Trial Statistical Analysis Plan

c31811315-01

BI Trial No.:	1245-0191
Title:	A phase III, randomised, double-blind, placebo-controlled, parallel group study of Empagliflozin (10 mg and 25 mg) administered orally once daily in combination with insulin with or without up to two oral anti-diabetic agents for 24 weeks in Chinese type 2 diabetic patients with insufficient glycemic control.
Investigational Product(s):	Empagliflozin (BI 10773)
Responsible trial statistician(s):	[redacted] Phone: [redacted]
Date of statistical analysis plan:	12 November 2021 SIGNED
Version:	Final

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2 LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
AESI	Adverse event of special interest
ALQ	Above Limit of Quantification
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ASA	Acetylsalicylic acid
AST	Aspartate transaminase
ATC	Anatomical-Therapeutic-Chemical classification
BI	Boehringer Ingelheim
BIcMQ	BI-customised MedDRA query
BLQ	Below Limit of Quantification
BMI	Body mass index
CEC	Clinical event committee
CRF	Case report form
CT	Concomitant therapy
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBP	Diastolic blood pressure
DKA	Diabetic Ketoacidosis
ECG	Electrocardiogram
eCCr	Estimate creatinine clearance
eGFR	Estimated glomerular filtration rate
EoT	End of treatment
FPG	Fasting plasma glucose
FPI	Fasting plasma insulin
HbA1c	Glycated haemoglobin
HOMA-IR	Homeostatic model assessment - insulin resistance
HOMA-β	Homeostatic model assessment - β
ICH	International Conference on Harmonisation
IPD	Important protocol deviation
IRT	Interactive Response Technology

Term	Definition / description
LOCF	Last observation carried forward
LQ	Limit of Quantification
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
mITT	Modified intention to treat
MMRM	Mixed-effect Model Repeated Measures
MQRM	Medical Quality Review Meeting
MTT	Meal tolerance test
NCF	Non-completers considered failure
OAD	Oral antidiabetic drug
OC	Observed case
OC-AD	Observed cases – all data
OR	Original results
PK	Pharmacokinetics
PPG	Post parandial glucose
PPS	Per protocol set
PT	Preferred term
PD	Protocol deviation
Q1	Lower quartile
Q3	Upper quartile
REML	Restricted maximum likelihood
RPM	Report planning meeting
SBP	Systolic blood pressure
SCR	Screened set
SAE	Serious adverse event
SD	Standard deviation
SDL	Subject data listing
SMQ	Standardised MedDRA query
SOC	System Organ Class
TOC	Table of contents
TSAP	Trial statistical analysis plan

Term	Definition / description
UACR	Urine albumin-to-creatinine ratio
ULN	Upper limit of normal
UTI	Urinary tract infection

3 INTRODUCTION

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

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

SAS® Version 9.4 or later version will be used for all analyses.

4 CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

There are no changes in this TSAP compared to the statistical methods described in the CTP.

5 ENDPOINTS

5.1 PRIMARY ENDPOINT

The endpoint will be used as defined in CTP Section 2.1.2.

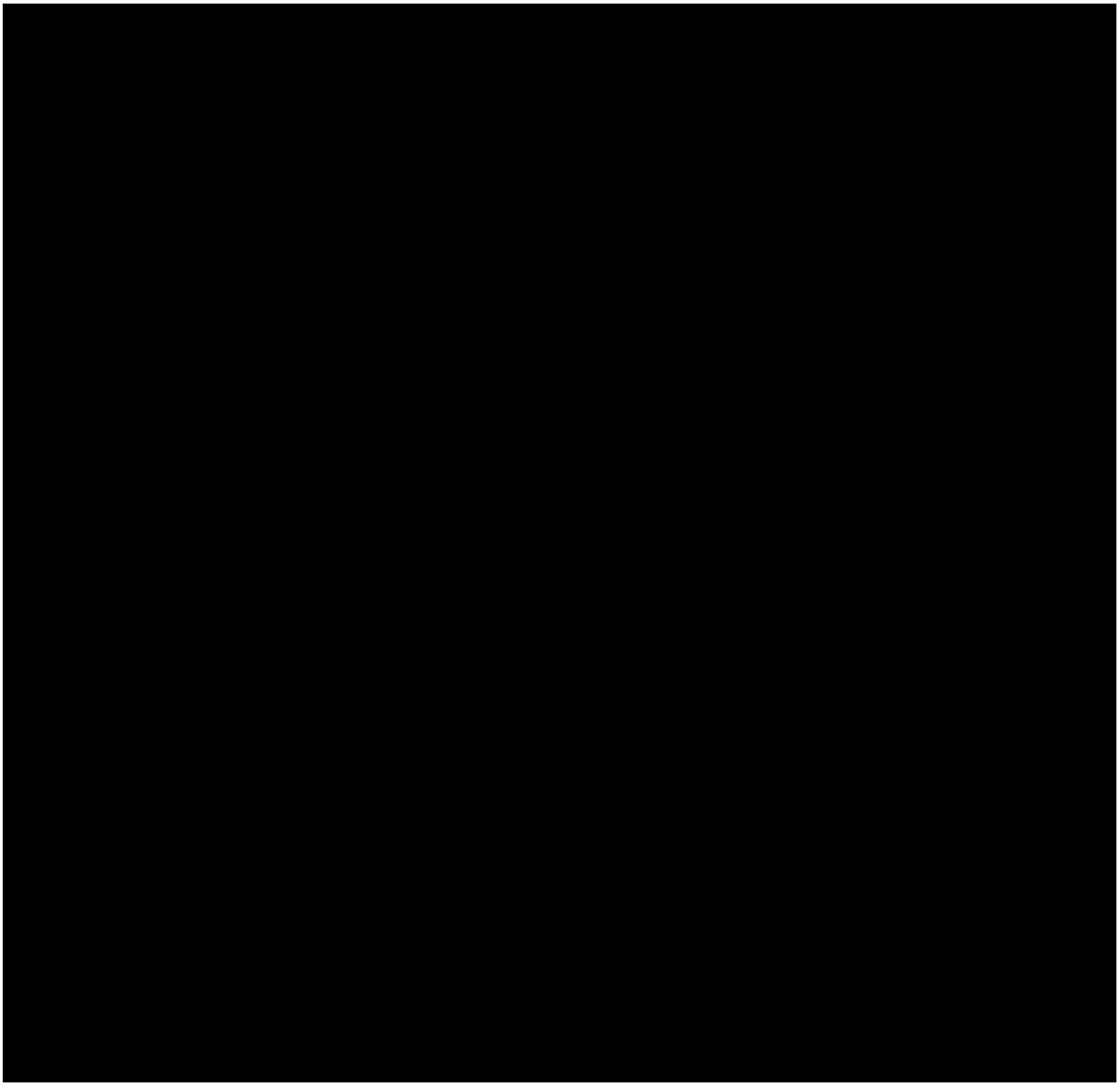
5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

Since there are no key secondary endpoints specified in the CTP, this section is not applicable.

5.2.2 Other secondary endpoints

The endpoints will be used as defined in CTP Section 2.1.3.



6 GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

There will be five treatment study phases in this trial: screening, placebo run-in, double-blind study treatment phase (with empagliflozin and matching placebo), post-treatment and post-study.

Table 6.1:1 Treatment regimens / study intervals

Label	Interval	Start date	Start time
Screening	Screening	Date of informed consent	00:00
Run-in	Run-in	Date of first administration of run-in medication	Time of first administration of run-in medication, 12:00 if missing
Placebo/ Empagliflozin 10mg/ Empagliflozin 25mg	Treatment	Date of first administration of double-blind study medication	Time of first administration of double-blind study medication, 12:00 if missing
Post-treatment	Post-treatment	Date of last intake of study medication +X+1 (see definition of X below)	00:00
Post-study	Post-study	Start date= Last contact date, defined as the maximum of (Trial completion date, last study medication intake + X) +1	00:00

The purpose of the definitions above is to describe all the different study/treatment intervals, to which a patient can be assigned during the course of the trial. Note that the term “treatment regimen” can also cover time periods with no active treatment.

In general, for safety analyses, data up to 7 days after last study medication intake will be considered as on-treatment for AEs, 3 days for laboratory values and 1 day for pulse rate: To clarify:

- Pre-treatment: before the first intake of any study medication.
- On treatment: begins from the date of first administration of the initial randomised study medication to last intake of study medication + X days (inclusive), where X=1, 3 or 7 days for pulse rate, safety laboratory, and AE respectively.

- Post-treatment: begins from the last intake of study medication + X days + 1 day up to the last contact date (inclusive). Last contact date is defined in Table 6.1:1. Post treatment period is not applicable for patients with last contact equal to 'last intake + X + 1 days' where X is 1, 3, or 7 days as previously specified.
- Post-study: From day after last contact defined in Table 6.1:1. If period starts at end of on-treatment period, then post-treatment period is not applicable.

For efficacy analyses, data up to 7 days after last treatment intake will be considered as on-treatment for HbA_{1c} and waist circumference and 1 day for all other efficacy endpoints. For further details, see Table 6.7:1.

The efficacy analyses will follow the intention-to-treat (ITT) principle in assigning patients to treatment groups, i.e. patients will be analysed in the treatment group they were randomized to.

Safety analyses will assign patients to the treatment group as initially treated.

In addition, AEs with an onset during the time of the incorrect study treatment will be listed separately.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Not all important protocol deviations (IPDs) will generate exclusion from the per protocol population. Deviations that lead to exclusion from analysis populations are indicated as such in Table 6.2:1.

IPD definitions will include consideration of, among others, important deviations of entry criteria, treatment non-compliance, treatment dispensing errors, prohibited concomitant medication and premature unblinding.

The decision about which protocol deviation (PD) could generate exclusion from analysis sets will be taken during the course of the study and finalised at the last report planning meeting (RPM), i.e. before unblinding.

The following table defines the different categories of IPDs. The final column describes which analysis set will the patients be excluded from.

Table 6.2:1 Important protocol deviations

IPD Code	IPD Category & brief description	Example/Comment	Exclude from which analysis set
A	Entrance criteria not met		
A1	Target indication not met		
A1.01	No type 2 diabetes	Inclusion criterion #2 not met	PPS
A1.02	Antidiabetic background therapy not as required	Inclusion criterion #3 not met	PPS
A2	Inclusion criteria not met		
A2.01	HbA1c out of range	Inclusion criterion #4 not met	PPS
A2.02	Age out of range	Inclusion criterion #1 not met	None
A2.03	Body mass index out of range	Inclusion criterion #6 not met	None
A2.04	Fasting C-peptide out of range	Inclusion criterion #5 not met	None
A3	Exclusion criteria met		
A3.01	Uncontrolled FPG level	Exclusion criterion #4 met	None
A3.02	Additional background therapy	Exclusion criterion #2, #9, #11, #12, #14 met	PPS
A3.03	Relevant concomitant diagnoses	Exclusion criterion #1, #6, #7, #20, #23 met	None
A3.04	Bariatric or other relevant gastrointestinal surgery within the past two years	Exclusion criterion #8 met	PPS
A3.05	Blood dyscrasias or any disorders causing hemolysis or unstable red blood cell count	Exclusion criterion #15 met	PPS
A3.06	Indication of liver disease	Exclusion criterion #13 met: ALT or AST or alkaline phosphatase > 3xULN at V1	None
A3.08	Treatment with protocol excluded anti-obesity drugs	Exclusion criterion #10 met	PPS
A3.09	Renal insufficiency or renal impairment (assessed by eGFR)	Exclusion criterion #3 met	PPS
A3.10	Treatment with protocol excluded systemic steroids or recent change in thyroid hormone dose	Exclusion criterion #16, #17 met	PPS
A3.11	Relevant alcohol or drug abuse and other conditions affecting study compliance	Exclusion criterion #18 met	PPS
A3.12	Any other clinical condition unsafe for participation that would jeopardise patient safety while participating in this clinical trial	Exclusion criterion #5, #22, #24, #25, #26 met	None
A3.13	Renal insufficiency or renal impairment (assessed by eCcR)	Exclusion criterion #19 met	PPS
A3.14	Known allergy or hypersensitivity to empagliflozin or other SGLT-2 inhibitors	Exclusion criterion #21 met	None

Table 6.2 :1 Important protocol deviations (cont.)

IPD Code	IPD Category & brief description	Example/Comment	Exclude from which analysis set
A3.15	Women who are pregnant, nursing, or who plan to become pregnant while in the trial.	Exclusion criterion #27 met	None
B	Informed Consent		
B1	Informed consent not available/not done	Inclusion criterion #7 not met	All
B2	Informed consent too late	Date of informed consent not obtained prior to any study related procedure. Minimum requirement <= date of Visit 1/date of any study procedure	None
C	Trial medication and randomisation		
C1.01	No study medication taken	Patient randomised according to IRT system but no medication taken according to eCRF/IVRS	TS, mITT, PPS
C1.02	Incorrect trial medication taken	Wrong medication taken, i.e. eCRF kit number does not match kit number assigned by IVRS* [Needs unblinding to determine if kit was same medication as assigned or not – so, will be finally judged after DBL]	PPS
C2.01	Treated without randomisation	Patient treated according to eCRF, but not randomised according to IVRS	mITT, PPS
C3.01	Non-compliance with study drug intake	Overall study compliance outside 80% and 120% (exclusive) or study treatment compliance below 80% in the last visit interval before primary endpoint assessment. [Final decision at the DBL meeting based on medical judgement.]	PPS
C4.01	Medication code broken at site without just cause	Medication code was broken for no valid reason.	PPS
D	Concomitant medication		
D2.01	Background antidiabetic therapy not taken as specified in the protocol	Review of eCRF for prohibited medication and check whether other than protocol defined rescue medication was taken* [Final decision at the DBL meeting based on medical judgment]	PPS
E	Missing data		
E1.01	No baseline HbA1c value	No valid baseline HbA1c value	mITT, PPS

6.3 SUBJECT SETS ANALYSED

The following analysis sets will be defined for this trial.

- *Screened patients set (SCR):*

This patient set includes all patients screened for the trial, with informed consent given and who completed at least one screening procedure at Visit 1.

- *Treated set (TS):*

  This patient set includes all patients who are randomized and treated with at least one dose of study medication. The assignment of patients to treatment groups will be based on the actual first study medication intake in the double-blind treatment period. The TS is the basis for safety analyses.

- *Modified Intention-to-Treat (mITT) set:*

  This patient set includes all randomized patients who are treated with at least one dose of the study medication and have a baseline HbA1c assessment and at least one on treatment HbA1c value. The assignment of patients to treatment groups will be based on the planned randomised study medication at the time of randomisation. The primary efficacy analysis will be performed on mITT set with patients who have a baseline HbA1c and at least one on treatment HbA1c measurement during randomized period.

- *Per-protocol set (PPS):*

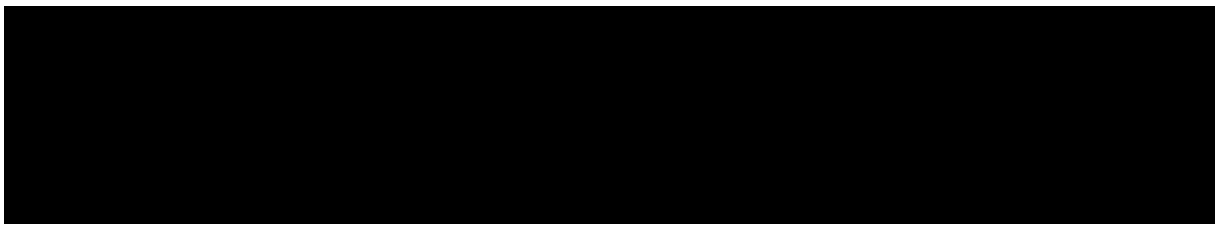
  This patient set includes all patients in the mITT set who do not have any important protocol deviations (iPDs) which can be expected to have a distorting influence on the assessment of the primary endpoint. iPDs are detailed in Table 6.2:1.

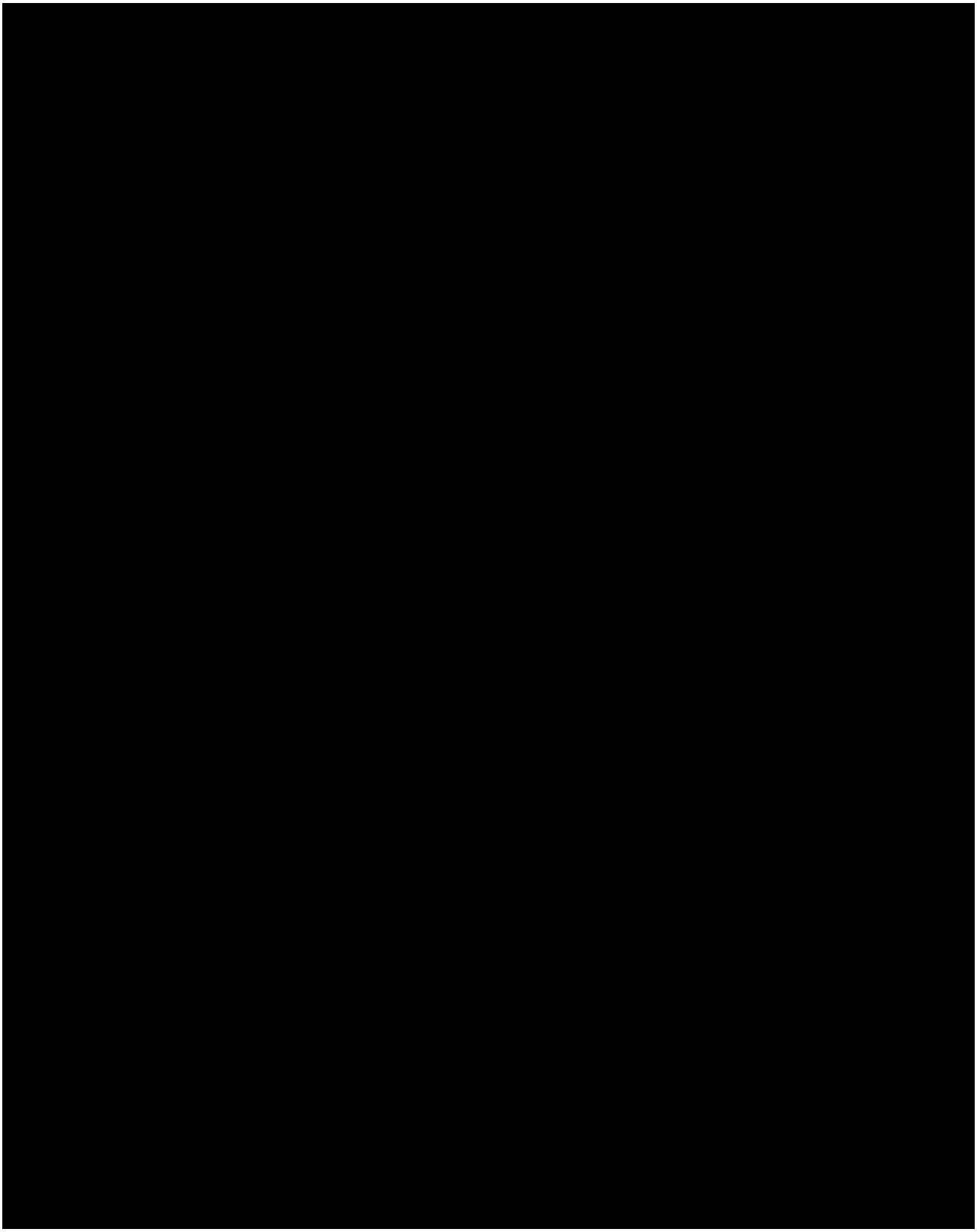
In Table 6.3:1 the data sets which are to be used for each category class of endpoint are illustrated.

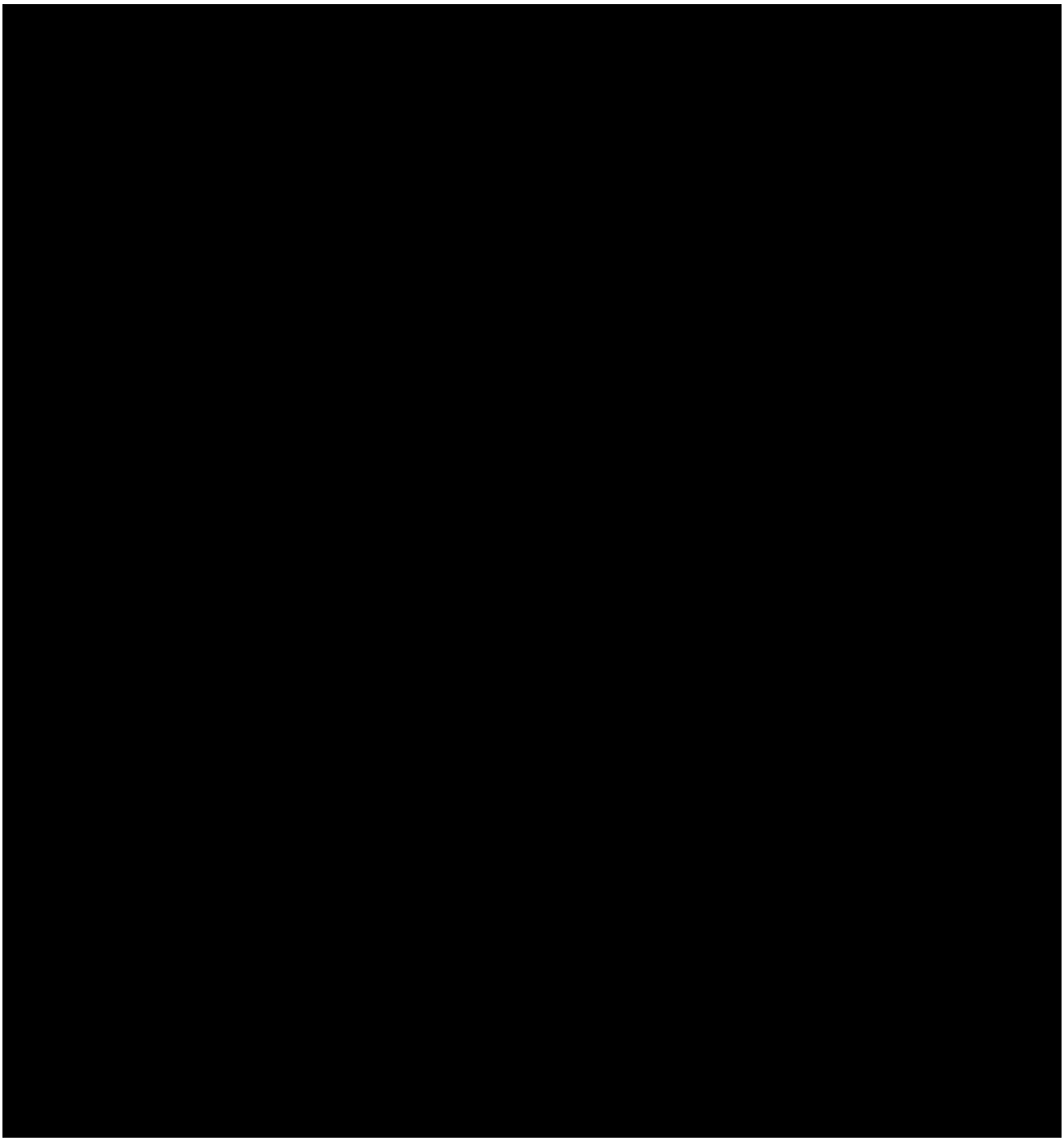
Table 6.3:1 Summary of which data sets will be used for which class of endpoints

Class of endpoint	Subject sets			
	SCR	TS	mITT	PPS
Disposition	OR			
Demographics		OR		
Baseline variables		OR		
Background total daily insulin dose/concomitant medications		OR		
Concomitant diagnoses/relevant medical history		OR		
Exposure/ compliance		OR		
Primary endpoints			Primary analysis (OC) & Secondary analyses (MI, OC-AD)	OC
Secondary and further efficacy endpoints-continuous			OC, OR#	
Secondary and further efficacy endpoints-binary			NCF	
Subgroup analyses			OC	
Safety endpoints		OR		

SCR=screened set, mITT set=modified intention-to-treat set, PPS=per protocol set, TS=treated set; patient sets are defined in Section 6.3
OR=original results, OC=observed cases on treatment, OC-AD=observed cases-after discontinuation and rescue therapy, NCF=Non-completers considered failures. Handling of missing data is described in Section 6.6
#OR results will only be presented for time to first rescue medication and number of patients with rescue.







6.5 POOLING OF CENTERS

This section is not applicable because center is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Based on the different reasons of patients' data missing for different endpoints, various methods will be used to assess the impact of missing data on the efficacy endpoints of this trial, depending upon the type of the endpoint (see Table 6.3:1).

6.6.1 Definition of rescue therapy for censoring

For some of the imputation methods defined below, values after first rescue medication will be set to missing. In this context, the following three situations are defined as use of rescue medication:

- Additional antidiabetic medication used for ≥7 consecutive days
- For insulin, a change of >10% (increase/decrease) from the last dose recorded prior to the baseline visit (Visit 3) taken for ≥7 days
- For OADs, a change in dose (increase/decrease) compared with the baseline dose for ≥7 consecutive days

This approach will be used when considering which data to exclude from the OC analyses.

6.6.2 Methods of data selection

Original result (OR) analysis

Original result analysis implies the analysis of data exactly as observed. OR analysis will be performed on endpoints that are either not affected by patients' antidiabetic rescue medication use or if it is not meaningful to apply any imputation rule on them for replacing the missing values.

Observed cases (OC) analysis

For all efficacy endpoints, it is planned to analyse only the available data that were observed while patients were on treatment, i.e., excluding the missing data. In other words, OC analysis will be performed and missing data in this analysis will not be replaced.

For all efficacy endpoints, this OC-technique will set all values measured after antidiabetic rescue medication taken to missing (antidiabetic rescue medication as defined in section 6.6.1).

Observed cases analysis including data after treatment discontinuation and rescue therapy (OC-AD)

To mimic an intent-to-treat (ITT) analysis, post-treatment as well as post-rescue measurements may also be included. This will be done as a secondary analysis of the primary endpoint with OC as the imputation rule.

Non-completers considered failure (NCF)

For binary endpoints, like a treat to target response of HbA1c <7.0%, a conservative method to replace missing values is to consider them as "failures". Missing data due to early discontinuation per the completer definition will be replaced as "failure" (i.e. HbA1c ≥ 7.0%) up to the planned final visit to be reached by all patients. Values obtained after rescue medication was started are also replaced as "failure".

A multiple imputation (MI) approach will also be used as a sensitivity analysis for the primary endpoint. Further details can be found in Section 7.4.2.

6.6.3 Safety and other variables

Missing safety data will not be replaced.

An analysis of the changes from baseline to the last available value under treatment and the minimum and maximum post baseline will be determined for quantitative safety laboratory variables.

6.6.4 Missing dates and times

Missing or partial date information for AEs will be replaced according to general BI rules described in the BI guidance for handling of missing and incomplete AE dates (1).

If the date of first drug administration is missing but the patient was randomised, 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.

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 08:00 o'clock in the morning.

As a general rule, a missing drug stop date will be imputed according to the following principles:

- If an End of Treatment (EoT) visit, visit 8, is documented, it should be the date of the EoT visit
- If the date is incomplete with only month and year and the EoT visit is missing, it should be the first day of the following month.
- If the patient is lost to follow-up, it should be the date of the last visit + the longest treatment duration based on drug supply + 1 day.
- If a patient died during the course of the trial and no additional information about drug stop date are available, the date of death will be used as drug stop date assuming that the patient took the medication until the day of death.
- All other cases need to be assessed by the trial team on an individual basis, trying to use the points above as guidance.

For partial start and stop dates for concomitant therapies (CT) and additional antidiabetic drugs, the following derivations will be used to impute 'worst case' values.

- If the day of the end date is missing then the end date is set to last day of the month.
- If the day and month of the end date are missing then end date is set to 31st December of the year
- If the day of the start date is missing the start date is set to first day of the month
- If the day and month of the start date are missing then the start date is set to 1st January of the year.

All other cases need to be assessed by the trial team on an individual basis, using the above points as guidance.

In case of missing visit date for a compliance record, the following hierarchy will be used to select a date to impute the missing visit date:

- The visit date registered in the IRT system
- The date of the vital sign measurement for the same visit

- The date of the safety laboratory sampling for the same visit

All other cases need to be assessed by the trial team on an individual basis, using the above points as guidance.

6.6.5 Values below/above limits of quantification

For biomarkers (C-peptide, insulin) reported values below the limit of quantification (BLQ) will be replaced with 2/3 times lower LQ. This is approximately the median of the expected 'true' value if the biomarker follows a normal distribution. The inverse of the factor 2/3 will be used to replace values above the upper LQ, resulting in 1.5 times upper LQ. The analysis dataset will contain flags to indicate that the value was BLQ and a variable for the value of the LQ. With this approach, even a change of the method with different LQs can be handled within a trial. The number of samples above and below the limit of quantification will be included in the biomarker tables.

6.6.6 HOMA-β

Please refer to CTP Section 5.4.1 for the definition of HOMA-β. For FPG values <3.5 mmol/L, HOMA-β assumes extreme negative values for FPG values only slightly smaller than 3.5. For FPG=3.5 mmol/L, the ratio is not defined. Therefore, HOMA- β will only be calculated for FPG>3.5 mmol/L and set to missing for lower values.

6.7 BASELINE, TIME WINDOWS, AND CALCULATED VISITS

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

Measurements taken prior to the first intake of randomised study medication will be considered pre-treatment values. Pre-treatment values will be assigned to a visit according to the nominal visit number as recorded on the eCRF or as provided by the laboratory.

In general, 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 medication will be considered on-treatment values if they have been obtained up to end of the parameter specific follow-up period as defined in Table 6.7:1 below and will be assigned to the randomised study medication for efficacy analyses and to the first study medication taken for safety analyses.

Table 6.7:1 Endpoint specific follow-up period for the assignment to treatment phase

Endpoint	Last day of assignment to treatment phase (days after study medication stop date)
Efficacy	
HbA_{1c}	7
FPG	1
Body weight	1
Blood pressure (systolic, diastolic)	1
PPG	1
MDG	1
C-peptide	1
Biomarkers of insulin resistance and secretion	1
Waist circumference	7
Safety	
Adverse events	7
Safety laboratory measurements	3
Pulse rate	1

Measurements taken after the end of the endpoint specific follow-up period and after the last intake of study medication will be considered post-treatment values.

On-treatment efficacy and safety measurements 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 medication (see Table 6.7:2).

Table 6.7:2 Time windows for on-treatment efficacy measurement scheduled for each on treatment visit

			Time window (actual days on treatment)	
Visit number	Visit label	Planned days	Start	End[A]
3	Baseline	0	NA	1[B]
4	Week 4	28	2	42
5	Week 8	56	43	70
6	Week 12	84	71	105
7	Week 18	126	106	147
8	Week 24/EOT	168	148	Study medication stop date + X days

[A] In case of premature discontinuation of the study medication an early EoT visit has to be performed. If such an EoT Visit falls into the time window of a previous visit, measurements will be assigned to this previous visit and the visit value will be determined as described below. In this case the time window for the visit that includes the early EoT visit will end X days after the study medication stop date, including Day X. The definition of X is endpoint specific, cf. Table 6.7:1. Patients will then be asked to continue in the study according to the visit schedule. Off-treatment measurements will be assigned to visits in the same manner. No time window for optional visit is planned.

[B] Only values taken prior to the start of treatment with randomised study medication can be considered baseline values. Time windows will be used for assignment of measurements to scheduled visits.

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

- If first intake of study medication shows a large delay by e.g. more than one week after the date of randomisation, a measurement taken four weeks after randomisation rather reflects the drug effect after three weeks than after four weeks and thus may underestimate the treatment effect at this visit.
- With large delays of the introduction of study medication after the randomisation, the time window for the first on-treatment visit could include times the patient was not yet on study medication.

The time window for the first visit after randomisation starts on the day after the first intake of study medication. This maximises the number of measurements used in by visit analyses may lead to an underestimation of the treatment effect at the first visit for parameters that react slowly on treatment.

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 (Table 6.7:1).

Repeated and unscheduled efficacy and safety measurements will be assigned to the nominal visits and listed in the SDL according to the time windows described above. Only one observation per time window will be selected for analysis at an on-treatment 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 an observation is available on the last day of treatment, this observation will be preferably selected over any later observation that is still within the time window (not applicable for standard laboratory summaries). 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.

Data prior to randomisation will be based on nominal visits and time windowing will not be applied. For these time points, data from the scheduled visit will always be selected if they are collected correctly. Unscheduled visits will only be considered if no correct data from the scheduled visit is available. If no correct data from a scheduled visit is available and multiple unscheduled correct values are available for a visit, the first correct value will be selected.

7 PLANNED ANALYSES

Disposition of the patient population participating in the trial will be analysed by treatment groups and presented in the clinical trial report as a frequency-distribution. The number of patients participating in the study will also be analysed by treatment group and presented as a frequency distribution.

A frequency of patients with iPDs, also summarised by whether the iPD led to exclusion from the PPS, will be presented by treatment group for treated set. The frequency of patients in different analysis sets will also be presented for each treatment group.

For in-text tables presenting descriptive analysis of the endpoints and other variables (analysed in original scale), the set of summary statistics is: N (number of patients with non-missing values), mean, standard deviation (SD).

For end-of-text tables, the set of summary statistics is: N (number of patients with non-missing values) / Mean / SD / Min / Q1 (lower quartile) / Median / Q3 (upper quartile) / Max.

For the in-text, end-of-text and appendix tables presenting descriptive analysis of the endpoints and other variables (analysed on logarithmic scale), the respective summary statistics (e.g., gMean, gCV, etc.) will be used.

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" (2). Patient level results for the calculated endpoints HOMA-IR will be presented to one decimal place. HOMA-β will be presented as full integers. The summary statistics of these parameters will follow the aforementioned guideline.

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 if and only if there are actual missing values. Percentages will be based on all patients in the respective patient set whether they have non-missing values or not.

In all specified statistical analyses, treatment comparisons will be made between each randomised empagliflozin group (10mg and 25mg) and placebo.

7.1 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Descriptive analysis of the following demographic variables measured at baseline will be presented:

Sex, age (years) (continuous and categories), race, ethnicity, BMI (kg/m^2) (continuous and categories), height (cm), smoking history and alcohol status, time since diagnosis of diabetes (years) (continuous and categories), background medication, background insulin type, eGFR MDRD (mL/min/1.73 m^2) (continuous and categories) and UACR (mg/g) (continuous and categories).Categories for baseline characteristics are defined in Table 6.4:1.

Descriptive analysis of the following variables measured at baseline will be presented:

HbA1c (%) (continuous and categories), FPG (mg/dL)(continuous and categories), weight (kg) (continuous and categories) , waist circumference (cm), blood pressure (mmHg) (categories), fasting serum C-peptide, HOMA-IR and HOMA-β.

Both demographic and baseline characteristics tables will be presented on treated set by treatment groups.

A summary of the number of patients in each randomisation stratum per treatment will also be shown. This will be based upon the data received from the IRT provider. Analyses will be based on actual information collected via the CRF / central laboratory, not via IRT.

7.2 CONCOMITANT DISEASES AND MEDICATION

Descriptive statistics are planned for this section of the report using the treated set. Concomitant medication use will be summarised by Anatomical-Therapeutic-Chemical classification level 3 (ATC3) and preferred name. Summaries will be presented for concomitant therapies taken during screening, taken during randomised treatment and those taken at baseline. Separate summaries of antidiabetic treatment at enrolment, use of antihypertensives, acetylsalicylic acid (ASA) or lipid lowering drugs at enrolment by preferred name will be presented. The display categories and defining ATC levels and ATC code are shown in Section 9.1.

Concomitant diseases will be summarised by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). Relevant diabetic medical history by treatment group will also be presented. Both summaries will be presented using the treated set.

7.3 TREATMENT COMPLIANCE

Descriptive statistics are planned for this section of the report. The number and percentage of patients with overall compliance will be reported. Overall compliance will be calculated as a weighted average of reported compliance. The sum of all reported compliance over the planned visits (disregarding run-in) will be divided by the total duration (until last visit where medication is returned). The treated set will be considered. Refer to Section 6.6.4 for how to handle a single missing visit date for a compliance record, in the overall compliance calculation.

If compliance is missing at more than one on-treatment visit (>1), the overall compliance will be set to missing.

If a patient prematurely discontinues from treatment, compliance will be calculated until last study medication intake. Missing compliance values for off-treatment visits will not be considered in the calculation for overall compliance.

7.4 PRIMARY ENDPOINT

The primary endpoint in this trial is the change in HbA1c (%) from baseline after 24 weeks of treatment.

7.4.1 Primary analysis of the primary endpoint

The primary analysis is a restricted maximum likelihood (REML)based mixed model repeated measures (MMRM) approach comparing the change from baseline in HbA1c after 24 weeks of treatment. The analysis will be performed on the mITT set (OC) with treatment assignment as randomized and include on-treatment HbA1C only. If a patient misses a visit,

the missing data will not be imputed. The mixed effect model will handle missing data based on a likelihood method under the "missing at random" assumption.

The statistical model will be:

Change in HbA1c (%) from baseline to the end of 24 weeks

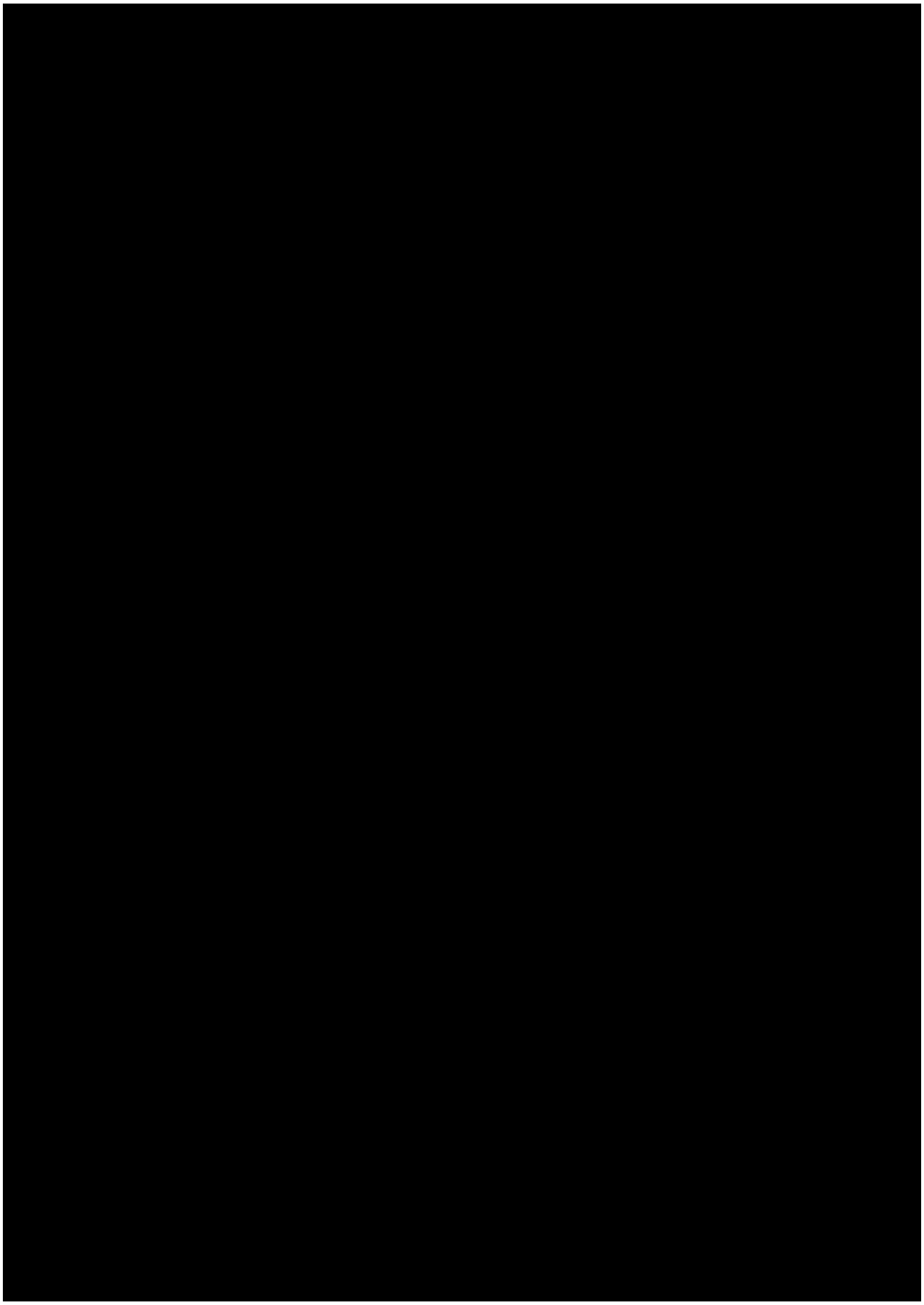
= overall mean + treatment + background therapy + baseline HbA1c + baseline eGFR + visit + treatment-by-visit interaction + baseline HbA1c-by-visit interaction + random error.

The analysis will include treatment (Empagliflozin 10 mg, Empagliflozin 25 mg, placebo), background therapy (insulin only, insulin with OADs), and visit as fixed classification effects, baseline HbA1c and baseline eGFR as the linear covariates, treatment by visit interaction, and baseline HbA1c by visit interaction.

For each patient, the error terms from all the visits represent the within-patient variability and are assumed to follow a multivariate normal distribution with an unstructured covariance matrix. The random error is assumed to be normally distributed with mean 0 and unknown variance σ_j^2. If an unstructured (co)variance structure fails to converge, the following structures will be tested in order: compound symmetry, variance components and Toeplitz. The (co)variance structure converging to the best fit, as determined by Akaike's information criterion, will be used.

The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom and adjust standard errors.

A hierarchical testing sequence will be used as defined in the protocol. Superiority will be tested using the p-value of the treatment effect (least-squares means) and a two-sided 95% confidence interval for the treatment difference.



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7.4.4 Supplementary analysis

The same MMRM analysis method as described in Section 7.4.1 will be applied on the mITT set (OC) to compare the change from baseline in HbA1c after 24 weeks of treatment between pooled Empagliflozin doses (10 mg q.d. and 25 mg q.d.) and placebo. The model includes treatment (Empagliflozin, placebo), background therapy (insulin only, insulin with OADs), and visit as fixed classification effects, baseline HbA1c and baseline eGFR as the linear covariates, treatment by visit interaction, and baseline HbA1c by visit interaction.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

This section is not applicable as no key secondary endpoints have been specified in the CTP.

7.5.2 Other secondary endpoints

The secondary endpoints for this study are described in CTP Section 2.1.3.

7.5.2.1 Responder analysis

The HbA1c responder analyses will be performed on mITT (NCF) by determining the percentage of patients that fulfil responder criteria (for the definition of treat to target and relative efficacy response, see Section 5.2.2) by treatment. Non-completers considered failures (NCF) imputation-technique will be used to impute the missing data for this analysis strategy.

Each analysis will consist of a tabulation by treatment of the percentage of patients meeting the response criteria along with 95% exact confidence intervals for the percentage. Additionally, a logistic regression model with treatment, background therapy, baseline eGFR and continuous HbA1c will be fitted on the binary response variable to calculate the estimate of the odds ratio of each dose to placebo. Estimate of odds ratios and 95% confidence intervals (Wald) will be presented along with the p-values for each comparison.

7.5.2.2 Change from baseline in body weight, SBP, DBP and FPG

The MMRM models constructed for the primary endpoint will also be conducted for continuous secondary endpoints of change from baseline in body weight, SBP, DBP and FPG at week 24. Analyses will be performed on the mITT set (OC). The model will include the baseline value of the corresponding endpoint and its interaction with visit as covariates.

7.5.2.3 Change from baseline in 2-hour PPG

A valid 2-hour PPG sample has to be taken between 1:50 and 2:10 h after the start of the meal in the MTT . To be eligible for use as baseline, the 2-hour PPG sample has to be taken prior to the intake of the first dose of the randomised study medication.

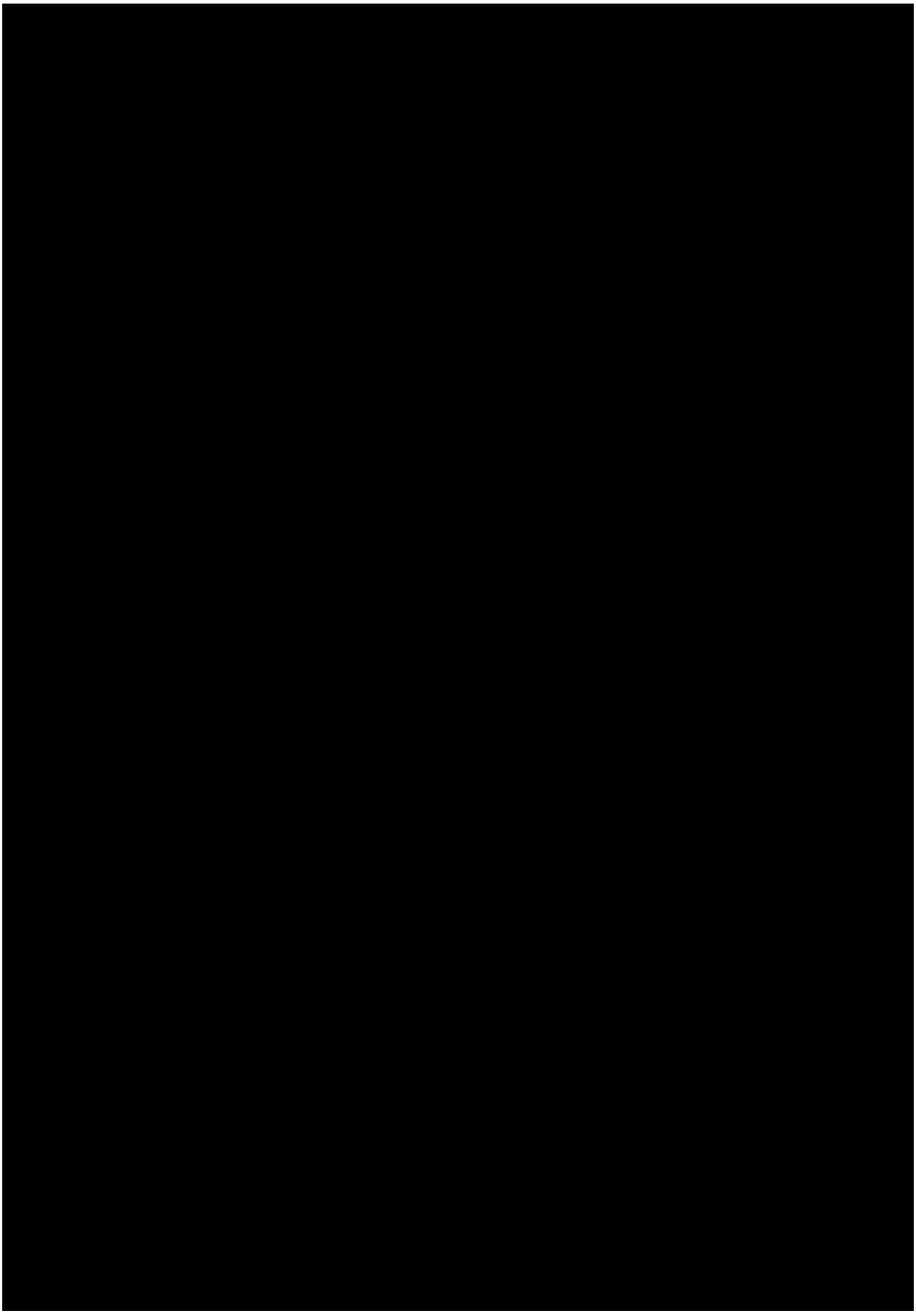
For continuous secondary endpoint of change from baseline in 2-hour PPG at week 24, ANCOVA will be performed based on the mITT (OC) set. The respective model will include treatment and background therapy as classification effects, baseline HbA1c, baseline PPG and baseline eGFR as the linear covariates.

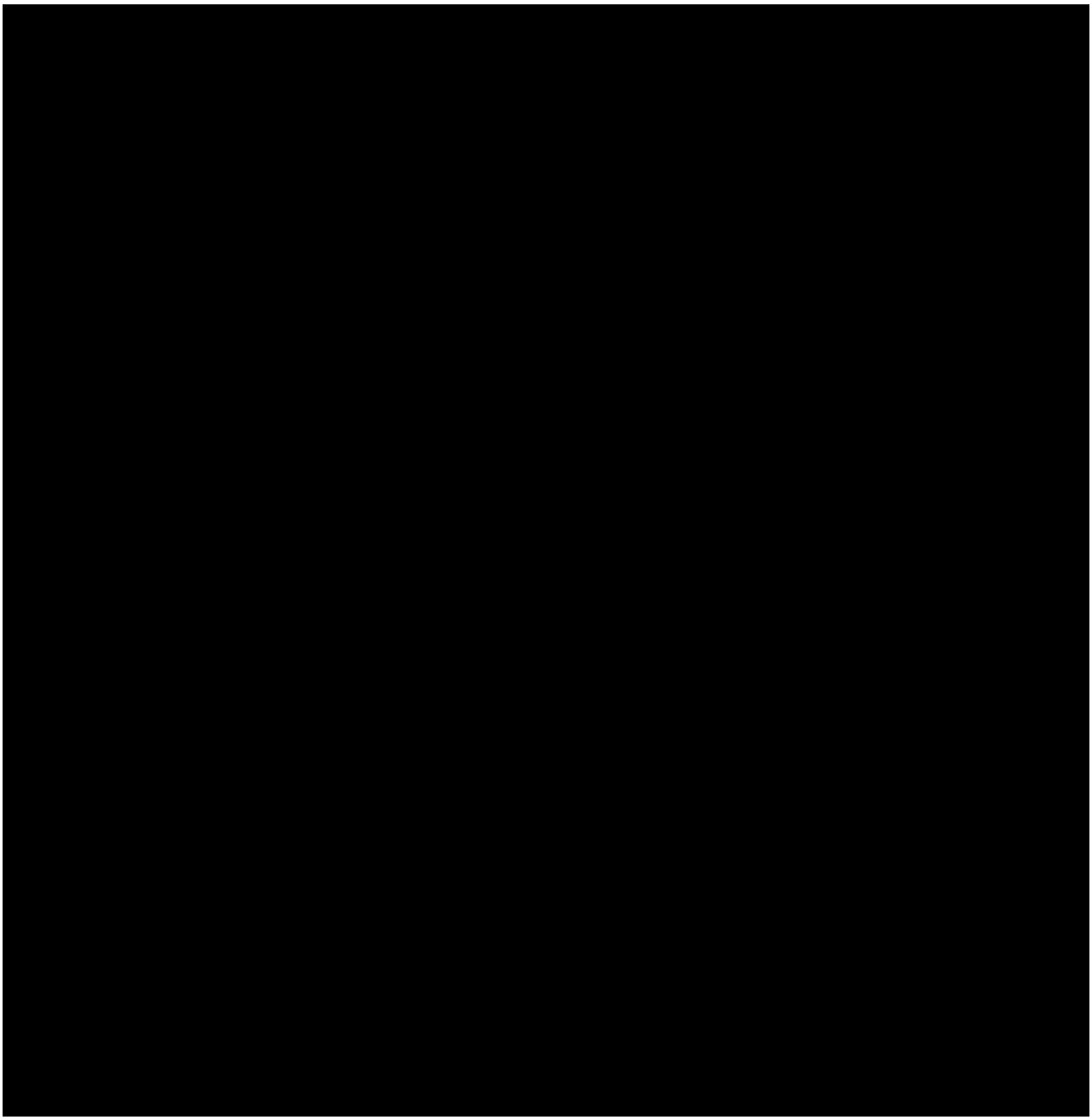
7.5.2.4 Occurrence of hypoglycemic events and adjudicated DKA events

Number of patients with confirmed hypoglycemic events and adjudicated DKA events will be tabulated in frequency tables by treatment groups. Logistic regression will be performed to compare the occurrence of confirmed hypoglycemic events and adjudicated DKA events between empagliflorin groups (10 mg and 25 mg, respectively) and placebo. Odds ratios and their respective 95% confidence intervals and p-values will be obtained. Baseline HbA1c value and treatment will be included in the model. Time to the onset of the first event will be analysed by Kaplan-Meier estimates.

Summaries of hypoglycemic events will include total number of hypoglycemic events, descriptive hypoglycemic event rate, number of episodes per patient, severity and intensity of the worst episode, action taken, minimum glucose level of worst episode, and time to onset of first episode. Hypoglycemic events will also be summarised by background medication, type of insulin, age group and use of rescue medication.

Different tables will be shown for (i) patients with investigator defined asymptomatic or symptomatic hypoglycemia reported as AE or non-AE, and (ii) patients with confirmed hypoglycemic adverse events, i.e. hypoglycemic adverse events that had a plasma glucose concentration ≤ 70 mg/dL or required assistance.





7.7 EXTENT OF EXPOSURE

A descriptive statistics table with mean, SD, median and range of the number of days a patient was on treatment will be provided for the treated set. The tables will also provide the sum total of the time (in years) that all patients pooled together were on treatment. A separate listing will be created of any patients that switched treatment at any time indicating exposure to each treatment.

A frequency table of number and percent of patients belonging to each categorical range of exposure weeks will be provided as well. The following are the categories of exposure-ranges (in weeks):

>0 to 4 weeks, >4 to 8 weeks, >8 to 12 weeks, >12 to 18 weeks, >18 to 24 weeks, >24 weeks.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

7.8.1 Adverse events

AEs will be coded using the latest version of the MedDRA coding dictionary at database lock.

Definitions of Boehringer Ingelheim customized MedDRA Queries (BIcMQs) for new MedDRA versions are maintained by the BI dictionary maintenance group.

Any clinically significant new finding in the physical examination, vital signs (blood pressure and pulse symptoms) and in the 12-lead ECG starting after visit 3 (randomisation visit) will be considered as an AE and will be reported as such.

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 the first step, AE occurrences, i.e. AE entries on the CRF, 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. Exceptions: (i) Hypoglycemic events are only collapsed if they occur within 12 hours of each other. The 12-hour period will begin with the first hypoglycemia onset time. If another event occurs outside this initial 12-hour window a new period for collapsing will begin. (ii) Genital infection events will not be collapsed if they are representative of different types (i.e. fungal balanitis or vulvovaginitis versus other than fungal balanitis or vulvovaginitis). (iii) Sepsis events will not be collapsed if they are representative of different sources of infection (i.e. urinary tract (urosepsis) versus other than urinary tract)
- 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’.

7.8.1.1 Assignment of AEs to treatment

In general, 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 drug intake will be assigned to the on treatment. All adverse events occurring before first drug intake will be assigned to 'pre-treatment' and all adverse events occurring

after last drug intake + 7 days will be assigned to 'post-treatment' (for listings only). For details on the treatment definition, see Section 6.1.

In general, in-text AE tables will only present AEs assigned to the first treatment taken except drug-related AEs which will be presented as actual treatment taken at each given timepoint. End-of-text tables will display in addition AEs observed 'pre-treatment' (including AEs observed during screening and placebo run-in regardless of treatment group). AEs and serious adverse events (SAEs) are assigned to the following phases: Screening, placebo run-in, each treatment group, post-treatment for each treatment group will be listed.

7.8.1.2 Analysis of other significant AEs

Other significant AEs will be reported and summarised according to ICH E3 criterion (3). Thus, AEs classified as 'other significant' will include those non-serious adverse events with:

- ‘action taken = discontinuation’ or ‘action taken = reduced’, or
- Marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Medical Quality Review meeting or Blinded Report Planning Meeting.

7.8.1.3 AE summaries

An overall summary of adverse events will be presented.

The frequency of patients with adverse events will be summarised by treatment, primary SOC and PT. AEs will also be reported by intensity. Separate tables will be provided for patients with other significant AEs according to ICH E3 (3), for patients with adverse events of special interest (AESI), for patients with serious adverse events, for patients with AEs leading to discontinuation, and for patients with drug-related AEs.

The SOC will be sorted alphabetically, preferred terms will be sorted by frequency (within SOC). Customized sorting orders may also be used based on trial needs, e.g. SOC sorted by frequency.

7.8.1.5 AEs of special interest (AESIs)

The protocol defines the following adverse events that for analysis purposes will be considered as AESIs:

- Hepatic injury
- Decreased renal function
- Diabetic ketoacidosis (DKA)
- Events leading to lower limb amputation

Events of these AESIs are identified through the AE being flagged by the investigator as an AESI on the case report form (CRF) and based on SMQs/BIsMQ.

Hepatic injury

Adverse events reported as AESIs relating to hepatic injury as specified in the protocol will be summarised.

Additionally, hepatic injury AEs will be summarized based on an SMQ based definition. From SMQ Drug related hepatic disorders (20000006) the following narrow sub-SMQs will be used:

- Liver related investigations, signs and symptoms: 20000008 (narrow SMQ)
- Cholestasis and jaundice of hepatic origin: 20000009 (narrow SMQ)
- Hepatitis, non-infectious: 20000010 (narrow SMQ)
- Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions: 20000013 (narrow SMQ)

A table with frequencies of patients with these AEs by treatment, primary SOC and PT will be provided. Hepatic injury SAEs and hepatic injury AEs leading to discontinuation based on the above SMQ definition will be presented.

Patients with hepatic injury will be listed.

Decreased renal function

Adverse events reported as AESIs relating to decreased renal function as specified in the protocol will be summarised, i.e. patients with elevated creatinine ≥ 2 x baseline and above upper limit of normal (ULN)

A frequency table of patients with AEs of acute renal failure by treatment, primary SOC and PT will additionally be provided based on the narrow standardized MedDRA query (SMQ) Acute renal failure (20000003).

SAEs and AEs leading to discontinuation based on the SMQ Acute renal failure (20000003) will be presented.

Patients with decreased renal function will be listed.

[redacted]

Events leading to lower limb amputation

A frequency table of patients with AEs leading to lower limb amputation as identified by the investigator by treatment, primary SOC and PT will be provided.

A separate table for AEs leading to lower limb amputation which lead to discontinuation will be presented.

SAEs will also be presented.

Patients with lower limb amputation will be listed.

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

An independent external CEC regularly reviews events suspected of DKA and evaluates whether pre-specified criteria for these adjudication endpoints are met. Details on composition of the CEC, responsibilities and clinical event definitions are provided in a separate CEC Charter.

The CEC will be provided with additional, specified background material on the patients with these events and perform an assessment of the events.

Adjudication assessments will be incorporated to the database. Frequency tables will be provided for the preferred terms in the specified SMQs of events and for the adjudication endpoints. Tables will be provided for events qualifying for adjudication and then separately the events that were confirmed or non-assessable.

7.8.1.7 AEs while patients taking wrong medication

A listing using the TS will be provided for AEs that occurred while a patient was taking the wrong medication.

7.8.2 Laboratory data

For continuous safety laboratory parameters standardized and normalized values will be derived as well as the differences to baseline. The process of standardization 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 (4). All analyses considering multiple of times upper limit of normal (ULN) will be based on original and not normalized data.

Baseline for safety laboratory parameters will be the last available measurement before the start of randomised or re-randomised study medication. In general, laboratory measurements taken up to 3 days after the last administration of randomised study medication will be considered as on-treatment. The exception will be for the liver enzyme elevation analysis (see Section 7.8.2.1).

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

7.8.2.1 Elevated liver enzymes

The frequency of the number of patients with AST/ALT elevations >= 3xULN, >= 5xULN, >= 10xULN, and >= 20xULN will be displayed.

To support analyses of liver related adverse drug effects, patients with AST and/or ALT ≥3xULN with concomitant or subsequent TBILI≥2xULN in a 30-day period after AST/ALT elevation are of special interest.

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 has no information available for the remaining parameter(s) at the same time-point or within the 30 day time window will not be listed under "ALT and/or AST ≥ 3xULN with Total Bilirubin ≥ 2xULN". An additional presentation including all events up to 30 days after the last dose of study treatment will also be included.

In a similar manner, patients with AST and/or ALT ≥5xULN with no concomitant or subsequent TBILI≥2xULN in a 30-day period after AST/ALT elevation will also be displayed. If no TBILI measurement is available in the 30-day period then the patient will not be listed.

7.8.2.2 Renal laboratory parameters

All calculations for the grading of renal function will be based on the originally measured laboratory values and the ULNs given by the laboratory, not on normalized values with BI standard reference ranges. The creatinine clearance and glomerular filtration rate will be estimated according to the formula and stored in the trial databases:

- Cockcroft-Gault formula (mL/min): eCcr = (140 – age) x (weight in kg) x (0.85 if female) / (72 x creatinine (mg/dL))
- MDRD formula (mL/min/1.73m²): eGFR = 175 x (creatinine (umol/L) / 88.4)$^{-1.154}$ x [age]$^{-0.203}$ x (0.742 if female)

For the analysis of eGFR and for the covariates in the statistical modelling the values calculated from the above formula using the serum creatinine values from the central laboratory will be used, not the eGFR values provided by the central laboratory. For the assignment of PDs based on renal function the central laboratory values will be used.

7.8.3 Vital signs

In addition to the analysis of SBP and DBP as secondary endpoints. Only descriptive statistics are planned for the summary of pulse rate (bpm), change from baseline in pulse rate after 24 weeks of treatment.

7.8.4 ECG

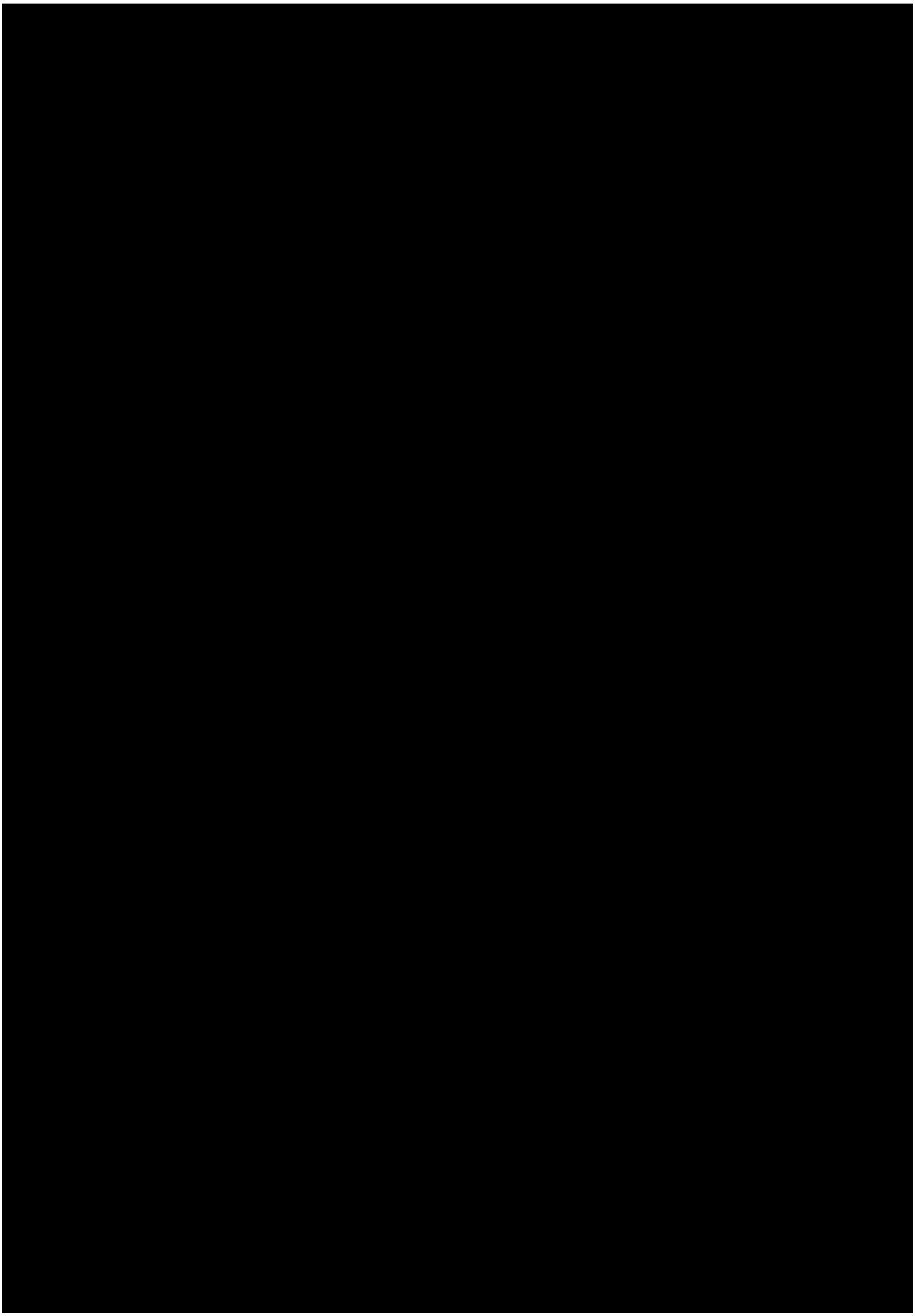
12-lead ECG measurements will be taken at baseline (Visit 3) and at EoT (Visit 8). Any clinically significant new findings in the ECG measurement after the first ECG will be considered as AEs and analyzed as planned in Section 7.8.1.

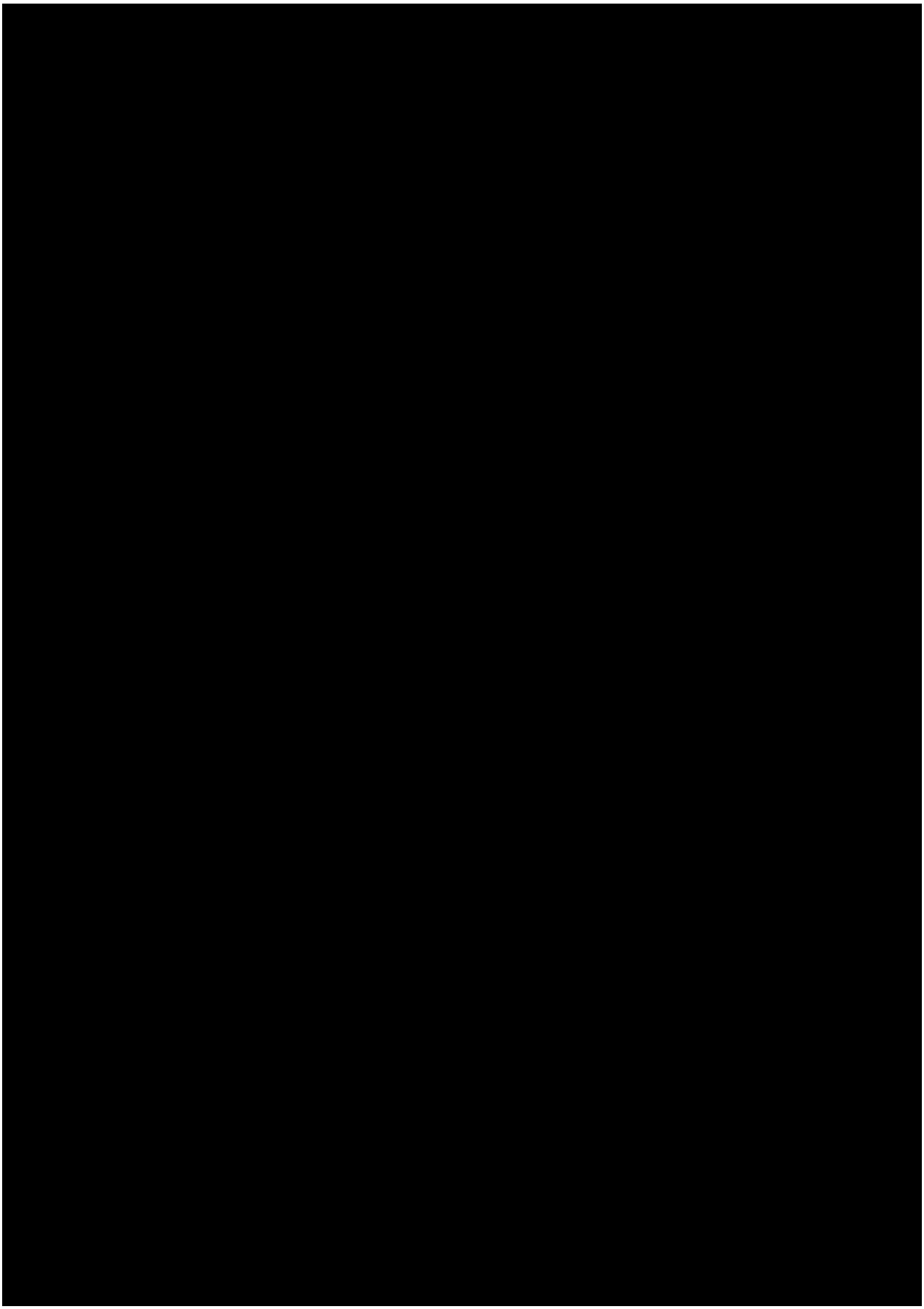
7.8.5 Creatinine and eGFR time curve analysis

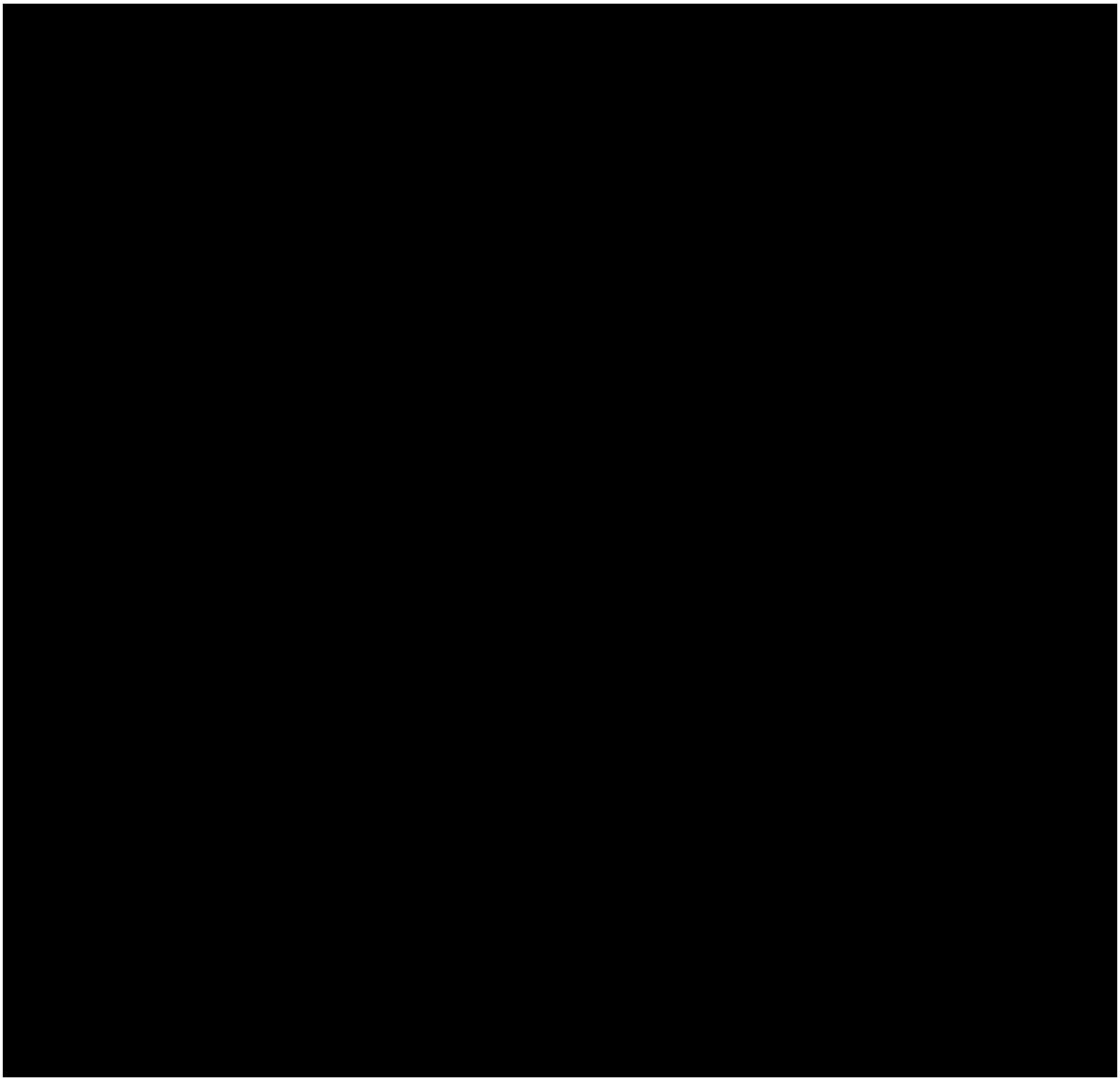
Descriptive statistics will be created for creatinine and eGFR values over time by treatment and presented in tables. Descriptive statistics for eCcr will be presented. These data will be used to create plots of the parameters over time.

8 REFERENCES

1	*BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED.
2	*Corp Guideline,* "Reporting of Clinical Trials and Project Summaries", current version, in: DMSM; BI Intranet: rdmnet.
3	*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.
4	*001-MCG-157:* "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.







10 HISTORY TABLE

Table 10:1 History table

Version	Date (DDMMMYY)	Author	Sections changed	Brief description of change
Final	12-Nov-21	[redacted]	None	This is the final TSAP without any modification