# Trial Statistical Analysis Plan

**c02152478-04**

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|---|---|
| **BI Trial No.:** | 1218.74 |
| **Title:** | A multicentre, international, randomised, parallel group, double blind study to evaluate **Car**di**o**vascular safety of **lina**gliptin versus glimepiride in patients with type 2 diabetes mellitus at high cardiovascular risk.<br><br>The **CAROLINA** Trial.<br><br>Including Global Protocol Amendments 1-6 [c01618200-19] |
| **Investigational Product(s):** | Linagliptin |
| **Responsible trial statistician(s):** | Phone:<br>Fax: |
| **Date of statistical analysis plan:** | 16 March 2018 REVISED |
| **Version:** | Revised |

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# 2. LIST OF ABBREVIATIONS

| Term | Definition / description |
|---|---|
| ADS | Analysis data set |
| AE | Adverse event |
| AESI | Adverse events of special interest |
| ALT | Alanine transaminase |
| ANCOVA | Analysis of covariance |
| AR(1) | first-order autoregressive |
| ASA | Acetylsalicylic Acid |
| AST | Aspartate transaminase |
| ATC | Anatomical-Therapeutic-Chemical |
| BI | Boehringer Ingelheim |
| BMI | Body mass index |
| BRPM | Blinded report planning meeting |
| CABG | Coronary Artery Bypass Graft |
| CARE | Clinical data Analysis and Reporting Environment |
| CEC | Clinical Event Committee |
| CI | Confidence Interval |
| CRA | Clinical Research Associate |
| CRF | Case Report Form |
| CS | Compound symmetry |
| CTP | Clinical Trial Protocol |
| CTR | Clinical Trial Report |
| CV | Cardiovascular |
| DBL | Database Lock |
| DBP | Diastolic Blood Pressure |
| DM&SM | Boehringer Ingelheim Data Management and Statistics Manual |
| DMC | Data Monitoring Committee |
| 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 |

| Term | Definition / description |
|---|---|
| EX | Exclusion criterion |
| FAS | Full analysis set |
| FPG | Fasting Plasma Glucose |
| GAD | Glutamic acid decarboxylase |
| HbA1c | Glycosylated haemoglobin |
| HDL | High Density Lipoprotein |
| HR | Hazard Ratio |
| IA-2 | Tyrosine phosphatase-like Insulinoma Antigen 2 |
| IAA | Insulin Auto Antibodies |
| IC | Informed Consent |
| ICA | Islet Cell Autoantibody |
| ICH | International Conference on Harmonisation |
| IDEA | International Document management and Electronic Archiving system |
| IN | Inclusion criterion |
| IPV | Important Protocol Violation |
| IRC | Independent Review Committee |
| ITT | Intention-to-treat |
| IXRS | Interactive Voice and Web-based Response System |
| KM | Kaplan Meier |
| LADA | Latent autoimmune diabetes of adults |
| LDL | Low Density Lipoprotein |
| LOCF | Last observation carried forward |
| MACE | Major Adverse Cardiovascular Event |
| MDRD | Modification of Diet in Renal Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Myocardial infarction |
| MMRM | Mixed Model Repeated Measures |
| mRS | modified Rankin Scale |
| N | Number of patients |
| NCF | Non completers considered failure |
| O*C | Oracle Clinical |
| OR | Odds Ratio |
| OS | On treatment set |

| Term | Definition / description |
|---|---|
| PCI | Percutaneous Coronary Intervention |
| PPS | Per protocol set |
| PR | Pulse Rate |
| PT | Preferred term |
| PV | Protocol violation |
| RAGe | Report Appendix Generator system |
| REML | Restricted Maximum Likelihood |
| Q1 | Lower quartile |
| Q3 | Upper quartile |
| SA | Statistical Appendix |
| SAP | Statistical Analysis Plan |
| SBP | Systolic Blood Pressure |
| SD | Standard deviation |
| SE | Standard error |
| SMQ | Standardised MedDRA query |
| SNC | Serious Non-compliance |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| SU | Sulfonylurea |
| TIA | Transient ischemic attack |
| TOC | Table of contents |
| TS | Treated set |
| TSAP | Trial statistical analysis plan |
| UACR | Urine albumine to creatinine ratio |
| ULN | Upper limit of normal |
| WHO-DD | World Health Organization Drug Dictionary |
| 3P-MACE/ 4P-MACE | 3 Point- Major Adverse Cardiovascular Event, 4 Point- Major Adverse Cardiovascular Event |

# 3. INTRODUCTION

As per ICH E9 (9), 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 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 study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomisation.

**CTP:** *The primary objective is to demonstrate non-inferiority (by means of comparing the upper limit of a two-sided (1-2*alpha)*100% confidence interval with the non-inferiority margin of 1.3) of treatment with linagliptin in comparison to glimepiride (as monotherapy or as add-on therapy) with respect to time to first occurrence of any of the adjudicated components of the primary composite endpoint (i.e. cardiovascular death, non-fatal stroke, or non-fatal myocardial infarction (excluding silent MI)) in patients with type 2 diabetes mellitus. If the noninferiority hypothesis with margin 1.3 has revealed a significant result, then secondly, the primary composite endpoint will be tested with a superiority hypothesis. If the superiority test has revealed a significant result, then thirdly the first key secondary endpoint of time to first occurrence of any of the adjudicated components of cardiovascular death, non-fatal stroke, non-fatal myocardial infarction (excluding silent MI) or hospitalisation for unstable angina pectoris will be tested hierarchically with a superiority hypothesis. If the test of the first key secondary hypothesis has revealed a significant result, then fourthly the second key secondary endpoint will be tested hierarchically. If the test of the second key secondary hypothesis has revealed a significant result, then fifthly the third key secondary endpoint will be tested hierarchically.*
*Other objectives are to compare HbA1c change from baseline, the incidence of hypoglycaemia, weight gain and treatment sustainability defined as the proportion of patients that are on study treatment at study end without need for rescue medication, that at Final Visit maintain glycaemic control (HbA1c ≤ 7.0%).*

# 4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

In the following the changes to the CTP and additional analyses are described:

4. For the first key secondary endpoint another sensitivity analysis on the 30DTS will be performed considering events until earliest date of treatment stop + 30 days or end of observation.

5. For the endpoints of occurrence of 4P-MACE and 3P-MACE sensitivity analysis on the FAS, PPS and 30DTS will be performed. For these analyses events until earliest date of treatment stop + 30 days or end of observation will be considered.

7. The time to overall mortality will be defined as the time to death, not the date of onset of a fatal event.

8. The eGFR of patients from Japan that are of Asian Race will be calculated as described in Section 7.8.2.

9.

Further aspects are clarified as follows:

1. In general rescue medication is not only considered during study medication intake. Rescue medication is defined as any dose increase of anti-diabetic background medication or introduction of new anti-diabetic treatment after first study medication intake until the time as specified in Section 6.8. Short term use of any insulin- up to two weeks - will not count as rescue medication.

2. The endpoint of change from baseline to final visit is to be investigated for urinary albumin (secondary diabetes related endpoints).
   Any transition in albuminuria classes will be investigated based on UACR, in order to allow correction of albumin for creatinine concentration.

4. The censoring rules including those for 4P-MACE are described in detail in Section 6.8.3.

In the following the changes and additional analyses as compared to the first signed Trial Statistical Analysis Plan from 22 JAN 2014 are described. This includes any changes based on clinical trial protocol amendments 5 and 6.

1. Based on the clinical trial protocol amendment 6 the definitions of the primary and first key secondary endpoints were updated throughout this document.
   Details on control of the type I error are defined in Section 7.4.1.
   Following the exchange of the primary and first key secondary endpoint in CTP amendment 6, and the first interim analysis performed for time to first 4P-MACE, the allocation of alpha for the second interim analysis and the final analysis is defined in Section 7.4.1.

Date of onset of silent MI and censoring of patients without silent MI was updated accordingly in Section 6.8.2 and 6.8.3.

Derivation of time to event and censoring was updated accordingly in Section 6.8.1, 6.8.2 and 6.8.3. The approach for the analyses of these endpoints was defined in Section 7.6.

5. Definition of important protocol violations in Table 6.2: 1 was updated. Criteria A1.2, A2.2, A2.3, A2.5, A2.6, A2.10 from initial TSAP have been removed as IPVs leading to exclusion from the PPS, as violations of these entry criteria are not expected to influence primary and key secondary CV outcome.
   IPV criterion C3.1 from initial TSAP was removed, as sensitivity analyses with respect to study drug exposure are addressed via analyses of the 30DTS and the 'on-treatment' analyses on the FAS.
   IPV criterion D1.1 from initial TSAP was revised to allow for a tolerance window of 35 days (i.e. first planned visit following randomisation at 28 days + 7 days visit window) to stop the use of glinide or SU when taken at baseline.
6. The definition of the 30-days-treatment set in Section 6.3 was updated to require a cumulative exposure of at least 30 days to study drug.

9. Section 6.7.3 was updated to include assignment of follow-up measurements
10. Details on censoring with regard to the date of IC withdrawal were updated to allow use of information as allowed by local law. Date of PCI/CABG was added into derivation of censoring date.
11. Sensitivity analyses considering events until 7 days after last permanent treatment discontinuation or date of last documented study visit, whichever comes first, were added for time to first 3P-MACE and time to first 4P-MACE in Section 7.4.2 and 7.5.1.
12. Addition of cumulative incidence function for adjudicated CV endpoints accounting for competing risk.

14. For all adjudicated CV endpoints including all-cause mortality additional sensitivity analysis will be performed on the FAS considering events until 30 days after last permanent treatment discontinuation or date of last documented study visit, whichever comes first.
15. OC analyses were added for total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, creatinine, urinary albumin, UACR, eGFR and weight in Section 7.5.2.2.1.
    MMRM analyses following the ITT approach (OC-ALL) were added for secondary/tertiary diabetes related endpoints.
    Analysis of follow-up measurements was added.

16. Additional approaches for the investigation of adverse events were added in Section 7.8.1.1 and 7.8.1.3.2.
17. Further details including serious adverse events and adverse events leading to discontinuation will be presented for the adverse events of special interest as defined in Section 7.8.1.4. Further adverse events as outlined in Section 7.8.1.7 will be analysed.
18. Analysis of adjudicated pancreatic events was added in Section 7.8.1.8.
19. Analysis of assessment results for cancer events was added in Section 7.8.1.9.
20. A shift table based on KDIGO categories as defined in Section 7.8.2 will be prepared. Investigation of amylase and lipase was added in Section 7.8.2.
21. Vital signs will be analysed as a continuous parameters only as outlined in Section 7.8.3. Heart rate as defined in Section 7.8.4 will be analysed in addition.
22. For the analyses of first disabling or fatal stroke (based on the Modified Rankin scale), a supporting analysis will be performed, with no data imputation (Section 7.8.5).

Below all changes since the Trial Statistical Analysis Plan was signed on 11 August 2016 are listed. These include changes based on FDA feedback for CARMELINA (1218.22) as well as clarifications regarding analysis specifications added to the text.

1. To align the definitions with CARMELINA (1218.22), all endpoints will be analysed on treated set (TS), which means no change in content as outlined below. Patients considered for FAS – the previously defined primary population – need to be randomised and have received at least one dose of study medication. Patients considered for TS have received at last one dose of study medication (Section 6.3). Since all patients that had treatment assigned before IXRS was called are considered as forced randomised (Section 6.1.1) the FAS population and TS population of this study are identical.
2. Population 30-days-treatment set (30DTS) is re-named on-treatment set (OS) to align terminology with CARMELINA (Section 6.3).
3. Based on FDA feedback for CARMELINA an additional censoring timepoint +0 is added for analysis. Censoring rules aligned with CARMELINA based on FDA advise (Section 6.8.3). Sensitivity analysis for 3P-MACE and 4P-MACE will be conducted on TS+0.

6. Sensitivity analysis for diabetes related endpoints specified for parameters HbA1c, FPG and weight. MMRM model up to week xxx will be applied (Section 7.5.2.2.1).
7. Arthralgia and bullous conditions are considered as safety endpoints (further adverse events) only. Since the TSAP was signed in August 2016, both medical concepts have been further investigated and assessed on project level. In accordance with the trial protocol, arthralgia and bullous conditions are no adverse events of special interest (AESI).

8. Definition of medical concept for immunological reaction, malignancy and bullous condition added (Section 7.8.1.7).

# 5. ENDPOINTS

The study is set up with prospective adjudication of all cardiovascular, cerebrovascular and pancreatic trigger events.
The prospectively defined adjudication process will ensure the assessment of cardiac and neurological vascular events through an independent, blinded, external Clinical Event Committee (CEC). Details on the composition of the committee, its procedures and interactions are provided in a separate CEC Charter.

The primary and first key secondary endpoints are based on adjudicated (i.e. CEC confirmed) events.

Additionally, a separate independent, blinded, external committee will be set up for adjudication of pancreatic events. The adjudication process for these events will be clarified in another charter.

For all time to event analyses, the time to the (first) occurrence of an endpoint will be computed as described in Section 6.8.

## 5.1 PRIMARY ENDPOINT

The primary endpoint in this trial is time to the first occurrence of any of the following CEC confirmed adjudicated components of the primary composite endpoint: CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI),or non-fatal stroke.
This endpoint will be further referred to also as time to first 3-Point-MACE (3P-MACE).

To clarify: Silent MI is not an endpoint to be confirmed by adjudication. Any investigator reported silent MI that is adjudicated and confirmed as being an MI by the CEC will be counted as MI.

## 5.2 SECONDARY ENDPOINTS

### 5.2.1 Key secondary endpoints

The key secondary efficacy endpoints are:

- time to the first occurrence of any of the following CEC confirmed adjudicated components of CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI), non-fatal stroke or hospitalisation for unstable angina pectoris
  This endpoint will be further referred to also as time to first 4-Point-MACE (4P-MACE).

  To clarify: Silent MI is not an endpoint to be confirmed by adjudication. Any investigator reported silent MI that is adjudicated and confirmed as being an MI by the CEC will be counted as MI.
- composite endpoint of (treatment sustainability defined as the proportion of patients that are on study treatment at study end, that at Final Visit maintain glycaemic control (HbA1c $\leq$ 7.0%) without need for rescue medication (between end of titration [Visit 6]

and Final Visit) and patients without any moderate/severe hypoglycaemic episodes (between Visit 6 and Final Visit) and without > 2% weight gain at Final Visit (between Visit 6 and Final Visit))
(A patient fulfilling all these criteria is considered a 'responder'.)

- composite endpoint of (treatment sustainability defined as the proportion of patients that are on study treatment at study end, that at Final Visit maintain glycaemic control (HbA1c ≤ 7.0%) without need for rescue medication (between Visit 6 and Final Visit) and patients without > 2% weight gain at Final Visit (between Visit 6 and Final Visit))
(A patient fulfilling all these criteria is considered a 'responder'.)

Study end/ Final visit for second and third key secondary endpoints

Please refer to Section 7.5.1 for the derivation.

Rescue medication in general:

Rescue medication is defined as any dose increase of anti-diabetic background medication (as compared to one day prior to first drug administration) or introduction of new anti-diabetic treatment, for insulin any new onset and intake for at least 15 days, starting from the date of first drug administration until the time as specified in Section 6.8.3.
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.
If a patient switches to or adds protocol defined background medication at or after the date of first trial drug intake, this will be considered rescue medication. (The same applies for a change from metformin or alpha-glucosidase inhibitor to metformin + alpha-glucosidase inhibitor.)

Moderate and severe hypoglycaemic episodes are defined as follows:

A moderate hypoglycaemic event is defined as documented symptomatic hypoglycaemia with plasma glucose concentration ≤ 70 mg/dL, without the need for external assistance.

A severe hypoglycaemic event is defined as documented hypoglycaemic episode requiring assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions need for external assistance.

### 5.2.2 (Other) Secondary endpoints

5.2.2.1 Secondary cardiovascular endpoints

Secondary CV endpoints are:

- occurrence of at least one of the following CEC confirmed adjudicated components of CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI), non-

fatal stroke and hospitalisation for unstable angina pectoris
This endpoint will be further referred to also as 'occurrence of 4P-MACE'.

- occurrence of at least one of the following CEC confirmed adjudicated components of CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI) and non-fatal stroke
  This endpoint will be further referred to also as 'occurrence of 3P-MACE'.

- occurrence of and time to the first occurrence of any of the following components of the composite endpoint of all CEC confirmed adjudicated events of:

  - CV death (including fatal stroke and fatal MI)
  - non-fatal MI
  - non-fatal stroke
  - hospitalisation for unstable angina pectoris
  - TIA
  - hospitalisation for congestive* heart failure
  - hospitalisation for coronary revascularization procedures (CABG, PCI)

*refers to all heart failure events as adjudicated and confirmed by CEC and will be referred to as 'heart failure' in the CTR

#### 5.2.2.2 Secondary diabetes related endpoints

Secondary diabetes related endpoints include change from baseline to Final Visit in the following laboratory parameters:

- $HbA_{1c}$
- Fasting plasma glucose
- Total cholesterol
- LDL cholesterol
- HDL cholesterol
- Triglycerides
- Creatinine
- eGFR (MDRD formula)
- Urinary albumin

In addition any transition in albuminuria classes will be investigated by using UACR. Please refer to Table 7.8.2: 2 for the definition of classes.

For these endpoints, the final visit value refers to the last value obtained on treatment. Parameter-specific on-treatment phases are defined according to Section 6.7.2. The intake of rescue medication is considered as described in Section 5.2.1.

# 6. GENERAL ANALYSIS DEFINITIONS

## 6.1 TREATMENTS

The following treatments are investigated in this study:

Table 6.1: 1 Treatments and labels used in the analysis

| Treatment | | Short label |
|---|---|---|
| A | Linagliptin tablet 5 mg / Placebo Glimepiride capsule 1-4 mg | Lina |
| B | Glimepiride capsule 1-4 mg / Placebo Linagliptin tablet 5 mg | Glim |

### 6.1.1 Treatment regimens / study intervals

The treatment setup in the O*C database will contain the following study intervals: screening (starting with the date of informed consent at 0:00 h), run-in (starting with the date of run-in medication, time 0:00 h), linagliptin and glimepiride (each of the treatments starting with the date and time of first drug administration), off-treatment (starting with any date and time of last drug administration + 1 day, time 0:00 h, if the study drug is re-started afterwards), post-treatment (starting with the last date and time of last drug administration + 1 day, time 0:00 h), and post-study (starting with the date of trial completion + 1 day, time 0:00 h).

During the study treatment phase, patients are allowed to go off study drug and subsequently re-start study drug. This may happen not at all or repeatedly for a given patient, as this study is expected to go on for a number of years. This is reflected by the off-treatment phase. Further, a patient might die or discontinue from the study.

If the date of last drug administration is identical to the date of trial completion, post-treatment starts with the date of trial completion + 1 day and post-study period starts with the date of trial completion + 2 days, both at time 0:00 h.

For specific safety and efficacy parameters the duration of the on-treatment phase is given in Section 6.7.2.
For detailed information on the handling of the treatment in the O*C views and the definition of analysis treatments refer to Technical TSAP ADS plan.

A summary table will display the actual dose of glimepiride at the different visits, including the number of patients on each dose and the mean, SD, median and mode of dose per visit. However, none of the treatment comparisons will take into account the actual doses of glimepiride, only the treatment groups ‘glimepiride’and ‘linagliptin’ will be displayed.

Patients will be analysed as randomised for all analyses (safety and efficacy).
If the Interactive Voice and Web-based Response System (IXRS)-assigned study medication is not available at the site, a forced randomisation will occur, and the IXRS will assign a

treatment that is available at the site. Also, if a site assigns treatment to a patient before calling the IXRS, this is considered a forced randomisation. In both cases, that patient will receive the same treatment for the remainder of the trial.

(If a patient erroneously receives the wrong trial drug, patients are asked to return to the site and dispensed correct drug as soon as possible.)

## 6.2 IMPORTANT PROTOCOL VIOLATIONS

Data discrepancies and deviations from the CTP will be identified for all patients randomised and/or treated.
A protocol violation (PV) is important, if it affects the rights or safety of the study patients or if it can potentially influence the primary and/or key secondary outcome measures for the respective patients in a way that is neither negligible nor in accordance with the study objectives.

This second category of important PV forms the basis for the decision of whether a patient belongs to an analysis set.
The following table contains the categories which are considered to be important protocol violations in this trial. If the data show other important PVs, this table will be supplemented accordingly, latest at the BRPM.

The important PVs will be described in the CTR. A listing of patients with medication code broken will be provided, although this is not defined as IPV.

Table 6.2: 1 Important Protocol Violations

| **Category / Code** | | **Description** | **Comment/Example** | **Affects rights or safety (R/S) or primary/ key secondary outcome (E)** | **Excluded from** |
|---|---|---|---|---|---|
| A | | Entrance Criteria Not Met | | | |
| | | Inclusion criteria violated | | | |
| | A1.1 | No type 2 diabetes | Inclusion criterion IN1 ticked „No“ | E | PPS |
| | | Exclusion criteria violated | | | |
| | A2.1 | Type I diabetes | Exclusion criterion EX1 ticked „Yes“ | E | PPS |
| | A2.4 | Preplanned planned coronary artery re-vascularization (PCI, CABG) | Exclusion criterion EX7 ticked „Yes“ | E | PPS |
| | A2.7 | Congestive heart failure of NYHA class III or IV | Exclusion criterion EX10 ticked „Yes“ | E | PPS |
| | A2.8 | Specific exclusion criterion for premenopausal women violated | Exclusion criterion EX17 ticked „Yes“ | R/S | None |
| | A2.9 | Patient considered unreliable by the investigator for safe participation in the study | Exclusion criterion EX18 ticked „Yes“ | E | PPS |

Table 6.2: 1 (cont'd.) Important Protocol Violations

| Category / Code | | Description | Comment/Example | Affects rights or safety (R/S) or primary/ key secondary outcome (E) | Excluded from |
|---|---|---|---|---|---|
| B | | Informed Consent | | | |
| | B1 | Informed consent not available | Inclusion criterion IN6 ticked „No“<br>or<br>Date of informed consent missing<br>or<br>No signature on patient's “Declaration of Informed Consent” (to be identified by CRA) | E, R/S | TS, OS, PPS, Screened patients |
| | B2 | Informed consent given too late | Date of informed consent for the study not obtained prior to any study related procedure.<br>Minimum requirement for initial informed consent <= date of Visit 1a/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 | TS, OS, PPS |

Table 6.2: 1 (cont'd.) Important Protocol Violations

| Category / Code | | Description | Comment/Example | Affects rights or safety (R/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 of a patient.<br>This is identified by the medication kit number recorded in eCRF as well as the medication kit number as assigned by IXRS.<br>Can also be manually identified by investigator or CRA.<br>Can only be finally judged after DBL since unblinding information is required. | E | PPS |
| C2 | | Randomisation not followed | | | |
| | C2.1 | Treated before calling IXRS | Date of randomisation call after date of study drug intake at visit 2 | E | PPS |
| C3 | | Non-compliance | | | |
| | C3.2 | Non-compliance with criteria for removal from study medication | This includes only the following case: although a patient is pregnant, she is treated. A missing pregnancy test does not qualify as IPV. | R/S | None |

Table 6.2: 1 (cont'd.) Important Protocol Violations

| Category / Code | | Description | Comment/Example | Affects rights or safety (R/S) or primary/ key secondary outcome (E) | Excluded from |
|---|---|---|---|---|---|
| D | | Concomitant Medication | | | |
| D1 | | Improper medication washout | | | |
| | D1.1 | Glinide or SU not stopped until 35 days after first study drug intake | For patients on SU/glinide at baseline: Date of termination of glinide or SU > Date of first trial drug intake + 35 days | E | PPS |
| D2 | | Prohibited medication use during the treatment period of the trial | Not applicable. | | |
| D3 | | Mandatory medication not taken | Not applicable. | | |
| E | | Missing data | Not applicable. | | |
| F | | Incorrect timing | Not applicable. | | |
| G | | Trial specific protocol violations | | | |
| | G1.1 | Previous participation within this study | | E, R/S | PPS |
| | G1.2 | Serious non-compliance potentially affecting primary endpoint* | | E, R/S | 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

- Treated set (TS):
  All patients treated with at least one dose of study drug. The TS is the basis for all efficacy and safety analyses.

- Per protocol set (PPS):
  Patients included in the TS who have important protocol violations will be excluded from the PPS. A protocol violation will be considered important if it can be expected to have a distorting influence on the assessment of the primary endpoint and/or key secondary endpoints.

- On-treatment set (OS):
  The 30-days-treatment set will include all randomised patients with a minimum treatment duration of 30 days. It is 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 Patient sets for analyses

| | | Patient set | |
|---|---|---|---|
| Endpoint | TS | PPS | OS |
| Primary/Key secondary endpoints | X | X* | X* |
| Occurrence of 4P-MACE, 3P-MACE | X | X* | X* |
| Occurrence of and time to the first occurrence of composite endpoint of all CEC confirmed adjudicated events/ Tertiary CV endpoints/ non-CV death | X | | |
| Secondary/Tertiary diabetes related endpoints | X | | |
| Adverse events, safety laboratory, vital signs, hypoglycaemia related endpoints | X | | |
| Other endpoints not mentioned above (excluding adverse events, safety laboratory, vital signs, hypoglycaemia related endpoints, non-CV death) | X | | |
| Demographic/baseline characteristics | X | | |
| Important PVs | X | | |

Disposition is based on enrolled (defined as patients with signed informed consent), randomised and treated patients. Patient analysis sets are displayed on all randomised patients.
* Sensitivity analysis

Note that the number of patients with available data for an endpoint may differ. For details, see section “Handling of missing data”.

### 6.3.1 Serious non-compliance potentially affecting primary endpoint

If an individual site is closed for serious non-compliance (SNC), any decisions regarding the use of the data will be made as detailed in (6) before unblinding and documented separately.

Further, any decisions with respect to inclusion/exclusion from the PPS will be documented separately.

The analysis of data from patients who participated at more than one investigator site in this study will be described in a separate document.

## 6.5 POOLING OF CENTRES

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

A pooling of centres is not planned; primary and key secondary endpoints will be explored by geographical region only.

## 6.6 HANDLING OF MISSING DATA AND OUTLIERS

Every effort will be made to collect data as complete as possible. Missing data will be handled as outlined below.

For time to event analysis, patients who do not have a specific event will be censored (for details, refer to Section 6.8).

Different methods will be used to handle missing data for diabetes related endpoints of this trial. The following paragraphs outline the general approach. Refer to Table 6.6: 1 below for more details.

Observed cases (OC)

Only the available data that were observed while patients were on study medication (defined as time from first drug intake until last permanent treatment stop date plus the endpoint specific follow-up time) will be considered. Missing data will not be replaced. Any values taken after rescue medication intake will be set to missing.

Observed cases – Rescue observed cases (OC-ROC)

Only the available data that were observed while patients were on study medication (defined as time from first drug intake until last permanent treatment stop date plus the endpoint specific follow-up time) will be considered. Missing data will not be replaced. Any values taken after rescue medication intake will be kept.

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. Any values taken after rescue medication intake will be kept.

Last observation carried forward (LOCF)

Any values taken after rescue medication intake will be set to missing.
The last observed on-treatment value (within the time window from first drug intake until last permanent treatment stop date plus the endpoint specific follow-up time) will be carried forward, whether or not it is selected/picked as the value for the respective previous week (if multiple measurements were performed within a time window for a visit, as described in Section 6.7.3). That means, for patients receiving rescue therapy the last on-treatment measurement prior to the intake of rescue therapy will be carried forward.
Missing values before baseline will not be imputed.

One missing value within a course of measurements on treatment will be interpolated based on the last observed value before the missing visit and the first observed value after the missing visit.
(This is independent from the selection of a value as the picked visit value to be used in the descriptive analysis by week, as described in Section 6.7.3).

Interpolation will be done according to the formula described below. Let:

$D_0$ = date of a visit with a missing value for an endpoint;

$D_1$ = date of the next visit, with endpoint value non-missing, after the visit with missing value;

$D_{-1}$ = date of the previous visit, with endpoint value non-missing, before the visit with missing value;

$E_i$ = endpoint values for visits $D_{-1}$, $D_0$, $D_1$ for i= -1, 0 and 1.

Then the missing value will be interpolated as:

$$E_0 = E_{-1} + \left( (E_1 - E_{-1}) \times \frac{D_0 - D_{-1}}{D_1 - D_{-1}} \right)$$

Replacement of missing values will be performed for all weeks up to the last planned week that could have been reached by a patient, based on individual randomisation into the trial. Refer to Section 7.5.1 for the definition of this planned final visit.
In general baseline results will not be carried forward in case of missing on-treatment values, but can be used for interpolation.
Only, if a patient receives rescue therapy before the first available on-treatment HbA1c measurement, the HbA1c baseline value will be carried forward.
For all other parameters, except HbA1c, no baseline values will be used to replace post rescue measurements.
All values documented after last permanent study treatment stop will be set to missing for the analysis; instead, values derived by on-treatment LOCF will be analysed. That means, post-treatment values following the last permanent study treatment stop will not be considered, not even for interpolation.

Last observation carried forward – Rescue observed cases (LOCF-ROC)

Any values taken after rescue medication intake will be kept. LOCF (as described above) will be applied thereafter.

The following table provides an overview of the different approaches.

Last observation carried forward - ALL (LOCF-ALL)

All available data will be considered, including values obtained on treatment and post-treatment. Any values taken after rescue medication intake will be kept.
Missing values will be replaced by LOCF (including interpolation for a missing value within a course of measurements).

Table 6.6: 1 Summary of imputation methods for diabetes related endpoints

| Imputation method | Endpoint | Handling of missing values | Handling of values after rescue therapy |
|---|---|---|---|
| OC | Continuous endpoints | No imputation | Excluded (considered missing) |
| LOCF | HbA1c (at each visit and change from baseline) | Missing values following the last on-treatment value are replaced by the last on-treatment value.<br>Missing values with subsequently available on-treatment values are imputed by interpolation.<br>Baseline values are not carried forward, but will be used in interpolation. | Values after the start of rescue therapy are replaced by the last available on-treatment measurement.<br>If no on-treatment HbA1c measurement prior to rescue therapy is available baseline values are carried forward. |
| | Other continuous endpoints | As for HbA1c. | Values after the start of rescue therapy are replaced by the last available on-treatment measurement.<br>If no on-treatment measurement prior to rescue therapy is available baseline values are *not* carried forward and consequently, in this case values in the LOCF analysis are missing. |
| OC-ROC | Continuous endpoints | No imputation | Included |
| LOCF-ROC | All continuous endpoints | As for LOCF of HbA1c. | Included |

Pro-insulin, C-peptide, antibodies

Only patients with available baseline values will be presented descriptively. Missing values will not be replaced.

Binary key secondary endpoints and binary tertiary diabetes related endpoints

*Binary diabetes related endpoints including the restriction as of being on treatment*

If a patient was off-drug before trial stop, without re-start, or already died prior to regular completion, the patient will be handled as non-completers considered failure (NCF).
For further details refer to Section 7.5.1.

*Binary diabetes related endpoints including HbA1c and/or weight*

If a patient did not permanently and prematurely discontinue from treatment and has a missing value of HbA1c and/or weight at the last on-treatment visit, the missing value will be imputed by LOCF-ROC (weight)/LOCF (HbA1c).

If a patient has a missing value for weight at week 16 (corresponding to visit 6), the latest value before the week 16 window start will be used.

For the sensitivity analysis of the second and third key secondary endpoints on the OS patients who prematurely discontinue study treatment will not be counted as non-responders. Instead, their last on-treatment value will be used.

Missing dates and times

*Adverse event data and non-fatal outcome events*

Missing or incomplete AE dates are imputed according to BI standards (see DM&SM "Handling of missing and incomplete AE dates").(1)
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.

*Missing information on the date of first administration of trial drug*

If a patient was randomised, but the date of first drug administration is missing, the date of the first drug administration will be set to the date of randomisation. If the date of first administration is partially missing with the month and year present, the day will be set to the date of randomisation, if randomisation was in the same month. 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.

*Missing information on the date of last administration of trial drug*

If this date is missing, it will be imputed by the date of the respective visit.
If the date is incomplete with only month and year and the respective visit date is missing, the date of last drug administration will be imputed by the last day of this month. If this would be later than the date of trial completion, then the date of trial completion will be used for imputation.
If a patient is lost-to-follow up, no date of last drug administration is reported and the date of the respective visit is not available, the date of last drug administration is set as the date of trial completion.
For a patient who dies in the treatment phase with no information on the date of last drug administration, the date 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 6.1.1.
If after imputation, the date of trial completion is before the date of last drug administration, the start of the post-study period is defined as the maximum of trial completion +1 day, the date of the last visit +1 day and the start of the post-treatment period+1 day.

*Missing information on other dates of administration of trial drug (excluding first and last administration)*

A missing date 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 the documented month is later than the month of the visit date, the day will be imputed by the 1st of the month.

*Missing information on date of randomisation*

If the date of randomisation differs between IXRS and eCRF, the randomisation date as in IXRS will be used. If the date of randomisation is missing in the eCRF, it will be imputed by the date obtained from IXRS.

*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 the midpoint of the possible interval will be used. That means, 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 trial completion (=last contact or date of death)*

If the date is completely missing the following rules will be applied:
If a patient did not die (no corresponding vital status and/or adverse event information), the date of trial completion will be imputed by the last date the patient was known to be alive.
If a patient died and has not withdrawn consent, this date will be imputed by the date of death.
If a patient has withdrawn informed consent, this date will be imputed by the date of IC withdrawal.

If the date is incomplete with only month and year reported, the date will be imputed by the first day of this month.
Exception:
If the date last known to be alive, or respectively date of IC withdrawal is after the imputed date, the date of trial completion is to be imputed by this date.
If a patient died and has not withdrawn consent and the date of death is known, the date of trial completion will be imputed by the date of death.

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.

If a patient has multiple hypoglyceamic 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).

Laboratory data

Missing safety laboratory data will not be replaced.

Laboratory data outside the limits of quantification

Biomarker measurements of HbA1c, fasting plasma glucose, pro-insulin and c-peptide below the limit of quantification will be imputed by 2/3 times the lower limit of quantification for analysis. Values above the upper limit of quantification will be replaced by 1.5 times the upper limit of quantification.

## 6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The actual number of visits that a patient attends depends on when the patient gave informed consent (randomisation period: Dec, 2010 to Dec, 2012).

### 6.7.1 Baseline

With regard to efficacy and safety endpoints, the term "baseline" refers to the last observed/available measurement prior to administration of any randomised study medication.

A missing baseline value at the randomisation (Visit 2) may be replaced by a value at the beginning of the placebo run-in period (Visit 1b).

The following rule applies to baseline laboratory and ECG measurements, if visit and date/time of lab/ECG sample is not in a corresponding sequence (i.e. earlier date/time documented for a later visit):
If such a discrepancy occurs before first study medication intake, then the observations are sorted by date, time and visit and the last observation up to and including the time of the first administration of study drug is selected as baseline value for analyses.

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 HbA1c, FPG, triglycerides, proinsulin, C-peptide and antibodies: the measurement will not be considered as baseline

b) For total cholesterol, HDL cholesterol, LDL cholesterol, creatinine, eGFR, urinary albumin, UACR and all safety 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 study drug 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 study drug will be considered on-treatment values if they have been obtained up to the end of the parameter-specific follow-up period as defined in Table 6.7.2: 1: they will be assigned to the randomised study drug for analyses.

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

Table 6.7.2: 1 Endpoint specific follow-up time for assignment to active treatment

| Endpoint | Last day of assignment to treatment (days after study drug stop date) |
|---|---|
| HbA1c | 7 |
| FPG | 1 |
| Body weight | 7 |
| Adverse events | 7 |
| Asymptomatic hypoglycaemia, that is not considered as adverse events | 7 |
| Laboratory measurements including eGFR and UACR | 7 |
| Vital signs | 7 |
| Waist circumference | 7 |

### 6.7.3 Time windows for assignment to visits in the on-treatment phase

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 on treatment (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.

On-treatment measurements of HbA1c, FPG, weight, Total cholesterol, LDL cholesterol, HDL cholesterol, Triglycerides, Creatinine, eGFR, urinary albumin, UACR, vital signs and waist circumference will be assigned to visits based on time windows around the planned visit dates.

These time windows are defined based on the planned number of days after the date of first administration of study drug (Visit 2).

The midpoint between two on-treatment visits defines the end of a time window, with the midpoint being included in the time window of the preceding visit. The end of the time window of the last on-treatment visit (end of treatment (EOT)) is endpoint dependent.

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

- If first intake of study drug 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 study drug after the randomisation, the time window for the first on-treatment visit could include times the patient was not yet on study drug.

The time window for the first visit after randomisation starts on the day after the first intake of study drug. This maximises the number of measurements used in by visit analyses and provides consistency with the planned last observation carried forward (LOCF) approach (as well as the approach to include patients with a baseline and at least one on-treatment measurement into the analysis).

Table 6.7.3: 1 shows the time windows for FPG, planned to be measured at every visit.

Table 6.7.3: 1 Time windows for visits for FPG

| Visit number | Planned days after randomisation | Planned days on treatment | Time window start* based on planned days on treatment | Time window end* based on planned days on treatment |
|---|---|---|---|---|
| 2 | 0 | 1 | NA | 1** |
| 3 | 28 | 29 | 2 | 43 |
| 4 | 56 | 57 | 44 | 71 |
| 5 | 84 | 85 | 72 | 99 |
| 6 | 112 | 113 | 100 | 169 |
| 7 | 224 | 225 | 170 | 281 |
| 8 | 336 | 337 | 282 | 393 |
| 9 | 448 | 449 | 394 | 505 |
| 10 | 560 | 561 | 506 | 617 |
| 11 | 672 | 673 | 618 | 729 |
| 12 | 784 | 785 | 730 | 841 |
| 13 | 896 | 897 | 842 | 953 |
| 14 | 1008 | 1009 | 954 | 1065 |
| 15 | 1120 | 1121 | 1066 | 1177 |
| 16 | 1232 | 1233 | 1178 | 1289 |
| 17 | 1344 | 1343 | 1290 | 1401 |
| 18 | 1456 | 1457 | 1402 | 1513 |
| 19 | 1568 | 1569 | 1514 | 1625 |
| 20 | 1680 | 1681 | 1626 | 1737 |
| 21 | 1792 | 1793 | 1738 | 1849 |
| 22 | 1904 | 1905 | 1850 | 1961 |
| 23 | 2016 | 2017 | 1962 | 2073 |
| 24 | 2128 | 2129 | 2074 | 2185 |
| 25 | 2240 | 2241 | 2186 | 2297 |
| 26 | 2352 | 2353 | 2298 | 2409 |
| 27 | 2464 | 2465 | 2410 | 2521 |
| 28 | 2576 | 2577 | 2522 | 2633 |
| 29 | 2688 | 2689 | 2634 | 2745 |
| 30 | 2800 | 2801 | 2746 | Study drug stop date + x days*** |

*actual days on treatment
**has to be pre-treatment value
***The definition of x is endpoint specific, cf. Table 6.7.2: 1.

As e.g. HbA1c and weight are 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 apply):

Table 6.7.3: 2 Time windows until visit 6 for e.g. HbA1c and weight

| Visit number | Planned days after randomisation | Planned days on treatment | Time window start* based on planned days on treatment | Time window end* based on planned days on treatment |
|---|---|---|---|---|
| 2 | 0 | 1 | NA | 1** |
| 6 | 112 | 113 | 2 | 170 |

*actual days on treatment
**has to be pre-treatment value

For further visits beyond visit 30 the same concept is applied.

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. 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.

For LOCF imputation (including interpolation), the last observed on-treatment value will be carried forward, whether or not it was selected in the previous time window (see Section 6.6).

The assignment of all measurements, including on-treatment and off-treatment measurements, to visits will be performed accordingly.
For all variables any measurement obtained in the window of +8 days to + 44 days after last study drug intake will be assigned as “Follow-up measurement”, corresponding to planned measurement at 30 days after last study drug stop.

## 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 study (under risk).
Consistent with that approach, the respective time intervals determine the start and end for the derivation of occurrence of a specific event.

For those patients with an event, the time to event is calculated as:
<date of event> - < start date> + 1
For those 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.
If study drug administration happened before calling IXRS, the date of first drug administration will be used as start date.

For the endpoints of time-to-first-rescue-medication, time-to-first-hypoglycaemia and time-to-AE analysis (refer to Section 7.8.1.3.2), time to first silent MI and laboratory based endpoints, the date of first drug intake will be considered as starting point. (The use of a different start date is justified as the general definition of rescue medication applies only to the time after first study drug intake and general AEs (including hypoglycaemia) 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 4P-MACE, 3P-MACE and time to the first occurrence of any of the components of the composite endpoint of all CEC confirmed adjudicated events, 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 date determined by the adjudication committee will be used; this can be different from the investigator reported date.
For the endpoints of time to CV death, time to all-cause mortality and time to non CV death 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 hypoglycaemia, the onset date of the first episode will be used. The same applies to time-to-AE analysis.
For time to rescue medication, the first intake of rescue medication (or respectively increase in background medication dose) will be used.

The time to first occurrence of endpoints based on 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, key secondary, secondary CV and tertiary CV endpoints (except stand-alone endpoints of CV death, all-cause mortality, non CV-death and silent MI) and time to first disabling or fatal stroke*

The underlying principle is that the censoring date should be the last date a patient was known to be free of an endpoint event (e.g. free of each component of the 4P-MACE).

Patients without occurrence of a specific endpoint (composite endpoint or individual components) will be considered censored at their last documented study visit*.

* This includes any dates as of

- adverse event/outcome event start dates (if non-fatal events),
- onset dates of adjudicated (confirmed and non-confirmed) events (if non-fatal event),
- date of PCI/CABG
- date of trial completion (defined as latest of date of last clinic visit, last telephone call, date of last contact if lost to follow-up).

Censoring is considered independent from study drug intake.
Any information as permitted by local law will be used in the analyses.

*Time to first rescue medication (overall and protocol-defined)*

Patients without rescue medication intake that have prematurely and permanently stopped trial drug intake will be considered censored at their last documented study visit* as described above.
Patients without rescue medication intake that have regularly completed trial drug intake until study end will be considered censored at their last treatment stop date.

*Primary endpoint sensitivity analyses*

Please refer to Section 7.4.2.

*Endpoints of CV death, non-CV death and all-cause mortality*

A patient who did not die/died from another event will be censored at the latest date of the dates as described above, (for e.g. the primary endpoint) 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).

Censoring rules and their application:

- 0-days censoring will be used for sensitivity analyis on TS (label: TS+0)
- 7-days censoring will be used for all adverse events - for hypoglycemia refer below (label: TS+7)
- 30-days censoring will be used for sensitivity analysis done on PPS (label: PPS) and OS (label: OS) and as additional sensitivity analysis regarding censoring on TS (label: TS+30)

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 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, whichever is earlier.

*Silent MI*

A patient without this event will be considered censored at the last documented study visit* as defined above.

*Time to first hypoglycaemia*

To keep the analysis of hypoglycaemia consistent with the overall AE analysis, a patient without an event will be considered censored at the date of last trial drug intake + 7 days or date of death, if earlier. For further details refer to Section 7.8.1.6.

*Time to first investigator reported heart failure (based on narrow SMQ cardiac failure)*

Censoring will be performed as described above for the primary endpoint.

*Endpoints based on laboratory data only*

Patients who already fulfil the respective condition at baseline are 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..

*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

If a patient could not be followed-up (vital status could not be collected) at the end of study (considering a certain close-out period), that patient will be flagged as Lost To Follow Up (LTFU). Patients who died are not considered LTFU.

# 7. PLANNED ANALYSIS

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 enroled, entered/randomised, treated as well as those who did/ did not prematurely discontinue trial medication, did/did not prematurely discontinue from trial.

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

For End-of-text tables and appendix tables, the set of summary statistics is: N / Mean / SD / Min / Median / Max. Q1 (lower quartile) and Q3 (upper quartile) will be shown, if appropriate.
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 will 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. Percentages will be rounded to one decimal place. The category missing will be displayed only if there are missing values.

Statistical parameters will be displayed to a defined number of decimal places as specified in the BI guideline “Reporting of Clinical Trials and Project Summaries” (3).

## 7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive analysis of the following demographic characteristics and variables measured at baseline will be presented by treatment groups and in total for the TS:

- Gender, race, ethnicity, country, age (continuous and categories of <55 years to >=85 in steps of 5 years),
- Height, weight (continuous and categorical), BMI (continuous and categorical), waist circumference
- Smoking history and Alcohol status
- Duration of formal education in years
- eGFR (continuous and categorical)
- Baseline HbA1c (continuous and categorical) and FPG (continuous and categorical)
- Time since diabetes mellitus type 2 was first diagnosed (continuous and categories of <=1 year, >1 to <=5 years, >5 to >= 10 years, >10 years)

## 7.2 CONCOMITANT DISEASES AND MEDICATION

Relevant medical history/concomitant diseases

Relevant medical history/concomitant diseases will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA).

Frequency tabulations of the following concomitant diseases as obtained at baseline will be presented by treatment group and in total based on the TS:

- Cardiovascular risk factor categories: Previous vascular disease, Evidence of vascular related end-organ damage, Multiple CV risk factors (hypertension, current smoking, dyslipidaemia, Type 2 Diabetes Mellitus >10 years) as well as combinations (Section 6.4)

- Relevant medical history (presence of baseline conditions within the previous 6 month: Diabetic retinopathy, Diabetic nephropathy, Diabetic neuropathy, Diabetic foot, Coronary artery disease, Peripheral artery occlusive disease, Cerebrovascular disease and Hypertension

The number of patients (including percentages) with at least one concomitant disease (except diabetes mellitus type 2) at baseline will be presented.
Concomitant diagnoses by MedDRA System Organ Class (SOC) or Preferred Terms at screening with incidence of >=1% in at least one treatment group will be summarised by treatment group and in total in a frequency table based on the TS.

Concomitant medication

All frequency tabulations will be performed on the TS.
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.

Overall concomitant medication use (excluding antidiabetic/background therapy) with an incidence of >=1% in at least one treatment group per WHO−DD preferred name will be summarised by Anatomical-Therapeutic-Chemical classification level 3 (ATC3). Summaries will be presented for concomitant therapies taken during screening and those taken after first drug intake.

Separate summaries of use of acetylsalicylic acid (ASA), antihypertensives, lipid lowering drugs, P−gp or CYP 3A4 inhibitors and anti−coagulants during screening and those taken after first drug intake will be presented.

Antidiabetic therapies including background therapies taken at screening as well as those started after the date of first trial drug intake will be presented, with categorisation into monotherapy/combination therapy and the number of (oral) antidiabetic drugs. Antidiabetic therapies at screening will be linked to the visit 1a HbA1c to reflect the different categories of inclusion criterion 2.

An antidiabetic therapy that is not a background therapy is considered as being taken at screening, if the start date was before the date of IC and the end date was not earlier than 10 weeks pior to IC. As the start and stop date of the protocol-defined background medication of alpha-glucosidase inhibitor and/or metformin is not recorded in the eCRF, it is assumed, that this background medication was already taken at screening.

Summaries on the total daily dose of metformin at the date before first trial drug intake and last date of trial drug intake will be provided, this includes a categorisation into ≤1500mg or >1500mg.
The number of patients with a change in background therapy at any time starting from the date of first intake of trial drug will be presented for metformin as well as alpha-glucosidase inhibitor.

## 7.3 TREATMENT COMPLIANCE

Compliance will be analysed descriptively
A table showing the frequency of patients within (yes) and respectively outside (no) of 80%-120% compliance will be given, presenting information for all visits for each treatment group, as well as for the total of all patients, based on the treated set.

The percent compliance was to be calculated by the investigator as described in Section 4.3 of the CTP.

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 means, that whenever compliance is documented due to premature treatment discontinuation, the information will be assigned to the respective week. That may result in varying denominators of patients with compliance information over time, as a patient might stop study drug permanently and restart again.

Whenever compliance information has been documented more than once within the same time window, the following rules apply:

- Compliance outside of 80-120% at least once in that window: This information is used and no is displayed
- Compliance always inside 80-120% in that window: This information is used and yes is displayed
- Compliance always missing in that window: Missing is displayed
- Compliance missing at least once in that window and the other values is inside the window: The compliance is considered as being inside 80-120%.

## 7.4 PRIMARY ENDPOINT

### 7.4.1 Primary analysis

For the primary endpoint of time to the first occurrence of any of the following CEC confirmed adjudicated components of the primary composite endpoint: CV death (including

fatal stroke and fatal MI), non-fatal MI (excluding silent MI), or non-fatal stroke an ITT-analysis (as randomised) on the TS will be performed. The analysis will be performed on TS with patients considered as randomised (intention-to-treat) and all events up to individual day of trial completion considered.
The randomised study treatment will be used to assign patients and events to treatment groups; all adjudicated events which occur until study end will be taken into account (i.e. independent of whether or not a patient was still on study medication).
The time to the primary endpoint will be derived from the date of randomisation.

The one-sided overall significance level will be alpha=2.5%. As described in the CTP, the DMC will perform formal interim analyses. The significance levels for the analyses are denoted by $\alpha_i$, i=1,…,K, where K is the total number of analyses.

The O'Brien & Fleming alpha-spending function defined the significance level for the first interim analysis on 4P-MACE.
Due to the change of the primary endpoint after the first DMC interim analysis a Bonferroni adjustment will be applied in addition, to control the overall alpha level. That means, the alpha spent at the first DMC interim analysis (performed for 4P-MACE and based on the O'Brien & Fleming alpha-spending function) is subtracted from the initial overall alpha. The O'Brien & Fleming alpha spending function based on the new overall alpha (after additional Bonferroni adjustment) defines the allocation of the still available overall significance level for the second interim analysis and the final analysis.

7.4.1.1 Statistical Methods

For the primary analysis a regression analysis using Cox's proportional hazards model including a term for treatment will be applied to compare linagliptin with glimepiride. Breslow's method will be used for dealing with ties.

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

$h_j(t) = \exp(\beta_1 x1_j)\, h_0(t)$, 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 $x1_j$
- $\beta 1$ is the (unknown) coefficient of the explanatory variable x1
- $x1_j$ is an indicator variable representing the treatment group for patient j=1,...,n.

The hazard ratio (HR) for the effect of treatment (linagliptin vs. glimepiride) will be presented with the corresponding $(1-2*\alpha_i)*100\%$ confidence interval (CI), the corresponding 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 for the null hypothesis of equality based on the Wald chi-squared statistic.

The proportional hazards assumption will be explored by plotting log(-log(survival function)) against the log of time by treatment group and checked for parallelism. The interaction of treatment 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(time).

The probability of the primary endpoint event over time will be displayed by treatment using Kaplan Meier (KM) estimates, which includes the presentation of certain quantiles of the failure times (e.g. 2.5%, 5%, 7.5% and 10% quantiles) and Kaplan-Meier rates after specific number of years.
Any pointwise $(1-2*\alpha_i)*100\%$ CIs for KM failure rates will be determined using Greenwood's variance estimate.
The two-sided p-value resulting from the log-rank test will be presented.

Tabular and graphical displays will present the (cumulative) number of patients at risk, failures as well as censored patients over time.

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.

7.4.1.2 Censoring for time to event endpoints for interim and final analyses

Please refer to Section 6.8 above.

7.4.1.3 Testing hierarchy

In the i-th analysis, i=1,…, K, the upper limit of the two sided $(1-2*\alpha_i)*100\%$ confidence interval of the hazard ratio will be compared with the non-inferiority margin of 1.3. Also the one-sided p-value of the non-inferiority test based on the Wald chi-squared statistic will be given. If the non-inferiority test is significant, i.e. non-inferiority within the margin of 1.3 has been demonstrated, a superiority test (Wald chi-squared statistic) will be performed. If the superiority test is significant, a superiority test on the first key secondary endpoint will be performed at the same significance level as used for the primary endpoint. If this superiority test is also significant, the second and third key secondary endpoints will be tested hierarchically. The second and third key secondary endpoints will be analysed with a Chi-Square test at the same significance level $(2*\alpha_i)*100\%$ as the primary endpoint.

7.4.1.4 Details on alpha-spending

The following details on alpha-spending will hold:

*a) Early stop of the study due to superiority or futility*

If the decision is to terminate the study after a formal DMC interim analysis due to superiority of linagliptin over glimepiride or futility, further endpoint events are expected to be documented before the study is stopped. These events will also be adjudicated and subsequently used for the final analysis.

The final, confirmatory analysis will be based on all (primary) endpoint events observed until study end. This analysis will be performed based on the same significance level $\alpha_i$ as the interim analysis that led to early stopping of the trial.

*b) Early stop of the study due to safety reasons*

If the study is terminated prematurely (before observation of 631 patients with primary endpoint events) as a consequence of DMC safety reviews, the remaining significance level alpha will be fully exhausted at this step (taking into account previous official interim analysis), and the analysis will be based on all observed and confirmed (primary) endpoints events.

*c) Underrunning at study end (not stopping prematurely)*

If, for logistical reasons, the study is terminated with fewer than 631 patients with primary endpoint events, the remaining significance level alpha will be fully exhausted at this step (taking into account previous official interim analysis).

*d) Overrunning at study end (not stopping prematurely)*

If, for logistical reasons, the study is terminated with more than 631 patients with primary endpoint events, the significance level alpha as determined for 631 patients with primary endpoint events will be used (taking into account previous official interim analysis).

### 7.4.2 Sensitivity analysis

7.4.2.1 Proportional hazards assumption violated

In case the proportionality assumption is violated, an attempt will be undertaken to identify groups of patients for which the proportionality assumption holds and a 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 (7) will be investigated.

7.4.2.2 General sensitivity analysis

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

Sensitivity analyses done on the PPS, OS population and on TS population in combination with censoring on day 30 will be performed based on events occurring within the time patients are on-treatment + 30 days after permanent treatment discontinuation or date of last documented study visit, whichever comes first.

This means patients will be considered censored at the date of last treatment stop + 30 days, if their last documented study visit was performed thereafter. If the last documented study visit was performed earlier than 30 days after last treatment stop, the patient will be censored at the last documented study visit (refer to Section 6.8.3).

The sensitivity analysis done on the TS in combination with censoring on day 0 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.

These sensitivity analyses will be performed as described in Section 7.4.1.1 at the significance level used for the primary analysis.

The following table provides an overview of the planned analyses.

Table 7.4.2.2: 1 Overview of analyses on the primary endpoint

| **Censoring mechanism** | **Analysis set** | | |
|---|---|---|---|
| | **TS** | **PPS** | **OS** |
| Individual day of trial completion | x | | |
| 0 days censoring | x | | |
| 7 days censoring | x | | |
| 30 days censoring | x | x | x |

For the details on censoring refer to Section 6.8.3.

For the primary endpoint an additional sensitivity analysis will be performed in addition on the TS considering all events that occurred between randomisation and 7 days after the last permanent treatment discontinuation or date of last documented study visit, whichever comes first. Accordingly, patients without an event will be considered censored at the earliest of the date of last treatment discontinuation + 7 days or last documented study visit.

The cumulative incidence for the time to first occurrence of the primary endpoint will be presented, accounting for the time to non-CV death as competing risk. In addition, a Cox's proportional hazards model will be fitted to compare the distribution of competing risks between treatment groups.

### 7.4.4 Interim analysis

The significance level alpha is determined as described in Section 7.4.1.
For the interim analysis patients without events will be considered censored as described in Section 7.4.1.2.

The DMC will perform formal interim analyses as outlined in the DMC charter. A separate Statistical Analysis Plan for the interim analysis will be provided.
The transfer of data is outlined in the Interim Analysis Logistics Plan (logistical aspects), as well as the Data Transmission Agreement signed by the DMC Statistician.

## 7.5 SECONDARY ENDPOINTS

### 7.5.1 Key secondary endpoints

*Primary analysis of key secondary endpoints*

The first key secondary endpoint of time to first 4P-MACE will be analysed on the TS as described in Section 7.4.1, at the same significance level $\alpha_i$ as the primary endpoint.

The second and third composite key secondary endpoints will be analysed with a Chi-Square test at the same significance level $\alpha_i$ as the primary endpoint, based on the TS.
The number and percentage of patients with response will be provided along with the 95% Wilson confidence intervals.
A logistic regression model will be applied including a term for ‘treatment’. The Odds ratio

(OR) along with the $(1-2*\alpha_i)*100\%$ Wald CI and the two-sided p-value for treatment comparison will be presented.

General definition of second and third key secondary endpoints

If a patient has terminated study treatment permanently (i.e. without subsequent re-start) before trial stop, the patient is considered a non-responder (except in sensitivity analyses).
A patient who stops study treatment and restarts later, can still fulfill the second and third composite key secondary 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.
HbA1c and weight and hypoglycaemia are only considered for the (parameter-specific) time on-treatment and not e.g. at/until a follow-up visit, because the follow-up visit is planned to be performed after treatment discontinuation.

*Sensitivity analysis of key secondary endpoints*

For the first key secondary endpoint of time to first 4P-MACE sensitivity analyses will be done on the PPS, the OS and TS+0, TS+30.
These sensitivity analyses will be performed based on events occurring within the time patients are on-treatment + 30 days after permanent treatment discontinuation or date of last documented study visit, whichever comes first.
For further details refer to Section 7.4.2.

For the time to first 4P-MACE an additional sensitivity analysis will be performed on the TS considering all events that occurred between randomisation and 7 days after the last permanent treatment discontinuation or date of last documented study visit, whichever comes first. Accordingly, patients without an event will be considered censored at the earliest of the date of last treatment discontinuation + 7 days or last documented study visit.

The cumulative incidence for the time to first 4P-MACE will be presented, accounting for the time to non-CV death as competing risk. In addition, a Cox's proportional hazards model will be fitted to compare the distribution of competing risks between treatment groups.

For the second and third key secondary endpoints sensitivity analyses will be done on the PPS and the 30-days-treatment set OS, including the same statistical procedures as described above for the TS.
For the sensitivity analysis on the PPS patients who prematurely discontinue study treatment will be counted as non-responders as in the primary analysis on the TS.
For the sensitivity analysis on the 30-days-treatment set patients who prematurely discontinue study treatment will not necessarily be counted as non-responders. The measurement of the last documented on-treatment study visit will be used in this case.
The significance level from the primary analysis of key secondary endpoints will be used.

### 7.5.2 (Other) Secondary endpoints

All other secondary 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 alpha=0.05.

#### 7.5.2.1 Secondary/Tertiary cardiovascular endpoints

For all secondary and tertiary CV 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.
For time to first investigator reported heart failure (based on narrow SMQ cardiac failure) only frequencies and incidence rates will be provided. For time to first investigator reported heart failure (based on narrow SMQ cardiac failure) another analysis will be performed on the TS based on events occurring until + 7 days after permanent treatment discontinuation or date of last documented study visit, whichever comes first. Accordingly, patients without an event will be considered censored at the earliest of the date of last treatment stop + 7 days or last documented study visit.

The cumulative incidence function for time to first occurrence of each adjudicated CEC confirmed CV endpoint (except all-cause mortality), accounting for any death that is not part of the endpoint as a competing risk, will be provided. In addition a Cox's proportional hazards model will be applied to the competing risk.

For the secondary CV endpoints of occurrence of 4P-MACE and 3P-MACE sensitivity analysis on the TS, PPS and OS will be performed, considering events until earliest date of treatment stop + 30 days or date of last documented study visit. This covers the presentation of number and percentage of patients with an event.

For all adjudicated CV endpoints including all-cause mortality additional sensitivity analyses will be performed on the TS based on events occurring until + 30 days after permanent treatment discontinuation or date of last documented study visit, whichever comes first. Accordingly, patients without an event will be considered censored at the earliest of the date of last treatment stop + 30 days or last documented study visit.

7.5.2.2 Secondary/Tertiary diabetes related endpoints and UACR

7.5.2.2.1 Continuous diabetes related endpoints (FPG, HbA1c, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, creatinine, urinary albumin, eGFR, weight and UACR)

Evaluation will be performed on standardized values. The analyses will be performed on the TS. Measurements will be assigned to 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.

Treatment-emergent evaluation

Patients with a baseline measurement and at least one on-treatment measurement will be included for analysis over time. Only values obtained until last permanent treatment stop will be considered. The assignment of values to be on-treatment is defined in Table 6.7.2: 1.

In general, for the evaluation of HbA1c and FPG, for patients receiving rescue therapy all on-treatment efficacy measurement after the start of rescue therapy will not be used for analysis and hence set to missing (OC, LOCF). If a patient receives rescue therapy before the first available on-treatment measurement, this patient will not be included in the analysis, except for HbA1c LOCF analysis.

For total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, creatinine, urinary albumin, UACR, eGFR and weight values before and after rescue therapy intake will be considered (OC-ROC, LOCF-ROC).
In addition, analyses following the OC concept will be performed.

For the following parameters, only values obtained in the fasted state will be used for analyses: FPG, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides.

For UACR log10 transformed data will be used within the ANCOVA or respectively MMRM model, the results will be back-transformed to the original scale.

*Change from baseline to final visit on-treatment*

For the investigation of continuous diabetes related endpoints at the final visit, the following analysis of covariance (ANCOVA) model will be applied:

Efficacy endpoint as absolute change from baseline = overall mean + treatment + baseline measurement + random error

This model includes effects accounting for the following sources of variation: ‘Treatment’, and ‘baseline’. ‘Treatment’ is a fixed classification effect and ‘baseline’ is a linear covariate. The random error is assumed to be normally distributed with mean 0 and variance $\sigma^2$.

The adjusted mean with SE for each treatment group, the adjusted mean difference with SE and the corresponding 95% CI will be reported.

Treatment-specific baseline will be investigated.

Descriptive statistics will be presented.

The analysis will be performed on OC and OC-ROC for HbA1c, FPG and ~~on OC-ROC~~ for Total cholesterol, HDL cholesterol, LDL cholesterol, Triglycerides, Creatinine, eGFR, urinary albumin, UACR and weight.

*Change from baseline over time – considering the design of the trial*

Only data up to the planned week that could theoretically be achieved by all patients will be included in this analysis. This time-point depends on the duration of the trial. If e.g. the trial would run for 7 years in total with 2 years for re-cruiting, the last patient randomised could theoretically only reach the visit at week 260. Then for all patients only the data up to planned week 260 will be included in this analysis.

*a) MMRM*

The change from baseline over time will be evaluated with a restricted maximum likelihood (REML) based mixed model repeated measures (MMRM) approach with the fixed, categorical effects of treatment, week, treatment-by-week interaction, with the continuous covariates of baseline and baseline-by-week interaction.
The baseline and the available longitudinal observations at each post baseline visit until last permanent treatment stop will be used for the analysis of these endpoints at each week.

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.
The average treatment difference over time will be provided in addition to the treatment difference per week for continuous endpoints.

An unstructured covariance structure will be used to model the within-patient errors.
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.
The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Type III sums of squares will be used.

The analysis will be performed on OC and OC-ROC for HbA1c, FPG and for Total cholesterol, HDL cholesterol, LDL cholesterol, Triglycerides, Creatinine, eGFR, urinary albumin, UACR and weight.

*b) LOCF*

The last observation carried forward (LOCF) approach will be performed to conduct a sensitivity analysis. The change from baseline after replacement by LOCF will be evaluated with the analysis of covariance (ANCOVA) model as described above for every week.

The adjusted mean with SE for every treatment group, the adjusted mean difference with SE and 95% CI will be reported.

The analysis will be performed on LOCF and LOCF-ROC for HbA1c, FPG and for Total cholesterol, HDL cholesterol, LDL cholesterol, Triglycerides, Creatinine, eGFR, urinary albumin, UACR and weight.

*c) Descriptive statistics*

Descriptive statistics will be provided based on OC data and after LOCF imputation (OC, OC-ROC, LOCF, LOCF-ROC).

*Change from baseline over time*

MMRM analyses on OC and OC-ROC will be performed as described above.
Simple descriptive statistics will be calculated for the change from baseline over time based on observed case data (OC and OC-ROC). All weeks will be considered.

*Sensitivity analysis for determination of influence of rescue medication and fasting*

For HbA1c and FPG and weight the above analyses considering the actual design of the trial applying MMRM analysis will be repeated including also data obtained after rescue therapy intake (OC-ROC and LOCF-ROC).
As stated above, approaches of OC and LOCF will also be performed for Total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, creatinine, eGFR, urinary albumin, UACR and weight.
For total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides a sensitivity analysis using descriptive statistics will be performed for the change from baseline over time and at final visit based on OC-ROC, considering all values, obtained in fasted and non-fasted state.

<u>Evaluation including all data independent of treatment</u>

MMRM analyses on OC-ALL considering the actual design of the trial will be performed as described above for HbA1c, FPG and weight.
Descriptive statistics will be calculated for the change from baseline over time and to study end based on all observed data. All data obtained before and after intake of rescue therapy and independent of treatment stop will be considered (OC-ALL).

Descriptive statistics will also be provided after applying LOCF including all data obtained up to the planned week that could theoretically be achieved by all patients.

An ANCOVA will be performed for the change from baseline to final week per patient using the model as described above for HbA1c, FPG and weight.
Treatment-specific baseline will be investigated for the change from baseline to final week.

Investigation of follow-up information obtained after treatment stop

A comparison of baseline, last value on-treatment and follow-up value will be performed for measures of SBP, DBP, pulse rate, FPG, eGFR.

A model including subgroup, subgroup-by-treatment interaction will be used.

7.5.2.2.2 C-peptide, plasma pro-insulin and antibodies

Descriptive statistics of baseline values will be provided based on the TS and include geometric mean and geometric coefficient of variation. For C-peptide and pro-insulin only values obtained in fasted state will be considered.

7.5.2.2.3 Binary diabetes related endpoints

The Chi-Square test is used to compare the two treatment groups and a logistic regression with factor treatment is performed to report the OR along with the 95% CI. The number and percentage of patients with response will be provided along with the 95% Wilson confidence intervals. The analysis will be performed on the TS.

7.5.2.2.4 Time to and occurrence of antidiabetic rescue therapy

Time to first rescue therapy use among patients will be analysed by Kaplan-Meier estimates and compared using a log-rank test based on the TS.

The time to first rescue medication will be calculated as date of first intake of rescue therapy minus the date of first intake of randomised study drug plus one day.
For censoring refer to Section 6.8.

The number and percentage of patients with rescue medication will be provided along with the 95% Wilson confidence intervals. The analysis will be performed on the TS.

## 7.7 EXTENT OF EXPOSURE

Extent of exposure to active study medication will be calculated as the difference between the date of last intake of study drug (or respectively date of death) and the first administration of study drug + 1 day (i.e. including off-treatment periods) per patient.

The end of time in study is defined as the latest date as of the date of last documented study visit (defined in Section 6.8.3) and the date of vital status (if alive)/ date last known to be alive (if LTFU)/ date of death (if died). The time in study is the difference between the end of time in study and the date of randomisation.

A descriptive statistics table of the treatment exposure and time in study will be provided. This table will also include the total exposure/time in study summed over all patients within each treatment group and transformed to patient years as obtained by:

$$\text{Patient years} = \frac{\Sigma \text{ (individual patient total exposure/time in study in days)}}{365.25 \text{ days}}$$

In addition, the table will include the sum of exposure/time in study without/prior to rescue medication [years] and the sum from first intake of rescue medication [years] per treatment group.

A frequency table of number and percentage of patients with exposure/time in study for specific time periods will be provided by treatment group.

A Kaplan-Meier plot will be provided for exposure time and time in study.

## 7.8 SAFETY ANALYSIS

Safety analyses of adverse events and laboratory data will be performed on the treated set.

### 7.8.1 Adverse events

AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

The analyses of adverse events will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs (not the number of AEs). For this purpose, AE data will be combined in a 2-step procedure into AE records.

In a first step, AE occurrences, i.e. AE entries on the eCRF, will be collapsed into AE episodes provided that all of the following applies:

- The same MedDRA lowest level term was reported for the occurrences
- The occurrences were time-overlapping or time-adjacent. Time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence.
- Treatment did not change between the onset of the occurrences OR treatment changed between the onset of the occurrences, but no deterioration was observed for the later occurrence

In a second step, AE episodes will be condensed into AE records provided that the episodes were reported with the same term on the respective MedDRA level and that the episodes are assigned to the same treatment. For further details on summarization of AE data, please refer to the guideline 'Handling and summarization of adverse event data for clinical trial reports and integrated summaries' (2).

The general AE analysis will include all adverse events (including outcome events).

For the hypoglycaemic events (reported as adverse events or separately) further evaluation is performed on episodes. The occurrences are only collapsed if they occur within ≤60 minutes of each other. The period will begin with the first hypoglycaemia onset time. If another event occurs outside this initial 60 minutes window a new period for collapsing will begin. Hypoglycaemic episodes with a missing onset time will be counted as separate episodes, regardless of other episodes on the same day.

#### 7.8.1.1 Assignment of AEs to treatments

The analysis of adverse events will be based on the concept of treatment emergent adverse events. That means that all adverse events occurring between first drug intake until 7 days after last permanent treatment stop will be considered as on-treatment (see Table 6.7.2: 1), which means, that possible treatment interruption phases of a patient will be part of the on-treatment phase.
All adverse events occurring prior to first drug intake will be assigned to 'screening/run-in'.
All adverse events occurring after last drug intake + 7 days will be assigned to treatment related 'post-treatment', whereby the post-treatment phase according to the previous treatment will be used (post-Lina and post-Glim respectively). Adverse events reported after the latest date as of the date of last documented study visit (defined in Section 6.8.3) and the date of vital status (if alive)/ date last known to be alive (if LTFU)/ date of death (if died)+ 1 day will be assigned to post-study. For details on the treatment definition, see Section 6.1.
Patients who died before last drug intake + 7 days will have their on-treatment phase assigned until the date of death.

In section 15, only adverse events assigned to on-treatment phase of linagliptin or glimepiride of the respective drug will be displayed. Further tables including also adverse events which occurred during screening/run-in and post-treatment phase will be included in Appendix 16.1.9.2 and 16.2.7.
All AEs observed during the study starting from first treatment intake will be presented in further tables.
A listing of patients with on-treatment adverse events with an onset during the non-randomised treatment will be provided.

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

- For cancer and pancreatic cancer in addition to the '7-day-on-treatment 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 reactions all adverse events that occurred between first study drug intake up until treatment stop + 30 days will be presented based on the treated set.
- For pancreatitis all adverse events that occurred between first study drug intake up until study end will be presented based on the treated set.
- Investigator reported cardiac failure will be analysed following the '7-day-on-treatment approach' and also considering all events up to individual day of trial completion (refer to Section 7.5.2.1).

#### 7.8.1.2 Analysis of other significant AEs

According to ICH E3 (8), 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
(iii) lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Blinded Report Planning Meeting.

#### 7.8.1.3 AE summaries

##### 7.8.1.3.1 Frequency of patients with adverse events

Frequency of patients with adverse events will be summarised by treatment, primary system organ class (SOC) and preferred term. 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). No inferential analysis is planned for routine safety comparisons.

An overall summary of patients with adverse events will be presented (including patients with any AE, severe AEs, investigator defined drug-related AEs, other significant AEs, AEs leading to discontinuation of trial drug, serious AEs).

The frequency of patients with adverse events will be summarised by treatment, primary system organ class and preferred term. Separate tables will be provided for patients with other significant adverse events according to ICH E3 (8), for patients with serious adverse events, for patients with drug-related adverse events, patients with adverse events leading to treatment discontinuation, patients with fatal adverse events, and by AE intensity.

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

7.8.1.3.2 Adverse event incidence rates, rate ratio and rate difference

In addition to the frequency tabulations, time-adjusted adverse event analyses will be performed for certain types of events (severe AEs, investigator defined drug-related AEs, other significant AEs, AEs leading to discontinuation of trial drug, serious AEs, and adverse events of special interest and further adverse events) by SOC and PT, respectively HLT and PT.

Therefore, the time at risk in patient years is derived as follows:

- Patients with AE:
  time at risk (AE) in days = date of start of AE with specified PT/SOC – study 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 + 7 days and date of death, if applicable.
  Depending on the specific approach for how long adverse events are assigned to treatment, '+30 days' or respectively the date of trial termination may be used for the derivation of time at risk.

Total AE-specific time at risk per treatment group is then derived as:
Time at risk (AE) [years] = 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 = date of start of AE with specified PT in a SOC – start of study treatment + 1.

The AE incidence rate per 1000 patient years can then be calculated as follows:

Incidence rate [1/1000 Patient years (pt-yrs)] = 1000 * number of patients with AE / time at risk (AE) [years].

Further the rate ratio of the incidence rates and the rate differences with the 95% CIs will be presented for hypoglycaemia. The estimates and confidence intervals for incidence rate ratios are based on a Cochran-Mantel-Haenszel option, while estimates and confidence intervals for incidence rate differences are derived as follows:

The rate difference is defined as

$\hat{\delta} = \frac{x}{n} - \frac{y}{m}$, where

x denotes the number of patients with event in treatment 1,

y denotes the number of patients with event in treatment 2,

n denotes the number of patient days at risk with treatment 1 and

m denotes the number of patients days at risk with in treatment 2.

The estimated variance of $\hat{\delta}$ is defined as: $\hat{\text{var}}(\hat{\delta}) = \frac{x \cdot m^2 + y \cdot n^2}{(nm)^2}$.

Assuming normal distribution of $\hat{\delta}$, an approximate 95% confidence interval is given as follows, where $z_{0.975}$ is the 97.5% quantile of the standard normal distribution:

$$CI = [\hat{\delta} \pm z_{0.975} \cdot \sqrt{\hat{\text{var}}(\hat{\delta})}].$$

7.8.1.4 AEs of special interest (AESI)

Analysis of protocol specified AEs (=events of special interest)

According to the CTP the following events are considered as adverse events of special interest (AESI):

- Hypersensitivity reactions such as angioedema, angioedema-like events, and Anaphylaxis (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 events (defined by narrow SMQ 20000003 ‘acute renal failure’)
- Pancreatitis (defined by narrow SMQ 20000022 ’acute pancreatitis’ and PT ’Pancreatitis chronic’)

Patients with these AESIs will be tabulated by treatment group.

Further, patients with pancreatic cancer (defined based on narrow BIcMQ) will be tabulated by treatment group.

For all AESIs, in addition frequency tables for serious adverse events (except for pancreatic cancer as these events are on the always-SAE list), adverse events leading to discontinuation from trial drug, drug related adverse events and adverse events by severity and outcome will be presented.

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

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

Tabulations with frequency of patients with adverse events triggering CEC adjudication (based on specified SMQs according to CEC charter and manually identified) will be provided by treatment/overall, primary SOC and preferred term ~~and result of adjudication~~. 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 strokes, stent thrombosis and all not assessable cases will be presented.

#### 7.8.1.6 Analysis of hypoglycaemic 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 with additional information to assess the intensity of the hypoglycaemic event.

For asymptomatic hypoglycaemia with a measured plasma glucose concentration >=3.0 and <=3.9 mmol/L (>=54 and <=70 mg/dL), if not considered as adverse event, the plasma glucose levels values will be recorded in the CRF.

Analyses on hypoglycaemic events will be performed on the TS.

Different tables will be shown for (i) patients with investigator defined asymptomatic or symptomatic hypoglycaemia reported on the CRF, and (ii) patients with (by the investigator) confirmed hypoglycaemic adverse events and (iii) asymptomatic hypoglycaemia.

The number of patients with investigator defined hypoglycaemia (adverse events) will be tabulated by treatment group. 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.

The number of patients with hypoglycaemic events and investigator defined hypoglycaemia adverse events will be shown by age group and by use of rescue medication (yes, no).

Time to the onset of the first hypoglycaemia and first hypoglycaemia adverse event will be analysed by Kaplan-Meier estimates. A log rank test will be performed. For the details on censoring refer to Section 6.8 and 7.8.1.3.2.

#### 7.8.1.7 Further adverse events

Patients with the following adverse events will be tabulated by treatment group: Malignancies (defined by broad BIcMQ 'Malignancy'), Immunological reaction (only on SOC level, 'Immune System Disorder'). Analysis regarding malignancies as defined by broad BIcMQ 'Malignancy' will be presented separately by narrow SMQ 'Malignant tumours' and SMQ 'Tumours of unspecified malignancy' and overall.

In addition, frequency tables will be provided for the following 'AE-concepts':

- angioedema (defined by narrow SMQ 20000024 'angioedema')
- arthralgia (defined by HLGT 'Joint disorders') (by HLT and PT)
- bullous conditions (by HLT 'bullous condition' and PT)

For all these 'AE concepts' in addition frequency tables for serious adverse events (except for cancer as these events are on the always-SAE list), adverse events leading to discontinuation from trial drug, drug related adverse events and adverse events by severity and outcome 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 PDMAP.

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

A separate independent, blinded, external committee regularly reviews events suspected of acute pancreatitis, chronic pancreatitis, asymptomatic pancreatic hyperenzymemia and pancreatic malignancy and will evaluate whether pre-specified criteria for these adjudication events are met. Details on composition of the CEC, responsibilities and clinical event definitions are provided in the corresponding CEC charter.

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 considering the individual day of trial completion and 'on-treatment + 7 days'.

For CEC confirmed 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 all events up to individual day of trial completion.

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 tumour malignancy as defined in the charter.

The analysis will be performed on all events up to individual day of trial completion.

### 7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards. The process of standardisation and normalisation as well as standard analyses for safety laboratory data are described in the BI guidance for the Display and Analysis of Laboratory Data: (see DM&SM: Display and Analysis of Laboratory Data)(4).

Laboratory measurements will be assigned to trial phases screening/run-in, treatment period of Linagliptin or Glimepiride and post-treatment Linagliptin, post-treatment Glimepiridie, post-study period as described in Section 6.1.1 and 6.7.

Laboratory measurements will be analysed with an on-treatment approach. Further analyses will be provided summarizing on-treatment and post-treatment measurements per treatment group.

Baseline for safety laboratory parameters will be the last available measurement before the start of randomised study drug. The last measurement taken between the first intake of randomised trial drug and seven days after the last administration of trial drug will be analysed as the last value on-treatment. In case of repeated measurements per visit, the worst value will be used.

Only patients with at least one available baseline and on-treatment value will be included in the analysis of an individual laboratory parameter.

Descriptive statistics of continuous laboratory data for safety purposes will be based on normalised values.

Laboratory values will be compared to their reference ranges (and multiples of their reference ranges) and frequency tables will be provided for the number of patients within and outside the reference range at baseline, over time and the last measurement on treatment (continuous parameters). Descriptive statistics for changes from baseline will be provided by treatment group for baseline, over time, the minimum and maximum post baseline and last measurement on-treatment for continuous parameters.

Categorical laboratory data will be presented in frequency tables for baseline, over time and last value on treatment.
Further frequency tables will summarise the number of patients with possible clinically significant abnormalities.

Details on patients with potential Hy's law cases will be listed. For the summaries on patients with elevated liver enzymes see below. A summary will also be created representing the number of patients per treatment group who experienced a doubling in creatinine on treatment compared to baseline.
A shift table from baseline, over time and last value on treatment for eGFR (MDRD) and UACR will be provided.

For these analyses the continuous diabetes related endpoints will be included in the safety analyses with respect to the reference range and in the analysis of possible clinically significant abnormalities, as far as reference ranges and thresholds for potential clinical significance exist.

*Specific considerations for hepatic parameters*

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) >= 3 times upper limit of normal (ULN) with
- total bilirubin >= 2 x ULN and
- alkaline phosphatase <= 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 each liver enzyme elevation above the defined thresholds.

Patients who fulfil one or two of the criteria for ALT/AST or total bilirubin elevations above and have no information available for the remaining parameter(s) at the same timepoint or within the 30 day time windows will be presented as well.

All calculations for the grading will be based on the originally measured laboratory values and the ULNs given by the laboratory, not on normalised values with BI standard reference ranges.

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

- ALT/AST ≥ 3 x ULN
- ALT/AST ≥ 5 x ULN
- ALT/AST ≥ 10 x ULN

Frequency tables of patients with elevated liver enzymes defined by ALT and/or AST, total bilirubin and AP combinations will be provided. A scatter plot of peak ALT against peak total bilirubin will be presented with reference lines for 3 x ULN ALT and 2 x ULN total bilirubin, including an indicator for treatment received.

*Specific renal endpoints*

The frequency of patients with ≥2 fold increase of creatinine from baseline will be presented.

For non-Japanese adult patients, the glomerular filtration rate will be estimated 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 ~~the~~ National Institute of Health) as of October 2012. In the formula for non-Japanese, adult patients the factor of 175 accounts for IDMS traceable determination of creatinine:

- MDRD formula for adult, non-Japanese patients

  $$\text{eGFR (mL/min/1.73m}^2\text{)} = 175 \times (\text{creatinine (µmol/L)} / 88.4)^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black})$$

- eGFR formula for adult Japanese patients
  $$\text{eGFR (mL/min/1.73m}^2\text{)} = 194 \times \text{creatinine (mg/dL)}^{-1.094} \times \text{age}^{-0.287} \times (0.739 \text{ if female})$$

  A patient will be considered to be of Japanese origin if the patient was screened at a site located in Japan and is of Asian Race.

Calculation of age will be done by:

- age = (laboratory assessment date – date of birth + 1) / 365.25.

To support analysis of renal function, eGFR throughout the trial will be categorised according to the following MDRD staging and a shift table will be provided based on standardized observed values. (This shift table will be provided based on a treatment emergent approach and independent of treatment.)

Table 7.8.2: 1 MDRD staging

| **Stage** | **eGFR [mL/min/1.73m$^2$]** | **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 |

Only the albumine / creatinine ratio will be analysed as for urinary albumine and creatinine no normalised values can be derived.
The UACR will be determined (by the laboratory) based on urinary albumine and urinary creatinine measures from the same urine sample as:

UACR (µg/mg crea) = urinary albumine (mg/dL) / urinary creatinine (g/dL)
= urinary albumine (mg/dL) / (8.84 x urinary creatinine (mmol/dL))

For descriptive analyses log10 transformed UACR values will be derived and their change from baseline (as difference between log10 transformed values) will be determined.

A shift table will be provided based on standardized observed values. (This shift table will be provided based on a treatment emergent approach and independent of treatment.)

Table 7.8.2: 2 UACR categorisation

| Stage | UACR | Description | Label for displays |
|---|---|---|---|
| 1 | <30 | Normal UACR | <30 mg/g (normal) |
| 2 | >=30 to <=300 | Microalbuminuria | >=30 to <=300 mg/g (elevated) |
| 3 | >300 | Macroalbuminuria | >300 mg/g (high) |

In addition, a shift table based on the KDIGO categories will be provided from baseline to last value on treatment:

Table 7.8.2: 3 Prognosis of chronic kidney disease by GFR and albuminuria category

| | | UACR (mg/gcrea) | | |
|---|---|---|---|---|
| | | <30 | >=30 to <=300 | >300 |
| eGFR (MDRD) [mL/min/1.73m$^2$] | >=90 | 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 |

*Clinically significant abnormal laboratory values*

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 a clinically relevant decrease, a clinically relevant increase is not defined for this trial.

*Investigation of amylase and lipase*

Following analyses will be performed for amylase and lipase:

- Descriptive statistics for baseline, last value on-treatment and follow-up value
- Descriptive statistics for values over time (on-treatment including values before and after antidiabetic rescue therapy)
- Shift tables for baseline, last value on treatment and maximum value on treatment with categorisation of <LLN, LLN to ULN, ULN to <=3ULN, >=3*ULN and for every week

### 7.8.3 Vital signs

In-clinic pulse rate, SBP and DBP will be summarised by treatment group per week and as change from baseline to each week using descriptive statistics based on the treated set.

### 7.8.4 ECG

Clinically relevant abnormal findings will be reported as AEs or respectively as baseline conditions.
Any findings resulting in an assessment of silent MIs or adjudicated confirmed outcome events will be analysed as described in Sections 7.4 and 7.5. AE analysis will take place as planned in Section 7.8.1.
Heart rate will be summarised by treatment group per week and as change from baseline to each week using descriptive statistics based on the treated set.

### 7.8.5 Others

**Waist circumference**

Simple descriptive statistics over time is planned on the TS, based on observed values (without imputation).

**Modified Rankin scale**

The endpoint of occurrence of or time to first disabling or fatal stroke will be based on the MRS assessment. In case of a missing assessment, the grade will be set to 5, if the patient has not died, otherwise to grade 6. If an MRS assessment is available for a stroke, but has not been confirmed by the adjudication committee, this assessment will not be used for the endpoint of time and occurrence of first disabling or fatal stroke.

As a supporting analysis missing MRS assessments will not be imputed.

**Titration**

Overviews on titration including investigator’s reasons will be presented.

# 8. REFERENCES

1 001-MCG-156_RD-01: "Handling of missing and incomplete AE dates", current version; IDEA for CON.

001-MCG-156_RD-01: "Handling of missing and incomplete AE dates", version 2.0; IDEA for CON.

2 001-MCG-156: "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.

3 001-MCG-159: "Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.

4 001-MCG-157: "Display and Analysis of Laboratory Data", current version; IDEA for CON.

5 001-MCG-157_RD-02: " Handling, Display and Analysis of Laboratory Data: Standard Clinical Evaluation Criteria", current version; IDEA for CON.

6 001-MCS-80-606: " Handling of Non-Compliances in Medicine and QRPE", current version; IDEA for CON.

7 R07-4680: "Modelling Survival Data in Medical Research", Collet D (2003), Chapman and Hall.

8 CPMP/ICH/137/95: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version.

9 CPMP/ICH/363/96: "Statistical Principles for Clinical Trials", ICH Guidline E9; current version.

# 10. HISTORY TABLE

Table 10: 1 History table

| **Version** | **Date (DD-Mmm-YY)** | **Author** | **Sections changed** | **Brief description of change** |
|---|---|---|---|---|
| First | **22-Jan-14** | | None | This is the draft TSAP without any modification |
| Second final | **11-Aug-16** | | Refer to Section 4 | Refer to Section 4 |
| Revised | **16-March-18** | | Refer to Section 4 | Refer to Section 4, Reference for ICH E9 added |

**APPROVAL / SIGNATURE PAGE**

**Document Number: c02152478** **Technical Version Number:4.0**

**Document Name:** 8-01-tsap-core

**Title:** A multicentre, international, randomised, parallel group, double blind study to evaluate Cardiovascular safety of linagliptin versus glimepiride in patients with type 2 diabetes mellitus at high cardiovascular risk.

**Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|
| Author-Statistician | | 19 Mar 2018 08:46 CET |
| Approval-Medical Writer | | 19 Mar 2018 10:31 CET |
| Approval-Trial Clinical Monitor | | 19 Mar 2018 11:47 CET |
| Approval-Project Statistician | | 19 Mar 2018 14:05 CET |
| Approval-Team Member Medicine | | 20 Mar 2018 17:52 CET |

**(Continued) Signatures (obtained electronically)**

| **Meaning of Signature** | **Signed by** | **Date Signed** |
|---|---|---|