Trial Statistical Analysis Plan

c08934834-02

BI Trial No.:	1245.100
Title:	A double-blind, placebo controlled, cross-over renal mechanistic trial to assess the effect of adding empagliflozin versus placebo on renal hyperfiltration on a background of the angiotensin converting enzyme inhibitor (ACEi) ramipril: BETWEEN Study Including Protocol Amendment 3 [c03608483-05]
Investigational Product(s):	Jardiance®, empagliflozin
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2. LIST OF ABBREVIATIONS

Term	Definition / description
ABPM	Ambulatory blood pressure monitoring
ADRNa	Absolute distal sodium reabsorption rate
ADS	Analysis dataset
AE	Adverse event
AESI	Adverse events of special interest
AIx	Augmentation index
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
APR	Absolute proximal fluid reabsorption rate
APRNa	Absolute proximal sodium reabsorption rate
AST	Aspartate transaminase
BHB	Beta-hydroxybutyric acid
BICMQ	BI customised MedDRA query
BMI	Body mass index
BP	Blood pressure
BRPM	Blinded report planning meeting
BSA	Body surface area
cAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
CI	Cardiac index
CLI	Lithium clearance
CNa	Sodium clearance
CO	Cardiac output
CPO	Cardiac power output
CPOI	Cardiac power output index
CS	Compound symmetry
CSII	Continuous Sub-cutaneous Insulin Infusion
CT	Concomitant therapies
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DB	Double-blind

Term	Definition / description
DDNa	Distal sodium delivery
DKA	Diabetic ketoacidosis
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
DTA	Data transfer agreement
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EoT	End of Treatment
ERPF	Effective renal plasma flow
FAS	Full analysis set
FDRNa	Fractional distal sodium reabsorption rate
FENa	Fractional sodium excretion
FELi	Fractional lithium excretion
FF	Filtration fraction
FPG	Fasting plasma glucose
FPR	Fractional proximal fluid reabsorption rate
FWER	Family-wise error rate
GFR	Glomerular filtration rate
HbA1c	Glycated haemoglobin
HRV	Heart rate variability
ICH	International Conference on Harmonisation
IPD	Important protocol deviation
ITT	Intention to treat
LOCF	Last-observation-carried-forward
MAP	Mean arterial pressure
MAR	Missing at random
MDI	Multiple daily injection
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model repeated measures
NA	Not applicable
O*C	Oracle Clinical
OL	Open label
PD	Protocol deviation

Term	Definition / description
PG	Plasma glucose
PLi	Plasma lithium
PNa	Plasma sodium
PK	Pharmacokinetics
PPS	Per protocol set
PSTAT	Project Statistician
PT	Preferred term
PWV	Pulse wave velocity
Q1	Lower quartile
Q3	Upper quartile
RBF	Renal blood flow
REML	Restricted maximum likelihood
REP	Residual effect period
RIS	Run-in set
RMSSD	Root mean square successive index
RVR	Renal vascular resistance
SD	Standard deviation
SDNN	Standard deviation of normal-to-normal interval
SE	Standard error
SMQ	Standardised MedDRA query
SOC	System organ class
SV	Stroke volume
SVI	Stroke volume index
SVV	Stroke volume variation
T1D	Diabetes mellitus type 1
T2D	Diabetes mellitus type 2
TFC	Thoracic fluid content
ToC	Table of contents
TPR	Total peripheral resistance
TPRI	Total peripheral resistance index
TS	Treated set
TSAP	Trial statistical analysis plan

Term	Definition / description
ULi	Urine lithium
UNa	Urine sodium
ULN	Upper limit of normal
unGFR	Uncorrected glomerular filtration rate
UTI	Urinary tract infection
V	Urine flow rate
VI	Vagal index
WHO	World health organisation

3. INTRODUCTION

As per ICH E9 (1), 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.

In July 2019 it was decided to terminate the trial early due to recruitment futility based on the inability to find patients with renal hyperfiltration. The study terminates with 31 patients randomised and treated. The basis will be CTP Version 4.0 and the analysis plan will be driven by the current known status of the study, in terms of the types of patients randomised.

Changes and additions from CTP version 4.0 are outlined in Section 4.

SAS® Version 9.4 will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Below are the high level changes that have been made to both the recent versions of the protocol and to the deviation from the protocol analyses, following early trial termination in July 2019.

<u>High level changes to recent versions of protocol</u>:

The primary patient population was changed from diabetes mellitus type 1 (T1D) only to either T1D, diabetes mellitus type 2 (T2D) or obesity in CTP global amendment 3.

The primary analysis population was changed from non-responders to hyperfilterers, i.e. patients with a glomerular filtration rate (GFR) ≥ 135 mL/min/1.73m^2 at visit 4 instead of visit 8 in CTP global amendment 3. Consequently, a secondary analysis for the primary endpoint was planned to be performed on the non-responder subgroup. Further, in the secondary analysis of the primary endpoint on all patients in the full analysis set, the gradient of the treatment effect will be calculated based on randomization baseline GFR values that are centred around the mean baseline value instead of the originally anticipated value of 135 mL/min/1.73m^2, as with the changed population a baseline value of 135 mL/min/1.73m^2 is no longer considered a central value. In the first 31 patients randomized into the trial inulin was used to measure GFR for the primary endpoint analysis. However, as inulin will no longer be available, iohexol would have been used to measure GFR for the remaining patients to be randomized into the trial.

In CTP global amendment 3 the secondary endpoint filtration status was changed from a threshold of < 135 mL/min/1.73m^2 to < 120mL/min/1.73m^2 in line with the lower baseline GFR values expected in the new primary analysis population of hyperfilterers compared to non-responders.

The further endpoints “protein intake” and “ratio of GFR to baseline” were removed and the further endpoint “24hour urea” was added in CTP global amendment 1.

The further endpoint “urine albumin / creatinine ratio” was removed and the further endpoints “glomerular pressure”, “efferent resistance”, “afferent resistance” and “ketones/BHB” were added in CTP global amendment 3.

Because the primary analysis population for the primary endpoint was changed in CTP global amendment 3, the sample size section was adapted accordingly.

<u>High level changes to TSAP compared to protocol version 4.0:</u>

The main deviation from the protocol-defined efficacy analyses will be on the analysing populations. In addition, one planned analysis for the primary endpoint will be removed and some further endpoints added. Subgroup analyses are now included for the eight renal haemodynamic parameters and for the 24-hour ambulatory blood pressure monitoring (ABPM) of systolic blood pressure (BP), diastolic BP and pulse rate.

Since no patients were randomised under the iohexol clearance method, reference will be made to inulin clearance only.

Primary endpoint analysis

Analyses on subgroups of GFR hyperfilterers (n=2), GFR responder (n=2) and GFR non-responder (n=0) groups are not possible because there are too few patients per group. Therefore, it is not possible to test the null hypothesis of the study.

Subsequently, no per protocol set (PPS) will be determined, however, the important protocol deviations will still be identified prior to unblinding.

The subgroup of normofilterers (n=29) is very similar to the overall set of patients in the full analysis set (FAS) (n=31) and therefore, only the overall set of patients will be analysed.

For the overall set of patients, all pre-specified analyses will be implemented, except for the pre-specified analysis using screening GFR and the screening GFR by treatment interaction. Due to the high correlation between screening GFR and baseline (pre-randomisation) GFR, it is expected that this would lead to similar findings, compared to the analysis (with interaction) using pre-randomisation GFR as baseline.

The assumptions behind the models will be investigated by way of model diagnostics and the potential period effect by graphics. Otherwise, the analyses will be as per protocol.

Secondary endpoint analysis

The secondary endpoint of proportion of patients with GFR < 120 mL/min/1. 73m^2 will be analysed on the FAS only, and with an additional investigation of the GFR status (< 120 vs ≥ 120 mL/min/1.73m^2) at baseline, given that many of the patients are already <120 mL/min/1.73m^2 at baseline.

Further endpoint analysis

With regard to the further efficacy endpoints, these will be conducted according to protocol. For the planned analyses on the treated set (TS), only the full TS will be used.

Additional further endpoints for Tubular sodium handling will be added:

- Fractional sodium excretion (FENa)
- Absolute proximal fluid reabsorption rate (APR)
- Absolute proximal sodium reabsorption rate (APRNa)
- Fractional proximal fluid reabsorption rate (FPR)
- Absolute distal sodium reabsorption rate (ADRNa)
- Fractional distal sodium reabsorption rate (FDRNa)

Additional further endpoints for Cardiovascular and blood pressure parameters will be added:

- Cardiac index (CI)
- Stroke volume variation (SVV)
- Stroke volume index (SVI)
- Total peripheral resistance index (TPRI)
- Cardiac power output (CPO)
- Cardiac power output index (CPOI)
- Thoracic fluid content (TFC)

The plan for the analysis of the ABPM parameters will be outlined in the TSAP, as already indicated in the protocol. However, additional further endpoints will be created from the data collected. Since the ABPM data is collected automatically over a 24 hour period, the following endpoints will be determined for each of systolic blood pressure, diastolic blood pressure and pulse rate, and grouped accordingly:

- 24-hourly mean
- Night time mean, Day time mean
- Awake time mean, Sleep time mean
- Trough to peak ratio

Subgroup analysis

There will be descriptive subgroup analyses to investigate the relationship between the 8 renal haemodynamic parameters (GFR and the 7 further efficacy endpoints) and screening GFR subgroups with categories (≤115 vs >115 mL/min/1.73m^2). The value of 115 mL/min/1.73m^2 approximately represents the median GFR at screening baseline.

Additionally, the relationship between the 24-hourly mean ABPM parameters (systolic BP, diastolic BP and pulse rate) and the two subgroups of baseline body mass index (BMI) (≤median, >median) and baseline blood pressure (low, high) will be conducted. The specific values of low and high will be defined in the subgroup analysis Section 7.9.

For each of these 11 endpoints, a small selection of the main graphical displays will be split by these subgroups, to try to identify patterns.

For the renal haemodynamic parameters only, a mixed-effect model repeated measures (MMRM) will be conducted.

5. ENDPOINTS

This study comprises an open-label run-in treatment period with ramipril, followed by a double-blind (DB) treatment period. The DB treatment period further comprises: 1) two crossover periods, during which either empagliflozin or placebo is taken in addition to open-label ramipril (determined according to the randomised treatment sequence); 2) a washout period between the two crossover periods, during which only open-label ramipril is taken.

To avoid all ambiguity, the term "baseline" should not be used without further qualification. Measurements taken prior to the start of open-label ramipril treatment will be referred to as "screening baseline". Measurements taken prior to randomisation to one of the two double-blind treatment sequences will be referred to as "randomisation baseline".

Owing to the proposed data capture in this trial (as per CTP flowchart), a need to consider separate "period baselines" (i.e. baseline values prior to each of the two crossover periods) in all analyses is not envisaged. For select safety laboratory data, period baseline will be used where available.

5.1 PRIMARY ENDPOINT

The primary endpoint is GFR under euglycaemic conditions after 4 weeks of double-blind treatment (either empagliflozin or placebo added to ramipril).

GFR is measured in units of mL/min/1.73m^2 (=mL•min^{-1}•1.73m^{-2}). GFR will be calculated by the local laboratory using the inulin clearance method and then entered by the study site onto the electronic case report form (eCRF). The required euglycaemic conditions are those imposed by the clamp used in the trial.

Inulin method for post baseline visits: Two clearance measurements are taken in the derivation of each GFR reading, scheduled at 90 minutes and 120 minutes after the start of infusion respectively. The mean of the pair of GFR measurements at the relevant 4-week visits (visits 11 and 15) will be calculated and used as the primary endpoint value. If only one GFR measurement is available, the primary endpoint will be that single value.

All recorded GFR measurements on the eCRF will be considered eligible for derivation of the primary endpoint and will be included in the FAS analysis. However, any values measured outside of the visit window (see Table 6.7: 2) will not be used and will therefore not contribute to the primary endpoint derivation.

It will be assumed that any GFR values which are technically implausible or otherwise incorrect will be removed from the trial database during data cleaning prior to analysis.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

Not applicable.

5.2.2 Secondary endpoint

The secondary endpoint is filtration status after 4 weeks of double-blind treatment (either emplagliflozin or placebo added to ramipril). Filtration status is defined as whether a patient has normal filtration status (GFR < 120 mL•min^{-1}•1.73m^{-2}, "yes"), or not (GFR ≥ 120 mL•min^{-1}•1.73m^{-2}, "no"). GFR is calculated as for the primary endpoint.

No inferential analysis strategy with family-wise error rate (FWER) control is considered. Therefore, p-values for the secondary endpoint analysis can just be regarded as a descriptive measure of the degree of consistency of observed treatment differences with random variability. Likewise, confidence intervals can be regarded as a descriptive measure of the plausibility range of the effect size.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

There will be a maximum of eight treatment periods for patients included in this trial: screening, Ramipril run-in, ramipril post-treatment, on-treatment (crossover) period 1 (with either empagliflozin or matching placebo), treatment x wash-out period, on-treatment (crossover) period 2 (with either empagliflozin or matching placebo), treatment x post-treatment period, and post-study. The definitions of each of these treatment periods are defined in Table 6.1: 1 below. (**Note:** 'double-blind medication' refers to either empagliflozin or placebo and 'any study medication' refers to either ramipril, empagliflozin or placebo.)

Table 6.1: 1 Definitions of treatment periods

Period	Start date	End date
Screening	Informed consent	Start date of open-label ramipril run in period – 1 day
Ramipril run-in	First administration of open-label Ramipril	Start date of DB on-treatment period 1 – 1 day, or, Date of last intake of open-label ramipril + x (for those patients who were not treated with DB medication)
Ramipril post treatment#	Date of last intake of open-label ramipril + x + 1	Last study contact.
On-treatment period 1 'Period 1' or 'Empa 25mg' or 'Placebo'	Date of first administration of first DB medication	Date of last administration of first DB medication + x
Treatment x washout 'Empa 25mg washout' or 'Placebo washout'	Date of last intake of first DB medication + x + 1	Start date of second DB on-treatment period – 1 day. Date is not defined for patients who did not receive DB medication in period 2
On-treatment period 2 'Period 2' or 'Empa 25mg' or 'Placebo'	Date of first administration of second DB medication	Date of last administration of second DB medication + x
Treatment x post treatment 'Empa 25mg post treatment' or 'Placebo post treatment'	Date of last administration of DB medication + x + 1 day	Date of last study contact + 1 day
Post study	Date of last study contact + 1 day	Date of trial database lock. Date is not defined for a patient that is lost to contact whilst still receiving study medication.

For efficacy, x=1 day, for AE x=7 days and for laboratory parameters x=3 days as defined in Section 6.7.
This time period is defined only for patients treated with open label ramipril but not DB medication (and therefore not in the TS).

For certain efficacy and safety analyses, as well as for laboratory data, measurements will still be considered on-treatment during a follow-up period of e.g. X = 7 days (see Section 6.7). This will be applied programmatically where needed and not used in trial database set up; for the latter X = 0 will be used.

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 medication, the patient will be analysed according to the actual trial medication received. In addition, AEs with an onset during the time of the incorrect study treatment will be tabulated and listed separately.

The open-label ramipril run-in period will be labelled as the single treatment arm "OL Ramipril" on relevant outputs.

The first and second double-blind on-treatment periods will be labelled "Empa 25mg" and "Placebo" according to the medication assigned to or taken in that period (note: the additional background ramipril will not, therefore, form part of the double-blind treatment labels).

Demographic and baseline summaries will be presented by assigned treatment sequence, which will be labelled as "Empa25/Pbo" and "Pbo/Empa25" respectively. On these summaries a "Total" column will be presented, which is the sum of the number of patients in the two treatment sequence columns.

In general, on efficacy and safety tables presenting double-blind treatment, a "Total" column will not be added, noting in any case that for a crossover design, "Total" is not the sum of the number of patients displayed under "Empa 25mg" and "Placebo".

A limited number of exploratory outputs may also display the crossover period as well as the double-blind treatment. For this purpose, the labels used will be "Period 1" and "Period 2".

6.2 IMPORTANT PROTOCOL DEVIATIONS

There are two aspects that qualify a deviation of the protocol to be important (IPDs):

First, there are PDs that potentially affect the rights or safety of study patients. In this case, the sponsor needs to react immediately to such PDs to prevent recurrence. In most cases, these PDs do not have an impact on whether a patient can be included in an analysis, but they need to be described in the report.

Second, a PD can potentially influence the primary outcome measure for the respective patients in a way that is neither negligible nor in accordance with the study objectives. Therefore, such PDs potentially affect the main study results and conclusions. This second category of IPDs forms the basis for the decision of whether a patient does or does not belong to an analysis set. Further, for a crossover study, certain categories of IPD may affect only one of the two crossover periods, which raises the further possibility of whether the patient should

be retained in the analysis set with data from one of the two crossover periods excluded. Even though this trial has terminated early and there will be no PPS, this second set of IPDs will still be determined.

All other PDs are of minor importance and it is not necessary to describe or list these PDs in the integrated clinical trial report (CTR).

The following table defines the different categories of IPDs. The final column describes which IPDs will be used to exclude patients and/or individual measurements from the analysis sets (see also Section 6.3).

Table 6.2: 1 Important protocol deviations

Category/Code		Description	Example/Comment
A		**Entrance criteria not met**	
A1		**Target indication not met**	
	A1.02	Antidiabetic background therapy not as required for T1D patients	Inclusion criterion 3 not met No insulin recorded on eCRF for T1D patients Or CSII T1D patients: fewer than 3 months experience of using the pump prior to Visit 1.
	A1.03	No Type 1 Diabetes, Type 2 Diabetes or non-diabetic obesity	Inclusion criterion 2 not met; no diagnosis of T1D, T2D or obesity.
	A1.05	Time since diagnosis out of range for T1D patients	Inclusion criterion 2 not met, with a date of diagnosis < 6 months prior to Visit 1 for T1D patients.
A2		**Inclusion criteria not met**	
	A2.01	HbA1c out of range for T1D and T2D patients	Inclusion criterion 4 not met HbA1c <6.3% or > 11.2% at Visit 1 prior to CTP global Amendment 3 for T1D patients. HbA1c <6.5% or > 11.% at Visit 1 after CTP global Amendment 3 for T1D and T2D patients
	A2.02	Age out of range	Inclusion criterion 6 not met Age < 18 years at Visit 1.
	A2.03	BMI out of range	Inclusion criterion 7 not met BMI <18.5 kg/m^2 or > 35.0 kg/m^2 at Visit 1 prior to CTP global Amendment 3 for T1D patients. BMI <18.5 kg/m^2 at Visit 1 after CTP global Amendment 3 for T1D, T2D or obesity patients.

Table 6.2 : 1 Important protocol deviations (cont.)

Category/Code		Description	Example/Comment
	A2.04	eGFR out of range	Inclusion criterion 8 not met eGFR < 60 mL/min/1.73m^2 according to CKD-EPI formula derived using central laboratory creatinine value at Visit 1.
	A2.07	BP out of range	Inclusion criterion 9 not met Average systolic/diastolic BP ≤ 90 or 60 mmHg, or average systolic/diastolic BP > 140 or 90 mmHg at Visit 1
A3		**Exclusion criteria not met**	
	A3.02*	Additional background therapy	Exclusion criteria 1, 2, 10 or 13 checked Or any of the following: • Any SGLT-2 inhibitor within 30 days of Visit 1. • Any antihyperglycaemic drug (e.g. metformin, AGI, GLP-1 analogues, pramlintide, inhaled insulin, pre-mixed insulins etc.) except an SGLT-2 inhibitor, subcutaneous basal or bolus insulin recorded on eCRF within 3 months prior to Visit 1 for T1D patients. • Any concomitant medication at visit 1 known to interfere with the RAAS activity and/or renal function based on investigator judgment (e.g. ACEi, ARBs, aldosterone inhibitors, renin inhibitors etc.). • Weight loss surgery or aggressive diet regimen leading to unstable body weight (based on Investigator's judgment) 3 months prior to Visit 1. • Treatment with anti-obesity drugs 3 months prior to Visit 1 for T1D patients.

Table 6.2 : 1 Important protocol deviations (cont.)

Category/Code		Description	Example/Comment
	A3.03*	Relevant concomitant diagnoses	Exclusion criteria 3, 4, 5, 6, 8 or 20 checked Or any of the following: • Severe hypoglycaemia involving coma and/or seizure that required hospitalisation or hypoglycaemia related treatment by an emergency physician or paramedic within 3 months prior to Visit 1*. • Hypoglycaemia unawareness based on Investigator judgment or frequent episodes of unexplained hypoglycaemia (2 or more unexplained episodes within 3 months prior to Visit 1)*. • Occurrence of DKA within 3 months prior to Visit 1 or until Visit 3. • Acute coronary syndrome (non-STEMI, STEMI and unstable angina pectoris), stroke or transient ischaemic attack (TIA) within 3 months prior to Visit 1*. • Diagnosis of brittle diabetes*. • Medical history of cancer within the last 5 years (except resected basal cell carcinoma)*.
	A3.05*	Blood dyscrasias or any disorder causing haemolysis or unstable red blood cell count	Exclusion criterion 16 checked Or Relevant diagnosis (e.g. malaria, babesiosis, haemolytic anaemia) at Visit 1*.
	A3.06	Indication of liver disease	Exclusion criterion 9 checked Or ALT, AST or alkaline phosphate > 3xULN at Visit 1.
	A3.07*	Contraindication to any of the drugs in the study regime	Exclusion criterion 11 checked Or Any contraindication to Altace® (ramipril) per local product monograph, including: • History of angioedema • History of haemodynamically relevant bilateral renal artery stenosis or unilateral renal artery stenosis in a single kidney • History of hypotension or haemodynamically unstable states • History of hypersensitivity reaction to ramipril or to any other ACEi, or to any ingredient in the ramipril formulation

Table 6.2 : 1 Important protocol deviations (cont.)

Category/Code		Description	Example/Comment
	A3.10*	Treatment with protocol excluded systemic steroids or recent change in thyroid hormone dose	Exclusion criteria 14 or 15 checked Or Treatment with systemic steroids or planned initiation of such therapy at Visit 1 (excluding inhaled or topical use of corticosteroids). Or Change in dose of thyroid hormone within 6 weeks prior to Visit 1 or planned change or initiation of such therapy at Visit 1*.
	A3.11*	Intake of other investigational drug in another trial within 30 days prior to intake of study medication in this trial	Exclusion criterion 19 checked Or Intake of another investigational drug in another trial within 30 days prior to Visit 1*. Final decision at DBL meeting based on medical judgment.
	A3.12*	Specific exclusion criterion for pre-menopausal women violated	Inclusion criterion 10 or Exclusion criterion 17 checked Or Women who are pregnant, nursing, or who plan to become pregnant whilst in the trial*.
	A3.13*	Relevant alcohol or drug abuse and other conditions affecting study compliance	Exclusion criterion 18 checked Or Alcohol or drug abuse within 3 months prior to Visit 1*.
	A3.14*	Any other clinical condition unsafe for participation that would jeopardise patient safety while participating in this clinical trial	Exclusion criterion 22 checked Or Any other clinical condition that, based on Investigator's judgment, would jeopardise patient safety during trial participation or would affect the study outcome*. Final decision at DBL meeting based on medical judgment.
	A3.22*	Diagnosis of severe gastroparesis	Exclusion criterion 7 checked Or Relevant diagnosis recorded as a baseline condition in the eCRF.
	A3.45*	History of Organ Transplant	Exclusion criterion 12 checked Or History of organ transplant, including pancreas, pancreatic islet cells or renal transplant.
	A3.46*	Inability to comply with study requirements	Exclusion criterion 21 checked Or Patient not able to understand and comply with study requirements, based on Investigator's judgment*.
B		**Informed consent**	
	B1	Informed consent not available	Inclusion criterion 1 not met Or Informed consent date missing.
	B2	Informed consent too late	Informed consent date was after Visit 1 date or after any study related procedure.

Table 6.2 : 1 Important protocol deviations (cont.)

Category/Code		Description	Example/Comment
C		**Trial medication and randomisation**	
C1		**Incorrect trial medication**	
	C1.02	Incorrect trial medication taken	Wrong double-blind medication taken (different medication than the patient was allocated to for that period was taken, i.e. drug kit recorded in eCRF is from a different treatment group than the drug kit assigned by IRT). Can only be judged after DBL as requires unblinding information.
	C1.03*	Incorrect background medication dose taken during run-in	Wrong dosage of ramipril dosage consistently taken during run-in period. Final decision at DBL meeting based on medical judgment.
	C1.04*	Incorrect background medication dose taken after randomisation	Wrong dosage of ramipril dosage consistently taken during a treatment period following randomisation. Final decision at DBL meeting based on medical judgment.
C2		**Randomisation not followed**	
	C2.01	Treated without randomisation	Patient treated by double-blind medication according to eCRF, but not randomised according to IRT.
C3		**Non-compliance**	
	C3.01	Non-compliance with randomized study drug intake	Compliance for empagliflozin or placebo over one or both 4 week on-treatment periods <80% or >120% (single compliance value for each treatment period).
	C3.04	Non-compliance with background medication during run-in period.	Average ramipril compliance outside of 80-120% during run-in period (calculated from two compliance values recorded during this period)
	C3.05	Non-compliance with background medication following randomisation	Ramipril compliance outside of 80-120% during a double-blind treatment period or the washout period
C4		**Medication code broken**	
	C4.01*	Medication code broken without just cause	Medication code broken whilst on-treatment without valid reason*. Final decision at the DBL meeting based on medical judgment.
D		**Concomitant medication**	
D2		**Prohibited medication use**	
	D2.01*	Use of prohibited medication during run-in or randomized treatment periods	Review of eCRF for contraindicated drugs*. Final decision at the DBL meeting based on medical judgment.

Table 6.2 : 1 Important protocol deviations (cont.)

Category/Code		Description	Example/Comment
G3		**Other trial specific deviation**	
	G3.43*	Errors in measurement of randomisation baseline GFR value	Protocol for taking clearance measurements (used to calculate GFR) not followed and likely to cause significant error in measurement of visit 8 value*. e.g. Unsuccessful euglycaemic clamp. Final decision on measurement exclusion at the DBL meeting based on medical judgment.
	G3.44*	Errors in measurement of other GFR value	Protocol for taking clearance measurements (used to calculate GFR) not followed and likely to cause significant error in measurement*. e.g. Unsuccessful euglycaemic clamp. Final decision on measurement exclusion at the DBL meeting based on medical judgment.
	G3.45	Randomisation baseline GFR measured outside of visit window	Visit 8 GFR measurement taken < 14 days after start of first intake of ramipril
	G3.46	Treatment period GFR measured outside of visit window	GFR measurement taken < 14 days after start of treatment period
	G3.47	Insufficient washout	The washout period was < 14 days.

*Manual IPD (e.g. IPD that is too complex to program or cannot be detected through the data stored in the trial database). Some IPDs may need a combination of manual and programmed checks.

6.3 PATIENT SETS ANALYSED

Since this study terminated early, there will be no analyses on the protocol defined subgroups of hyperfilterers, non-responders, responders and normofilterers. Instead, all patients will be analysed together, according to the analysis sets defined below:.

- Screened 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. This patient set is not specifically defined in CTP.

- Run-in set (RIS):

  The run-in set (RIS) includes all patients from the SCR who were treated with at least one dose of study medication (ramipril, empagliflozin, placebo).

- Randomised set (RIS):

This patient set includes all patients from the SCR who were randomized to double-blind treatment. This patient set is not specifically defined in CTP.

- Treated set (TS):

  The treated set (TS) includes all patients who were randomised and treated with at least one dose of double-blind study medication (empagliflozin, placebo).

- Full analysis set (FAS):

  This patient set includes all patients who were randomised and treated with at least one dose of double-blind study medication (empagliflozin, placebo), and who provided a randomisation baseline (visit 8) GFR measurement and at least one post-randomisation GFR measurement.

- Per protocol set (PPS):

  There will be no PPS in this study, however, IPDs will still be defined prior to unblinding. IPDs are detailed in Table 6.2: 1.

  Table 6.3: 1 below provides an overview of which analysis sets are to be used for the various endpoints and analysis of the endpoints.

Table 6.3: 1 Patient sets analysed

		Class of Endpoint				
Patient Set	**Subgroup**	**Primary**	**Secondary**	**Further**	**Safety**	**Demographics**
FAS	All patients	2° Analyses	2° Analyses			X
TS	All patients			X	X	
RIS	All patients			One endpoint only	X	X

6.5 POOLING OF CENTRES

This section is not applicable, because the study is performed in only one 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.

6.6.1 Efficacy analysis

If one of the pair of scheduled GFR measurements (or other similarly recorded data) is missing, the endpoint will be defined as the single remaining non-missing value, as specified in Section 5.1. If both of the scheduled GFR measurements (or other similarly recorded data) are missing, then the endpoint is missing at that visit.

All GFR measurements available on the trial database after data cleaning activities have been completed (or other similarly recorded data) will be assumed to be technically plausible and eligible for use in the analysis, i.e. will not be set to missing programmatically in any cases.

In the event that GFR values (or other similarly recorded data) at a particular visit are outside the relevant visit window specified in Section 6.7, the values will be retained in analysis datasets, but not used in any analysis.

In the event that randomisation baseline GFR is missing, or both double-blind treatment period GFR values are missing, such a patient will be excluded from the FAS by definition, and therefore, excluded from all analyses of GFR after 4 weeks of double-blind treatment. Since ramipril is given to lower GFR in the run-in period, under no circumstances will a missing randomisation baseline GFR be imputed by screening baseline GFR, if randomisation baseline GFR is missing after data cleaning activities have been completed.
For all continuous endpoints (including GFR after 4 weeks of double-blind treatment), any patient with only one available value will still be included in the mixed model analyses in which patient is fitted as a random effect (including the primary analysis of GFR). Missing data for one of the crossover periods is implicitly handled in this type of statistical model under the missing at random (MAR) assumption. This also means that all patients in the FAS will be included in the primary analysis of the primary endpoint. Such a patient will be excluded from other analyses in which patient is fitted as a fixed effect. If it is the first crossover period where the missing value occurs, such a patient will also be excluded from any analysis which only uses data from the first double-blind treatment period.

Since only one value per double-blind treatment period is expected for the endpoints in this trial, performing imputations is not needed (e.g. last-observation-carried-forward, LOCF) within treatment periods, and it will not be appropriate to perform imputations across treatment periods.

For binary endpoints, only patients with data from both double-blind treatment periods contribute to the McNemar test statistic. Consequently, patients with missing values for one or both periods are implicitly excluded from this analysis.

Rescue medication is not used in this trial, and therefore there is no need to set missing values following rescue medication use in any analysis.

Any changes to the above (including the handling of any unresolvable but technically implausible GFR values on the trial database) will be documented in the final blinded report planning meeting (BRPM) minutes.

6.6.2 Safety and other variables

Missing safety data will not be replaced.

6.6.3 Missing dates and times

Missing or incomplete AE dates are imputed according to BI standards (see “Handling of missing and incomplete AE dates”) (2).

If the date of first period double-blind drug administration is missing, but the patient was randomized, the date of first double-blind drug administration will be set to the date of randomisation, unless there is evidence that no first period drug was taken at all (e.g. all

dispensed drug returned unused). If the date of first double-blind drug administration is partially missing with the month and year present, the date of randomisation will be used if it was in the same month, and the first day of the month will be used otherwise.

If the date of second period double-blind drug administration is missing, but the patient was randomized and completed the washout period, the date of second double-blind drug administration will be set to the date of Visit 12, unless there is evidence that no second period drug was taken at all (e.g. all dispensed drug returned unused). If the date of second double-blind drug administration is partially missing with the month and year present, the date of Visit 12 will be used if it was in the same month, and the first day of the month will be used otherwise.

If the date of first open-label ramipril administration is missing, but the patient was confirmed eligible, the date of first open-label ramipril administration will be set to the date of Visit 4, unless there is evidence that no ramipril was taken at all (e.g. all dispensed drug returned unused). If the date of first open-label ramipril administration is partially missing with the month and year present, the date of Visit 4 will be used if it was in the same month, and the first day of the month will be used otherwise.

If the date of a subsequent ramipril dose change is missing but a changed ramipril dose has been recorded (including zero dose), it will be imputed by the date of new dose prescription (or date of dose interruption) by the site if this can be obtained. If this cannot be obtained, no dose change will be assumed. If the date of a subsequent ramipril dose change is partially missing with the month and year present, the first day of the month will be used in the absence of other information.

All missing times of first drug administration will be imputed as 08:00 in the morning.

Missing drug stop dates will be imputed according to the following principles:

- For a missing first period double-blind medication end date, if an End of Treatment (EoT) visit is documented only, then the date of the EoT visit will be used. If a Visit 11 is documented only, or is documented along with an EoT visit or a Visit 15, then the date of Visit 11 will be used.
- If the first period double-blind medication end date is incomplete with the month and the year present, and the EoT visit and Visit 11 are missing, then the first day of the following month will be used.
- For a missing second period double-blind medication end date, if an EoT visit is documented (in addition to Visit 11), then the date of the EoT visit will be used. If a Visit 15 is documented (in addition to Visit 11), then the date of Visit 15 will be used.
- If the second period double-blind medication end date is incomplete with the month and the year present, and the EoT visit and Visit 15 are missing, then the first day of the following month will be used.
- If the patient is lost to follow up, or continues in the trial without the expected visit for imputation being available at all (e.g. Visit 11 is missing, but Visit 12 and/or Visit 15

present), then the date of the previous double-blind drug dispensing visit + longest possible treatment duration based on drug supply at that visit + 1 day will be used.

- If the ramipril end date is missing, then the date of the previous ramipril dispensing visit + longest possible treatment duration based on drug supply at that visit + 1 day will be used.
- If the ramipril end date is incomplete with the month and year present, then the first day of the following month will be used.
- If a patient died during the course of the trial and no additional information about drug stop date(s) is (are) available, then the date of death will be used as drug stop date(s) assuming that the patient took the medication(s) 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 partial start and stop dates for concomitant therapies (CT) 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.

For other incomplete date information 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.

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

To avoid all ambiguity, the term “baseline” should not be used without further qualification. Measurements taken prior to the start of open-label ramipril treatment will be referred to as “screening baseline” (Visit 4). Measurements taken prior to randomisation to one of the two double-blind treatment sequences will be referred to as “randomisation baseline” (Visit 8).

Randomisation baseline will be at visit 8 and prior to intake of any double-blind study drug. If more than one value is recorded at visit 8, the value taken at timepoint -0:05 will be used. These will be referenced to explicitly within Section 5.3 Further endpoints.

Period baseline is the baseline prior to intake of any double-blind study drug, within each of the two cross-over periods. For period 1, this is the same as randomization baseline. For period 2, this is prior to the intake of double-blind study drug in the second sequence of the cross-over. This value has not always been recorded, but is often available for laboratory data.

Time windows for visits will be defined in general relative to the start of the relevant treatment period (and not relative to the start of any treatment or to randomisation). The date and (where relevant) clock time of the first drug administration for that treatment period will be used to determine the visit windows. The notable exception to this is the washout period, which is defined based upon the date and time of the last intake of the first period double-blind medication.

Measurements taken prior to the first intake of any study medication (ramipril, empagliflozin or placebo) will be considered pre-treatment or screening 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. Measurements taken after the first intake of ramipril but before intake of double-blind medication will be considered run-in or randomization baseline values. Measurements taken after the last intake of the first double-blind medication but before the intake of the second double-blind medication will be considered washout values.

Measurements taken after the first intake of any study medication (ramipril, empagliflozin or placebo) will be considered on-treatment values if they have been obtained up to the end of the endpoint-specific follow-up period X, as defined in Table 6.7: 1 below. Measurements taken after the last intake of study medication and after the endpoint-specific follow-up period X will be considered off-treatment values for the treatment in question.

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

Treatment phase	Endpoint(s)	Last day of assignment to treatment phase (days after study drug stop date)
Open-label ramipril run-in (for patient not subsequently randomised)	GFR	1
	HbA1c	7
	Waist circumference	7
	All other further endpoints	1
	Adverse events	7
	Safety laboratory measurements	3
Open-label ramipril run-in (for patient subsequently randomised)	GFR	0
	HbA1c	0
	Waist circumference	0
	All other further endpoints	0
	Adverse events	0
	Safety laboratory measurements	0
Double-blind treatment (both periods)	GFR	1
	HbA1c	7
	Waist circumference	7
	All other further endpoints	1
	Adverse events	7
	Safety laboratory measurements	3

Visit window definitions for each treatment phase and time point, based on the relevant anchor date to define relative days, are shown in Table 6.7: 2. These visit windows will be used in all analyses and summaries of endpoints at specific time points.

Further details on the specific handling of GFR values outside these visit windows, or of insufficient washout, with regard to IPDs and PPS analysis are given in Section 6.2.

Table 6.7: 2 Time windows for scheduled visits

Nominal visit number[B]	Treatment phase	Visit label	Anchor date	Planned days	Time window (actual days from anchor date) Start	End
8	Run-in (OL Ramipril)	OL Week 4	First ramipril administration	28	15	42
11	Period 1 (Empa 25mg/Placebo)	Week 4	First period 1 medication administration	28	15	42
12	Washout	NA	Last period 1 medication intake	28	15[A]	42
15	Period 2 (Placebo/Empa 25mg)	Week 4	First period 2 medication administration	28	15	42

[A] Note that the washout period itself commences on the $(X+1)^{th}$ day after visit 11 so at least (X+1) days are required for there to be any washout period at all.

[B] Any values from EOT visits also need to be assigned to the correct treatment phase and appropriate visit window, in addition to values from nominal visits 8, 11, 12 and 15.

7. PLANNED ANALYSIS

Disposition of the patient population participating in the trial will be analysed as follows:

- Open-label ramipril run-in disposition will be summarized using the screened patients set
- Double-blind disposition will be summarized by treatment using the randomized set (no “Total” column)
- Double-blind disposition per period will also be summarized by treatment sequence using the randomized set (“Total” column will be included).

Disposition summaries by region, country and site are not applicable for this single-centre trial.

IPDs during the randomized treatment period will be listed only.

The frequency of patients in different analysis sets will be summarised in total, and by treatment sequence.

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

For end-of-text and appendix 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" (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 or treatment sequence (as applicable and unless otherwise specified; all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive summaries of the following demographic variables, as measured at screening, will be presented:

Table 7.1: 1 List of demographic variables at screening and their categorisation

Demographic variable at screening	**FAS**	**RIS**
Sex	x	x
Race	x	x
Ethnicity	x	x
Age (year)	x	x
*Age categories (18 to 23, 24 to 28, ≥29 years)	x	x
*BMI categories (<25, 25 to <30, ≥30 kg/m^2)	x	x
Height (cm)	x	x
Smoking history	x	x
Alcohol status	x	x
Time since diagnosis of diabetes (year)	x	x
*Time since diagnosis of diabetes (≤5, >5 to ≤10, >10 to ≤25, >25 year)	x	x
eGFR	x	x
*eGFR categories (75 to ≤115, 115 to ≤125, 125 to ≤140 mL/min/1.73m^2)	x	x
UACR (mg/g)	x	x

By treatment sequence and Total

*Definitions of categories are subject to change.

Descriptive summaries of the following variables measured at screening baseline (visit 4) will be presented:

Table 7.1: 2 List of baseline characteristic variables at screening and their categorisation

Baseline characteristics at screening	**FAS**	**RIS**
GFR (mL/min/1.73m^2)	x	x
*GFR categories (≤115, >115 mL/min/1.73m^2)	x	x
HbA1c (%)	x	x
*HbA1c categories (<8.5, ≥8.5%)	x	x
FPG (mg/dL)	x	x
*FPG categories (<54, 54 to ≤70, 70 to ≤126, 126 to ≤140, 140 to <200, ≥200 mg/dL)	x	x
Weight (kg)	x	x
*Weight categories (≤50, >50 to ≤70, 70 to ≤90, >90 kg)	x	x
Waist circumference (cm)	x	x
Systolic blood pressure (bpm)	x	x
Diastolic blood pressure (bpm)	x	x
*Blood pressure categories (SBP≥140 or DBP≥90, SBP<140 and DBP<90)	x	x

By treatment sequence and Total

*Definitions of categories are subject to change.

The table on baseline characteristics at screening (Table 7.1: 2) will be reproduced for randomization baseline, even though the randomization baseline for the continuous part of these variables will also be presented together with the respective further endpoint.

Categories for baseline characteristics are defined in Section 6.4.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant medication use will be summarised by Anatomical-Therapeutic-Chemical classification level 3 (ATC3) and preferred name.

Descriptive summaries of concomitant medication will be presented for:

- Screening period (Pre-treatment) for the RIS; by OL ramipril
- Run-in period for the RIS; by OL ramipril
- Run-in period for the FAS; by treatment sequence and "Total"
- Double-blind treatment (including washout) for the FAS; by treatment sequence and "Total"
- Double-blind treatment (excluding washout) for the FAS; by treatment.

Separate summaries of use of antihypertensives, ASA or lipid lowering drugs will be presented:

- At screening baseline for the RIS
- At randomisation baseline for the FAS; by treatment sequence and "Total"

The displayed categories and defining ATC levels and ATC codes are shown in Table 9.2: 1.

Background pre-existing insulin therapy, including a categorisation of patients using MDI versus CSII will be presented for the RIS.

Background total daily insulin dose at screening baseline and randomisation baseline respectively will be presented in a summary table in insulin 'unit' and 'units/kg' as units of insulin per kg body weight at baseline. The table will also display the total daily basal insulin dose and the total daily bolus insulin dose at the relevant baseline. The number of insulin injections at the relevant baseline will be presented for multiple daily injection (MDI) patients. These tables will be presented for the RIS and FAS, by treatment sequence and "Total" respectively.

Total daily ramipril dose at the start of the open-label ramipril run-in is assumed to be 5mg from the data captured (that is, the protocol-specified initial dose 5mg qd), and so will not be summarized.

Total daily ramipril dose prior to the start of the double-blind treatment period will be summarized for the FAS, by treatment sequence and "Total".

Total daily ramipril dose prior to the start of each treatment crossover period will be summarized for the FAS, by treatment.

Concomitant diseases will be summarised by MedDRA System Organ Class (SOC) and preferred term (PT). Both concomitant diseases and relevant diabetic medical history will be presented for the RIS and for the FAS, by treatment sequence and "Total" respectively.

7.3 TREATMENT COMPLIANCE

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

Frequency distribution of patients with an overall open-label ramipril compliance between 80% and 120% (inclusive) will be reported for the RIS, as well as the patients outside this range. Overall compliance for this purpose will be calculated as a weighted average of reported OL ramipril compliance (from Visits 5 and 8 on the eCRF).

Frequency distribution of patients with an overall double-blind ramipril compliance between 80% and 120% (inclusive) will be reported for the FAS, by treatment sequence, as well as the patients outside this range. Overall compliance for this purpose will be calculated as a weighted average of reported DB ramipril compliance (from Visits 11, 12 and 15 on the eCRF).

It is also noted that ramipril dose may change throughout the trial, and therefore the recorded ramipril compliance on the eCRF needs to take account of this. Since this is handled using the compliance worksheet and instructions given to the site, further details are not given here.

Frequency distribution of patients with a double-blind empagliflozin/placebo compliance between 80% and 120% (inclusive) will be reported for the FAS, by treatment, as well as the patients outside this range. Since a single compliance value is recorded on the eCRF at the end of each treatment crossover period (Visit 11/EoT and Visit 15/EoT respectively), this single value will be used. No weighted average needs to be calculated.

In the above, where an overall compliance is calculated from more than one visit, if compliance is missing at more than one of these visits, then overall compliance will be set to missing.

7.4 PRIMARY ENDPOINT

The primary endpoint in this trial is GFR measured after 4 weeks of double-blind treatment with either empagliflozin or placebo.

7.4.1 Primary analysis of the primary endpoint

The protocol planned primary analysis of the primary endpoint in this early terminated trial cannot be performed, because data are too sparse in the predefined subgroup of hyperfilterers.

7.4.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the primary endpoint

The primary endpoint will be analysed on all patients in the FAS, only. This was a predefined secondary analysis of the primary endpoint according to the protocol. No further sensitivity

analyses are planned. The plan for the analysis of the primary endpoint by subgroups are outlined in Section 7.9.

7.4.2.1 Random effects crossover model MMRM1

This predefined secondary analysis of the primary endpoint is analogous to the CTP predefined primary analysis of the primary endpoint on the subgroup of hyperfilterers, now removed, but just on all patients in the FAS. The aim of this analysis is to investigate the treatment effect, whilst adjusting for baseline GFR.

This is a random effects crossover model, which is a Mixed-Effects Model for Repeated Measures (MMRM) for a crossover design using restricted maximum likelihood (REML). The model is as described in the CTP Section 7.3.1.1 with a random effect for patient, fixed effects for the class variables treatment and period, and a fixed effect for the continuous variable randomisation baseline GFR. For ease of terminology, it will be referred to as MMRM1. The model structure also gives rise to an implicit compound symmetry covariance structure for between patient variance, and consequently within patient and between patient variance is assumed to be independent under this model.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.050$ (two-sided 95% confidence intervals). The residuals are assumed to have a multivariate normal distribution with zero means and covariance matrix of the type specified above.

The primary treatment comparison will be the least squares mean contrast between treatments (empagliflozin minus placebo). The treatment contrast, its two-sided 95 % confidence interval and its p-value will be reported. The model predicted GFR values for each of the baseline GFR values and treatment will be presented graphically. Descriptive tables of the GFR values by period and treatment and condensed over the two treatment periods will be presented. Baseline and change from baseline will be included in the summary.

7.4.2.1.1 Model diagnostics

Model diagnostics will be limited and based on a standard investigation of the studentized residuals.

7.4.2.1.2 Examination of potential period effect

The potential period effect will be examined graphically. Firstly, presenting the mean GFR on the y-axis against the period on the x-axis, split by treatment and each of the treatments joined by a line. Secondly, the within patient differences will be examined by individual patient profiles, one for each treatment sequence. Each plot will present the GFR on the y-axis versus the period on the x-axis (patients joined from period 1 to period 2) and the mean GFR at each period superimposed.

7.4.2.1.3 Examination of treatment effect

To investigate the treatment effect graphically, a scatter plot will be produced, displaying one treatment on the y-axis versus the other treatment on the x-axis, including a 45-degree line

and the mean of the two treatments superimposed. In addition, a boxplot showing the distribution of the GFR at week 4 by treatment will be included.

7.4.2.1.4 Examination of relationship between GFR at baseline and week 4, by treatment

To investigate the relationship between baseline GFR and GFR at week 4, by treatment, there will be a scatter plot with GFR at week 4 on the y-axis and baseline GFR on the x-axis using different symbols for each of the two treatments. In addition, GFR at week 4 will be presented by subgroups of GFR at baseline, split into three approximately equally sized groups (<107, ≥107 to <120, ≥120) using boxplots with one display per treatment group. The overall GFR (irrespective of baseline) will also be included.

7.4.2.2 Random effects crossover model including the treatment by baseline interaction MMRM2

This was also a predefined secondary analysis of the primary endpoint, on all patients in the FAS. It assumes that any treatment effect is linearly dependent upon randomisation baseline (visit 8) GFR. This will be done using the analysis model and assumptions described in Section 7.4.2.1, with an additional term for the treatment-by-baseline GFR interaction. For ease of reference, it will be referred to as MMRM2.

The gradient of the treatment effect with respect to randomisation baseline GFR will be estimated, along with its 95% confidence interval and nominal p-value. Estimates for the treatment effects and their 95% CIs will be provided for a range of selected randomisation baseline GFR values (100, 115 and 130 mL/min/1.73m^2).

The same set of limited model diagnostics as in Section 7.4.2.1.1 will be produced.

7.4.2.3 Random effects crossover model on the natural logarithmic scale MMRM3

The primary analysis as described in described in Section 7.4.2.1, will be repeated on all patients in the FAS with the modification that all GFR measurements (endpoint and randomisation baseline values) will be replaced by their natural logarithms (loge). Estimates from this model will be back-transformed and the estimate of the treatment effect reported as the ratio of geometric means for GFR (empagliflozin/placebo), together with its 95% CI and nominal p-value. A value of less than 1 for the ratio of geometric means therefore represents a lower mean GFR on empagliflozin compared to placebo.

For ease of reference, this will be referred to as MMRM3.

In order to examine the treatment effect, the same graphical displays (scatter plot and boxplot) as defined in Section 7.4.2.1.3 will also be produced on the natural log scale.

7.4.2.4 Analysis of period one ANCOVA1

An ANCOVA analysis will be conducted on the primary endpoint GFR measurements from crossover period 1 only, for all patients in the FAS. This will be referred to as ANCOVA(1).

This is to provide an estimate of the treatment effect that cannot possibly be affected by any potential carryover effect, albeit on half of the sample size compared to when both periods are included.

The data will be limited to period one data only and the statistical model will include a fixed effect for the class variable of first period treatment, and randomisation baseline GFR as a linear covariate.

In order to examine the treatment effect within period one, the same graphical displays (scatter plot and boxplot) as defined in Section 7.4.2.1.3 will also be produced.

There are no planned sensitivity analyses in this early terminated study.

7.5 SECONDARY ENDPOINT

7.5.1 Key secondary endpoint

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 Secondary endpoint

The secondary endpoint is filtration status (GFR < 120 mL/min/1.73m^2) after 4 weeks of double-blind treatment with either empagliflozin or placebo.

7.5.2.1 Primary analysis of the secondary endpoint

The protocol planned primary analysis of the secondary endpoint in this early terminated trial cannot be performed, because data are too sparse in the predefined subgroup of hyperfilterers.

7.5.2.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the secondary endpoint

The secondary endpoint will be analysed on all patients in the FAS, only. This was a predefined secondary analysis of the secondary endpoint according to the protocol. No further sensitivity or subgroup analyses are planned for this endpoint.

The endpoint will be analysed using McNemar's test, as well as the odds ratio, 95 % CI and nominal p-value. A table will be presented showing the number of concordant and discordant pairs with each filtration status (<120, ≥120), by treatment. The number of patients omitted due to a missing value will be separately recorded. Descriptive statistics showing the concordant and discordant pairs will also be produced by the filtration status (<120, ≥120), at randomisation baseline and treatment.

The proportion of patients with each filtration status by both treatment and period will be summarised descriptively.

7.7 EXTENT OF EXPOSURE

A descriptive statistics table with mean, SD, median and range of the number of days a patient was on open-label ramipril run-in treatment will be provided for the RIS. The tables will also provide the sum of the total time (in years) that all patients pooled together were on open-label ramipril run-in treatment, as well as descriptive statistics for the mean, minimum and maximum total daily ramipril dose for each patient during the run-in period.

Similar tables will be produced for exposure to ramipril across the whole trial for the RIS.

A descriptive statistics table with mean, SD, median and range of the number of days a patient was on double-blind treatment will be provided for the TS, by treatment. The tables will also provide the sum of the total time (in years) that all patients pooled together were on each double-blind treatment.

A separate listing will be created of any patients that switched treatment at any time during double-blind treatment.

In the above summary tables, the number and percent of patients belonging to each categorical range of exposure weeks will also be provided using the following cumulative categories:

≥ 1 day, ≥ 1 week, ≥ 2 weeks, ≥ 3 weeks, ≥ 4 weeks (for open-label ramipril and double-blind treatment)

≥ 1 day, ≥ 1 week, ≥ 2 weeks, ≥ 3 weeks, ≥ 4 weeks, ≥ 8 weeks, ≥ 12 weeks, ≥ 16 weeks (for total trial ramipril exposure).

Descriptive statistics for the total daily ramipril dose at the start of each double-blind treatment period will be provided for the TS, by treatment. The number and percent of patients who received a total daily ramipril dose less than 10 mg for at least one day during double-blind treatment (excluding washout period) will also be summarised by treatment.

7.8 SAFETY ANALYSIS

Unless otherwise specified below, all safety analysis specified will be performed separately for the open-label ramipril run-in period (on the RIS) and the double-blind treatment period (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 (pulse symptoms) and in the 12-lead ECG starting after visit 4 (start of open-label ramipril run-in) will be considered as an AE and will be reported as such.

Unless otherwise specified, the analyses of adverse events will be descriptive in nature and analyses of AEs will be based on the number of patients with AEs (not the number of AEs).

For analysis of AE attributes such as duration, severity, etc. multiple AE occurrence data 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 may apply:
    - Genital infection 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);
    - 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);
    - Severe hypoglycaemia endpoint confirmed by adjudication will not be collapsed;
    - Hypoglycamia adverse events will not be collapsed (except in case of occurrences with identical onset date, time and glucose value).
- 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.

For further details on summarization of AE data, please refer to (5).

7.8.1.1 Assignment of AEs to treatment

The analysis of adverse events will be based on the concept of treatment emergent adverse events. To this end, all AEs occurring on or within the respective treatment period will be considered ‘treatment-emergent’. For adverse events, the REP is defined as 7 days after the last dose of treatment (see Table 6.7: 1).

Owing to the trial design consisting of an open-label ramipril run-in period and the double-blind crossover periods, where periods are defined in Table 6.1: 1, adverse events will be determined as treatment-emergent according to the following rules:

- For the AE summaries of the open-label ramipril run-in period, adverse events will be considered “on-treatment” if they lie on or within the run-in period, as defined in Table 6.1: 1.
- For the AE summaries of the double-blind treatment period, adverse events will be considered “on-treatment” or ‘treatment emergent’ if they lie on or within on-treatment period 1 or on-treatment period 2, as defined in Table 6.1: 1.

AEs occurring on or within the screening period will be referred to as “screening AEs”.

AEs occurring during the treatment x washout period will be assigned to "Treatment x washout".

AEs occurring on or within the treatment x post treatment period will be assigned to "Treatment x post-treatment".

AEs occurring on or within the post study period will be assigned to 'Post study'.

AEs occurring on or within the ramipril post treatment period will be assigned to 'ramipril post treatment'.

Section 15 summaries of treatment-emergent AEs in the open-label ramipril run-in period will be presented for the RIS.

Section 15 summaries of treatment-emergent AEs in the double-blind treatment period will be presented for the TS, by treatment.

Additional summaries of AEs including off-treatment study periods will be included in Appendix 16.1.9.2.

Malignancy and bone fracture events

For malignancy (and respectively bone fracture), in addition to the standard '7-day-on-treatment approach' detailed above, all malignancy (respectively bone fracture) adverse events that occurred between first study drug intake up to study end will be pooled and analysed together in Section 15.

7.8.1.2 Analysis of other significant AEs

Other significant AEs will be reported and summarised according to the ICH E3 criterion. Thus, AEs classified as 'other significant' will include those non-serious and non-significant 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 for both the open-label ramipril run-in period and the double-blind treatment period.

The frequency of patients with adverse events will be summarised by treatment, primary system organ class and preferred term. AEs will also be reported by intensity. Separate tables will be provided for patients with other significant adverse events according to ICH E3, 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 system organ classes will be sorted according to the standard sort order specified by EMA; preferred terms will be sorted by frequency (within system organ class).

Appendix 16.1.9.2 will also include an analysis on the frequency of patients with non-serious adverse events occurring with incidence in preferred term greater than 5 % by double-blind treatment, for disclosure on clinicaltrials.gov website.

7.8.1.4 AEs of special interest

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

- Decreased renal function: creatinine shows a >= 2 fold increase from baseline and is above the upper limit of normal (ULN)
- Hepatic injury defined by the following alterations of liver parameters after randomization:
    - An elevation of AST and/or ALT >= 3 fold ULN combined with an elevation of total bilirubin >= 2 x ULN measured in the same blood sample
    - An isolated elevation of AST and /or ALT ≥ 5 fold ULN irrespective of any bilirubin elevation.
- Diabetic ketoacidosis (DKA)
- Severe hypoglycaemic episodes

For further details on the definition of DKA and severe hypoglycaemic episodes, refer to Section 5.3.6.1 of the CTP.

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

The AESI ‘Decreased renal function’ will be identified by the narrow SMQ “Acute renal failure: 20000003”.

This display will be replicated for present serious events and then events leading to discontinuation.

Acute renal kidney injury will also be discussed based on the creatinine laboratory data increase as detailed in Section 7.8.2.

The AESI ‘Hepatic injury’ will be identified by the narrow SMQs:

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

This display will be replicated for present serious events and then events leading to discontinuation.

Further laboratory analyses will support the hepatic evaluation. See Section 7.8.2 for further details on elevated liver enzyme analyses.

The AESI 'Diabetic ketoacidosis (DKA)' will be identified by using both the CEC confirmed ketoacidosis events and the investigator defined Ketoacidosis events.

A frequency table will first summarize the results of the CEC adjudication committee for ketoacidosis events (refer to Section 7.8.1.6 for further details on the adjudication process). This summary will present the number of patients with CEC:

- certain ketoacidosis
- potential ketoacidosis
- unlikely ketoacidosis
- unlikely ketoacidosis but ketosis
- unclassifiable events

by worst severity and requirement of hospitalisation.

A second frequency analysis will be created and will display the characteristics of ketoacidosis for patients with CEC certain ketoacidosis. These characteristics will include outcome, severity of the worst episode, time to onset of first episode, and lowest blood pH. This analysis will be successively repeated for ketoacidosis endpoints considered by the CEC as potential, as well as for ketoacidosis endpoints considered by the CEC as certain or potential.

Additional analyses will be produced to assess the risk of ketosis. In particular the number of patients with any ketosis events (i.e. CEC confirmed unlikely ketoacidosis but ketosis, and ketosis events derived from the database that were not trigger events for the adjudication) will be summarised.

Other ketoacidosis endpoints as identified by the investigator will be analysed as above.

Frequency of patients with investigator defined AESI ketoacidosis will in addition be tabulated by SOC and PT, as well as using specified trigger search terms for DKA.

The analysis based on specified trigger search terms for DKA will also be restricted to CEC certain ketoacidosis, and to CEC potential ketoacidosis.

Two additional analyses will then be performed to distinguish patients with events based on trigger terms indicative of ketoacidosis and or diabetic ketoacidosis, from patients with events based on trigger terms indicative of acetonaemia.

Serious ketoacidosis will be summarised based on specified trigger search terms for DKA, as well as ketoacidosis leading to treatment discontinuation.

An overview table will first summarize the results of the CEC adjudication committee on ketoacidosis episodes by worst severity.

The CEC certain ketoacidosis episodes will be tabulated by treatment and characteristics of ketoacidosis (e.g. outcome, severity, pre-existing factors, blood pH).

The adjudication outcome results on the ketoacidosis episodes will also be summarised based on how the episode has been identified for adjudication.

Finally, the number of ketosis episodes will be summarised.

The investigator defined AESI ketoacidosis episodes will be summarised by event characteristics, as done on patient level.

The AESI 'Severe hypoglycaemic episodes' will be determined by using severe hypoglycaemia AEs reported by the investigator as AESI or severe hypoglycemia that has been confirmed by the adjudication committee.

Refer to Section 9.3 for further details on the derivation of the severe hypoglycaemia adverse event endpoints analysed in this section.

For the analysis of number of patients with severe hypoglycaemia adverse event, a frequency table will first summarize the results of the adjudication committee on hypoglycaemic events that had been sent to the CEC for adjudication.

Patients with CEC confirmed severe hypoglycaemia will be tabulated by treatment and characteristics of hypoglycaemia including minimum glucose level and time to onset of first episode. The frequency of severe nocturnal hypoglycaemia AE (i.e. any hypoglycaemia event with an onset from 0:00 midnight to 5:59 a.m.) will also be evaluated as part of these characteristics.

Patients with investigator defined AESI severe hypoglycaemia will also be summarised by treatment and event characteristics.

Patients with investigator defined AESI severe hypoglycaemia will be then summarised by SOC, PT and treatment group.

Finally, severe hypoglycaemia considered serious or requiring third person assistance will be tabulated using the narrow SMQ Hypoglycaemia. This analysis will be repeated for patients with CEC confirmed severe hypoglycaemia.

For the analysis of frequency of hypoglycaemic adverse events, the number of CEC confirmed severe hypoglycaemic episodes will be first tabulated by treatment and characteristics of hypoglycaemia.

In addition, the severe hypoglycaemic episodes that have been confirmed by the adjudication committee will be represented on a graph by hour of the day (from midnight to 11:59 pm).

The investigator defined AESI severe hypoglycaemic episodes will finally be summarised by event characteristics, as done on patient level.

7.8.1.5 Other specific adverse events

Hypoglycaemia adverse events

In this sub-section, only hypoglycemia reported by the investigator as adverse events will be discussed.

Refer to Section 7.8.1.4 for specifications on specific analyses on the AESI severe hypoglycaemia.

Refer to Section 9.3 for details on the derivation of the hypoglycaemia adverse event endpoints listed below.

Every episode of PG ≤ 70 mg/dL should be documented with the respective time and date of occurrence. This includes hypoglycaemia with glucose values < 54 mg/dL and all symptomatic and all severe hypoglycaemic events. On the basis of this information the hypoglycaemic adverse event will be classified according to the following protocol defined categories:

- Asymptomatic hypoglycaemia with PG ≤ 70 mg/dL
- Documented symptomatic hypoglycaemia with 54 mg/dL ≤ PG ≤ 70 mg/dL and typical symptoms
- Documented symptomatic hypoglycaemia with PG < 54 mg/dL and typical symptoms and no need for external assistance
- Severe hypoglycaemia, event requiring assistance (i.e. the CEC confirmed severe hypoglycaemia)

Analysis of number of patients with hypoglycaemia adverse events

The number of patients with hypoglycaemia according to investigator's judgment will be tabulated by treatment group.

The frequency of patients with protocol defined hypoglycaemia adverse event will be presented by treatment and characteristics of hypoglycaemia. The severity, action taken, minimum glucose level of worst episode, and time to onset of first episode will be displayed as part of the characteristics.

Urinary and genital infections

The following additional specific adverse events will also be assessed and tabulated by treatment:

- Genital infections
- Urinary tract infections (UTI)

Genital infections will be identified by: BIcMQ 'Infections', narrow sub-search 1.1 'Genital tract infections predisposed to by glucosuria'.

Urinary tract infections will be identified by: BIcMQ 'Infections', narrow subsearch 2.1 'UTI predisposed by glucosuria'.

The serious genital infection events as well as the genital infection events leading to treatment discontinuation will additionally be summarised using the narrow project defined PT list.

Similarly, the serious UTI events as well as the UTIs leading to treatment discontinuation will be summarised using the BIcMQ.

A frequency table for complicated urinary tract infections/pyelonephritis/urosepsis where 'complicated urinary tract infections' are defined as serious AEs from the narrow BIcMQ UTI, all events included in the sub-BIcMQ pyelonephritis and all events of preferred term urosepsis will in addition be provided.

Genital infections based on investigator assessment will additionally be summarised by type (fungal balanitis or fungal vulvovaginitis, genital infection other than fungal balanitis or fungal vulvovaginits), intensity (mild, moderate or severe), time to onset of first episode (within the first 3 months of treatment or after), duration (<7 days, 7-14 days and >14 days), how the event was treated (no treatment, therapy assigned, hospitalisation), treatment (0, 1, 2, >2 antimicrobials needed to treat), duration of treatment (≤7 days, >7 days), whether leading to discontinuation of treatment, and the number of episodes per patient.

Furthermore, the above mentioned displays on genital infections based on investigator assessment will be repeated by the type of infection (fungal balanitis or fungal vulvovaginitis, or genital infection other than fungal balanitis or fungal vulvovaginitis).

UTIs based on investigator assessment will additionally be summarised by intensity (mild, moderate or severe), time to onset of first episode (within the first 3 months of treatment or after), duration (<7 days, 7-14 days and >14 days), anatomical location (upper UTI, lower UTI), how the event was treated (no treatment, therapy assigned, hospitalisation), treatment (0, 1, 2, >2 antimicrobials needed to treat), duration of treatment (≤7 days, >7 days), whether leading to discontinuation of treatment, and the number of episodes per patient.

AESIs of genital infections and UTIs based on investigator assessment will additionally be summarised by sex.

<u>Acute pyelonephritis, sepsis, and asymptomatic bacteriuria</u>

The following specific adverse event based on investigator assessment will be tabulated by treatment:

- Acute Pyelonephritis: patient incidence overall and by intensity, and treatment required (0, 1, 2, >2 antimicrobials needed to treat)
- Sepsis: patient incidence overall and by source of infection

- Asymptomatic Bacteriuria: patient incidence overall

Bone fractures

The frequency of patients with bone fracture will be provided by event characteristics (e.g. type of fracture, intensity, and time to onset of first fracture). Bone fracture will also be displayed by SOC and PT using the BIcMQ.

Volume depletion

A frequency table of patients with volume depletion will be constructed based on preferred terms:

- Volume depletion: BIcMQ (sub-BIcMQ origin vascular narrow).

Malignancy

A frequency table will be created for malignancies based on the following narrow SMQs:

- Malignancies: The following Sub-SMQs of SMQ Malignancies (20000090) will be used: Sub-SMQ Malignant or unspecified tumors (20000091) and Sub-SMQ Malignancy related conditions (20000092), excluding PT "Acanthosis nigricans".

7.8.1.6 Events qualifying for external adjudication by the Clinical Event Committee

An independent external CEC regularly reviews cardiovascular, neurovascular, severe hypoglycaemia, hepatic and ketoacidosis events 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 separate CEC charters. Events qualifying for adjudication will be selected based on the latest CEC charter versions.

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.

Refer to Section 7.8.1.4 for details on analyses for severe hypoglycamia and for ketoacidosis.

A frequency table by treatment will be provided for the adjudicated cardiovascular and neurological endpoints and for the preferred terms in the specified SMQs of events. A table will also be provided for events that were confirmed or non-assessable.

The cardiovascular and neurovascular events qualifying for adjudication will be selected based on the following SMQs:

- Ischemic heart disease, excluding PTs “Blood creatine phosphokinase abnormal” and “Blood creatine phosphokinase increased”
- Cardiac failure, excluding PTs “Oedema”, “Oedema peripheral” and “Peripheral swelling” unless there are reported as serious events

- Torsade de pointes / QT prolongation
- Cerebrovascular disorders, excluding PT “Fahr's disease”
- Further simple preferred terms
- All fatal cases

7.8.1.7 AEs while patients were taking wrong medication

A listing 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 standardised and normalised values will be derived, as well as the differences to screening baseline for the open-label ramipril run-in period, and to both screening and randomisation baselines for the double-blind period.

If the period baseline for a particular laboratory parameter is available (see definition in Section 6.7), then this will be used, in place of the randomization baseline value. Throughout the remainder of this section, however, randomization baseline will be referred to.

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 (4). All analyses considering multiple of times upper limit of normal (ULN) will be based on original and not normalized data.

Analysis of further endpoints derived from specific laboratory parameters is described in Section 7.6.

Results of laboratory analyses will be presented based on both SI units and US conventional units.

Screening baseline for safety laboratory parameters will be the last available measurement before the start of OL ramipril treatment. Randomisation baseline for safety laboratory parameters will be the last available measurement before the start of double-blind treatment. Unless otherwise specified, laboratory measurements taken up to 3 days after the last administration of study drug will be considered as on-treatment (see Section 6.1 and Section 6.7).

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 General laboratory evaluation

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 for baseline, on-treatment values and for changes from baseline based on normalised values, as well as on the basis of standardized values for parameters with an incomplete reference range (e.g. lipids).

Descriptive statistics will in addition be calculated for the changes from screening and randomisation baselines in haematocrit over time, including during the follow-up period. In particular, statistics will be provided for last-value on-treatment, follow-up, change from baseline for last on-treatment value and follow-up, and change from last on-treatment assessment to follow-up.

Frequency tables will summarise the number of patients with potentially clinically significant abnormalities.

7.8.2.2 Elevated liver enzymes

Special attention will be paid to parameters characterising liver function. These include liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP)) and total bilirubin.

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 AST/ALT or total bilirubin 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 Total Bilirubin >= 2xULN".

Patients with elevations as defined above by ALT and/or AST, total bilirubin and AP combinations, will be summarised and stratified by Alkaline phosphatase < 2xULN and >=2xULN.

Details on patients with elevated liver enzymes will be listed.

7.8.2.3 Lipid parameters

Lipid parameters will be analysed using descriptive statistics only.

Descriptive statistics will be shown over time for the OL ramipril run-in period for the RIS including change from screening baseline.

Descriptive statistics will be shown over time for the double-blind treatment period by treatment for the TS including change from randomisation baseline.

7.8.2.4 Renal laboratory parameters

Creatinine and eGFR

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 glomerular filtration rate will be estimated according to the following CKD-EPI creatinine equation, and stored in the trial database:

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

Where:
- k is 0.7 for females and 0.9 for males,
- a is -0.329 for females and -0.411 for males,
- min indicates the minimum between (serum creatinine/k) and 1,
- max indicates the maximum between (serum creatinine/k) and 1.
- 'African origin' is the category ‚Black/African Amer.' on the CRF.

For any analysis using eGFR (CKD-EPI, creatinine), the values calculated from the above formula using the serum creatinine values from the central laboratory will be used, and not the eGFR values provided by the central laboratory.

The following additional rules will apply:

- In case of mixed race, if 'Black or African American' is one of the patient races, eGFR will be by default derived as if the patient is of African origin.
- 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. The age at a specific visit where eGFR is calculated will be derived as follows:

Age [years] = (date of eGFR laboratory measurement – birth date + 1) / 365.25

A shift table from screening baseline to both last value on treatment and minimum value on treatment will be provided for eGFR (CKD-EPI, creatinine) for the OL ramipril run-in period using the RIS.

A shift table from randomisation baseline to both last value on treatment and minimum value on treatment will be provided for eGFR (CKD-EPI, creatinine) for the double-blind treatment period by treatment using the TS.

Descriptive statistics will also be presented for creatinine and eGFR (CKD-EPI, creatinine) values over time, and their changes from screening baseline, for the OL ramipril run-in period using the RIS.

Descriptive statistics will also be presented for creatinine and eGFR (CKD-EPI, creatinine) values over time, and their changes from both screening and randomisation baselines, for the double-blind treatment period by treatment using the TS.

A summary will be created for the OL ramipril run-in period using the RIS of the number of patients that experienced a doubling in creatinine on treatment that was out of the normal range as compared to screening baseline.

A summary will be created for the double-blind treatment period by treatment using the TS of the number of patients that experienced a doubling in creatinine on treatment that was out of the normal range as compared to randomisation baseline.

7.8.3 Vital signs

Where not already covered by analyses of further endpoints in Section 5.3.6 and Section 7.6:

Descriptive summaries of systolic BP, diastolic BP and pulse rate over time, and their changes from screening baseline, will be produced for the OL ramipril run-in period using the RIS.

Descriptive summaries of systolic BP, diastolic BP and pulse rate over time, and their changes from both screening and randomisation baselines, will be produced for the double-blind treatment period by treatment using the TS.

7.8.4 ECG

No analysis is planned for ECG data. Any clinically relevant changes will be reported as AEs.

7.8.5 Others

Not applicable

7.9 SUBGROUP ANALYSIS

There will be limited subgroup analysis for this study. The combination of endpoints and subgroups to be examined is outlined in Table 6.4:1. In general, each endpoint will be analysed on the same population as the main analysis.

Subgroup analysis on renal haemodynamic parameters (8)by screening GFR subgroup(MMRMSG)
Descriptive graphical displays will take the form of boxplots and scatter plots. The boxplot will investigate the treatment effect alone and the scatter plot will investigate the baseline relationship with that particular parameter and treatment. Each will be split by the subgroup, which just has two categories.

In order to provide descriptive p-values for the treatment effect within each of the subgroups, a random effects crossover model, referred to as ‘MMRMSG’ will be used:

MMRMSG is an interaction model, analagous to MMRM2, but the interaction term will be for the treatment by subgroup combination. The model will include treatment, period,

baseline of renal parameter being modelled, the screening GFR subgroup and interaction of treatment by screening GFR subgroup as fixed effects, and patient as a random effect. For each of the subgroups the predicted treatment means and SE by baseline renal parameter will be presented graphically. Finally, for each of the two levels of subgroup the treatment different with 95% CI will be displayed in the form of a Forest plot. The same limited set of model diagnostics as per MMRM1 will be presented.

Subgroup analysis on ABPM 24-hourly mean endpoints by baseline BMI and blood pressure subgroups

The 3 ABPM 24-hourly endpoints for diastolic BP, systolic BP and Pulse rate will be analysed on the 2 subgroups of baseline BMI (≤median, >median) and baseline BP (high: Dia BP ≥90 AND Sys BP ≥140, Low: Dia BP<90 OR Sys BP <140). Since this is a lot of important information over time, the main mean (SE) plots over time will be reproduced on these groups.

For ABPM therefore, the exploration of the data within these subgroups will be descriptive in nature, only.

If any of the subgroups have less than 5 patients, then this data exploration will not be performed.

8. REFERENCES

1	CPMP/ICH/363/96: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2	001-MCG-156_RD-01: "Handling of missing and incomplete AE dates", current version: IDEA FOR CON. 001-MCG-156_RD-01: "Handling of missing and incomplete AE dates", Version 5.0; IDEA FOR CON.
3	001-MCG-159, "Reporting of clinical trials and project summaries", current version; IDEA FOR CON.
4	001-MCG-157: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.
5	BI-KMED-BDS-HTG-0041: "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; KMED.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**09-Oct-2019**		None	This is the final TSAP without any modification