Boehringer Ingelheim

Trial Statistical Analysis Plan

for Final Analysis

BI Trial No.:	1218.22
Title:	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. **CARMELINA**. Including Protocol Amendment 2 1218.22 [C02155180-06].
Investigational Product(s):	Linagliptin (BI 1356)
Responsible trial statistician(s):	Phone: Phone:
Date of statistical analysis plan:	18 DEC 2017
Version:	Revised

SIGNATURE PAGE

Statistical Analysis Plan (Revised version December 18th 2017) for Protocol 1218.22.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the TSAP

Term	Definition / description
ATC	Anatomical-Therapeutic-Chemical
CEC	Clinical Event Committee
CI	Confidence Interval
CKD	Chronic Kidney Disease
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
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOT	End Of Treatment

Term	Definition / description
HbA_{1c}	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
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
OR	Odds Ratio
PPS	Per Protocol Set
PT	Preferred Term
pt-yrs	Patient-years
PV	Protocol Violation
Q1	Lower quartile
Q3	Upper quartile

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

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) ≥ 40% from baseline), will be investigated separately with a test on superiority.

SAS® 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:

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.

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

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.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

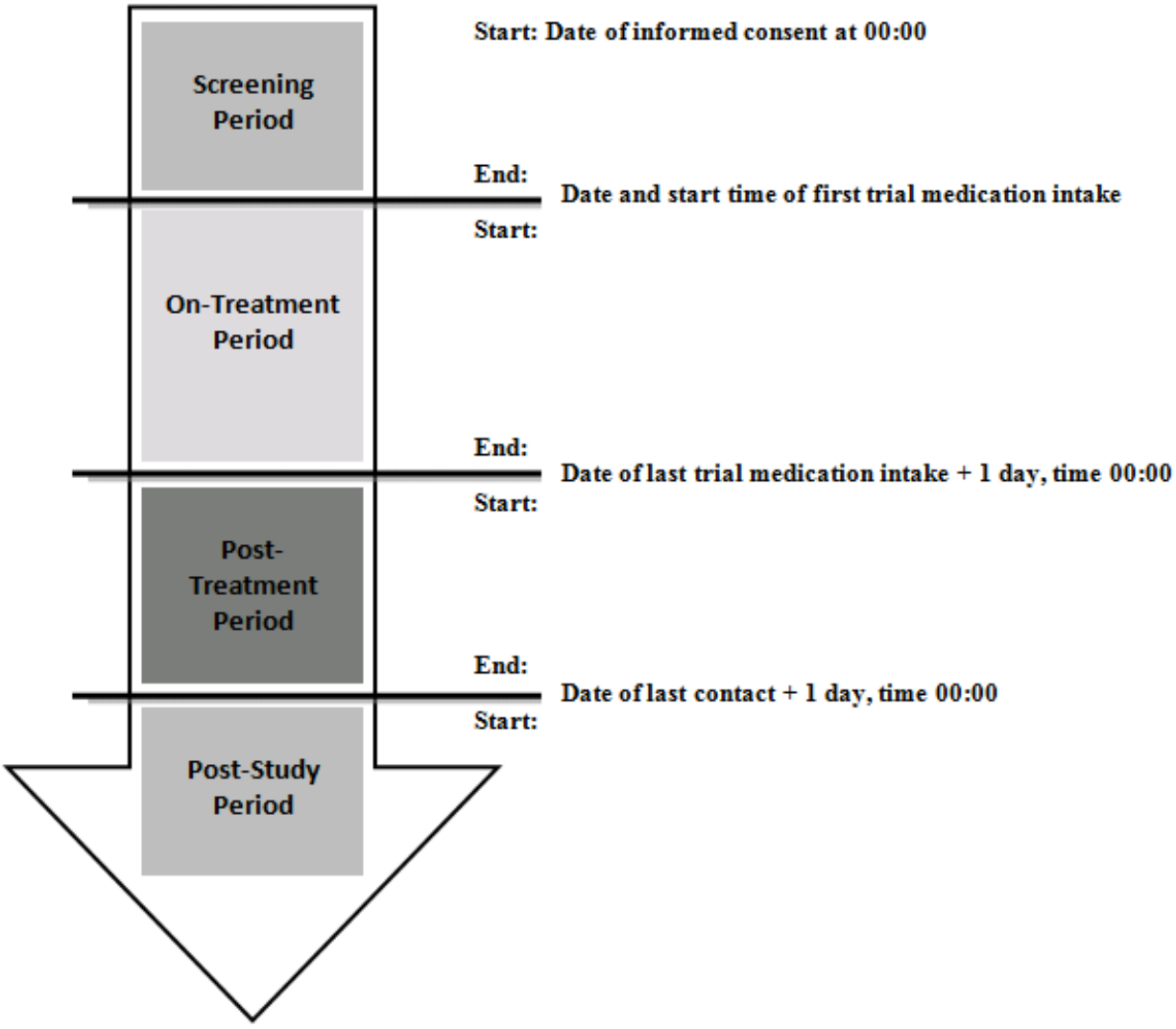
The following treatments are investigated in this trial:

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**
A		**Entrance Criteria Not Met**			
	A.1	**Inclusion criteria violated**			
	A1.1	No type 2 diabetes	Inclusion criterion IN1 ticked "No"	E	PPS
	A.2	**Exclusion criteria violated**			
	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 m²) or ESRD at Visit 1 and/or the need for maintenance dialysis	Exclusion criterion EX4 ticked "Yes" Or eGFR < 15 ml/min/1.73 m² 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 ≤ 2 months prior to Visit 1	Exclusion criterion EX12 ticked "Yes"	E	PPS
	A.2.7	Stroke or transient ischemic attack (TIA) ≤ 3 months prior to Visit 1	Exclusion criterion EX13 ticked "Yes"	E	PPS
B		**Informed Consent**			
	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.)

Category / Code		Description	Comment/Example	Affects rights (R)/ safety (S) or primary/ key secondary outcome (E)	Excluded from
	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
C		**Trial medication and randomisation**			
	C1	**Incorrect Trial Medication Taken**			
	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	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. This is identified by the medication kit number recorded in eCRF as well as the medication kit number as assigned by IRT. Can also be manually identified by investigator or CRA. Can only be finally judged after DBL since unblinding information is required.	E	PPS
	C2	**Randomisation not followed**			
	C2.1	Treated before randomisation	Date of randomisation after date of study medication intake at visit 2; Or Patient treated according to eCRF, but not randomised according to IRT.	E	PPS
	C3	**Non-compliance**			

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**
	C3.1	Non-compliance with criteria for removal from the trial	A missing pregnancy test does not qualify as IPV.	R/S	None
D		**Concomitant Medication**	Not Applicable		
E		**Missing data**	Not Applicable		
F		**Incorrect timing**	Not Applicable		
G		**Trial specific protocol violations**			
	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.

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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

	Patient Sets		
Endpoint	SCR	RS	TS
Disposition	X		
Patient analysis sets		X	
Primary/Key secondary endpoint			X
Other safety endpoints as per Section 5.3.2			X
Post stroke functional assessment as per Section 5.4.1			X

* Sensitivity analysis

^ 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.

6.5 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.

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).

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 ≤ Date of first drug administration ≤ 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

Condition	**Action**
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 1st 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.

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.

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.

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:
<date of event> - < start date> + 1

For patients without an event, the time at risk is calculated as:
<date of censoring> - < start date > + 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,

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

The dates determined by the adjudication committee will be used; these can be different from the investigator reported dates.

6.8.3 Censoring

Primary endpoints

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.

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 (
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.

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 1st and 99th 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: 1for 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.

7.4 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 α_1=2.5%.

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

$$h_j(t) = \exp(\beta_1 x1_j + \beta_2 x2_j)\, h_0(t),\ j=1,...,n,$$

where

- $h_0(t)$ is the non-negative baseline hazard function for a patient with a value of zero for the explanatory value $x1_j$ and $x2_j$
- $\beta 1$ is the (unknown) coefficient of the explanatory variable x1
- $x1_j$ is an indicator variable representing the treatment group for patient j=1,...,n

- $\beta 2$ is the (unknown) coefficient of the explanatory variable x2
- $x2_j$ is an indicator variable representing the geographical region for patient j=1,...,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 H0(Sup1) and H0(Sup2) will be tested separately, at the initial alpha-levels of 0.2*alpha for 3-point MACE and 0.8*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 H0(Sup2) is rejected at the alpha-level of 0.8*alpha, then H0(Sup1) can be tested at the full alpha-level of 2.5% (one-sided). If H0(Sup1) is rejected at the alpha-level of 0.2*alpha, then H0(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.

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.

7.5 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.

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 SOCs 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 clinicaltrial.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.

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.

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.

7.8.1.11 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 BIcMQ) (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.

7.8.3 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.

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.

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.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
Final	05 May 2017		None	Final version
Revised	18-DEC-2017		Refer to Section 4	Updated version based on FDA comments and minor clarifications (refer to Section 4)