CI will be reported at all timepoints.

An unstructured variance-covariance matrix will be specified for the within-subject covariance between weeks.

In the event that this analysis cannot be applied for mathematical reasons or fails to converge, the AR(1) covariance structure will be employed. If this fails to converge, the compound symmetry (CS) covariance structure will be employed.

Before use of another covariance structure, the ‘singular’ option in the model statement of PROC MIXED may be adjusted.

The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Type III sums of squares will be used.

The MMRM model will include only those visits where  $\geq 5\%$  of all patients of the treated set have a measurement.

The UACR values will be log<sub>10</sub> transformed prior to analysis within the MMRM model, and the results will then be back-transformed to the original scale.

The UACR will be determined by the central laboratory based on urinary albumin and urinary creatinine measures from the same urine sample.

For subgroup analyses in addition a model additionally including subgroup, subgroup-by-treatment interaction, subgroup-by-week interaction and subgroup-by-treatment-by-week interaction will be used. At minimum 5 patients per treatment group per subgroup category per visit are required, otherwise the respective visit will be dropped from the analyses starting with the last visit.

#### **7.6.4 eGFR slope**

The eGFR (MDRD and CKD-EPI) slope will be analysed as follows:

A random coefficient model allowing for random intercept and random slopes among patients will be used to investigate the difference in treatments.

The model will include the following factors: ‘Treatment’ and ‘geographical region’ as fixed classification effects and ‘time’ and ‘interaction of treatment-by-time’ as linear covariates and allow for randomly varying slopes and intercepts among patients.

For the analyses of eGFR slope from baseline to the value collected during follow-up visit all available measurements (i.e. obtained on-treatment or off-treatment) will be used.

For the analyses of eGFR slope from baseline to last value on-treatment all available measurements obtained on-treatment will be used.

A histogram of individual patient slopes derived from the model will be provided per treatment.

For subgroup analyses a model additionally including subgroup, subgroup-by-treatment interaction, subgroup-by-time interaction and subgroup-by-treatment-by-time interaction will be used.

#### **7.6.5 Transition in albuminuria and CKD class**

Shift tables will be provided to present the change from baseline to last value in study will be provided for:

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- UACR, using the albuminuria categories defined in [Table 7.6.5: 1](#)
- Combination of eGFR and UACR, using the CKD categories defined in [Table 7.6.5: 3](#) according to KDIGO
- eGFR (MDRD and CKD-EPI) categories of <15, 15 to < 30, 30 to <60, 60 to <90, ≥90,
- eGFR (MDRD and CKD-EPI) categories of <15, 15 to < 30, 30 to <45, 45 to <60, 60 to <90, ≥90 in [Table 7.6.5: 2](#)

Last value in study is defined to be the individual's last value in the study.

The shift tables will be provided by subgroups in addition.

Albuminuria classes are defined in the following table:

Table 7.6.5: 1 UACR categorisation

Stage	UACR [mg/g]	Description	Label for displays
1	< 30	Normal to mildly increased (Normalalbuminuria)	< 30 mg/g (normal)
2	≥ 30 to ≤ 300	Moderately increased (Microalbuminuria)	≥ 30 to ≤ 300 mg/g (elevated)
3	>300	Severely increased (Macroalbuminuria)	>300 mg/g (high)
	Not available	Missing	Missing

Albuminuria 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).

CKD classes are described in the following table.

Table 7.6.5: 2 MDRD staging

Stage	eGFR [mL/min/1.73m <sup>2</sup> ]	Description
1	≥90	Normal renal function
2	60 to <90	Mild renal function impairment
3a	45 to <60	Moderate renal function impairment 3a
3b	30 to <45	Moderate renal function impairment 3b
4	15 to <30	Severe renal function impairment
5	<15	Kidney failure

Table 7.6.5: 3 Prognosis of chronic kidney disease by GFR and albuminuria category

UACR (mg/gcrea)



eGFR (MDRD) [mL/min/1.73m <sup>2</sup> ]	>=90	<30	>=30 to <=300	>300
		low risk	moderately increased risk	high risk
	60 to <90	low risk	moderately increased risk	high risk
	45 to <60	moderately increased risk	high risk	very high risk
	30 to <45	high risk	very high risk	very high risk
	15 to <30	very high risk	very high risk	very high risk
	<15	very high risk	very high risk	very high risk

The estimated glomerular filtration rate (eGFR) will be provided by the central laboratory according to the MDRD formula, consistent with the recommendation of the US NIH, NIDDK (National Institute of Diabetes and Digestive and Kidney Diseases of the National Institute of Health) as of October 2012.

In addition eGFR (CKD-EPI) will be estimated and derived according to the following CKD-EPI formula based on serum creatinine:

$$\text{eGFR (ml/min/1.73m}^2\text{)} = 141 \times \min(\text{serum creatinine [umol/L]/88.4/k, 1})^a \times \max(\text{serum creatinine [umol/L]/88.4/k, 1})^{-1.209} \times 0.993^{\text{Age}^c} \times [1.018 \text{ if female}] \times [1.159 \text{ if of African origin}]$$

where:

k is 0.7 for females and 0.9 for males,

a is -0.329 for females and -0.411 for males,

min indicates the minimum between (serum creatinine/k) and 1,

max indicates the maximum between (serum creatinine/k) and 1.

### 7.6.6 Continuous endpoints of HbA1c, FPG, weight, waist circumference, heart rate

The analysis of change from baseline in those endpoints will be performed in the same way as specified in [Section 7.6.3](#) for eGFR on OC-ALL data.

Refer to [Section 6.6](#) for handling of missing data.

### 7.6.7 Binary endpoints

For the binary endpoints (e.g. proportion of patient with ≤ 2% weight gain at the end of study etc) defined in [Section 5.3.1](#), the number and percentage of patients who fulfil the criteria of the endpoint will be provided per treatment group.

For the endpoint of “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)” the following rules apply:

If a patient has terminated study treatment permanently (i.e. without subsequent re-start) before trial stop, the patient is considered a non-responder.

A patient who stops study treatment and restarts later, can still fulfill the endpoint criteria, independent from how long the patient was off drug. Only the last information on ‘termination of trial medication’ (i.e. last treatment stop date) is considered. If a patient died prior to completing the trial regularly, the patient is considered as non-responder.

For patients who regularly complete the study on study medication (i.e. last on-treatment visit  $\geq$  date of announced study closure), off-treatment information following last study medication intake is not considered (refer to [Section 6.7.2](#)).

#### **7.6.8 Administration of insulin and time to first initiation of insulin and daily dose of insulin**

The number and percentage of patients who initiated insulin after baseline, relative to the number of patients who were not on insulin at baseline, and the number and percentage of patients treated with insulin at baseline will be provided.

Descriptive statistics with mean, SD, median, Q10, Q25, Q75, Q90, range (min and max) and interquartile range (IQR) will be provided for time (days) to initiation of insulin will be presented for all patients of the treated set and patients not on insulin at baseline.

Absolute change from baseline in total daily dose of insulin will be presented descriptively for patients on basal insulin or mixed insulin at baseline.

Kaplan Meier estimates will be provided for time to first initiation of insulin. Only the initiation of basal insulin or mixed insulin is considered.

### **7.7 EXTENT OF EXPOSURE**

The extent of exposure will be presented on the TS.

Extent of exposure to trial medication will be calculated as the difference between the date of last intake of trial medication (respectively date of death if the patient did not discontinue trial medication) and the first administration of trial medication + 1 day per patient. This includes the off-treatment periods.

The time in study, i.e. time from randomisation to last contact will be calculated as the difference between the date of the last assessment/contact of a patient (including the date of vital status (if alive)/ date last known to be alive (if LTFU)/ date of death (if died)) and the date of randomisation + 1 day.

Descriptive statistics with mean, SD, median, Q10, Q25, Q75, Q90, range (min and max) and interquartile range (IQR) will be provided for both treatment exposure and time in study.

This table will also include the total exposure and total time in study summed over all patients within each treatment group and transformed to patient years (divided by 365.25 days).

A frequency table of number and percentage of patients with treatment exposure of at least certain months (e.g. 3 months, 6 months, 9 months, etc.) will be provided. The same analysis will be done for time in study.

A Kaplan-Meier plot will be provided for time to last study medication stop and time to end of study.

## **7.8 SAFETY ANALYSIS**

All safety analyses will be performed on the TS and displayed as randomised. Assignment of preferred terms to HLGT and SOC will be according to MedDRA “primary path”.

### **7.8.1 Adverse events**

AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) at database lock.

The analyses of adverse events will primarily be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs (and not on the number of AEs). The general AE analysis will include all AEs (including outcome events as reported by the investigator).

#### **7.8.1.1 Assignment of AEs to treatment**

The analysis of AEs will be based on the concept of treatment-emergent adverse events (TEAE). That means that all AEs occurring between first study drug intake until 7 days after last permanent study drug stop will be considered as on-treatment, i.e. possible treatment interruption phases of a patient will be part of the on-treatment phase.

All AEs occurring prior to first study drug intake will be assigned to “screening”. All AEs occurring after last study drug intake + 7 days will be assigned to “post-treatment”, whereby the post-treatment phase according to the previous treatment will be used (post-Lina and post-Placebo respectively). AEs reported after the date of last contact + 1 day will be assigned to “post-study”.

Patients who died before last drug intake + 7 days will have their on-treatment phase assigned until the date of death.

In addition to the primary treatment emergent approach displaying the on-treatment phase and post-treatment phase separately, all AEs after the first dose of study medication will be included in an additional analysis by treatment group.

*Further additional approaches will be implemented for the presentation of adverse events:*

- For cancer and pancreatic cancer in addition to the ‘TEAE approach’ on the treated set, all adverse events that occurred between first study drug intake up to study end will be presented.

There will be additional analyses including all patients who had a minimum cumulative study drug exposure of 6 months (excluding treatment gaps), using following two approaches:

- considering all AEs starting from the date when 6 months cumulative exposure was reached up to last drug stop + 7 days
  - considering all AEs starting from date when 6 months cumulative exposure was reached up to individual day of trial completion
- For renal events, hepatic events, pancreatitis and skin lesions all adverse events that occurred between first study drug intake up until treatment stop + 30 days will be presented based on the treated set.
  - Heart failure adverse events (based on narrow SMQ cardiac failure 20000004) will be analyzed following the ‘TEAE approach’ (all AEs occurring between first study drug intake until 7 days after last permanent study drug stop will be considered as on-treatment) and the concept where all AEs from first study drug intake up to study end are assigned to treatment.

For the subgroup analyses of adverse events (as specified in [Section 6.4](#)), all adverse events occurring between first drug intake until 7 days after last permanent treatment stop will be considered with the following exception: for subgroup analyses of pancreatic cancer all adverse events that occurred between first study drug intake until study end will be considered based on the treated set.

For these subgroup analyses, frequencies and incidence rates will be provided.

#### 7.8.1.2 Intensity

Intensity is classed as mild/moderate/severe (increasing intensity). If a patient reports an AE more than once within that system organ class (SOC)/ Preferred term (PT), the AE with the worst case intensity will be used in the corresponding intensity summaries.

#### 7.8.1.3 Relationship to trial medication

Relationship, as indicated by the Investigator, is classified as “not related” or “related”. If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to trial medication will be used in the corresponding relationship summaries.

#### 7.8.1.4 Analysis of other significant AEs

According to ICH E3 (4), AEs classified as ‘other significant’ will include those non-serious adverse events with:

- (i) 'action taken = discontinuation' or 'action taken = reduced', or
- (ii) marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator

The identification of category (ii) will be done by medical advisor based on the eCRF data prior to database lock.

#### 7.8.1.5 AE summaries

##### 7.8.1.5.1 Frequency of patients with adverse events

No confirmatory analysis is planned for routine safety comparisons.

An overall summary of patients with TEAEs will be presented by treatment, including patients with any AE, severe AEs, investigator defined drug-related AEs, AEs leading to discontinuation of trial drug, serious AEs (SAEs), AEs leading to death, AEs of Special Interest (AESI) and other significant AEs.

Separate tables will be provided for patients with SAEs, for patients with drug-related AEs, for patients with AEs leading to treatment discontinuation, for patients with fatal AEs, for patients with AESI, and for patients with other significant adverse events. AEs will also be reported by intensity.

The frequency of patients with TEAEs will be summarized by treatment, primary SOC and PT. The SOC's will be sorted according to the standard sort order specified by the European Medicines Agency (EMA), preferred terms will be sorted by frequency (within SOC).

Frequency tables of patients with cancer (broad BICMQ) by treatment, High level term (HLT) and preferred term will be provided.

For handling of missing or incomplete data refer to [Section 6.6](#).

In addition, an analysis will be done on AEs and SAEs which are assigned to the following phases: screening, treatment, and post-treatment for each treatment group.

An overview of adverse events from patients screened, but not treated, will be included.

A table showing the frequency of patients with non-serious TEAE occurring with PT incidences > 5% within at least one treatment group will be presented by treatment and preferred term for disclosure on [clinicaltrials.gov](http://clinicaltrials.gov) website. Additionally, the following analyses will be reported for disclosure on EudraCT:

- AEs per arm: This analysis includes the number of patients with serious AEs, patients with non-serious AEs >5%, as well as the total number of deaths (all causes), and the total number of deaths resulting from drug-related adverse events.
- Number of patients with serious AEs on preferred term level (grouped by standard SOC terms)

#### 7.8.1.5.2 Adverse event incidence rates

In addition to the frequency tabulations, time-adjusted adverse event analyses will be performed by SOC and PT, or respectively HLT and PT for TEAEs, severe TEAEs, investigator defined drug-related TEAEs, other significant TEAEs, TEAEs leading to discontinuation of trial drug, serious TEAEs, TEAE leading to death and AESI and further events (defined in [Section 7.8.1.11](#)).

The time at risk in patient years is derived as follows:

Patients with AE:

time at risk (AE) [days] = start date of event with specified PT/SOC – treatment start date + 1

Patients without AE:

time at risk (AE) in days = end date of time at risk – study treatment start date + 1, where end date of time at risk is the minimum of date of last study drug intake + x days and date of death, if applicable.

The standard approach will be x=7 days, but for certain AEs in addition other approaches will be used.

Total AE-specific time at risk per treatment group is then derived as:

Time at risk (AE) [years] =

$$\frac{\text{Sum of time at risk [days] over all patients in a treatment group}}{365.25}$$

For ‘each row of a table’ (e.g. displaying an SOC), time at risk is calculated using start of first AE summarized in this row; e.g. for patient with AE in a specified SOC:

Time at risk = start date of AE with specified PT in a SOC – treatment start date + 1.

The AE incidence rate per 100 patient years can then be calculated as follows:

Incidence rate [1/100 Patient years (pt-yrs)] =

$$\frac{100 * \text{number of patients with AE}}{\text{time at risk (AE)[years]}}$$

#### 7.8.1.6 Adverse events of special interest (AESI)

According to the protocol the following events are considered as AESI:

- Hypersensitivity reactions (defined by narrow SMQ 20000214 ‘hypersensitivity’)
- Skin lesions (defined by narrow SMQ 20000020 ‘severe cutaneous adverse reactions’)
- Hepatic events (defined by narrow sub-SMQ 20000010 ‘hepatitis, non-infectious’,

narrow sub-SMQ 20000013 ‘hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions’, narrow sub-SMQ 20000008 ‘liver related investigations, signs and symptoms’, narrow sub-SMQ 20000009 ‘cholestasis and jaundice of hepatic origin’)

- Renal adverse (defined by narrow SMQ 20000003 ‘acute renal failure’)
- Pancreatitis (defined by narrow SMQ 20000022 ‘acute pancreatitis’ and PT ‘Pancreatitis chronic’ (resp. based on updated MedDRA version corresponding term for that )
- Thyroid neoplasm (benign) (BICMQ Thyroid Neoplasms narrow BICMQs, restricted to diagnoses (exclude symptoms) by TM DS (manual review))
- Thyroid cancer (presentation in table of cancer events by HLT and PT; and also under “Thyroid neoplasm” as defined above)
- Pancreatic cancer (based on narrow BICMQ)

Patients with these AESIs will be tabulated by treatment group.

For all AESIs, in addition frequency tables for serious adverse events (except for thyroid neoplasm (benign), thyroid cancer, pancreatic cancer as always-serious events) and adverse events leading to discontinuation from trial drug will be presented.

The most recent version of the definitions of these AESIs at the time of the DBL will be used to be in line with the respective most recent AESI definition in the current MedDRA version. These will be stored in the CTMF.

#### 7.8.1.7 Events qualifying for external adjudication by the Clinical Event Committee (CEC)

Tabulations with frequency of patients with AEs triggering CEC adjudication (based on specified Standardized MedDRA Queries (SMQs) according to CEC charter and manually identified) will be provided by treatment group and overall, by primary SOC and preferred term. All events will be taken into account from first study drug intake up to study end. This table will be provided separately for cardio/neuro, renal, pancreatic adjudication and oncological assessment.

Further, outcome events captured by the investigators will be contrasted with those defined by the adjudication committee.

All by adjudication confirmed events will be summarised.

For cardio- and cerebrovascular events the components as listed in [Section 5.3.1](#) as well as the types of CV deaths, the types of non-fatal MIs, types of fatal and non-fatal strokes, stent thrombosis and all not assessable cases will be presented. The category of other cardiovascular causes will be presented with subcategories of “other assessable CV causes” and “presumed CV death”.

#### 7.8.1.8 Events qualifying for external adjudication by the Clinical Event Committee (CEC) for pancreatic events (CECP)

Based on the CECP adjudication results, the number of patients for each of the following events will be summarized in frequency tables (overall and by adjudication trigger i.e. lab or AE):

- Acute pancreatitis (with organ failure)
- Acute pancreatitis (without organ failure)
- Chronic pancreatitis (with organ failure)
- Asymptomatic pancreatic hyperenzymemia
- Pancreatic malignancy

The analysis will be performed on TS.

The analysis will be performed using all events from study treatment start until study end and in addition the 'on-treatment + 7 days' approach.

For adjudicated acute pancreatitis a Kaplan Meier curve for time to first event will be presented along with a Hazard ratio and 95% CI from Cox regression based on the TS.

#### 7.8.1.9 Events qualifying for external assessment by the Oncologic Assessment Committee (oncAC)

A separate independent, blinded, external committee regularly reviews all events suspect of solid cancer and assesses whether the cancer case is drug related or not. Details on composition of the oncAC, responsibilities and clinical event definitions are provided in the corresponding oncAC charter.

Frequency tables summarizing the relatedness will be provided.

In addition possibly related, not related and not assessable events will be presented.

A frequency table will be provided for trigger events that cannot be confirmed as a solid tumor malignancy as defined in the charter.

The analysis will be performed on TS using all events from study treatment start until study end.

#### 7.8.1.10 Analysis of hypoglycemic events

All symptomatic hypoglycaemic events, all asymptomatic events with glucose levels less than 3.0 mmol/L (or less than 54 mg/dL) and all asymptomatic hypoglycaemic events that are considered as adverse events by the investigator have to be recorded as an adverse event. Analyses on hypoglycaemic events will be performed on the TS.

Different tables will be shown for

- (i) hypoglycaemic adverse events based on narrow SMQ hypoglycaemia,
- (ii) patients with hypoglycaemia (reported as AE or non-AE),



by treatment group.

Table (i) will include the presentation of patients with confirmed hypoglycaemic adverse events (based on narrow SMQ hypoglycaemia), i.e. hypoglycaemic adverse events that had a plasma glucose concentration  $\leq 70$  ml/dL or required assistance.

In addition, the number of patients with different characteristics of hypoglycaemic events, including severity, symptoms, glucose level, minimum glucose level of the worst episode, number of episodes per patient as well as time to first hypoglycaemic episode will be presented.

For the treatment-time adjusted frequencies the time at risk in patient years is derived as described in [Section 7.8.1.5.2](#), with the date of the first episode of any hypoglycaemic event used as the onset date of the hypoglycaemic event.

Time to the onset of the first hypoglycaemia adverse event (i) will be analysed by Kaplan-Meier estimates.

For the details on censoring refer to [Section 6.8.3](#).

For the subgroups specified in [Section 6.4](#) for hypoglycaemia subgroup analysis the number of patients with hypoglycaemia adverse event (i) will be presented (including different characteristics of hypoglycaemic events).

#### 7.8.1.11 Further adverse events

Patients with the following adverse events will be tabulated by treatment group:

- arthralgia (defined by HLGT 'Joint disorders') (by HLT and PT)
- cancer (broad B1cMQ) (by HLT and PT)

For this 'AE concept' of arthralgia in addition frequency tables for serious adverse events and, adverse events leading to discontinuation from trial drug will be presented.

The most recent version of the definitions of these AEs according to the respective most recent MedDRA version will be used. These will be stored in the CTMF.

#### 7.8.1.12 Adverse events occurring after wrong medication intake

A listing of patients with on-treatment adverse events with an onset during the non-randomised treatment will be provided.

## 7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature. Summaries will generally be provided based only on the central laboratory data, with the exception of the analysis of hepatic enzyme elevations, as described below.

Laboratory measurements will be analysed by assigning the trial phases screening, treatment period of linagliptin or placebo and post-treatment linagliptin, post-treatment placebo, follow-up period as described in [Section 6.7.2](#).

For baseline definition refer to [Section 6.7.1](#). For the assignment of last value on-treatment refer to Section 6.7.2.

For general safety laboratory analyses: In case of repeated measurements per visit, the worst value will be used.

Laboratory measurements will be analysed with an on-treatment approach. Only patients with at least one available baseline and on-treatment value will be included in the analysis of an individual laboratory parameter. All individual data will be presented in listings.

Analyses of laboratory data for safety purposes will be based on values in conventional units. In addition analyses on SI units will be provided for the parameters where SI units differ from the conventional units.

Continuous laboratory values will be compared to their reference ranges and frequency tables will be provided for the number of patients within and outside the reference range at baseline (with the categories “High”, “Normal” and “Low”), over time and on the last measurement on treatment.

Descriptive statistics will be provided for baseline, measurements over time, changes from baseline by treatment group over time, and last measurement on-treatment and their changes from baseline.

Only for lipids (i.e. total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides) an additional MMRM analysis will be performed.

Categorical laboratory data will be presented in frequency tables for baseline, over time and last value on treatment.

For the continuous parameters, the analysis of possible clinically significant abnormalities will be tabulated, as far as reference ranges and thresholds for potential clinical significance exist. The definition of clinically significant abnormal laboratory safety values will follow the BI standard rules (5) except for fasting plasma glucose. A fasting plasma glucose value less than 54 mg/dL (<3.0 mmol/L) will be considered as a clinically relevant decrease, a clinically relevant increase is not defined for this trial.

For an evaluation of follow-up after discontinuation of trial medication an additional summary of all measured laboratory data will be produced. This summary will include descriptive statistics for baseline, last value on-treatment, change from baseline to last value on-treatment, follow-up value, and change from last value on-treatment to follow-up value, change from baseline to follow-up value.

*Specific considerations for hepatic parameters*

For the analyses on hepatic parameters described in the following central and local laboratory data will be used.

To support analyses of liver-related adverse drug effects, potential Hy's law cases are defined by the combination of the following events within one sample:

- any on-treatment value of ALT or AST (or both)  $\geq 3$  x ULN with
- total bilirubin  $\geq 2$  x ULN

Further, it will be investigated if the above events occurred within a time span of 30 days. The start of the 30-day time span is triggered by elevation of ALT or AST above the defined thresholds.

In addition, the combination of the following events within one sample will be presented:

- any on-treatment value of ALT or AST (or both)  $\geq 3$  x ULN with
- total bilirubin  $\geq 2$  x ULN
- alkaline phosphatase  $\leq 2$  x ULN.

Further, it will be investigated if the above events occurred within a time span of 30 days. The start of the 30-day time span is triggered by elevation of ALT or AST above the defined thresholds.

Patients who fulfil one or two of the criteria for ALT/AST elevations, but no information on total bilirubin is available within the 30 day time window will be presented in a listing.

All calculations will be based on the originally measured laboratory values and the ULNs given by the laboratory.

In addition ALT/AST will be used to investigate elevated liver enzymes:

- On-treatment ALT/AST  $\geq 3$  x ULN
- On-treatment ALT/AST  $\geq 5$  x ULN
- On-treatment ALT/AST  $\geq 10$  x ULN
- On-treatment ALT/AST  $\geq 20$  x ULN

Frequency tables of patients with elevated liver enzymes (see above) will be provided.

A scatter plot of peak ALT against peak total bilirubin (for measurements within one sample and in addition within the 30 day time window) will be presented with reference lines for 3 x ULN ALT and 2 x ULN total bilirubin, including an indicator for treatment received.

#### *Investigation of lipase*

The following analyses will be performed for lipase:

- Descriptive statistics for baseline, last value on-treatment and follow-up value
- Descriptive statistics for values over time on-treatment (OC-OT)

- Shift tables for baseline, last value on treatment and maximum value on treatment with categorisation of <LLN, LLN to ULN, ULN to  $\leq 3ULN$ ,  $\geq 3*ULN$  and for every visit
- Time to first increase of  $\geq 3*ULN$  (will be analysed by Kaplan-Meier plot, frequencies and incidence rates) on the treated set and in following subgroups: Patients with baseline lipase  $\leq ULN$  vs. Patients with baseline lipase  $>ULN$  to  $< 3*ULN$ .

*Investigation of acute pancreatitis in relation to pancreatic enzyme levels (lipase):*

Time to first adjudicated acute pancreatitis (Kaplan-Meier plot, frequencies and incidence rates) will be presented for following subgroups considering all events until treatment stop + 7 days:

- Lipase baseline value  $\leq ULN$
- Lipase baseline value  $>ULN$

### **7.8.3 Vital signs, waist circumference, weight**

Descriptive statistics will be displayed for the summary of blood pressure (BP) (mmHg), pulse rate (bpm), change from baseline in BP, and change from baseline in pulse rate over time. The analyses will be performed on the TS.

Descriptive statistics will be performed for weight over time on the TS, based on observed values (without imputation). In addition MMRM analyses will be performed for weight.

### **7.8.4 ECG**

Clinically relevant abnormal findings will be reported as AEs or respectively as baseline conditions.

AE analysis will take place as planned in [Section 7.8.1](#).

Heart rate will be summarised by treatment group per planned week and as change from baseline to each planned week using descriptive statistics on the treated set.

### **7.8.5 Others variables**

#### **Cognitive function**

The details on the analysis of cognitive function are specified in a separate Statistical Analysis Plan. The results will be reported separately from the Clinical Trial Report.

## **8. REFERENCES**

- 1 General Guideline and Template, “Global Biostatistics Standard Output Conventions”, current version; Output Conventions – OD BS0206.
- 2 R07-4680 Collet D (2003) Modeling Survival Data in Medical Research. Chapman and Hall.
- 3 Bretz F, Maurer W, Brannath W, Posch M (2009) A graphical approach to sequentially rejective multiple test procedures. Statist Med; 28:586-604
- 4 ICH Guideline Topic E3, “Structure and Content of Clinical Study Reports”, current version; Note For Guidance on Structure and Content of Clinical Study Reports (CPMP/ICH/137/95).
- 5 Reference Document of Corp Guideline, " Handling, Display and Analysis of Laboratory Data: Standard Clinical Evaluation Criteria", current version; IDEA for CON: 001-MCG-157\_RD-02.

## 9. ADDITIONAL SECTIONS

### 9.1 DETAILED DESCRIPTION OF REGIONS AND COUNTRIES

The below table (continued on the next page) summarizes to which regions countries are assigned.

Table 9.1: 1                      Regions and countries

<b>Region</b>	<b>Country</b>
Asia	China
	Japan
	Malaysia
	South Korea
	Taiwan
Europe	Bulgaria
	Croatia
	Czech Republic
	Germany
	Hungary
	Israel
	Netherlands
	Poland
	Portugal
	Romania
	Russia
	Spain
	South Africa
	Ukraine
United Kingdom	
Latin America	Argentina
	Brazil
	Chile
	Colombia
	Mexico
North America	Canada
	United States

## **9.2 COUNTRY SPECIFIC ANALYSES**

Appendix of the CTR will contain country specific analyses of disposition, demographics and baseline characteristics including concomitant diagnoses and therapies, exposure, primary and key secondary data, further endpoints data, AEs and laboratory data. The country specific analysis will be provided for China, Japan, Taiwan, Korea, East Asia (defined as Japan, Taiwan, Korea or China) and Mexico as analyses based on the specific subpopulation. The country specific analyses for Asian countries will only include Asian race patients, as indicated on the eCRF, from the country in question. The country specific analyses will not be described in the main CTR but described in country specific addendums, where needed.

For US, patients (yes/no) subgroup analyses will be performed based on the TS as described above, with the difference that the primary endpoint, key secondary endpoint and selected by adjudication confirmed time-to-event endpoints will be analysed with a Cox regression including terms for subgroup and the interaction of subgroup and treatment.

## 10. HISTORY TABLE

Table 10: 1 History table

<b>Version</b>	<b>Date (DD-Mmm-YY)</b>	<b>Author</b>	<b>Sections changed</b>	<b>Brief description of change</b>
Final	05 May 2017	Michaela Mattheus Thomas Perretti	None	Final version
Revised	18-DEC-2017	Sven Yannik Schnaidt Thomas Perretti	Refer to Section 4	Updated version based on FDA comments and minor clarifications (refer to Section 4)