Trial Statistical Analysis Plan

c02669320-02

BI Trial No.:	1245.29
Title:	1245.29: A randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of empagliflozin (10 mg, 25 mg) administered orally, once daily over 24 weeks in hypertensive black/African American patients with type 2 diabetes mellitus Clinical Phase IIIb Including protocol revision- **[c01945509-06]**
Investigational Product:	empagliflozin
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[redacted]

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2 LIST OF ABBREVIATIONS

Term	Definition / description
ABPM	Ambulatory blood pressure measurements
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ASA	Acetylsalicylic acid
AST	Aspartate transaminase
ATC	Anatomical-Therapeutic-Chemical classification
BICMQ	BI-customised MedDRA query
BMI	Body mass index
BRPM	Blinded report planning meeting
CI	Confidence interval
CEC	Clinical event committee
CRF	Case report form
CT	Concomitant therapy
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBP	Diastolic blood pressure
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
DMG	Dictionary Maintenance Group
ECG	Electrocardiogram
EMA	European medicines agency
eCCr	Estimate creatinine clearance
eGFR	Estimated glomerular filtration rate
EoT	End of treatment
FAS	Full analysis set
FPG	Fasting plasma glucose
GI	Genital infection
HbA_{1c}	Glycated haemoglobin

Term	Definition / description
ICH	International Conference on Harmonisation
iPV	Important protocol violation
ITT	Intention to treat
IVRS	Interactive Voice Response System
LOCF	Last observation carried forward
LOCF-IR	Last observation carried forward, including values after rescue
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect Model Repeated Measures
MQRM	Medical Quality Review Meeting
NCF	Non-completers considered failure
OC	Observed case
OR	Original results
PK	Pharmacokinetics
PPS	Per protocol set
PT	Preferred term
PV	Protocol violation
Q1	Lower quartile
Q3	Upper quartile
RS	Randomised set
SBP	Systolic blood pressure
SCR	Screened set
SD	Standard deviation
SDL	Subject data listing
SMQ	Standardised MedDRA query
SOC	System Organ Class
SSC	Special search category
TBL	Total bilirubin
TOC	Table of contents
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
UTI	Urinary tract infection

Term	Definition / description
WHO	World health organisation

3 INTRODUCTION

As per International Conference on Harmonisation (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 have been four amendments to the protocol.

The TSAP is written according to the changes reported in protocol amendment 4 (1) (c01945509-06, 18 JUL 2016).

The following additional endpoints or modifications to pre-specified endpoints have been defined:

- Urinary tract infections (UTIs), genital infections (GIs), malignancies and volume depletion have been added as AEs of special interest (AESIs)
- Orthostatic blood pressure test result at week 24

5 ENDPOINT(S)

Note that several imputation methods will be used for the analysis of efficacy endpoints. Further details can be found in Section 6.6.

Throughout the TSAP, the following should be considered:

- Successful is defined by the vendor BioClinica Inc. as a set of ambulatory blood pressure measurements (ABPM) readings meeting all of the following criteria:
    - Start time must be between 07:00 and 11:00
    - Minimum duration of 24 hours after beginning of the test
    - Minimum of 70% valid readings in the period
    - Total Required Hours is 18 (minimum valid readings for Required Hour is 1)
    - Total Exception Hours is 6 (minimum valid readings for Exception Hour is 0)
    - Total Consecutive Exception Hours is 2
- Valid is defined by the vendor BioClinica Inc. as a reading meeting all of the following criteria:
    - Systolic blood pressure (SBP) between 60 mmHg and 261 mmHg inclusive
    - Diastolic blood pressure (DBP) between 40 mmHg and 151 mmHg inclusive

- Usable is defined as a reading within 24 hours of the beginning of test.
- All ambulatory endpoints will be calculated by using successful, valid and usable ambulatory blood pressure (BP)/HR readings only. If any ambulatory BP/HR reading is not successful, valid or usable, then the corresponding ambulatory BP/HR measurements will also be set to not successful, valid or usable.
- All 24-hour means are defined as the mean of hourly means (based on clocktime) of successful, valid and usable readings.

[redacted]

- Mean trough ambulatory BP is defined as the mean of successful, valid and usable readings measured from 22:00 until 23:59 hours after the beginning of the test.
- Trough seated BP is defined as the mean of the seated/in office vital signs measurements including those taken after the removal of the ABPM device taken on the day of the clinic visit prior to trial drug intake.

[redacted]

- PP is defined as (SBP - DBP).

[redacted]

5.1 PRIMARY ENDPOINTS

The primary endpoint in this study is the change from baseline in HbA_{1c} (%) at week 24. HbA_{1c} will additionally be analysed in mmol/mol.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint(s)

Key secondary endpoints of this study are:

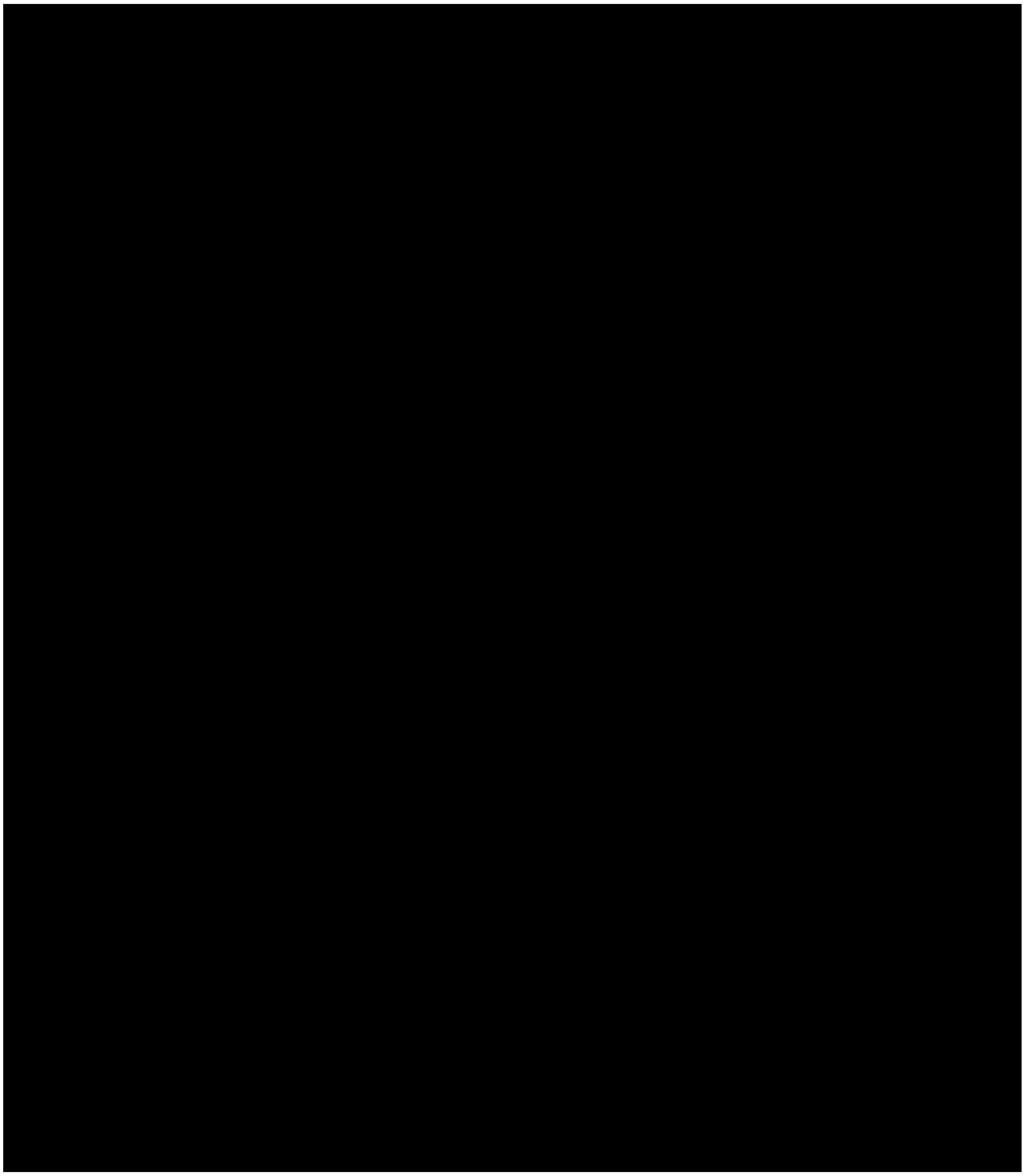
- Mean 24-hour ambulatory SBP (mmHg): Change from baseline at week 12
- Mean trough ambulatory SBP (mmHg): Change from baseline at week 12
- Body weight (kg): Change from baseline at week 24
- Trough seated SBP (mmHg): Change from baseline at week 12

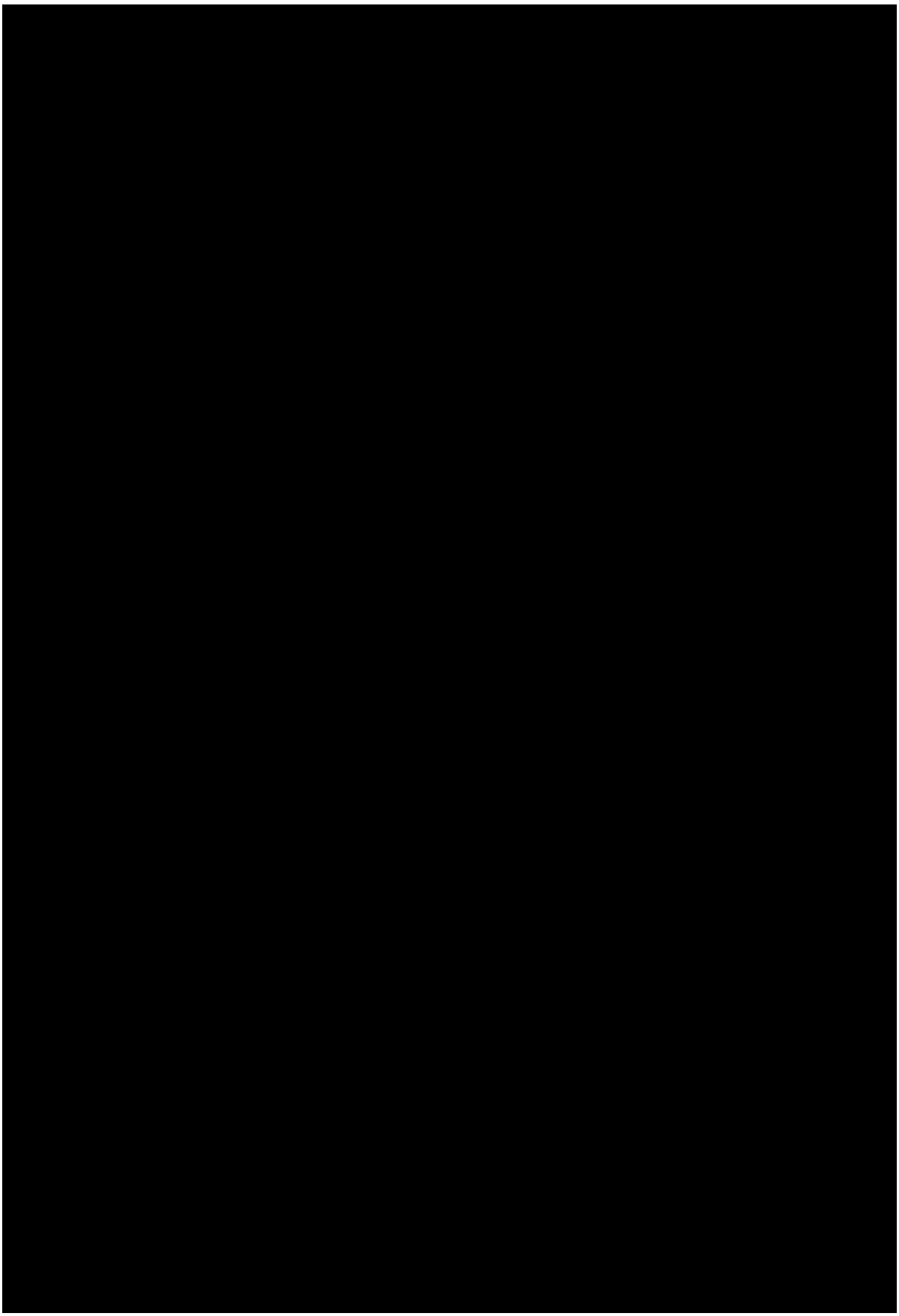
5.2.2 (Other) Secondary endpoint(s)

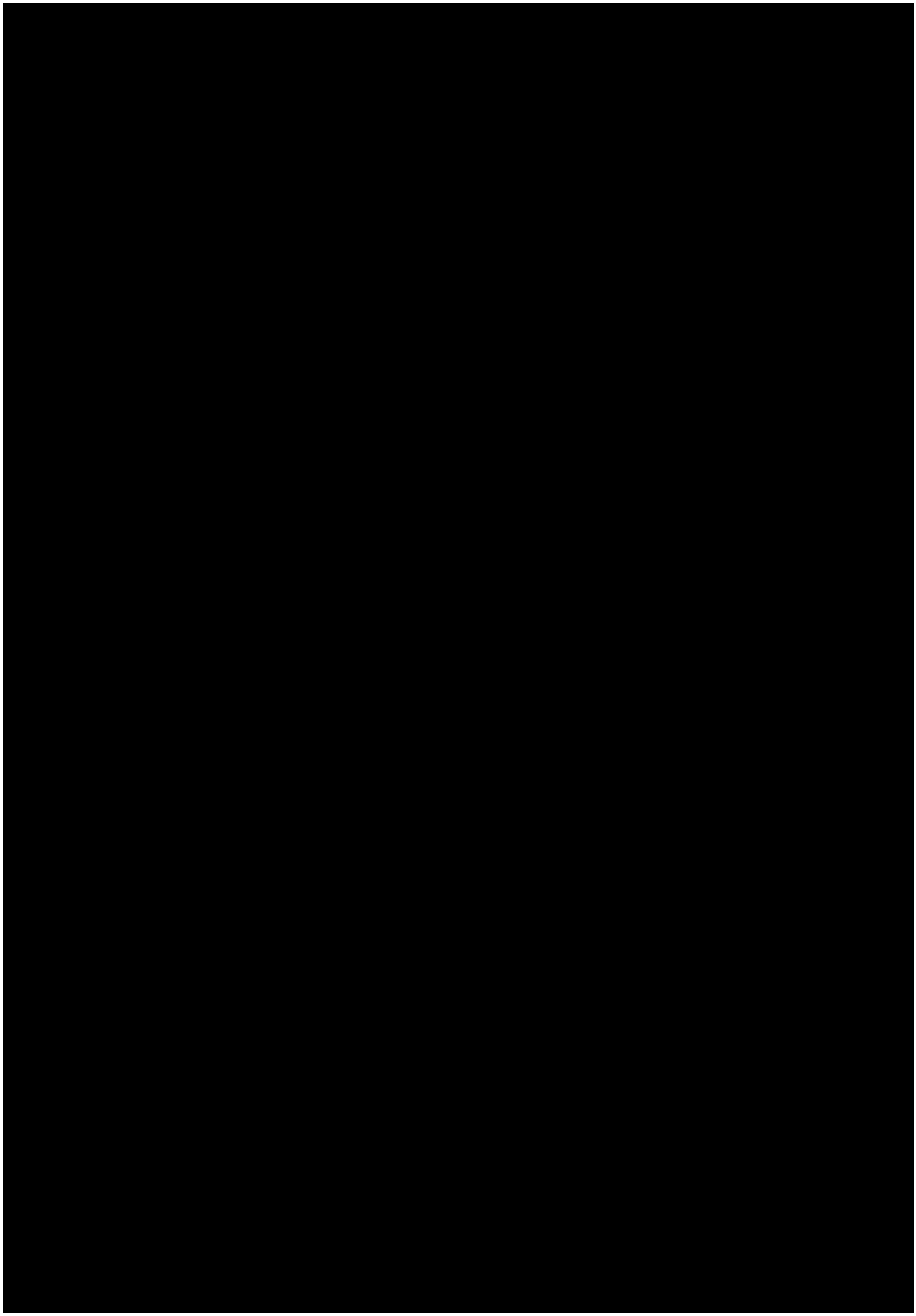
Other secondary endpoints of this study are:

- Change from baseline in mean 24-hour ambulatory SBP (mmHg) at week 24
- Change from baseline in mean 24-hour ambulatory DBP (mmHg) at week 12

- Change from baseline in mean 24-hour ambulatory DBP (mmHg) at week 24
- Change from baseline in trough seated SBP (mmHg) at week 24
- Change from baseline in trough seated DBP (mmHg) at week 12
- Change from baseline in trough seated DBP (mmHg) at week 24







6 GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

There will be 5 treatment study phases in this trial: screening, placebo run-in, study treatment phase (with either empagliflozin, matching placebo), post-treatment and post-study.

Table 6.1: 1 Treatment regimens / study intervals

Label	**Interval**	**Start date**	**Start time**
Screening	Screening period	Date of informed consent	00:00
Run-in	Run-in	Date of first administration of run-in medication	00:00
Placebo Empagliflozin	Double-blind treatment period	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 trial drug + X* +1 day	00:00
Post-study	Post-study	Last contact date~+1 day	00:00

* The endpoint specific follow-up periods for the assignment to active treatment are presented in detail in Section 6.7. This is relevant for the statistical programming team only.

The purpose of the definitions above is to describe all the different study/treatment intervals, in 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.

The endpoint-specific follow-up periods for the assignment to active treatment are presented in detail in Section 6.7.

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

Safety analyses will assign patients to the treatment group as treated. If a patient erroneously receives the wrong trial drug, the patient will be analysed as per the first treatment received. Drug-related AEs are analysed according to actual medication taken. Actual medication taken refers to medication at onset of AE. In addition, AEs with an onset during the time of the incorrect study treatment will be listed separately.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Not all important protocol violations (iPVs) will generate exclusion from the per protocol set (PPS). Violations that lead to exclusion from analysis populations are indicated as such in Table 6.2: 1.

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

Table 6.2: 1 List of important protocol violations

PV Category/ Code		**Description**	**(Comments)**	**Criterion to check for PV**	**Exclusion from**
A	**Entrance criteria not met**				
A1	**Target indication not met**				
	A1.01	No type 2 diabetes	Inclusion criterion checked	I1	PPS
A2	**Inclusion criteria not met**				
	A2.01	HbA_{1c} out of range	HbA_{1c} out of range for inclusion (see individual inclusion criterion) by >0.2% i.e. inclusion only if value is in [7.3-11.2%] interval	I3, for Protocol Version 4 the range has changed (>=**7.0** % instead of 7.5% so values within [6.8-11.2%]) will be included from Protocol Version 4 onwards	PPS
	A2.02	Age out of range (at V1)	See individual inclusion criterion	I7	None
A3	**Exclusion criteria violated**				
	A3.01	Uncontrolled FPG level	Exclusion criterion checked	E1	None
	A3.02	Additional anti-diabetic background therapy	Exclusion criterion checked	E2 (different definitions for Protocol Version 1+2 compared to Protocol Version 3 [with regards to background therapy])	PPS

Table 6.2: 1 List of important protocol violations (cont.)

PV Category/ Code		Description	(Comments)	Criterion to check for PV	Exclusion from
	A3.03	Relevant concomitant diagnoses	Exclusion criterion checked or see individual exclusion criterion	E8, E9, E10, E11, E15, E17	None
	A3.04	Bariatric or other relevant and other gastrointestinal surgery within the last two years	Exclusion criterion checked	E14	PPS
	A3.05	Blood dyscrasias or any disorders causing hemolysis or unstable red blood cell count	Exclusion criterion checked	E16	PPS
	A3.06	Indication of liver disease	Exclusion criterion checked	E12 + data check for any issues[1]	None
	A3.07				
	A3.08	Treatment with protocol excluded antiobesity drugs	Exclusion criterion checked or Treatment with anti-obesity drugs 3 months prior to informed consent or any other treatment at the time of screening (i.e. surgery, aggressive diet regimen, etc.)	E18 (protocol version 2), E19 (protocol version 1)	PPS
	A3.09	Renal insufficiency or renal impairment (assessed by eGFR)	Exclusion criterion checked	E13 + data check for any issues[1]	PPS

Table 6.2: 1 List of important protocol violations (cont.)

PV Category/ Code		Description	(Comments)	Criterion to check for PV	Exclusion from
	A3.10	Treatment with protocol excluded systemic steroids or recent change in thyroid hormone dose	Exclusion criterion checked or current treatment with systemic steroids at time of informed consent or change in dosage of thyroid hormones within 6 weeks prior to informed consent or any other uncontrolled endocrine disorder except T2DM. (Treatment with local and inhaled steroids is allowed)	E19 (protocol version 2), E20 (protocol version 1)	PPS
	A3.11	Intake of an investigational drug within 30 days prior to intake of study medication in this trial	Exclusion criterion checked (Medical judgment), depending on the type of drug given in the prior trial (only if investigational drug interferes with glucose metabolism).	E22 (protocol version 2), E23 (protocol version 1)	PPS Final decision at DBL meeting
	A3.12	Specific exclusion criterion for premenopausal women violated	Exclusion criterion checked	E20 (protocol version 2), E21 (protocol version 1)	None

Table 6.2: 1 List of important protocol violations (cont.)

PV Category/ Code		Description	(Comments)	Criterion to check for PV	Exclusion from
	A3.13	Relevant alcohol or drug abuse and other conditions affecting study compliance	Exclusion criterion checked	E21 (protocol version 2), E22 (protocol version 1)	None
	A3.14	Any other clinical condition unsafe for participation that would jeopardise patient safety while participating in this clinical trial	Exclusion criterion checked	E23 (protocol version 2), E24 (protocol version 1)	None
	A3.17	Diagnosis of autoimmune diabetes	As defined in protocol	E7	None
B	**Informed consent**				
	B1	Informed consent not available	Date of informed consent missing or No signature on patient's "Declaration of Informed Consent". *Patient's data will not be used at all.*	I8[1] data check or manual	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	I8[1] data check or manual	None
C	**Trial medication and randomisation**				
C1	**Incorrect trial medication taken**				

Table 6.2: 1 List of important protocol violations (cont.)

PV Category/ Code		**Description**	**(Comments)**	**Criterion to check for PV**	**Exclusion from**
	C1.01	No study medication taken	Patient randomised but no study medication taken	[1]	TS, FAS, PPS
	C1.02	Incorrect trial medication taken	Wrong medication taken for more than 20% of the overall treatment duration or for more than 20% of the last visit interval before the primary endpoint assessment (different medication than the patient was randomized to taken i.e. drug kit recorded in eCRF from different treatment group than drug kit assigned by IVRS) [manual check PV].	Can only be finally judged after DBL since unblinding information is required. [1]	PPS
C2	**Randomisation not followed**				
	C2.01	Treated without randomisation	Patient treated according to eCRF, but not randomised according to IVRS.		PPS
	C2.02	Randomization without successful completion of baseline ABPM	Patient randomized without successful completion of baseline ABPM with a mean SBP 135-175 mmHg as required.	I5	None
C3	**Non-compliance**				

Table 6.2: 1 List of important protocol violations (cont.)

PV Category/ Code		Description	(Comments)	Criterion to check for PV	Exclusion from
	C3.01	Non-compliance with trial drug intake	Overall study treatment compliance outside 80% and 120% (inclusive) or study treatment compliance below 80% in the last visit interval before primary endpoint assessment. Overall compliance will be calculated as a weighted average of reported compliance. The weighted sum of all reported compliance over the actual visits will be divided by the total duration until visit where all medication is returned.	[1]	PPS
	C3.03	Last treatment more than 7days prior to next visit	Last treatment more than 7 days prior to next visit.	[1]	PPS
C4	**Medication code broken**				
	C4.01	Medication code broke without just cause	Medication code was broken for no valid reason. Final decision at the DBL meeting based on medical judgment.		PPS Final Decision at DBL Meeting
D1	**Concomitant medication**				
D2	**Prohibited medication use**				

Table 6.2: 1 List of important protocol violations (cont.)

PV Category/ Code		Description	(Comments)	Criterion to check for PV	Exclusion from
	D2.01	Use of prohibited medication during treatment period	Review of eCRF for prohibited medication. Final decision at the DBL meeting based on medical judgment.		PPS Final Decision at DBL Meeting
D3	**Mandatory medication not taken**				
	D3.01	Background antidiabetic therapy not taken as specified in the protocol	Antidiabetic background therapy dose changed.	[1]	PPS
E	**Missing data**				
	E.01	No baseline HbA_{1c} value	No valid baseline HbA_{1c} value	[1]	FAS
F	**Incorrect timing**				
G	**Trial specific violation**				
G1	**Inclusion criteria violated**				
	G1.10	No black/African American or antidiabetic background therapy not as required	Inclusion criterion checked, see individual inclusion criteria	I2 (different definitions for Protocol Version 1+2 compared to Protocol Version 3 [with regards to background therapy]), Protocol Version 4 has no minimum metformin dose any longer	PPS
	G1.11	Blood pressure at screening out of range	Mean seated SBP outside 140-180 mmHg or DBP outside 90-110 mmHg at Visit 1	I4[1], from Protocol Version 4 onwards no DBP criteria	PPS

Table 6.2: 1 List of important protocol violations (cont.)

PV Category/ Code		Description	(Comments)	Criterion to check for PV	Exclusion from
	G1.12	Use of none or more than 3 antihypertensive medications or use of antihypertensive medications for less than 4 weeks prior to randomization	See inclusion criterion (as specified in the protocol)	I6[1] Protocol Version 4 allows 4 antihypertensive treatments, in previous Versions not more than 3 were allowed	PPS
G2	**Exclusion criteria violated**				
	G2.20	Use of hypertension treatment with oral Minoxidil	See exclusion criteria	E3[1]	PPS
	G2.21	Blood pressure out of range at placebo run-in confirmed	Mean seated SBP ⩾181 mmHg or mean seated DBP ⩾111 mmHg during placebo run-in visit and confirmed by a 2nd measurement (not on same day) preferably within 1 day	E4[1] from Protocol Version 4 onwards SBP criteria only (no DBP criterion)	PPS
	G2.22	Upper arm circumference exceeds cuff size of BP measurement device	Upper arm circumference that exceeds the upper circumference level of the cuff size of either ABPM and/or BP measurement device	E5	PPS
	G2.03	Night shift worker	Night shift workers who routinely sleep during the daytime and/or whose work hours include midnight	E6	PPS

Table 6.2: 1 List of important protocol violations (cont.)

PV Category/ Code		Description	(Comments)	Criterion to check for PV	Exclusion from
	G2.23	Systolic blood pressure difference of >10 mmHg between the arms at screening	See exclusion criteria	E18 (protocol version 1 only)	PPS
G3	**Other trial specific violation**				
H	**Other safety related violations**				
H3	**Violation of CTP procedure possibly affecting BP measurement**				
	H3.01	Incorrect procedure for BP measurement	Not the same arm used for BP measurement for baseline and last value on-treatment	[1]	None
	H3.02	Incorrect device used	Incorrect device used for baseline or last value on-treatment	Manual	None
	H3.07	Incorrect sequence for study procedures related to blood pressure	BP measured after blood draw	Manual	None
I	**Other safety related violations**				
I2	**Pregnancy monitoring**				
	I2.01	Pregnancy	Pregnancy		None
	I2.02	Missing pregnancy test	Pregnancy test not done for woman of child bearing potential for at least one visit before treatment discontinuation	[1]	None

Note: Data check means that the IPV will be manually checked (i.e. derived programmatically)

[1] programming is involved for checking according to project standard

The decision about which PV could generate exclusion from analysis sets will be discussed during the course of the study and finalized at the last blinded report planning meeting (BRPM).

6.3 PATIENT SETS ANALYSED

The following analysis sets will be defined for this trial.

- Screened patients set (SCR): All patients screened for the trial, with informed consent given and who completed at least one screening procedure at Visit 1.
- Randomised set (RS): All patients from the SCR who were randomised to trial drug, regardless of whether any trial drug was taken.
- Treated set (TS): All patients who were randomised and treated with at least one dose of trial drug. The TS is the basis for the safety analyses in the double-blind period.
- Full analysis set (FAS): All patients randomised, treated with at least one dose of trial drug, and with a baseline and at least one on-treatment HbA_{1c} value. The FAS is the basis for the primary efficacy analysis.
- Per-protocol set (PPS): All patients in the FAS without iPVs leading to exclusion. See Table 6.2: 1.

No efficacy or safety analyses are planned for the RS. 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

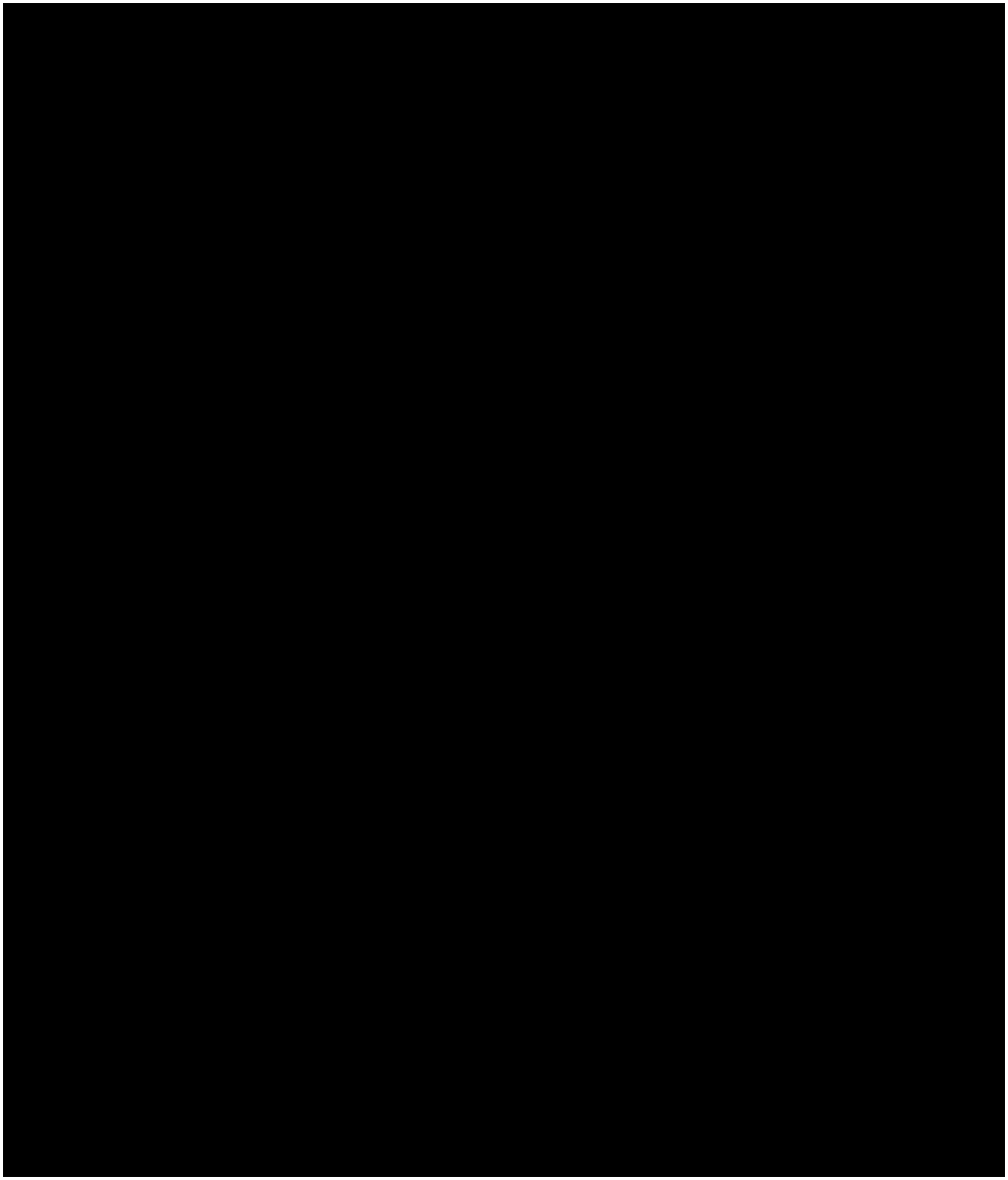
Class of endpoint	**TS**	**FAS**	**PPS**
Primary		OC OC-AD OC-IR LOCF MI	OC
Key secondary - BP endpoints - Other endpoints		 OC-AD (not for ABPM endpoints) OC-H OC-IR LOCF-H OC-AD OC OC-IR LOCF	
Subgroup analyses: - BP endpoints - Other endpoints		 LOCF-H OC-H OC	
Binary efficacy endpoints - BP endpoints - Other endpoints		 NCF-H NCF	
Other continuous efficacy endpoints - BP endpoints - Other endpoints		 OC-H LOCF-H OC LOCF OR#	
Safety endpoints	OR LOCF-IR^ OC-IR^		
Disposition	OR		
Demographics		OR	
Baseline efficacy		OC	

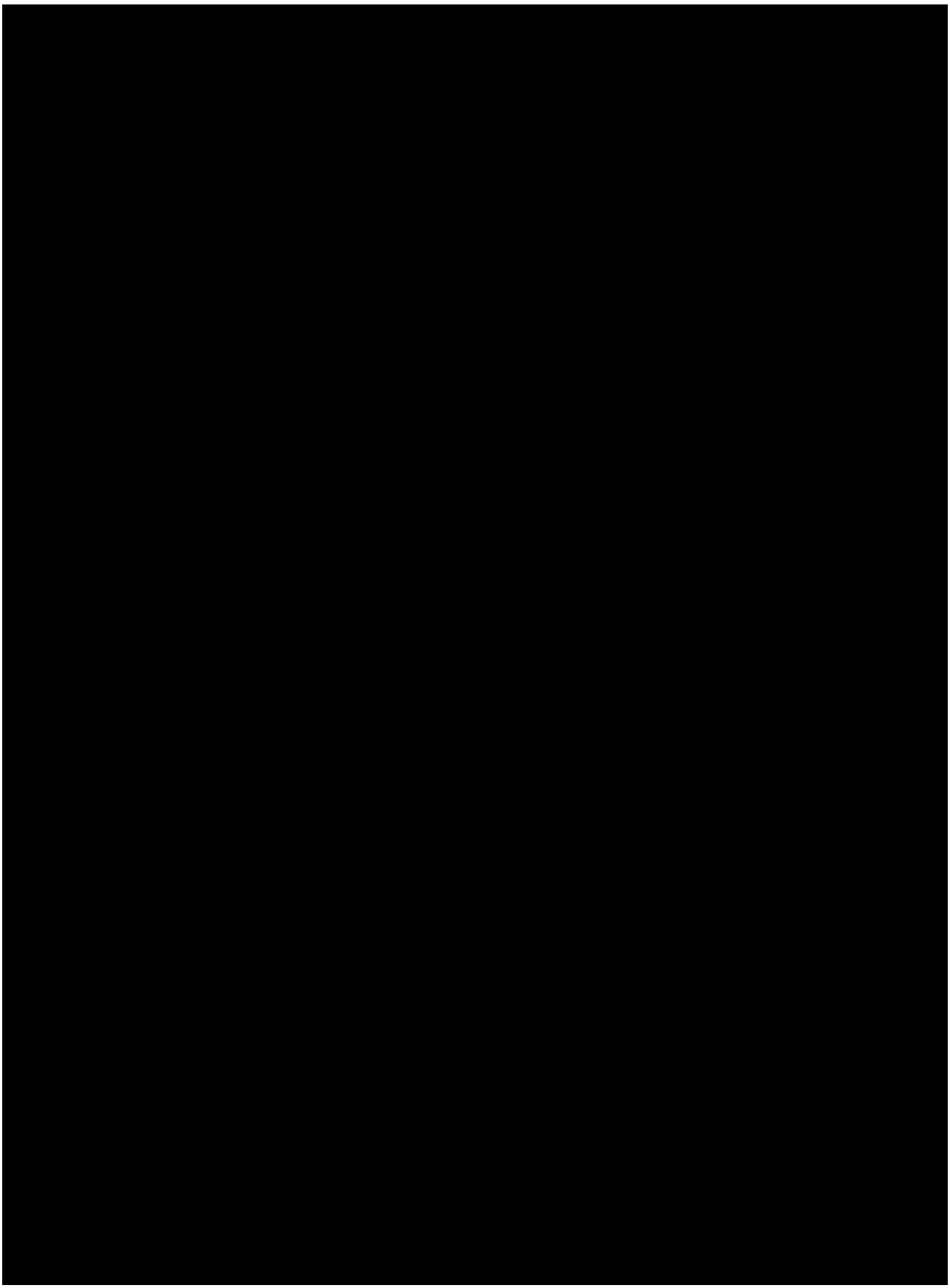
Note: LOCF=Last observation carried forward; OC=Observed cases; OR=Original result; MI=multiple imputation

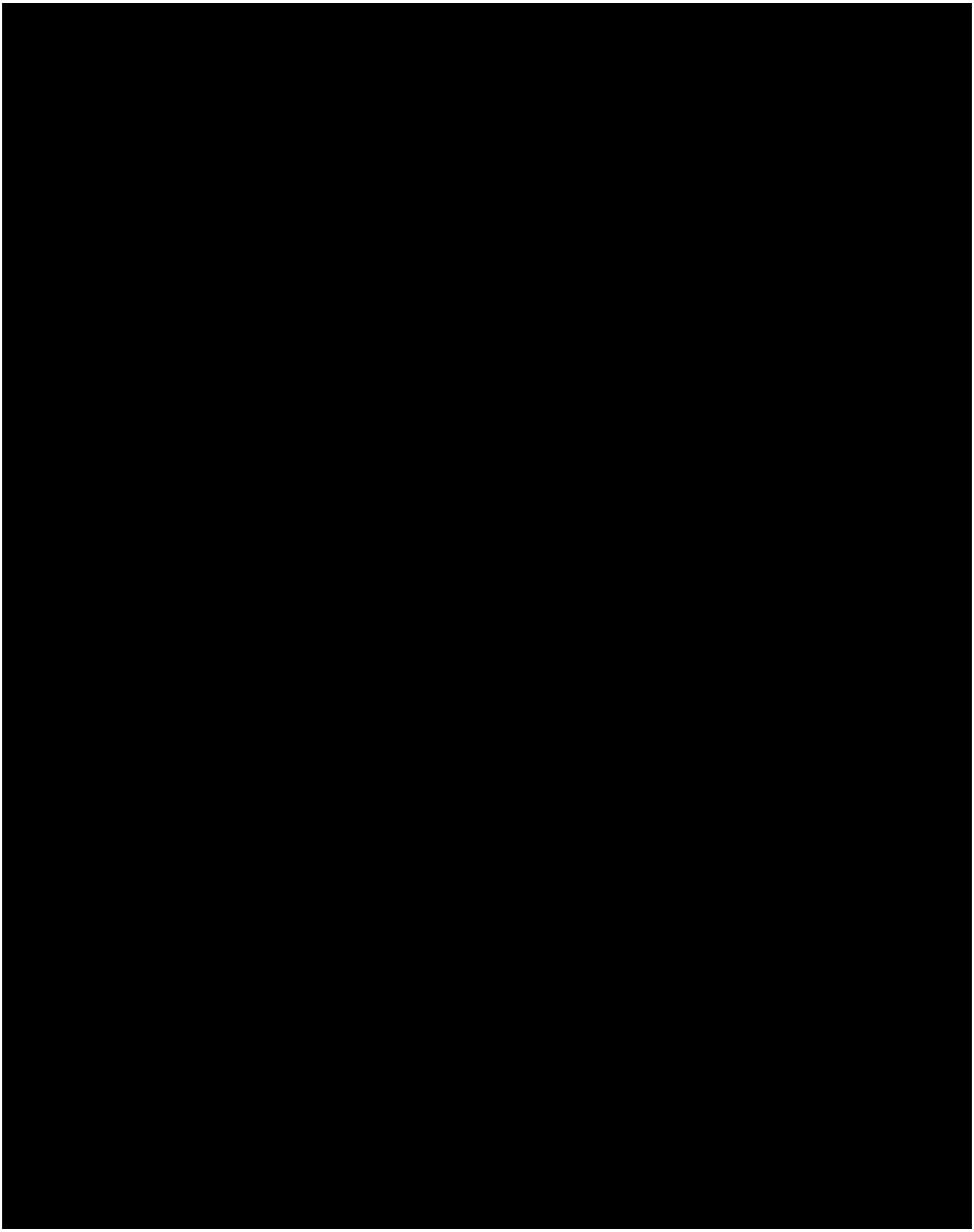
Further details of the imputation methods can be found in Section 6.6.

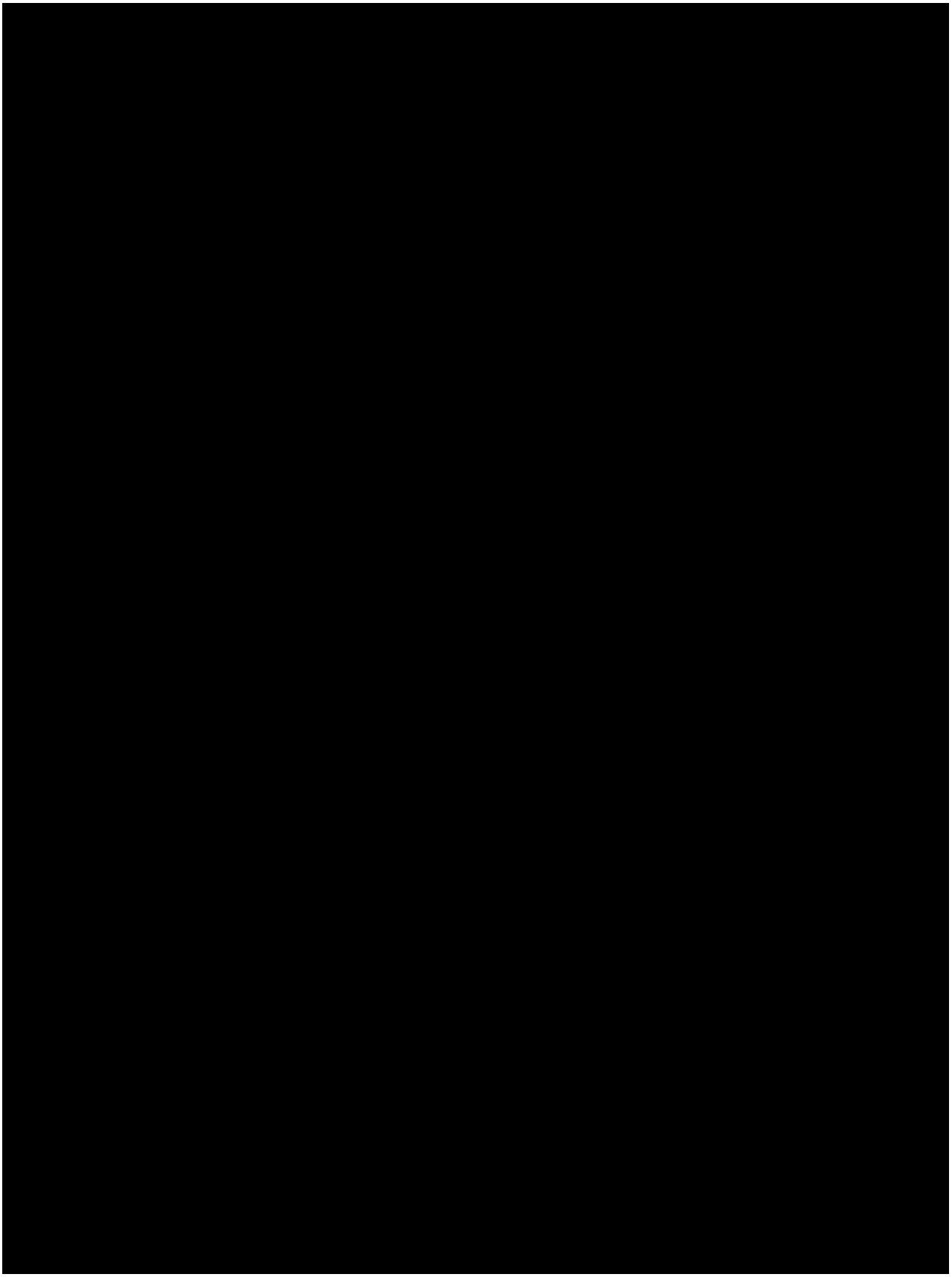
#OR results will only be presented for time to first rescue medication and number of patients with rescue.

^ LOCF-IR and OC-IR will only be used for lipids.









6.5 POOLING OF CENTERS

Endpoints will not be analysed by centre.

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 antidiabetic rescue therapy for censoring

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

- Additional antidiabetic medication used for ≥7 consecutive days
- Change in dose of antidiabetic background medication for ≥7 consecutive days

This approach will be used when considering which data to exclude from the OC and LOCF analyses. For the definition of antidiabetic rescue therapy as a further endpoint, please refer to Section 5.3.1.

For some other imputation methods, values after antidiabetic rescue and/or antihypertensive medication will be set to missing. For details on antihypertensive medication, refer to Section 5.3.2.

6.6.2 Imputation methods

6.6.2.1 Original result (OR) analysis

OR analysis implies the analysis of data exactly as observed. OR analysis will be performed on endpoints that are either not affected by antidiabetic rescue medication and/or change in antihypertensive therapy or if it is not meaningful to apply any imputation rule for replacing the missing values.

6.6.2.2 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 to missing (antidiabetic rescue medication as defined in Section 6.6.1).

For BP endpoints, the OC-technique will be adapted to set values measured after antidiabetic rescue medication and/or a change in antihypertensive therapy to missing (see Section 5.3.2 for the definition of a change in antihypertensive therapy). This technique will be called OC without values following a change in antihypertensive therapy (OC-H).

OC-H: For ABPM endpoints using data from two calendar days, no data will be excluded if the 24h collection starts before rescue medication or a change in antihypertensive therapy.

6.6.2.4 Last observation carried forward (LOCF)

An alternative method for quantitative endpoints is to replace missing values of a patient by her/his last observed measurement on-treatment.

The last observation on-treatment need not necessarily be a value selected as a visit value if multiple measurements were performed within a time window for a visit. In this case the last on-treatment value within the time window will be carried forward, while the visit value can be the value that was observed closest to the planned visit date or the first value observed in the time window (see Table 6.7: 2 for further details).

Missing values 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 visit.

Let:

D_0 = date of a visit with a missing endpoint value;

D_1 = date of the next visit (with endpoint value non-missing) after the visit with missing endpoint;

D_{-1} = date of a previous visit (with endpoint value non-missing) before the visit with missing endpoint;

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

Then the missing endpoint value can be interpolated as:

$E_0 = E_{-1} + ((E_1 - E_{-1}) \times (D_0 - D_{-1}) / (D_1 - D_{-1}))$.

In general, the values measured after antidiabetic rescue medication was taken during the active treatment period by the patients will be set to missing; and these missing values will be imputed by LOCF technique.

For BP endpoints, the values measured after antidiabetic rescue medication and/or a change in antihypertensive therapy will be set to missing before being imputed by LOCF technique. This adaptation of the LOCF technique will be called LOCF without values following antidiabetic rescue medication and/or a change in antihypertensive therapy (LOCF-H).

Missing data will only be imputed up to the planned visit to be reached by all randomised patients (week 24).

LOCF-H: For ABPM endpoints using data from two calendar days, no data will be excluded if the 24h collection starts before rescue medication or a change in antihypertensive therapy.

6.6.2.7 Non-completers considered failure (NCF)

For binary endpoints, like a treat to target response of HbA_{1c} <7.0%, a conservative method to replace missing values is to consider them as "failures". Missing data due to early discontinuation will be replaced as "failure" (e.g. $HbA_{1c} \geq 7.0\%$) up to the planned final visit to be reached by all patients. Values obtained after antidiabetic rescue medication was started are also replaced as "failure".

For BP endpoints, values obtained after antidiabetic rescue medication and/or a change in antihypertensive therapy will be replaced as “failure”. This adaptation of the NCF technique will be called NCF without values following antidiabetic rescue medication and/or a change in antihypertensive therapy (NCF-H).

For binary endpoints that are derived from quantitative endpoints (e.g. HbA_{1c}), missing values within a course of measurements on-treatment will be replaced on the basis of the corresponding imputed value of the underlying quantitative endpoint (interpolation for HbA_{1c}).

6.6.3 Safety and other variables

Missing safety data will not be replaced.

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

[redacted]

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 (2).

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, missing administration times at on-treatment visits will be imputed by 12:00 o'clock.

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

- If an EoT visit or visit 7.2 is documented, it should be the date of the EoT visit.
- 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.

If only the year of birth is known, the day and month of birth will be imputed as 01 January. For other incomplete date information always the midpoint of the possible interval will be used. If only the year is present the day and month will be imputed as 01 July, if year and month is present the day will be imputed as 15. If the year is missing, the date will be considered missing.

For partial start and stop dates (and dose change) 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 31 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 01 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.

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.

In general, the date and clock time of the first drug administration will be used to separate pre-treatment from on-treatment values; a notable exception to this rule is HbA_{1c} for which only the date will be used. Measurements taken after the first intake of randomised trial drug 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 trial drug for efficacy analyses and to the first trial drug taken for safety analyses.

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

Endpoint	**Last day of assignment to treatment phase (days after trial drug stop date)**
Efficacy	
HbA_{1c}	7
FPG	1
Body weight	1
BP	1
HR	1
Waist circumference	7
Safety	
AEs	7
Safety laboratory measurements	3

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

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

Visit number	Visit label	Planned days	Time window (actual days on treatment)	
			Start	End[A]
3	Baseline	0	NA	1[B]
4	Week 4	28	2	56
5	Week 12	84	57	105
6	Week 18	126	106	147
7	Week 24/EOT	168	148	Trial drug stop date + X days

[A] In case of premature discontinuation of the trial drug a Visit 7.2 has to be performed. If such a Visit 7.2 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 Visit 7.2 will end X days after the trial drug stop date, including Day X. The definition of X is endpoint specific, cf. Table 6.7: 1. No time window for optional visit is planned.

[B] Only values taken prior to the start of treatment with randomised trial drug will 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 trial 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 trial drug after the randomisation, the time window for the first on-treatment visit could include times the patient was not yet on trial drug.

The time window for the first visit after randomisation starts on the day after the first intake of trial drug. This maximises the number of measurements used in by visit analyses.

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 (EoT) is endpoint dependent (see Table 6.7: 1).

For variables where only one on-treatment value is obtained at the EoT visit the time window for the EoT visit, and only one on-treatment measurement, will begin at the midpoint between first and last on-treatment visit (day 168). For patients with no on-treatment value on or after day 168 they will have no on-treatment measurement assigned in the OC approach. For the LOCF imputation, the last value on-treatment will be carried forward regardless of whether before day 168.

Repeated and unscheduled efficacy and safety measurements will be assigned to the nominal visits and listed in the subject data listing (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.

For ABPM data only the first available successful ABPM reading at each of the ABPM time points (Visit 2.2, 5.1 and 7.1) will be used and not the closest to the protocol planned day. Data from a repeated second reading after a successful one at the same ABPM time point will be ignored for the analysis as no second reading should be conducted after one successful first attempt according to protocol and eCRF description.

Note: For LOCF imputation, the last observed on-treatment value will be carried forward within the applicable period, whether or not it was selected in the previous time window. For interpolation only selected values are to be used. For more details on LOCF refer to Section 6.6.

7 PLANNED ANALYSES

Disposition of the patient population participating in the trial will be analysed by study period and treatment groups and presented in the CTR as a frequency-distribution. The number of patients participating (screened, randomised, etc.) in the study will also be displayed.

A frequency of patients with iPVs, also summarised by whether the iPV led to exclusion from the PPS, will be presented by treatment group for the RS. The frequency of patients in different analysis sets will also be analysed 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 / lower quartile (Q1) / Median / upper quartile (Q3) / Max.

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).

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 actually 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 pooled Empagliflozin (10 mg, 25 mg) and placebo.

7.1 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

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

Sex, race, ethnicity, country, age (in years), age-groups, BMI (kg/m^2), BMI categories, height (cm), smoking history, alcohol status, antidiabetic background medication categories and renal impairment (eGFR [CKD-EPI] and eCCr).

Categories for demographic and baseline characteristics are defined in Section 6.4.

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

HbA_{1c} (%), HbA_{1c} (mmol/mol), HbA_{1c} categories, FPG (mg/dL), FPG categories, weight (kg), weight categories, [redacted] SBP (mmHg), mean 24-hour SBP (ABPM) (mmHg), [redacted] DBP (mmHg), mean 24-hour DBP (ABPM) (mmHg), [redacted] blood pressure control (SBP < 140 mmHg and DBP < 90 mmHg), [redacted]

[redacted]

Demographic and baseline characteristics will be presented for the FAS.

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 interactive voice response system (IVRS) provider.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report using the FAS.

Summaries will be presented for CTs taken during randomised treatment and those taken at baseline. Separate summaries of use of antihypertensives, ASA or lipid lowering drugs at baseline by preferred name will be presented. The displayed categories and defining anatomical-therapeutic-chemical classification (ATC) levels and ATC codes are shown in Table 9.3: 1. Additionally a descriptive table of changes in dose of antihypertensive medication will be shown.

Concomitant diseases will be summarised by 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 FAS.

7.3 TREATMENT COMPLIANCE

Only 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 FAS will be considered.

7.4 PRIMARY ENDPOINT(S)

7.4.1 Primary efficacy analysis

A hierarchical multiple testing procedure will be used to evaluate superiority of the primary endpoint, followed by the evaluation of superiority of the key secondary endpoints in the following pre-specified hierarchical sequence:

I. Primary endpoint: Change from baseline in HbA_{1c} (%) at week 24

II. Key secondary endpoint: Change from baseline in mean 24-hour ambulatory SBP (mmHg) at week 12

III. Key secondary endpoint: Change from baseline in mean trough ambulatory SBP (mmHg) at week 12

IV. Key secondary endpoint: Change from baseline in body weight (kg) at week 24

V. Key secondary endpoint: Change from baseline in trough seated SBP (mmHg) at week 12

Each step will be considered confirmatory if all previous steps were successful (superiority was achieved). If any of the previous steps were unsuccessful, the subsequent steps are regarded as exploratory.

The primary analysis is at 24 weeks and will be performed on the FAS (OC). It is a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach comparing the change from baseline in HbA_{1c} after 24 weeks of treatment. Missing data are handled directly by the fitted model. According to published literature, MMRM analysis appears to be a superior approach for controlling Type I error rates and minimizing bias as compared to single imputation approaches such as LOCF ANCOVA analysis particularly in the presence of missing completely at random (MCAR) or missing at random (MAR) data (4).

The statistical model will be:

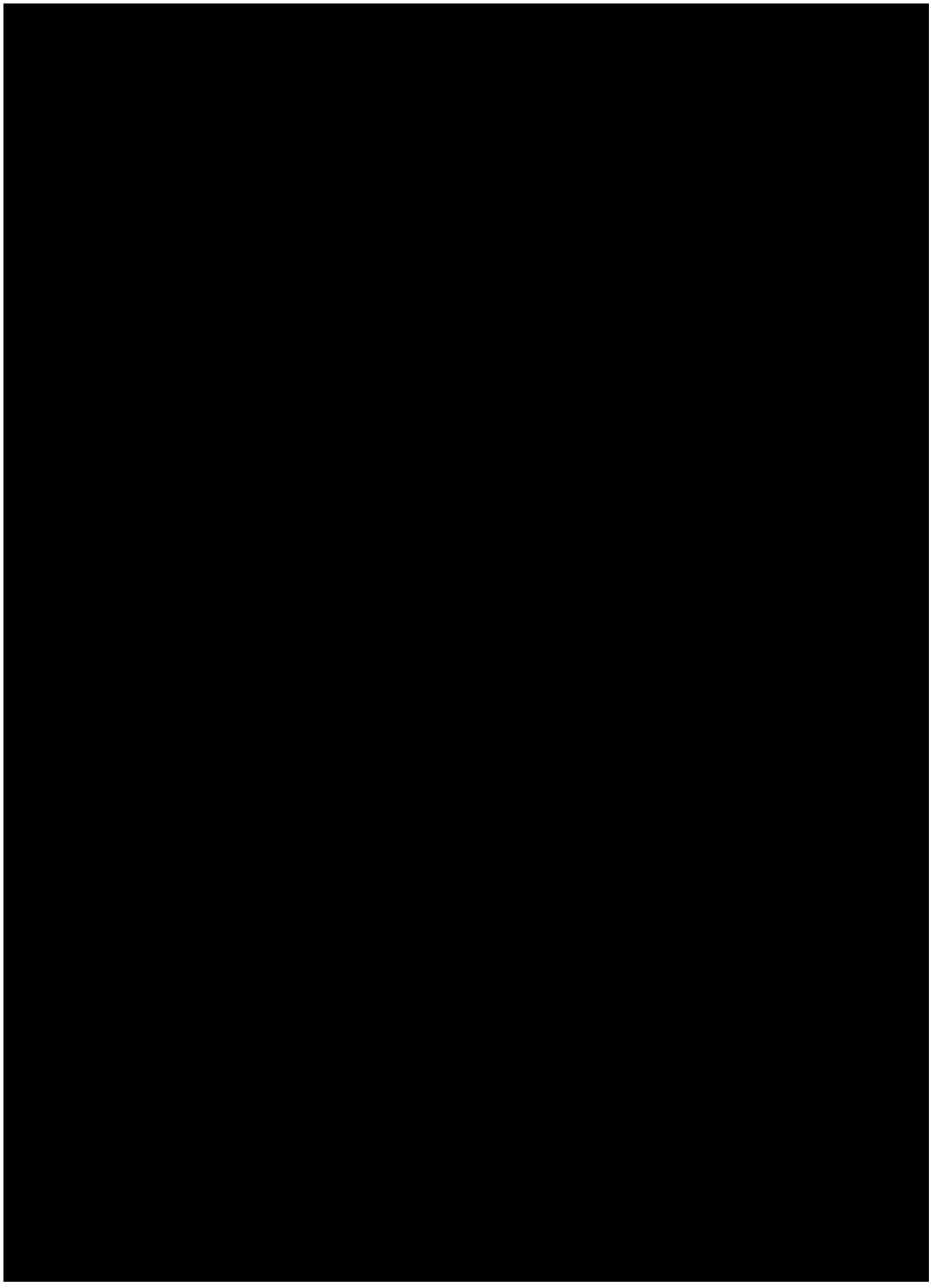
> HbA_{1c} change from baseline at each on-treatment visit = overall mean + HbA_{1c} baseline + treatment + renal function + pretreatment with metformin + visit + visit by treatment interaction + visit by HbA_{1c} baseline interaction + random error

This model includes effects accounting for the following sources of variation: 'HbA_{1c} baseline', 'treatment', 'renal function', 'pretreatment with metformin', 'visit', 'visit by treatment interaction' and 'HbA_{1c} baseline by treatment interaction'. 'Treatment', 'renal function', 'pretreatment with metformin', 'visit' and 'visit by treatment interaction' are fixed classification effects, and 'HbA_{1c} baseline' is a linear covariate. The interaction 'visit by HbA_{1c} baseline interaction' will be based on the linear covariate 'HbA_{1c} baseline'.

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. If the model first fails to converge using an unstructured (co)variance structure, then a hierarchical approach is applied until a (co)variance structure is obtained where the model converges. Therefore the following (co)variance structures are tested according to the pre-specified order: [1] unstructured, [2] Toeplitz, [3] variance components, [4] compound symmetry. As soon as one model converges this will be the final model used, therefore no further testing of subsequent (co)variance structures is required.

The treatment effect will be estimated on the basis of the least square mean treatment difference at week 24 extracted from the primary analysis model.

The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$ (two-sided 95% confidence intervals).

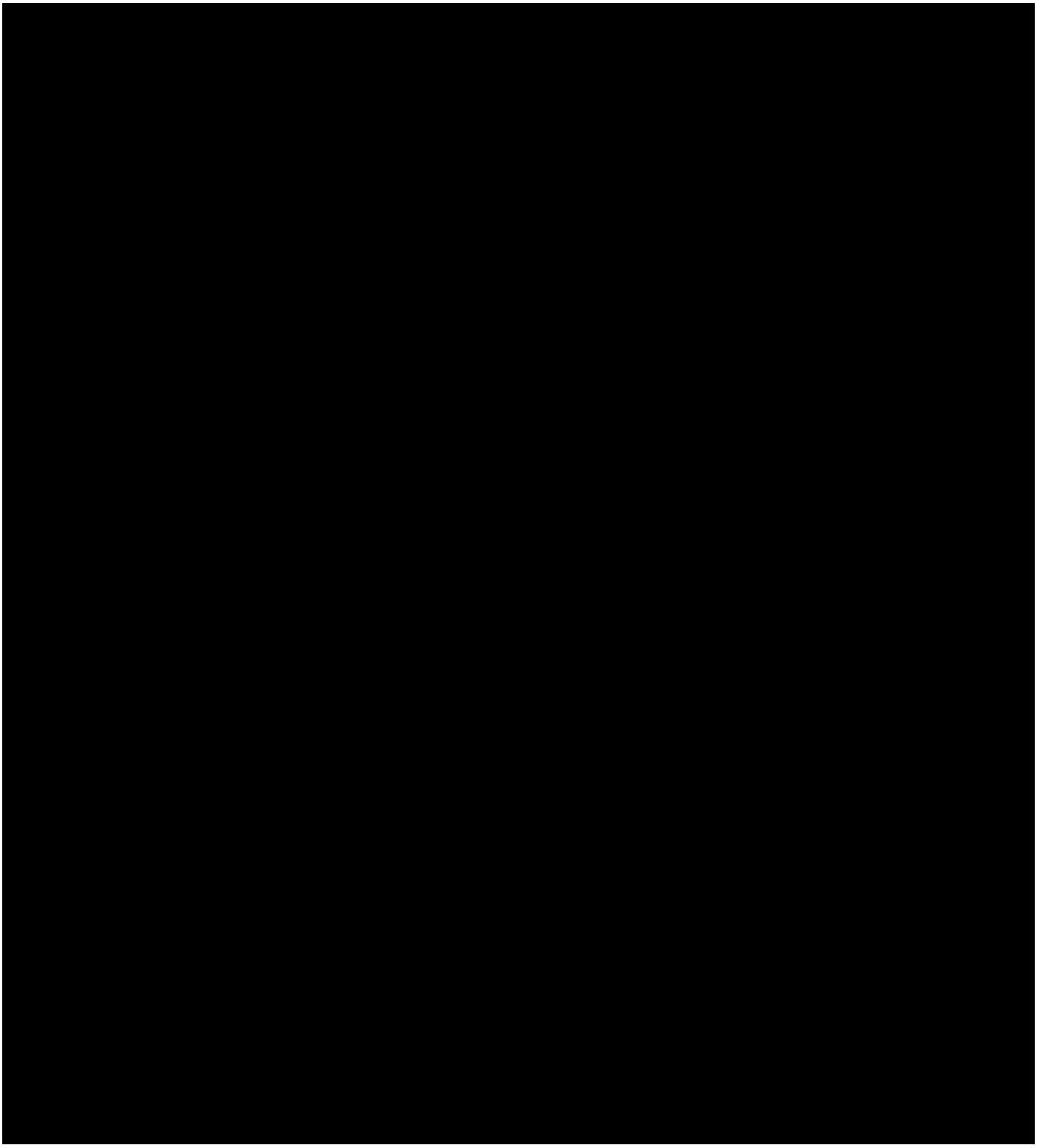


[redacted]

7.4.3 Effect of centre

Not applicable for this trial due to low patient numbers per site.

[redacted]



7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

The key secondary endpoints for this study are described in Section 5.2.

For the following key secondary endpoints:

- Change from baseline in mean 24-hour ambulatory SBP at week 12
- Change from baseline in trough mean ambulatory SBP at week 12

ANCOVAs will be performed based on the FAS (LOCF-H), [redacted] The respective model will include treatment, renal function, pretreatment with metformin, continuous baseline HbA_{1c} and continuous baseline of the respective secondary endpoint.

The results from these analyses will be presented graphically as for the descriptive values. As ambulatory measurements only provide one post-baseline assessment until week 12 (i.e. no repeated measurements), MMRM models will not be applied for these endpoints.

MMRM will be performed for the remaining key secondary endpoints (to be tested as third and fourth key secondary endpoints, respectively):

- change from baseline in body weight at week 24
- change from baseline in trough seated SBP at week 12

based on the FAS (OC) or FAS (OC-H), [redacted]. The model will be the same as that defined for the primary efficacy analysis with the addition of the continuous baseline key secondary endpoint as a covariate and visit by continuous baseline key secondary endpoint interaction.

[redacted]

[redacted]

Summary of hierarchical testing strategy for confirmatory analysis for superiority testing of treatment effect of Empa vs. Placebo (each step is tested at the two-sided alpha-level of 5%):

I. Primary endpoint: Change from baseline in HbA_{1c} (%) at week 24
   - Primary analysis: MMRM on FAS (OC)

II. Key secondary endpoint: Change from baseline in mean 24-hour ambulatory SBP (mmHg) at week 12
   - ANCOVA on FAS (LOCF-H)

III. Key secondary endpoint: Change from baseline in mean trough ambulatory SBP (mmHg) at week 12
   - ANCOVA on FAS (LOCF-H)

IV. Key secondary endpoint: Change from baseline in body weight (kg) at week 24
   - MMRM on FAS (OC)

V. Key secondary endpoint: Change from baseline in trough seated SBP (mmHg) at week 12
   - MMRM on FAS (OC-H)

7.5.2 (Other) Secondary endpoint(s)

The other secondary efficacy endpoints for this study are specified in Section 5.2.2.

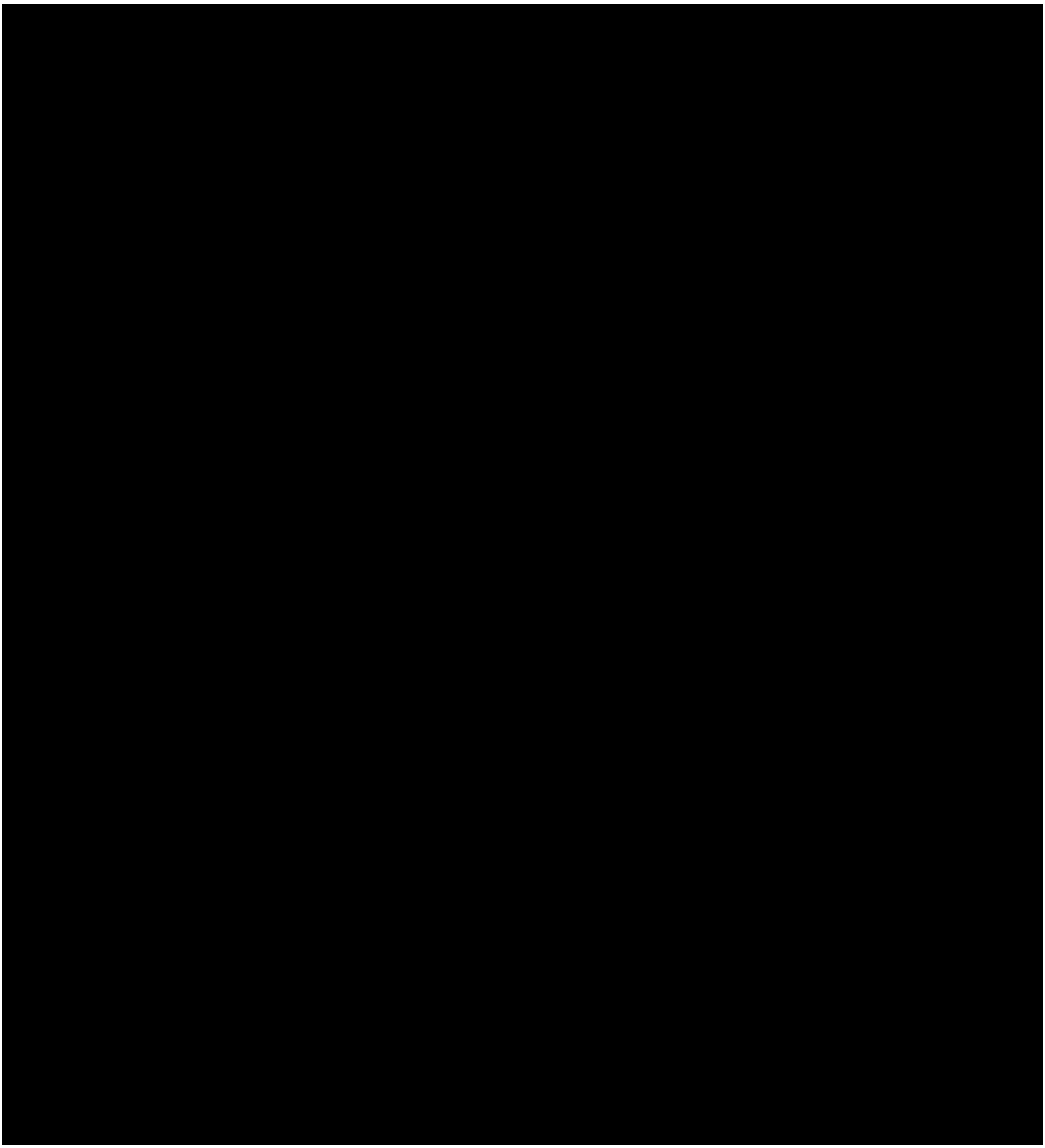
If not specified differently for a specific endpoint, the analysis of continuous endpoints and descriptive statistics will be provided by visit for the FAS (OC) or FAS (OC-H) if applicable including actual values and change from baseline.

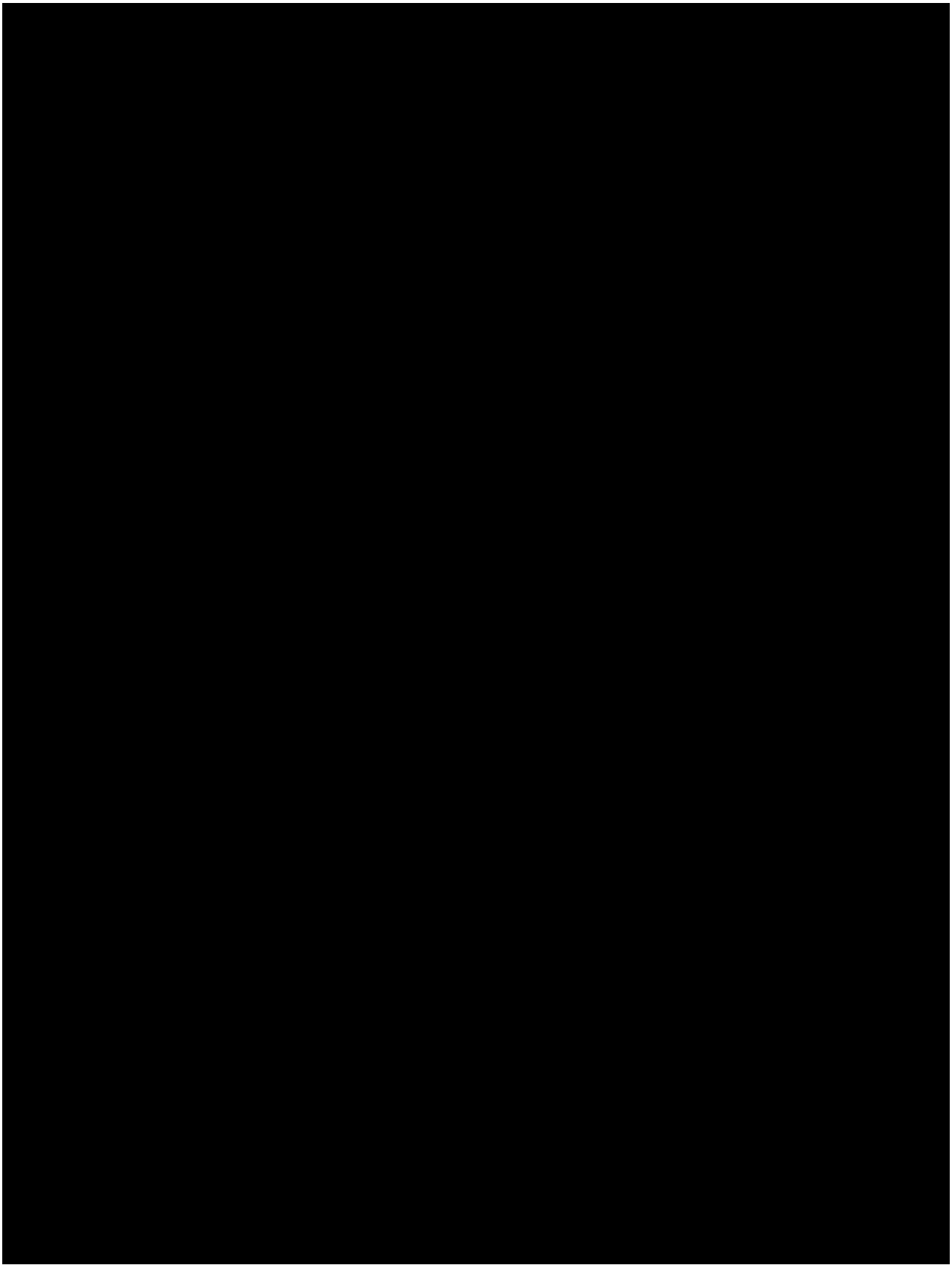
For the continuous exploratory endpoints (with more than one post-baseline assessment), MMRM analyses will be performed for the change from baseline at week 12 or week 24 (see Section 5.2.2) based on the FAS (OC) or FAS (OC-H) if applicable. For those endpoints with only one post-baseline assessment, an ANCOVA analysis will be performed on the FAS (LOCF) or FAS (LOCF-H) if applicable.

The respective MMRM model will include continuous baseline HbA_{1c}, continuous baseline of corresponding endpoint, treatment, renal function, pretreatment with metformin, visit by treatment interaction, visit by continuous baseline HbA_{1c} interaction and visit by continuous baseline of corresponding endpoint interaction. An unstructured covariance matrix for patient will be assumed; if this fails to converge, alternative matrices will be assessed as defined for the analysis of the primary efficacy endpoint in Section 7.4.1.

ANCOVA analyses will be performed based on the FAS (LOCF) or FAS (LOCF-H) if applicable. The respective model will include treatment, renal function, pretreatment with Metformin, continuous baseline HbA_{1c} and continuous baseline of the respective endpoint.

[redacted]





7.7 EXTENT OF EXPOSURE

A descriptive statistics table with mean, SD, Q1, median, Q3 and range of the number of days a patient was on-treatment will be provided for the TS. The tables will also provide the sum total of the time (in years) that all patients 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 8 weeks, >8 to 15 weeks, >15 to 21 weeks, >21 to 26 weeks, >26 weeks

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

7.8.1 Adverse events

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

Any clinically significant new finding in the physical examination, vital signs (BP and pulse symptoms) and in the 12-lead ECG starting after visit 2 (randomisation visit) will be considered as an AE and will be reported as such.

The analyses of AEs 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 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: [1] Hypoglycaemic events are only collapsed if they occur within 12 hours of each other. The 12 hour period will begin with the first hypoglycaemia onset time. If another event occurs outside this initial 12 hour window a new period for collapsing will begin. [2] GI events will not be collapsed if they are representative of different types (i.e. fungal balanitis or vulvovaginitis versus other than fungal balinitis or vulvovaginitis). [3] 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' (6).

7.8.1.1 Assignment of AEs to treatment

The analysis of AEs will be based on the concept of treatment-emergent AEs. This means that all AEs occurring between first drug intake until 7 days after last drug intake will be assigned to the first treatment received. All AEs occurring before first drug intake will be assigned to 'pre-treatment' and all AEs occurring after last drug intake + 7 days will be assigned to 'post-treatment'.

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). Appendix 16.1.9.2 will include an analysis where AEs and serious AEs (SAEs) are assigned to the following phases: Screening, placebo run-in, each treatment group, post-treatment for each treatment group.

7.8.1.2 Analysis of other significant AEs

Other significant AEs will be reported and summarised according to ICH E3 criterion (7). Thus, AEs classified as 'other significant' will include those non-serious and non-significant AEs with:

- ‘action taken = discontinuation’ or ‘action taken = reduced’, or
- marked haematological and other lab abnormalities or lead to significant CT as identified by the Clinical Monitor/Investigator at a Medical Quality Review meeting (MQRM) or BRPM.

7.8.1.3 AE summaries

An overall summary of AEs will be presented.

The frequency of patients with AEs 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, for patients with AESI, for patients with SAEs, for patients with AEs leading to discontinuation, and for patients with drug-related AEs.

The SOCs will be sorted according to the standard sort order specified by European medicines agency (EMA), PTs will be sorted by frequency (within SOC).

7.8.1.4 Analysis of hypoglycaemic events

The investigator will record for each AE whether it represents a hypoglycaemic AE and, if so, record additional information to assess the intensity of the hypoglycaemic AE. On the basis of this information the hypoglycaemic AE will be classified as:

- asymptomatic hypoglycaemia: event not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration < 3.0 mmol/L (< 54 mg/dL),
- documented symptomatic hypoglycaemia with a measured plasma glucose concentration ≥ 3.0 mmol/L and ≤3.9 mmol/L (≥ 54 mg/dL and ≤ 70 mg/dL): event accompanied by typical symptoms of hypoglycaemia,
- documented symptomatic hypoglycaemia with a measured plasma glucose concentration < 3.0 mmol/L (< 54 mg/dL): event accompanied by typical symptoms of hypoglycaemia but no need for external assistance,
- severe hypoglycaemic episode: event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions.
- symptomatic hypoglycaemia and plasma glucose concentration > 3.9 mmol/L (>70 mg/dL)
- symptomatic hypoglycaemia and plasma glucose concentration not measured

Asymptomatic hypoglycaemia with a measured plasma glucose concentration ≥ 3.0 mmol/L and ≤ 3.9 mmol/L (≥ 54 mg/dL and ≤ 70 mg/dL) will also be recorded by the investigator but will not be regarded as an AE.

The number of patients with hypoglycaemic AEs or non-AEs according to investigator's judgement will be tabulated by treatment group. A subgroup analysis of confirmed hypoglycaemic AEs with respect to age category, antidiabetic rescue therapy and renal function will be performed. Confirmed hypoglycaemic AEs are defined as hypoglycaemic AEs according to investigator's judgement confirmed with plasma glucose concentration ≤3.9 mmol/L (≤ 70 mg/dL) or required assistance.

The impact of treatment on the occurrence of hypoglycaemic AEs will be explored using logistic regression with model involving treatment, renal function, pretreatment with metformin and continuous baseline HbA_{1c}. Time to the onset of the first hypoglycaemic AE will be analysed by Kaplan-Meier estimates. The logistic regression and Kaplan-Meier analysis will be performed on confirmed hypoglycaemic AEs.

Summaries of hypoglycaemic events will include total number of hypoglycaemic events, descriptive hypoglycaemic 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. Hypoglycaemic events will also be summarised by baseline eGFR category (CKD-EPI) and age group.

In addition, the frequency of hypoglycaemic AEs characterized by the latest BIcMQ version terms will also be produced.

Different tables will be shown for (i) patients with investigator defined asymptomatic or symptomatic hypoglycaemia reported as AE or non-AE, (ii) patients with confirmed hypoglycaemic AEs, i.e. hypoglycaemic AEs that had a plasma glucose concentration ≤3.9 mmol/L (≤ 70 mg/dL) or required assistance, and, iii) patients with minor, confirmed hypoglycaemic AEs, defined as a hypoglycaemic event that had a plasma glucose concentration ≤ 3.9 mmol/L (≤ 70 mg/dL) but did not require assistance.

7.8.1.5 AEs of special interest (AESI)

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

- Decreased renal function: creatinine shows a ≥2 fold increase from pre-treatment/baseline and is above the upper limit of normal (ULN)
- Hepatic injury defined by the following alterations of liver parameters after randomization: AST and/or ALT ≥ 3 fold ULN and bilirubin ≥ 2 x ULN measured in the same blood sample, or isolated elevation of AST and /or ALT ≥ 5 fold ULN irrespective of any bilirubin elevation.
- Metabolic acidosis, ketoacidosis and diabetic ketoacidosis (DKA)

Events of these AESIs are identified through the AE being flagged by the investigator as significant on the case report form (CRF).

AE frequency tables will also be created for renal and hepatic events based on narrow SMQs.

Renal:

- Acute renal failure: 20000003 (narrow SMQ)

Hepatic:

- 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)

AE frequency tables will be created for the following AESI events based on narrow SMQs:

- Malignancies: (20000090) (narrow SMQ)

The following additional AESI will also be assessed and AE frequency tables constructed based on the latest MedDRA version at database lock:

- GI (BICMQ genital tract infections EMPA folder, investigator assessment)
- UTI (narrow BICMQ, investigator assessment)

AESIs of UTIs and GIs will additionally be summarised by age group, baseline HbA1c, intensity (mild, moderate or severe), whether leading to discontinuation of treatment, time of occurrence (in the first 3 months of treatment or after), duration (<7 days, 7-14 days and >14 days), sex, by how the event was treated (no treatment, therapy assigned, hospitalisation) and the number of episodes per patient.

The following AESIs based on investigator assessment will also be tabulated by treatment group:

- Acute pyelonephritis: patient incidence overall and by intensity, and treatment required (0, 1, 2, >2 antimicrobials)

- Sepsis: patient incidence overall and by source of infection
- Asymptomatic bacteriuria: patient incidence overall
- Bone fractures: patient incidence overall and by type of fracture, intensity, and time to onset of first fracture

In the number of episodes analysis of UTI and GI AEs will be collapsed within each special search category (SSC) regardless of PT with the collapsing following the description at the start of Section 7.8.1 but the condensing will not be conducted in order to maintain multiple episodes per patient.

Kaplan-Meier time to event analyses will also be presented for the UTI and GI AESIs. These analyses will also be presented by sex.

An additional AESI of volume depletion will be used and an AE frequency table constructed. The AESI will be based on the latest MedDRA version at database lock:

- Volume depletion: BICMQ (EMPA folder/sub-BICMQ origin vascular narrow)

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

For DKA events see Section 7.8.1.12.

7.8.1.7 Other AEs

Not applicable for this trial.

7.8.1.8 Pancreatic Events Qualifying for External Adjudication by the CEC

Not applicable for this trial.

7.8.1.9 AEs while patients taking wrong medication

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

7.8.1.10 Adjudicated Hepatic Injury Events

The assessments will be analysed on project level.

7.8.1.11 Adjudicated Cancer Events

The assessments will be analysed on project level.

7.8.1.12 Adjudicated DKA Events

The assessments will be analysed on project level.

7.8.2 Laboratory data

For continuous safety laboratory parameters, standardised and normalised values will be derived as well as the differences to baseline. 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 (8). All analyses considering multiple of times ULN will be based on original and not normalised data.

To support analyses of liver related adverse drug effects, patients with aspartate transaminase (AST) and/or alanine transaminase (ALT) ≥3xULN with concomitant or subsequent total bilirubin (TBL) ≥2xULN in a 30 day period after AST/ALT elevation are of importance. The start of the 30 day time span is triggered by each liver enzyme elevation above the defined thresholds. If the 30 day period for TBL spans both treatment periods, the event is assigned based on the date of AST/ALT elevation. Patients who fulfil one or two of the criteria for AST/ALT or TBL elevations above and have 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 TBL ≥2xULN" . An additional presentation including all events up to 30 days after the last dose of study treatment will also be included.

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 normalised values with BI standard reference ranges. The creatinine clearance and glomerular filtration rate will be estimated according to the two formulas 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))
    - Black female:
        - If serum creatinine ≤ 0.7

          CKD-EPI formula (mL/min/1.73m²): eGFR (mL/min/1.73m²) = 166 x [serum creatinine (mg/dL)/0.7]$^{-0.329}$ x 0.993^{age}
        - If serum creatinine > 0.7

          CKD-EPI formula (mL/min/1.73m²): eGFR (mL/min/1.73m²) = 166 x [serum creatinine (mg/dL)/0.7]$^{-1.209}$ x 0.993^{age}
    - Black male:
        - If serum creatinine ≤ 0.9

          CKD-EPI formula (mL/min/1.73m²): eGFR (mL/min/1.73m²) = 163 x [serum creatinine (mg/dL)/0.9]$^{-0.411}$ x 0.993^{age}
        - If serum creatinine > 0.9

          CKD-EPI formula (mL/min/1.73m²): eGFR (mL/min/1.73m²) = 163 x [serum creatinine (mg/dL)/0.9]$^{-1.209}$ x 0.993^{age}

Age will be considered as a discrete variable for the above calculations, and the age will be from the same visit as the other variables. If a value is not available, an interpolated value from the previous and subsequent visits will be used. If no subsequent value is available an LOCF approach will be used. Baseline values will not be interpolated and no interpolation will be done across study periods. See Section 6.6 for further information.

For the analysis of eGFR (CKD-EPI) 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 PVs based on renal function the central laboratory values will be used.

Table 7.8.2: 1 CKD-EPI staging

Stage	**eGFR (CKD-EPI) (mL/min/1.73m²)**	**Description**	**Label for displays**	***Additional labels#***
1	≥120	Normal renal function	≥120 (normal)	*≥120 (normal)*
2	<120 to >60	Mild renal impairment	<120 to >60 (mild)	*<120 to >60 (mild)*
3	≤60	Moderate/severe or end-stage renal impairment	≤60 (moderate/severe)	*≤60 (moderate/severe)*

Staging of the eCCr will be prepared with respect to the following categorisation and a shift table will be supplied for eCCr as well (Table 7.8.2: 2)

Table 7.8.2: 2 Cockcroft-Gault eCcr staging

Stage	**eCcr (mL/min)**	**Description**	**Label for displays**
1	≥90	Normal renal function	≥90 (normal)
2	60 to <90	Mild renal impairment	60 to <90 (mild)
3	30 to <60	Moderate renal impairment	30 to <60 (moderate)
4	<30	Severe renal impairment and beyond (e.g. End-stage renal disease)	15 to <30 (severe) + <15 (end-stage): <30 (severe to end stage)

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (see DM&SM: Display and Analysis of Laboratory Data) (8).

Baseline for safety laboratory parameters will be the last available measurement before the start of randomised trial drug. Laboratory measurements taken up to 3 days after the last administration of randomised trial drug will be considered as on-treatment or up to start of treatment with a new trial drug in the extension trial, whichever comes first.

Laboratory values will be compared to their reference ranges and frequency tables will be provided for the number of patients within and outside the reference range at baseline and the last measurement on-treatment. Descriptive statistics will be provided by treatment group for baseline, on-treatment values and for changes from baseline. Frequency tables will summarise the number of patients with potentially clinically significant abnormalities as defined for the new XLAB macro (version 2.03). Details on patients with elevated liver enzymes will be listed. Summaries will also be presented for patients with elevated liver

enzymes. A scatter plot of peak ALT against peak TBL will be presented with reference lines for 3xULN and 2xULN TBL, including an indicator for treatment received.

A summary will also be created representing the number of patients per treatment group that experienced a doubling in creatinine on-treatment compared to baseline that was out of the normal range.

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.

Urine creatinine does not have a reference range and is determined to calculate the albumin / creatinine ratio. Only the albumin / creatinine ratio will be analysed as for urine creatinine no normalised values can be derived. In cases where urine albumin values are reported to be below the quantification limits (e.g. <3 mg/L) the albumin / creatinine ratio is determined as missing and will not be replaced by estimated values. Additional summaries will be presented for the descriptive statistics of urine albumin/creatinine ratio by baseline value: normal (<30mg/g), microalbuminuria (30-≤300 mg/g) and macroalbuminuria (>300 mg/g), urine albumin by baseline value (<20mg/L, 20-<200mg/L and ≥200mg/L) and transitions from baseline based on the aforementioned categories.

A shift table from baseline to last value on-treatment for eGFR (CKD-EPI) will be provided in Section 15 of the CTR and eCCr (Cockcroft-Gault) will be provided in Appendix 16.1.9.2 of the CTR.

7.8.3 Vital signs

Analyses of SBP, DBP and PR are summarised in Section 15 of the CTR.

7.8.4 ECG

12-lead ECG measurements will be taken at baseline. ECG-findings before first intake of trial drug will be considered as baseline condition. In the event of any cardiac symptoms, an additional ECG will be recorded. Any clinically significant new findings in the ECG measurement after the first ECG will be considered as AEs and analysed as planned in Section 7.8.1.

7.8.5 Others

7.8.5.1 Creatinine and eGFR time curve analysis

Descriptive statistics will be created for creatinine and eGFR (CKD-EPI) values over time relative to pre-treatment and baseline separately by treatment and presented in tables. Descriptive statistics for eCCr will be presented in Appendix 16.1.9.2. These data will be used to create plots of the parameters over time. Subgroups tables of these descriptive statistics will also be presented for age subgroups.

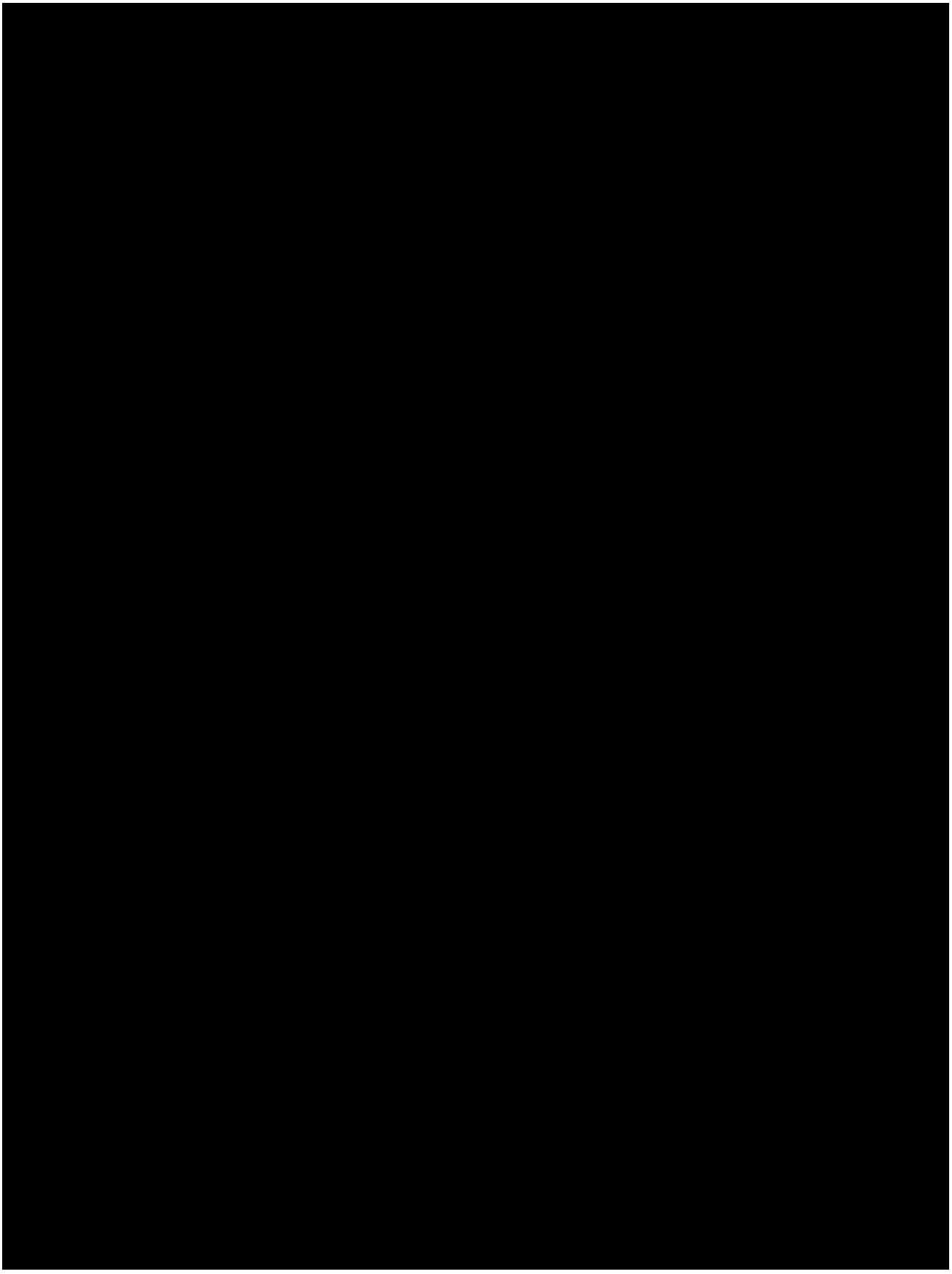
7.8.5.2 Lipid parameter analyses

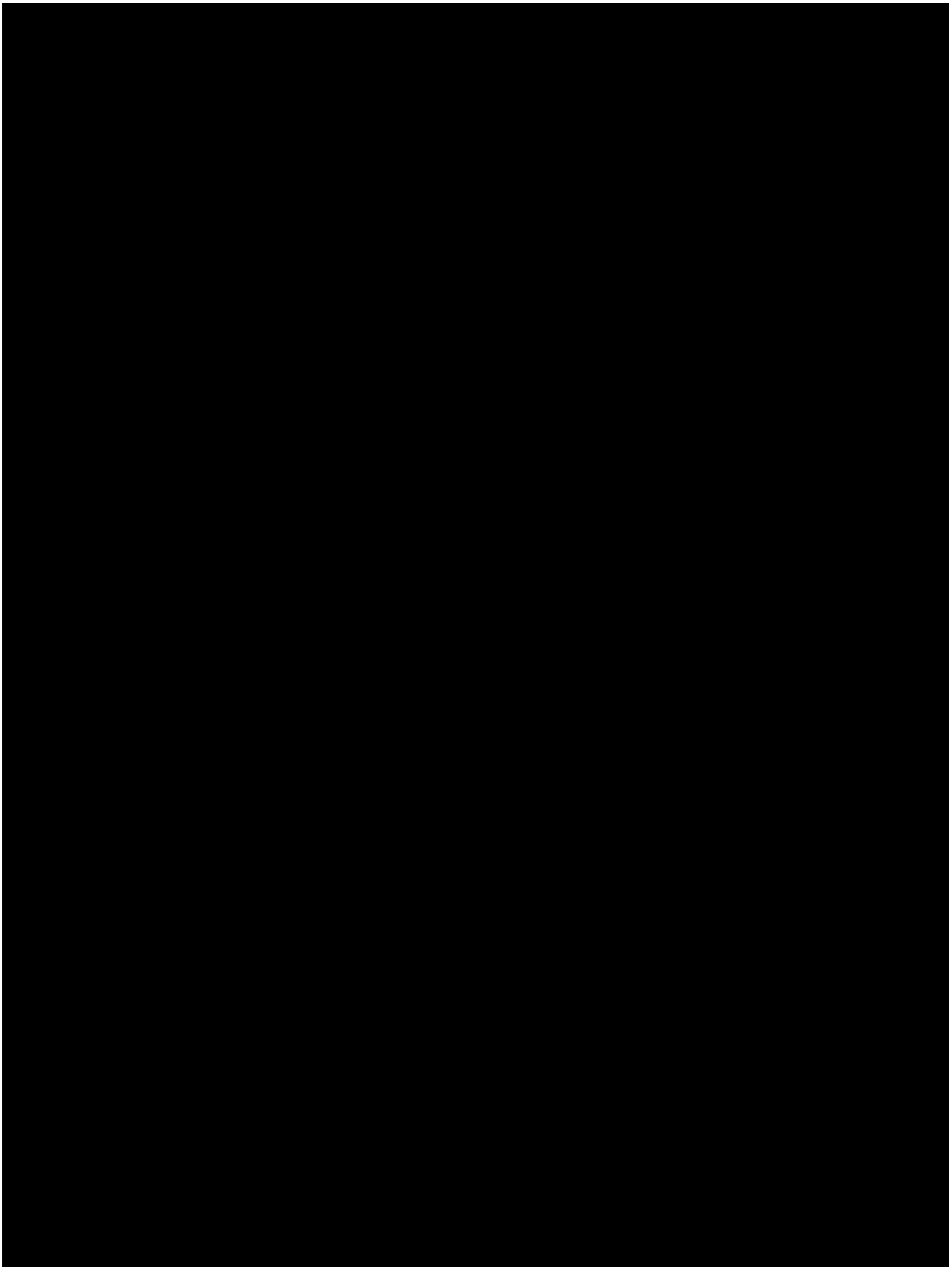
Lipid parameters will be analysed using descriptive statistics and MMRM modelling. [redacted] For each lipid parameter,

separate MMRM models will be fitted on the treated set [redacted] for both change from baseline at week 24 and percentage change from baseline at week 24 as dependent variables. The MMRM models will include baseline lipid and baseline HbA_{1c} as continuous covariates and renal impairment, pretreatment with metformin, treatment, visit, visit by treatment interaction, visit by baseline HbA_{1c} interaction and visit by baseline lipid interaction as fixed effects. They will be presented in both conventional and SI units.

8 REFERENCES

1	*c01945509-06:* "1245.29: Clinical Trial Protocol", BIRDS.
2	*001-MCG-156_RD-01*: "Handling of missing and incomplete AE dates", version 5.0; IDEA for CON.
3	*001-MCG-159*: "Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.
4	*R10-5462:* Siddiqui O, Hung J, O'Neill R. MMRM vs. LOCF: A comprehensive comparison based on simulation study and 25 NDA datasets. J. Biopharm. Stat. 2009; 19: 227–246
5	*R12-2378:* Rubin D.B.: Multiple Imputation for Nonresponse in Surveys. New York: John Wiley and Sons (1987)
6	*001-MCG-156*: Corp Guideline, "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", version 5.0; IDEA for CON.
7	*CPMP/ICH/137/95*: ICH Guideline Topic E3, "Structure and Content of Clinical Study Reports", current version; Note For Guidance on Structure and Content of Clinical Study Reports.
8	*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	Author	Sections changed	Brief description of change
Final	**16 AUG 2016**	[redacted]	None	This is the final TSAP without any modification
Revised	**24 MAR 2017**	[redacted]	Section 6.7 and Section 6.3, 6.6.2.6, 7.4.2, 7.4.5	Section 6.7: clarification for handling of repeated ABPM measurements if at least one successful reading is already available for a specific ABPM visit. [redacted]