TRIAL STATISTICAL ANALYSIS PLAN

c31460805-04

BI Trial No.:	1245.137
Title:	EMPA-KIDNEY: A multicentre international randomized parallel group double-blind placebo-controlled clinical trial of EMPAgliflozin once daily to assess cardio-renal outcomes in patients with chronic KIDNEY disease Including Protocol Amendment 1 <1245.137>-protocol-version-02 [c31394601]
Investigational Product:	Empagliflozin, BI 10773
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Date of statistical analysis plan:	15 JUL 2022 SIGNED
Version:	4

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
BI	Boehringer Ingelheim
BIcMQ	Boehringer Ingelheim customised MedDRA Query
BMI	Body Mass Index
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	Coronavirus Disease 2019
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DKA	Diabetic ketoacidosis
DM	Diabetes Mellitus
DMC	Data Monitoring Committee
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EoT	End-of-Text
ESKD	End Stage Kidney Disease
HbA1c	Haemoglobin A1c
HHF	Hospitalisation for Heart Failure
HLGT	High Level Group Term
HLT	High Level Term
HR	Hazard Ratio
ICH	International Conference on Harmonisation
iPD	Important Protocol Deviation
ITT	Intention-to-treat
KDIGO	Kidney Disease Improving Global Outcomes
KM	Kaplan-Meier

Term	Definition / description
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
Min	Minimum
MMRM	Mixed Model Repeated Measures
NT-proBNP	N-terminal pro B-type natriuretic peptide
OC-AD	Observed Case-All Data
OC-OT	Observed Case-On Treatment
PT	Preferred Term
Q1	Lower quartile
Q3	Upper quartile
RAS	Renin-angiotensin System
REP	Residual Effect Period
RS	Randomised Set
RS&I	Random Slope and Intercept
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SCR	Screened Set
SD	Standard Deviation
SI	International System of Units
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SOP	Standard Operating Procedure
TS	Treated Set
UACR	Urine Albumin Creatinine Ratio
UK	United Kingdom
UTI	Urinary Tract Infection

3. INTRODUCTION

As per the International Conference on Harmonisation (ICH) E9 guidance (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 regulatory TSAP predefines the statistical approaches to be used for regulatory authority submissions. It 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 Sections 2.3 “Data Analysis Plan” and 2.4 “Sample Size and Predicted Number of Events”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomisation.

Note, an earlier publication Data Analysis Plan (Standard Operating Procedure [SOP] 11) (2) was agreed by the Steering Committee for the trial, detailing the pre-specified analyses for presentation in the primary publication(s). Therefore, this regulatory TSAP replicates all the analyses from the primary publication(s) as pre-specified in SOP11 and, in addition, specifies a series of additional exploratory analyses/summaries to aid future potential regulatory submissions. The analyses common to both SOP11 and this regulatory TSAP are highlighted for ease of review.

SAS® Version 9.4 or a later version will be used for most analyses. R Version 4.0.1 (3) or a later version will be used where required.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

There are no changes in this TSAP compared to the statistical methods described in the CTP. The following clarifications and additions have been made:

- In February 2022 an error in the minimization process was discovered, indicating that minimization by region had not been performed correctly from late 2019. For this reason, the actual region patients were randomised from will be used in the main analysis models rather than the region from the minimization process. All other factors [age, sex, diabetes status, screening estimated glomerular filtration rate (eGFR) and screening urine albumin creatinine ratio (UACR)] will be fitted as planned from the minimization process. Note this change was made and documented prior to the Data Monitoring Committee (DMC) interim analysis.

- Standard Boehringer Ingelheim (BI) analyses of routine safety data have been included. Refer to Sections 7.8.1.2 and 7.8.2.2.
- Where considered appropriate, the potential impact of Coronavirus Disease 2019 (COVID-19) on the trial will be assessed by producing additional summaries of disposition, treatment compliance, efficacy, and adverse events (AEs). The start date for COVID-19 having an impact on the trial will be taken as the date of a discontinuation of the trial medication due to COVID-19, a COVID-19 related AE or the COVID-19 related global BI recruitment hold (17 MAR 2020), whatever comes first.
- Circumstances for delaying or cancelling the planned interim analysis are described in Section 9.2.

5. ENDPOINTS

Adjudication will be limited to all deaths and events initially reported as HHF, myocardial infarction (MI), stroke, liver injury, ketoacidosis, lower limb amputation, acute kidney injury and serious genital infections. Endpoints (and components) based on laboratory values will not be adjudicated. Receipt of a kidney transplant or initiation of maintenance dialysis will also not be adjudicated. Most hospitalisations will not be adjudicated. Further details on the adjudication process refer to SOP 9b: EMPA-KIDNEY: Adjudication Procedures (4). Where applicable adjudication data will take precedence over investigator data, for endpoint derivations. References to 'as adjudicated' within this document includes fully assessed events that have been confirmed by adjudication and provisionally assessed events that have not been refuted by adjudication. Other events that were not selected are not considered 'as adjudicated'.

For endpoints that involve eGFR the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula will be used. eGFR will be estimated from creatinine measured in the central laboratory. The exception being where a central measurement is expected but missing, the local creatinine value will be used, refer to Section 6.6 for further details.

Further details on the derivation of time to first occurrence endpoints are provided in Section 6.8.

5.1 PRIMARY ENDPOINT

The primary endpoint is a composite of time to the first occurrence of:

- Kidney disease progression [defined as ESKD, a sustained decline in eGFR to <10 mL/min/1.73m^2, 'as adjudicated' renal death, or a sustained decline of ≥40% in eGFR from randomisation]; or
- Cardiovascular (CV) death ('as adjudicated').

ESKD is defined as the initiation of maintenance dialysis or receipt of a kidney transplant. Dialysis will be considered as maintenance if it is required for ≥90 days or if the dialysis is stopped within 90 days for a reason of 'received kidney transplant', 'dialysis is futile' or 'subject refused dialysis'. Dialysis ongoing at the final follow-up visit or the last scheduled follow-up visit before death*, withdrawal of consent or loss to follow-up will also be considered as maintenance irrespective of duration. Where changes in dialysis modality are consecutive with one another durations will be summed for determining whether the maintenance duration has been met. Duration will be calculated as 'Dialysis stop – Dialysis start + 1'.

* For deaths within 90 days of starting dialysis the adjudicator will consider whether the dialysis would have been required long-term or only temporarily, if temporary then the outcome of dialysis will be changed from 'ongoing' to 'dialysis stopped for other reason' and not considered as an ESKD event.

To meet the requirement for a 'sustained' decline in eGFR, this will be taken to mean that it is either:

- Measured at two consecutive scheduled study follow-up visits (at least 30 days apart); or
- Measured at the final follow-up visit or the last scheduled follow-up visit before death, withdrawal of consent or loss to follow-up.

This 'sustained' rule will also apply to other endpoints defined below with these eGFR components. Further detail on defining 'sustained' eGFR declines is provided in Section 9.6.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

The key secondary endpoints are:

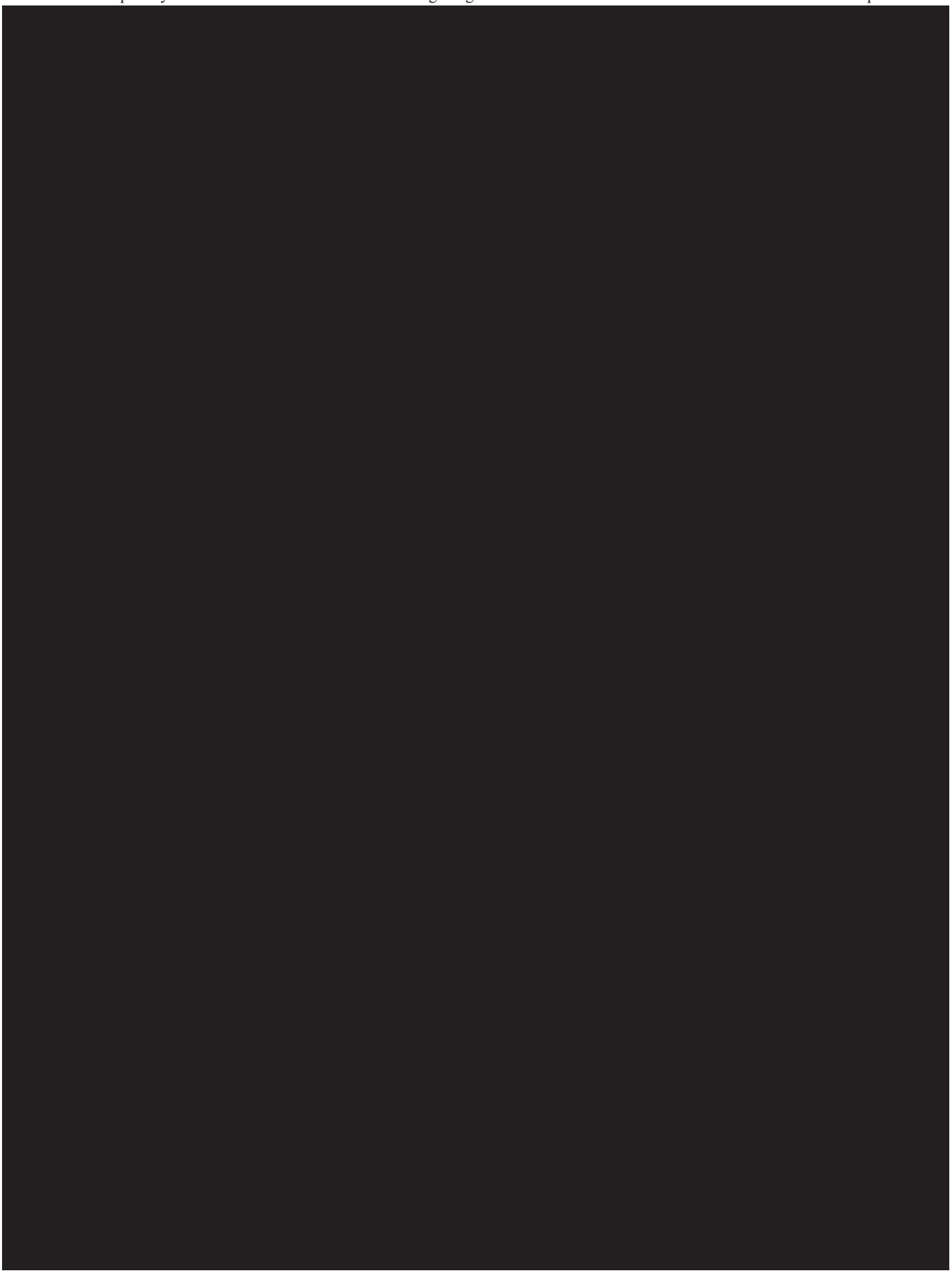
(i) Time to the first occurrence of HHF ('as adjudicated') or CV death ('as adjudicated')
(ii) Time to occurrences of all-cause hospitalisations (first and recurrent combined)
(iii) Time to death from any cause ('as adjudicated')

5.2.2 Secondary endpoints

Other secondary endpoints are:

(i) Time to the first occurrence of kidney disease progression
(ii) Time to CV death ('as adjudicated')
(iii) Time to first occurrence of CV death ('as adjudicated') or ESKD

[redacted]



5.4 OTHER VARIABLES

Trial-specific safety endpoints

Along with routine safety endpoints (refer to Section 7.8) the following trial-specific safety endpoints are defined (AEs will be coded using the MedDRA, version 20.1). Details on the PTs used to group the AEs for the AE-based endpoints below will be documented prior to database lock and listed in the Clinical Trial Report (CTR):

(i) Time to first occurrence of a serious adverse event (SAE) due to each of the following:
   a. Urinary tract infection (UTI)
   b. Genital infection ('as adjudicated')
   c. Hyperkalaemia
   d. Acute kidney injury ('as adjudicated')
   e. Dehydration

(ii) Time to first occurrence of an AE of special interest (AESI), 'as adjudicated':
   a. Liver injury [defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥5 x upper limit of normal (ULN) or the combination of ALT or AST ≥3 x ULN with bilirubin ≥2xULN (in the same blood sample)], overall and separately by cause
   b. Ketoacidosis
   c. Lower limb amputations, overall and by level (toe, forefoot, foot, below knee or above knee)

(iii) Time to first occurrence of other AEs relevant to the study question:

a. Bone fracture, overall and separately by site (long bones or non-long bones) and cause (high impact trauma, low impact trauma or other causes)
b. Severe hypoglycaemia (defined as low blood sugar causing severe cognitive impairment which requires assistance from another person for recovery)
c. Symptomatic dehydration (defined as whether or not a participant has experienced symptoms they attribute to dehydration, such as feeling faint or fainting)

(iv) Time to first occurrence of hospitalisation by specific causes based on the primary MedDRA System Organ Class (SOC)
(v) Time to first occurrence of SAEs, both overall and separately by primary SOC
(vi) Discontinuation of study treatment, both overall and by reason for discontinuation (SAEs [overall and by primary SOC], non-serious AEs [overall and by primary SOC] and all other reasons including those lost to follow-up)
(vii) Weight, systolic (SBP) and diastolic blood pressure (DBP) values at each scheduled visit during the follow-up period
(viii) Local laboratory measures of potassium at each scheduled visit during the follow-up period
(ix) Elevations in local laboratory measures of ALT and AST as defined by the categories of a) ALT or AST ≥5 x ULN b) ALT or AST ≥3xULN with bilirubin ≥2xULN (in the same blood sample)
(x) Haematocrit, haemoglobin, sodium, corrected calcium and phosphate at 18 months in the subset of surviving UK patients
(xi) Time to first occurrence of an SAE by each MedDRA HLGT (on the path to the primary SOC), exploratory endpoint

Extent of exposure

Treatment exposure (days) will be calculated as *Date of last administration of trial medication – Date of randomisation + 1*, note date of first administration of trial medication is not specifically collected but assumed to be the date of randomisation. Treatment exposure will include time when treatment is temporarily discontinued and subsequently reintroduced.

Observational period (days) will be calculated as *Date of final follow-up – Date of randomisation + 1*. The date of the final follow-up will be the date of the final follow-up visit if it was a direct visit or the date last known to be alive if it was an indirect visit or the date of death if the patient died prior to or on the day of the final follow-up visit.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

All summaries and analyses will assign patients to the treatment group that they were randomised to. The study has the following periods of interest:

- Screening/run-in period: from the day of informed consent to the day prior to randomisation
- Follow-up period: from the day of randomisation to the day of the final follow-up visit, split into the following:
    - On-treatment period: from the day of randomisation (note start date of study treatment is not specifically recorded, but assumed to be the randomisation date, as per protocol) to the day of permanently discontinuing study treatment + a residual effect period (REP), refer to Table 6.1: 1 below
    - Post-treatment period: from the day after the on-treatment period to the day of the final follow-up visit (for patients continuing on study treatment up to their final follow-up visit, no post-treatment period will exist)
- Post final follow-up period: from the day after the final follow-up visit to trial completion

There are two main data collection periods of interest for the efficacy and safety analyses:

Observed case including data after premature treatment discontinuation (OC-AD)
All data collected during the follow-up period (as defined above) will be considered. Later references during this document to the 'last/final scheduled follow-up visit' are within this period only. Unless stated otherwise data collected after the final follow-up visit will not be considered. Thus, following an intention-to-treat (ITT) analysis approach.

Observed case on-treatment (OC-OT)
Only data whilst a patient is on-treatment will be considered. The on-treatment period will include temporary off-treatment periods. The length of the REP depends upon the type of data being analysed and unless stated otherwise will be as detailed in Table 6.1: 1. Note it is possible for patients who permanently discontinue study treatment on or shortly prior to the day of the final follow-up visit to have a REP that would extend beyond the day of the final follow-up visit. In this instance for all trial-specific endpoints defined in Section 5, the REP will be truncated to ensure that the on-treatment period cannot extend beyond the day of the final follow-up visit. Whereas for the standard analyses of safety, described in Sections 7.8.1.2 and 7.8.2.2, the REP will be allowed to extend beyond the day of the final follow-up visit, where applicable.

Table 6.1: 1 Endpoint REP period for assigning to on-treatment period

Endpoint	**Residual Effect Period (days after study treatment stop date)**
eGFR and serum creatinine	1
HbA1c	7
Weight, BPs	1
Hip and waist circumference	7
EQ5D	7
Other laboratory parameters	3
AEs	7

6.2 IMPORTANT PROTOCOL DEVIATIONS

An important protocol deviation (iPD) is one that affects the rights or safety of the study patients or that can potentially influence the primary outcome measures for the respective patients in a way that is neither negligible nor in accordance with the study objectives.

Patients with an iPD will not be excluded from any analyses, the exception being patients not providing informed consent, who will be excluded from all analyses.

6.3 PATIENT SETS ANALYSED

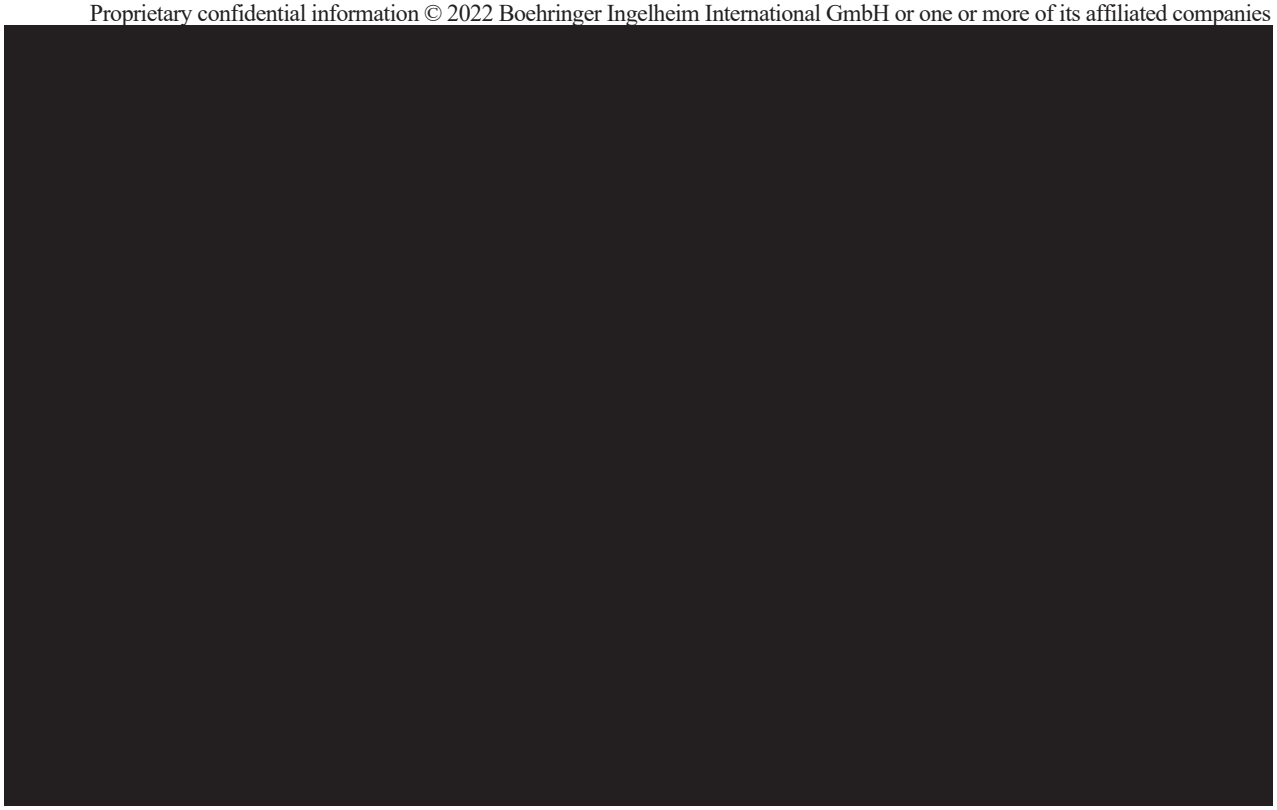
The following patient sets are defined:

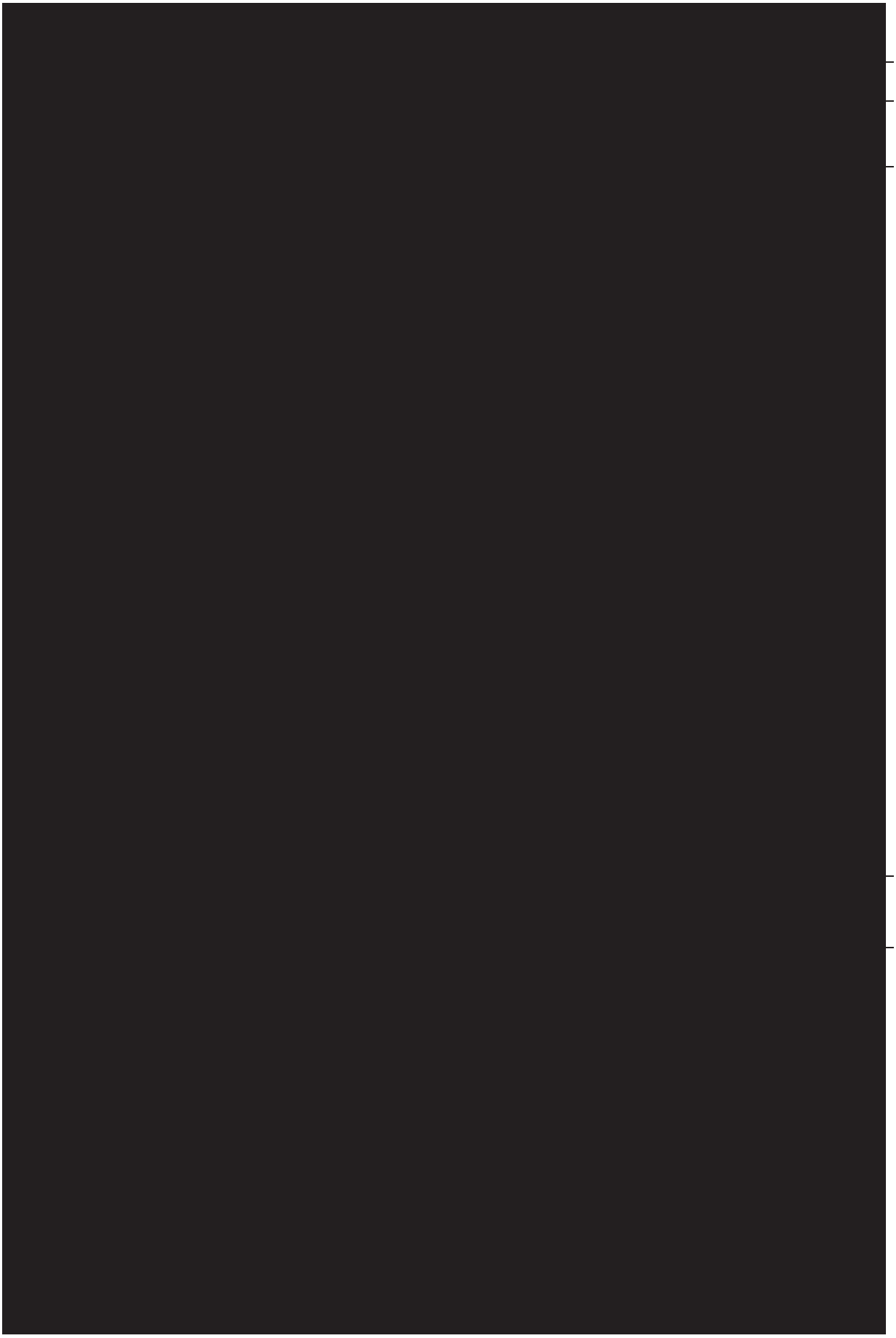
- Screened set (SCR)
  This patient set includes all patients screened for the trial and who provided informed consent.

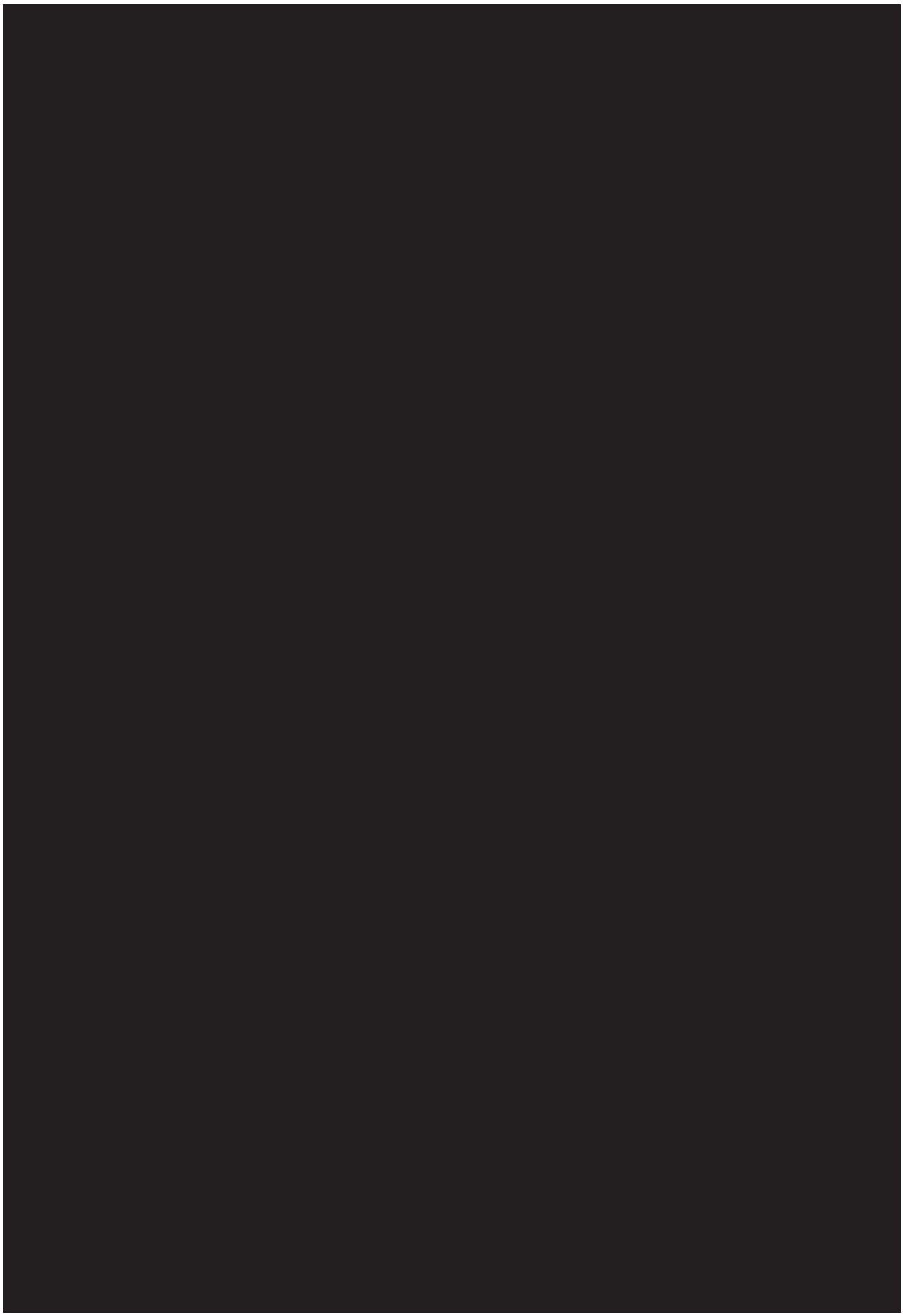
- Randomised set (RS):
  This patient set includes all randomised patients, whether treated or not.

- Treated set (TS):
  This patient set includes all patients who were dispensed randomised study medication.

Table 6.3: 1 summarises which endpoints are to be analysed for which analysis sets. RS analyses will use data from the OC-AD period of interest, unless specified otherwise. TS analyses will use data from the OC-OT period of interest, unless stated otherwise. Further details are provided in Section 6.1.







6.5 POOLING OF CENTRES

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

6.6 HANDLING OF MISSING DATA AND OUTLIERS

All efforts will be made to ensure patients attend all follow-up visits including the final follow-up visit, irrespective of whether patients are still on study treatment or not. At each follow-up visit, it is the aim to ascertain all components of all applicable endpoints.

For time to event endpoints, patients who are event-free but have dropped out of the trial prematurely (i.e. due to death, withdrawal of consent or loss to follow-up), will be censored according to the rules given in Section 6.8.2.

For the analysis of other endpoints, missing data will not be imputed unless detailed below. Note for endpoints analysed by mixed model repeated measures (MMRM) missing data will be handled via the methodology of MMRMs.

Missing central laboratory eGFR values

Note this section only applies to the handling of missing central laboratory eGFR for those efficacy endpoints that have time to a sustained decline in eGFR to <10 mL/min/1.73m^2 or time to a sustained decline of ≥40% in eGFR included as a component.

Table 6.7: 1 provides the expected study day for scheduled follow-up visits along with time windows defined for the purposes of analysis. If multiple central eGFR measurements are available in any one scheduled follow-up visit period, then the eGFR closest to the ideal follow-up day will be used to define the eGFR for that particular scheduled follow-up visit period.

eGFR will be estimated from creatinine measured in the central laboratory wherever possible. However, where a central laboratory eGFR measurement is expected but missing, the local blood creatinine measurement closest to the planned follow-up day within the scheduled follow-up visit period (if one exists) will be used to estimate the eGFR instead. Where a local eGFR is used, percentage change in eGFR will be calculated relative to the local randomisation visit value. The local eGFR measurement closest to the planned follow-up day of the next scheduled follow-up visit period will be used to assess the definition of a sustained decline. Using local measurements from previous scheduled follow-up visit periods for defining sustained declines will not be done (unless the central measurement is also missing at these visits). Therefore, to meet the sustained decline criteria, measurements must be from consecutive scheduled follow-up visit periods (at least 30 days apart) and from the same source (i.e. central or local). The exception being if the decline is observed at the last scheduled follow-up visit, in which case consecutive measurements are not required and a single local measurement could be used in the absence of a central one.

If the central eGFR measurement is missing at the randomisation visit, then the local measurement will be used. If both the central and local measurement are missing, then the latest locally measured pre-randomisation value will be used. Where a local eGFR is used, percentage change in eGFR will be based only on post-baseline local values.

Further detail on the handling of missing eGFR values and the derivation of sustained declines is provided in Section 9.6.

A sensitivity analyses for the primary endpoint will be performed solely on central laboratory eGFR measurements, to assess the impact of using local data when central data is missing. A similar sensitivity analysis will also be performed solely on local laboratory eGFR measurements, for completeness.

Missing information on event dates, AE onset dates and death dates

For such dates, month and year are required so only the handling of missing days is considered here. In general, a worst-case approach will be adopted, whereby the date will be assumed to have occurred as close to the date of randomisation as possible, i.e. the day of randomisation for dates within the same month of randomisation, or the first of the month for dates after the month of randomisation.

The exception will be for day of death, whereby if from other recorded dates it is known the patient was alive the latest of these dates will be used instead. Note during adjudication patients with an AE or AEs with a fatal outcome will have one AE selected as leading to the cause of death. The end date for this AE will be used to record the date of death and will be used for all applicable analyses/summaries.

In the unlikely event of the month and/or year also not being available dates will be imputed on a case-by-case basis and documented prior to breaking the blind.

Missing information on hospital discharge dates

This imputation is only required for the analysis of all-cause recurrent hospitalisations, when information on hospital duration is not provided and the corresponding AE end date (used as the hospital discharge date) is either partial or missing.

For these cases, if the day is missing then it will be assumed as the day that leads to the shortest hospital stay, i.e. the 1st of the month or the day of AE onset if the AE onset month is the same as the AE end month. If day and month are missing and AE onset/end dates are in the same year then the discharge date will be assumed as the day of AE onset, otherwise if in different years the 1st January will be used. If the AE end date is completely missing, then the discharge date will be assumed as the day of AE onset.

Missing information on the treatment stop date

If only month and year are present then the day will be assumed as the last day of the month, unless there is evidence of an earlier date of death, in which case the date of death will be used.

In the unlikely event of the month and/or year also not being available dates will be imputed on a case-by-case basis and documented prior to breaking the blind.

Handling of unquantifiable laboratory data

It is expected that some UACR (centrally and locally assessed) and NT-proBNP (centrally assessed) values may be too low to quantify, prior to any summaries of these data they will be imputed to a value approximately halfway between 0 and the lower limit of detection.

Some UACR (locally assessed only) values may also be too high to quantify, prior to any summaries of these data they will be imputed to the 95th percentile from the local baseline UACR values, after imputation of the too low to quantify values.

The exact values used for the imputations will be documented prior to the database lock.

Other instances of laboratory values being too low or high to quantify are expected to be seen rarely and if observed, likely to be unreliable. In such instances the values will be considered as missing for any summaries.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline will be defined as the last available measurement on or prior to the day of randomisation (excluding any pre-screening measurements). Per protocol, study treatment will start on the day of randomisation and baseline assessments will be taken prior to any intake of study treatment.

Where post-baseline efficacy or safety measurements need to be assigned to a specific follow-up visit, time windows around the planned visit day are defined. The midpoint between two scheduled visits defines the end of a time window, with the midpoint being included in the time window of the preceding visit, as detailed in Table 6.7: 1.

Study days will be assigned relative to the day of randomisation. The day prior to randomisation will be 'Day -1' and the day of randomisation will be 'Day 1'. Hence, 'Day 0' will not exist.

Table 6.7: 1 Time windows for post-baseline follow-up visits

Visit number	Follow-up visit	Planned day	Time window	
			Start	End
1	2 months	60	2	120
2	6 months	180	121	270
3	12 months	360	271	450
4	18 months	540	451	630
+ 1*	+ 6 months*	+ 180*	+ 180*	+180*

* Subsequent visits 6-monthly, add value to previous record in respective column

For summaries and analyses presented at a visit level only one observation per time window will be selected, this will be the value closest to the planned day. If there are two observations equidistant from the planned day then the earlier observation will be used, note only dates and

not times of assessments will be used in these calculations. For situations where we have two observations recorded on the same day a worst direction approach will be used to decide on the observation to select, refer to Section 9.4.

An exception to the above rule will be used for the handling of data collected at the final follow-up visit. If the final follow-up visit occurs within the same time window as the preceding visit, then the data collected at the final follow-up visit will take precedence, even if it is furthest from the planned day.

Time window for 4-week post final follow-up visit

For summaries of 4-week post final follow-up visit data only values measured >=7 days to <=42 days after the final follow-up visit will be considered. The value that is closest to the planned day of 28 days after the final follow-up visit will be used. The same approaches as defined above will be used for equidistant values and observations recorded on the same day.

6.8 CALCULATION OF TIME TO FIRST OCCURRENCE ENDPOINTS

All time to first occurrence endpoints will be reported in days and calculated as follows:

- For patients with the event of interest, the time to event is calculated as:

  <date of event> - <date of randomisation> + 1

- For patients without the event of interest, the time at risk is calculated as:

  <date of censoring> - <date of randomisation> + 1

For patients censored on the day of randomisation who are known not to have had any follow-up, their time at risk will be assigned as zero.

6.8.1 Date of event

For adjudicated events, the date determined by the adjudication committee will be used irrespective of whether this differs from the investigator reported date.

For composite outcomes, the earliest onset date of the corresponding components will be used. For the component of CV death or other death components, date of death will be used.

For ESKD, the earliest onset date of any episode of maintenance dialysis or kidney transplant will be used.

If the conditions for ‘sustained’ eGFR decline are met, the date of the event (i.e. laboratory test date) will be the date of the earlier of the two measurements (where applicable).

For events with multiple possible episodes, the onset date of the first episode will be used unless noted otherwise.

For the analysis of recurrent all-cause hospitalisations, the admission date of the hospitalisation will be taken as the AE onset date, and the discharge date as the AE onset date

+ the hospital duration. If the hospital duration is missing, then the discharge date will be taken as the AE end date. If this date is partial or missing the rules on missing hospital discharge dates detailed in Section 6.6 will be followed. Hospitalisations starting prior to randomisation will be ignored. Patients with overlapping hospitalisation events will have such events collapsed into one event, an overlapping event is one where the admission date of a hospitalisation is prior to or on the date of discharge of an earlier hospitalisation. The collapsing of hospitalisation events will take the earliest admission date and the latest discharge date.

For the OC-AD period of interest, all events occurring during the follow-up period will be considered. For the OC-OT period of interest, only events occurring during the on-treatment period will be considered. In all cases, events occurring after the final follow-up visit will not be considered.

6.8.2 Date of censoring

It is the aim at each scheduled follow-up visit to ascertain all components of all endpoints (where data is planned to be collected), with subsequent adjudication where applicable. Follow-up information will be collected from all patients, irrespective of whether they continue to take study treatment or not, usually at the scheduled follow-up visits, unless they withdraw consent. If patients are unwilling/unable to attend a scheduled follow-up visit the necessary information will be collected indirectly (e.g. via telephone). Every effort to collect a central blood sample will be made for each scheduled follow-up visit, but for those known to be alive who do not provide a blood sample, the most recent blood results will be recorded.

For patients who are alive with no evidence of the event being analysed at their last/final scheduled follow-up visit the date of the visit will be used as the date of censoring. The exception will be if the last/final scheduled follow-up visit is an indirect visit, in which case the date the patient is last known to be alive with no evidence of the event being analysed will be used (note this is the date of the telephone call if it was with the patient).

For composite endpoints that include a sustained decline in eGFR component, the above censoring dates will be used even if there is no eGFR value available at their last/final scheduled follow-up visit. This approach is being adopted as very few patients are expected to have a missing eGFR value at their final scheduled follow-up visit; it also avoids over complicated censoring rules for different components within a composite endpoint.

For patients that die during the follow-up period date of death can be used as a censoring date as long as there is no evidence of the event being analysed at the time of death. For example, if their death was not a CV death and they had not had a HHF, they would be censored at the time of death for the time to first occurrence of a HHF or CV death endpoint.

The above censoring rules apply to analyses of the OC-AD period of interest. For on-treatment (OC-OT) analyses, patients will be censored at the minimum of the OC-AD censoring date or the end of the on-treatment period.

7. PLANNED ANALYSIS

In general, the BI guideline 'Standards for Reporting of Clinical Trials and Project Summaries' (6) will be followed for the End-Of-Text (EoT) tables. In summary:

- The set of summary statistics for continuous data is: N / Mean / Standard Deviation (SD) / Minimum (Min) / lower quartile (Q1) / Median / upper quartile (Q3) / Maximum (Max). The geometric mean and geometric coefficient of variation will also be presented for summaries of parameters known to follow a log-normal distribution. The means, SDs, medians, Q1 and Q3 will be presented to one more decimal place than the raw data. Minima and maxima will be presented to the same number of decimal places as the raw data.

- Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all subjects in the respective subject 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.

- Standard errors (SEs) and confidence intervals (CIs) will be presented where appropriate and to one more decimal place than the raw data. P-values will be presented to four decimal places.

The trial is planned to continue until a minimum of 1070 first primary endpoint events have occurred, at which point patients will be invited to attend their final follow-up visit, this may occur earlier than their planned next 6-monthly visit.

A formal interim analysis may be conducted by the DMC when a minimum of 150 first ESKD events have occurred. If the pre-defined stopping criteria are met, then the trial will be stopped early for overwhelming efficacy. Further details are provided in the CTP, the DMC charter and Section 9.2 of this TSAP.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report, based on the RS of patients.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report, based on the RS of patients.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report, based on the TS of patients.

Appropriate summaries of compliance before and from the start of the COVID-19 disruption will be produced.

7.4 PRIMARY ENDPOINT

The primary estimand of this trial is the hazard ratio (HR) of the time to first occurrence of kidney disease progression or CV death in the target population, for patients randomised to empagliflozin 10 mg relative to those randomised to placebo on top of standard care. This estimand will ignore any non-fatal intercurrent events and is in the hypothetical absence of death from any cause not included in the endpoint.

The primary analysis will be based on the RS of patients using all available data from the follow-up period (OC-AD), data occurring after the final follow-up visit will not be considered.

7.4.1 Primary analysis of the primary endpoint

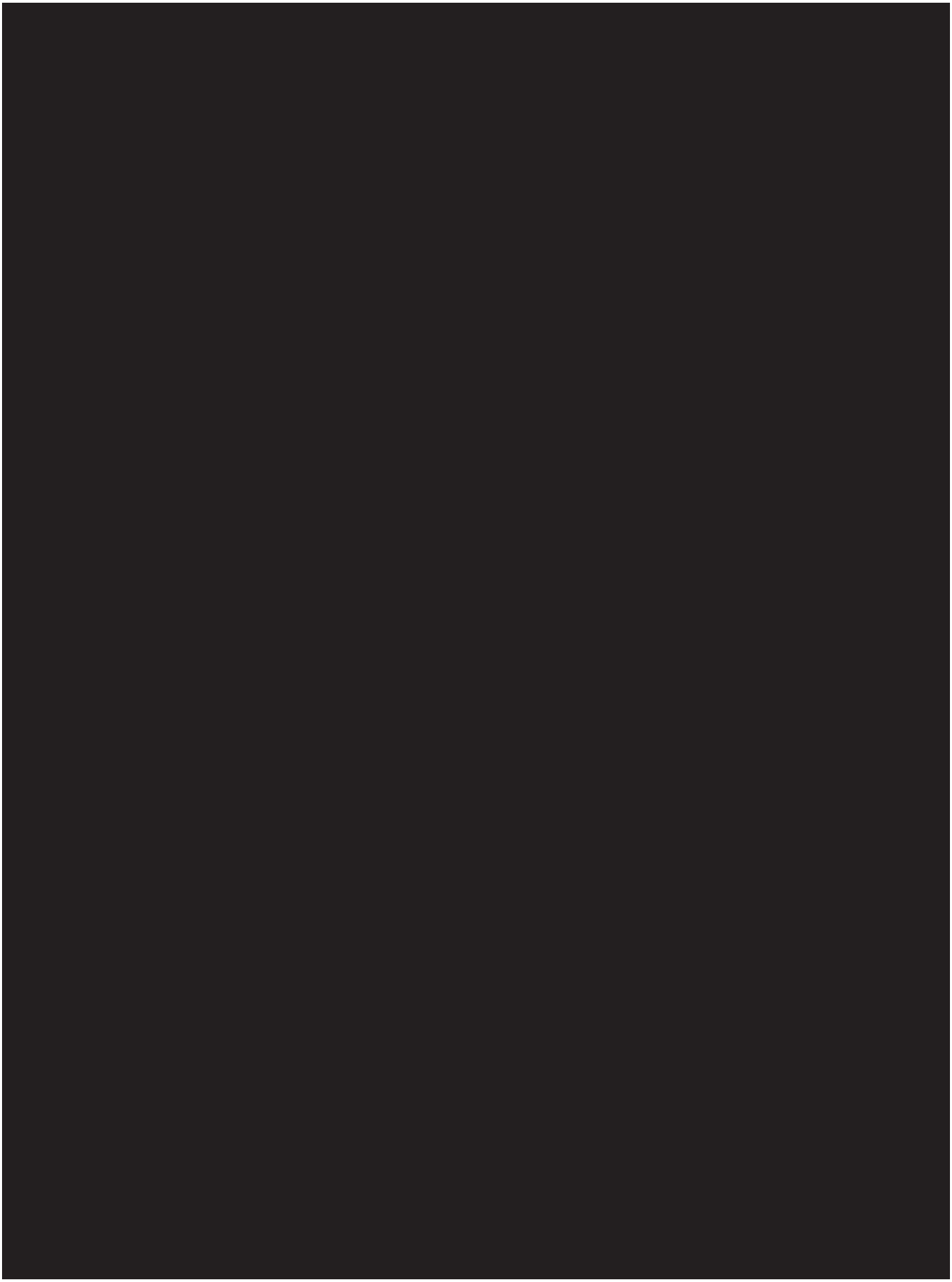
The primary endpoint will be analysed using a Cox proportional hazards regression model with factors of treatment (empagliflozin, placebo) and each of the variables used in the minimization algorithm for randomisation. The randomisation factors will be fitted according to the same categories used in the minimization; for age (<45, ≥45 to <55, ≥55 to <65, ≥65 to <75, ≥75), sex (male, female), DM status (yes, no), local screening eGFR (<30, ≥30 to <45, ≥45 to <60, ≥60 to <75 and ≥75) and local screening UACR (<20, ≥20 to <200, ≥200 to <500, ≥500 to <1000, ≥1000). However, for region (North America, Europe, Japan, Other Asia [China or Malaysia]) the actual region a patient was randomised from will be fitted.

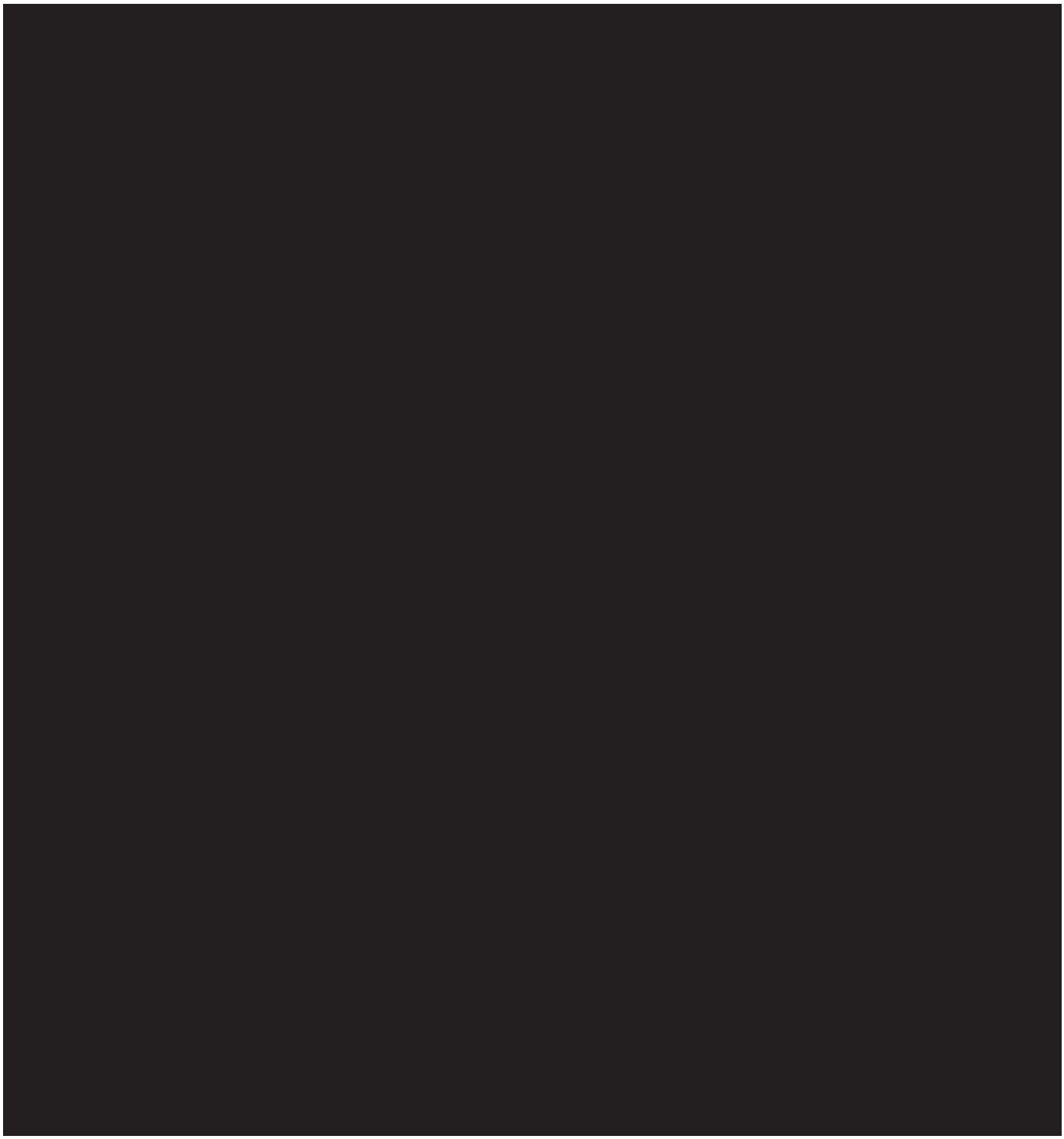
This model will be used to test the equality of the hazard rates via the Wald test for the treatment effect. The same model will used to estimate the HR of the treatment effect and the corresponding asymptotic two-sided 95% Wald CI. A HR of less than one favours empagliflozin. Breslow's method for handling ties will be used.

For the interim and final analyses of the primary endpoint the Hwang-Shih-DeCani alpha-spending function with parameter γ=-8 will be used to account for multiplicity. The required alpha-levels are expected to be 0.0020 and 0.0497 (two-sided) for the interim and final tests respectively, assuming 60% of the primary outcome events have accrued at the time of the interim analysis. The alpha-levels will be adjusted according to the actual proportion of primary outcome events observed at the interim. In addition to the 95% CIs described above, two-sided CIs based on the required alpha-levels will also be produced.

Cumulative incidence function (CIF) and/or Kaplan-Meier (KM) curves will also be produced to summarise the primary endpoint data. The number of events in each of the individual components that contribute to the overall number of primary composite events will also be summarised descriptively.

The proportional hazards assumption will be explored by plotting log (-log (survival function)) against the log of time by treatment group and visually inspected for parallelism. The interaction of treatment with log of time will be included in the primary endpoint model described above, as an exploratory analysis. Further, Schoenfeld residuals for each covariate and treatment will be plotted against time and log (time).





7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

If statistical significance is observed for the primary endpoint, then the key secondary endpoints will be formally analysed via the Hochberg ‘step-up’ procedure to control the familywise error rate. Note for formal analysis of the key secondary endpoints at the interim

time point, the additional criterion relating to time to CV death or ESKD will also need to be met, refer to the CTP for further details.

For the interim and final analyses the Hwang-Shih-DeCani alpha-spending function with parameter γ=0 will be used to account for multiplicity. The familywise error rate would be controlled at 3.0% and 3.1% for the interim and final tests respectively, assuming 60% of the primary outcome events have accrued at the time of the interim analysis. The error rates will be adjusted according to the actual proportion of primary outcome events observed at the interim.

The primary analysis of the key secondary endpoints will be based on the RS of patients using all available data from follow-up period (OC-AD).

7.5.1.1 Primary analysis of the key secondary endpoints

Time to first occurrence of HHF or CV death

The estimand is the hazard ratio (HR) of the time to first occurrence of HHF or CV death in the target population, for patients randomised to empagliflozin 10 mg relative to those randomised to placebo, ignoring any non-fatal intercurrent events and in the hypothetical absence of death from any cause not included in the endpoint.

The analysis of this endpoint will follow that of the primary endpoint, detailed in Section 7.4.1.

Time to occurrences of all-cause hospitalisations (first and recurrent)

The estimand is the hazard ratio (HR) of the time to occurrences of all-cause hospitalisations in the target population, for patients randomised to empagliflozin 10 mg relative to those randomised to placebo, ignoring any non-hospitalisation non-fatal intercurrent events and in the hypothetical absence of death from any cause.

All-cause hospitalisations will be analysed using a joint frailty model (JFM). The JFM is a semi-parametric model that accounts for the dependence between recurrent hospitalisations and all-cause death through a patient-specific frailty term (10). In summary:

Define $T_{i0} = 0$ and let $T_{i1}, T_{i2}, \ldots, T_{iNi}$ be the recurrent event times for person i, where N_i is the number of recurrent hospitalisation events before $X_i = \min(C_i, D_i)$, the minimum of an independent censoring time C_i and a dependent death time D_i. The JFM is defined through the hazard functions for the recurrent event process and death:

$$r_i(t \mid \omega_i) = \omega_i \, exp\{\beta_1 Z_i\} \, r_0(t)$$

$$\lambda_i(t \mid \omega_i) = \omega_i^{\alpha} exp\{\beta_2 Z_i\} \, \lambda_0(t)$$

The recurrent hospitalisations hazard function for the ith patient conditional on the patient specific random frailty, ω_i, is given by r_i and is proportional to the baseline hazard function, r_0. The conditional hazard function for time to death for patient i is given by, λ_i, with the

baseline hazard given by λ_0, and β_1, β_2 are the regression coefficients associated with vectors of covariates z_i. The same covariates as for the analysis of the primary endpoint will be used.

Patient specific independent random effects are denoted by ω_i and are assumed to follow a Gamma distribution with mean 1 and variance θ. The correlation of the recurrent events is quantified by θ, with higher values corresponding to greater within-patient correlation and greater between-patient variability. The parameter α determines the relationship between the recurrent hospitalisations and time to death. When $\alpha < 0$, higher frailty will result in a greater risk of recurrence and lower risk of terminal event (i.e. a negative correlation between the frailties), and when $\alpha > 0$, higher frailty will result in a greater risk of recurrence and is associated with a higher risk of terminal event (i.e. a positive correlation between the frailties). When $\alpha = 1$, the impact of frailty is identical on recurrent and terminating events, and $\alpha = 0$ means that the recurrent event process is independent of death, and the two outcomes can be analysed separately.

Let t_{ij} and x_i be the observed recurrent event times and follow-up, respectively. Denote by δ_{ij} and Δ_i, the indicator of the recurrent event at time t_{ij} and the indicator of death at time x_i, respectively. The likelihood for person i is then given by the following:

$$L_i = \int_{\omega_i} \prod_{j=1}^{N_i} [\omega_i r_i(t_{ij})]^{\delta_{ij}} \exp\left\{\int_0^{x_i} \omega_i r_i(t)dt\right\} [\omega_i^{\alpha} \lambda_i(x_i)]^{\Delta_i} exp\left\{\int_0^{x_i} \omega_i^{\alpha} \lambda_i(t)dt\right\} f_{\theta}(\omega_i)d\omega_i$$

Adopting piecewise constant hazards for the recurrent events and death allows estimation of the likelihood by Gaussian quadrature. The implementation of the adaptive Gaussian quadrature techniques is incorporated into PROC NLMIXED of SAS®, following the strategy outlined in (11) will be used. Sample code is provided in Section 9.5. The joint model will give two distinct hazard ratios:

- $HR_H = \exp\{\beta_{11}\}$ is the hazard ratio associated with the effect of treatment on the recurrent event rate of all-cause hospitalisations
- $HR_D = \exp\{\beta_{21}\}$ is the death hazard ratio

The HR_H will be the HR that is formally tested.

The size of the piecewise constant hazards are determined separately for the terminal and recurrent event process, each with 5 pieces. The nodes are defined by the empirical quintiles of the terminal or recurrent events, respectively. To fit the joint frailty model using the multiplicative parametrization with non-normal random effects, a likelihood-reformulation method will be used (12).

To improve convergence of the model, linear covariates (when no interaction with treatment is modelled) will be standardized prior to inclusion into the analysis and starting values for the model parameters will be determined using the following procedure:

1) An exponential model will be fitted for the terminal event and a poisson regression model the recurrent event process including the same covariates that are included in the final JFM to get the initial starting values for all parameters.

2) A simplified model without random effect ω that is otherwise equal (regarding covariates and baseline hazards) to the JFM fitted using the values from step (1) as starting values for the parameters. The estimated coefficients from the simplified model will be used as starting values for the parameters of the piecewise-constant JFM.

Estimates of HRs and corresponding 95% CIs will be provided for the hazard ratios.

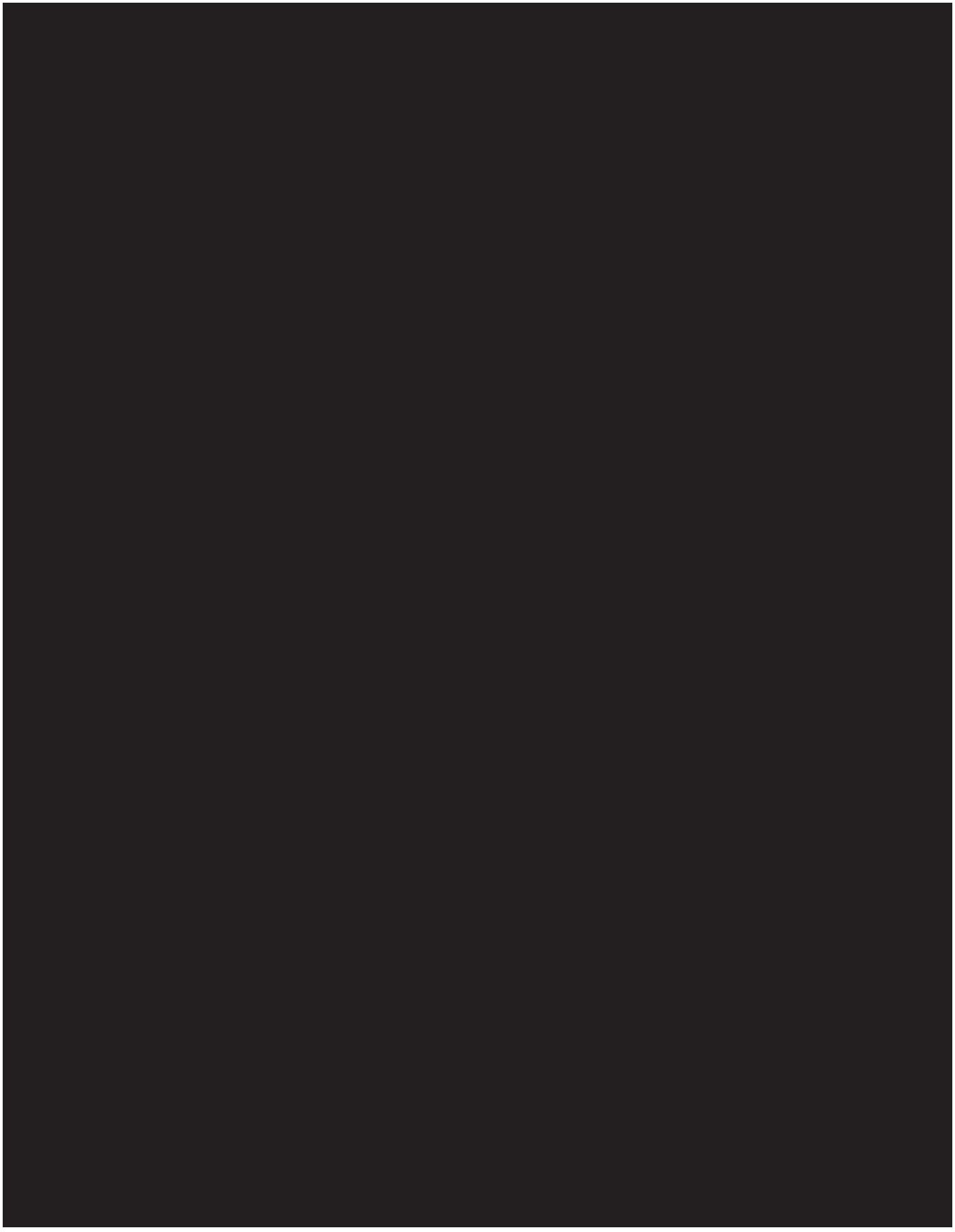
Pre-defined steps, to be documented prior to database lock, will be implemented to improve convergence of the semi-parametric JFM. If there are still convergence issues that cannot be resolved, as indicated by error or warning messages in the SAS® log, a parametric joint Gamma-frailty model will model the recurrent event component using a Poisson distribution and model the death component using an exponential distribution, conditional on the frailty parameter. Individual frailties are again assumed to follow a Gamma distribution. Thus, hospitalisation rates follow a negative binomial distribution and times to death a Lomax distribution (13).

Only in the situation where there are convergence issues as defined above will the parametric model replace the semi-parametric JFM for the confirmatory analysis.

Time to death from any cause

The estimand is the hazard ratio (HR) of the time to first occurrence of death from any cause in the target population, for patients randomised to empagliflozin 10 mg relative to those randomised to placebo, ignoring any non-fatal intercurrent events.

The analysis of this endpoint will follow that of the primary endpoint, detailed in Section 7.4.1.



[redacted]

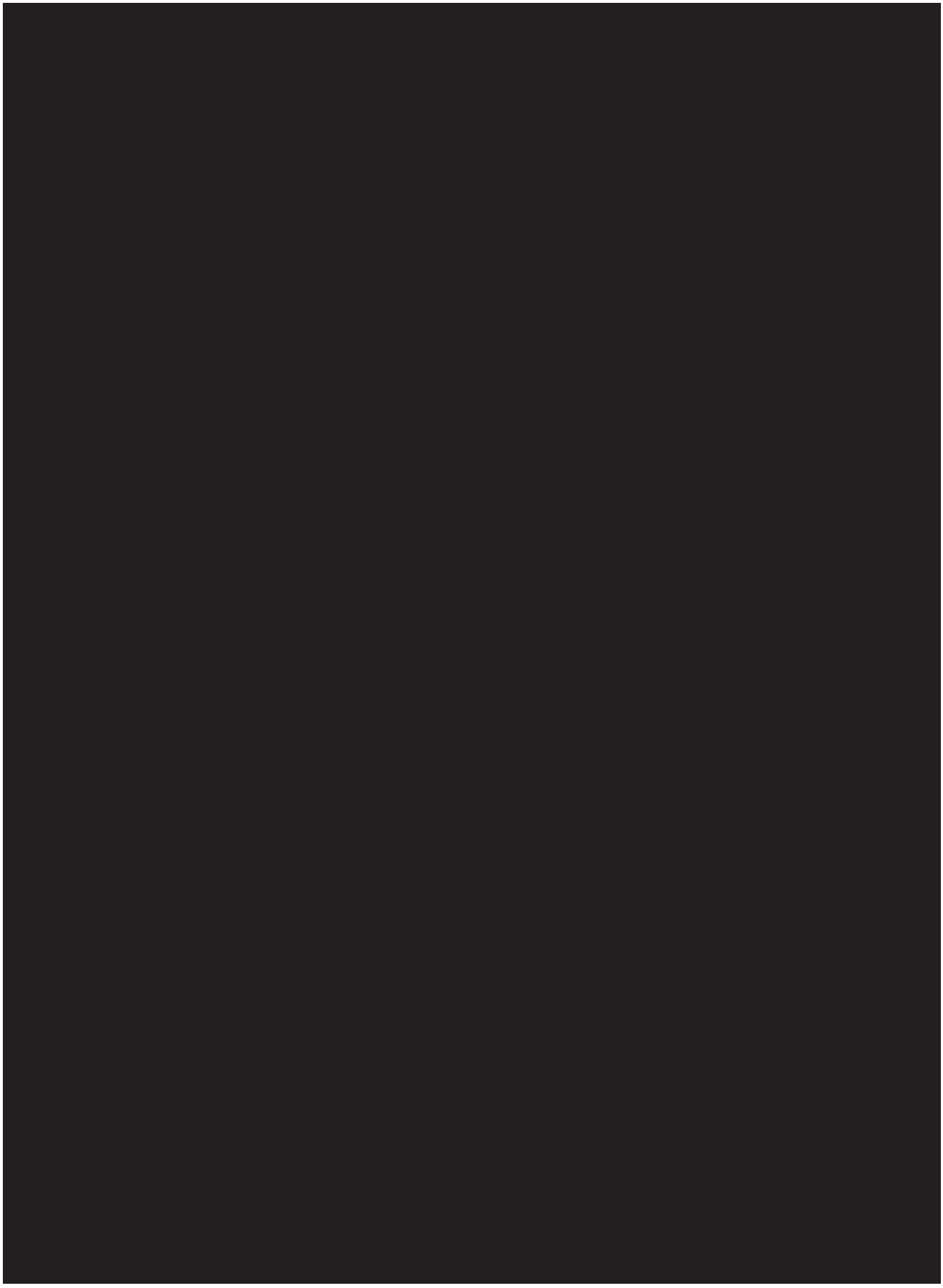
7.5.2 Other secondary endpoints

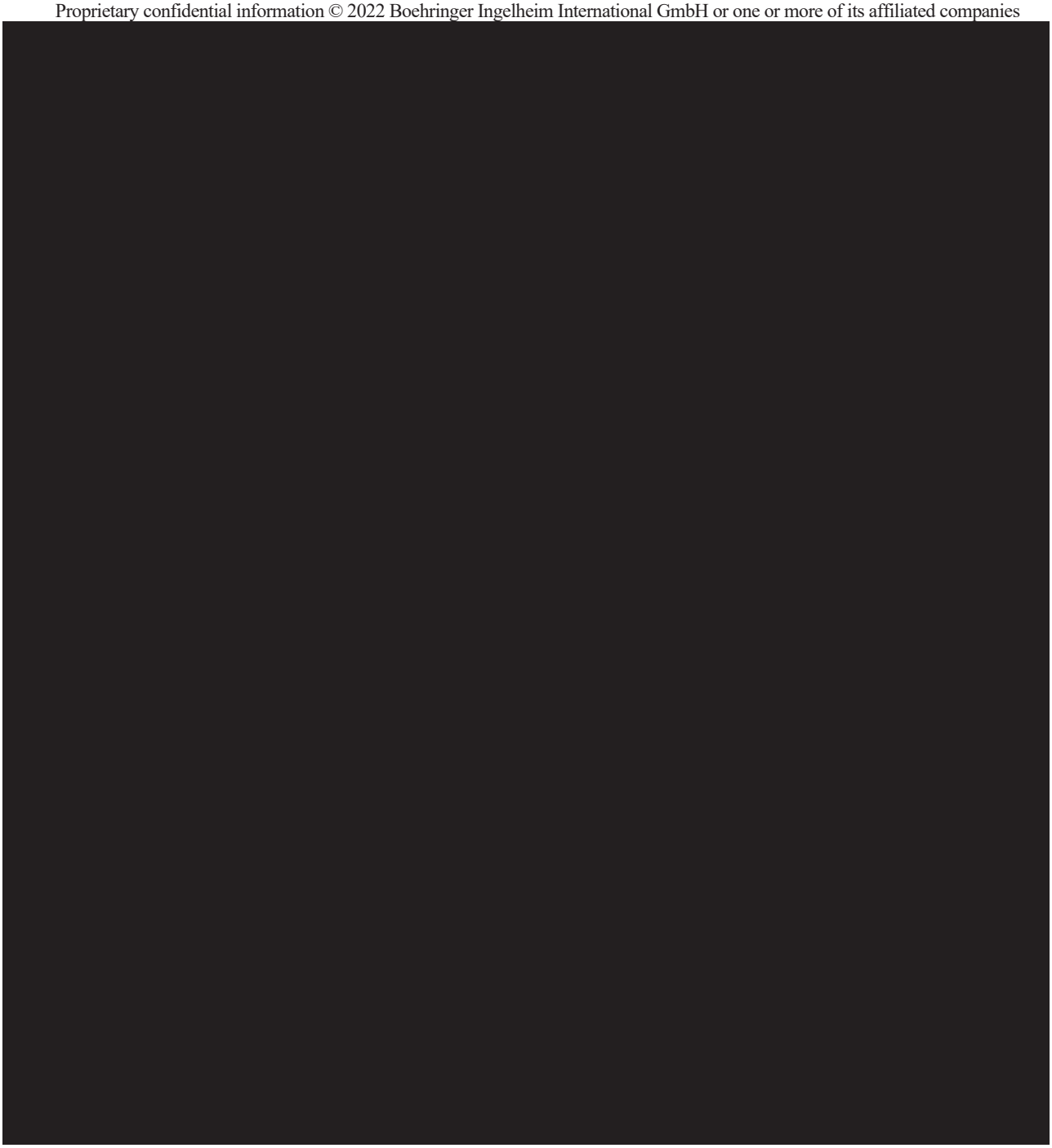
The other secondary endpoints defined in Section 5.2.2 will be analysed using the same methodology as for the primary endpoint. No formal hypothesis testing or adjustment for multiple testing will be performed for these endpoints, the analyses will be considered as supportive to the main analyses.

The analysis of all other secondary endpoints will be based on the RS of patients using all available data from follow-up period (OC-AD).

[redacted]

[redacted]





7.7 EXTENT OF EXPOSURE

A standard descriptive summary of the duration of treatment exposure and the duration of the observational period will be produced, the former on the TS and the latter on the RS. These tables will also provide the sum-total of the time (in years) exposed across all patients.

Frequency tables of the number and percentage of patients belonging to the categorical ranges of exposure (in weeks) will also be provided. The following categories are planned but may be adapted: ≥0 to <8, ≥8 to <26, ≥26 to <52, ≥52 to <78, ≥78 to <104, ≥104 to <130, ≥130 to <156 and ≥156 weeks.

7.8 SAFETY ANALYSIS

Where applicable, the sections below are divided into trial-specific safety endpoint analyses and BI/project standard analyses of routine safety data. The trial-specific safety endpoints are those specifically defined in the CTP and will be analysed for both the RS and TS. All BI/project standard analyses of routine safety data will be performed on the TS, treatment will be evaluated as randomised. Unless stated otherwise the RS analyses will use data from the OC-AD period of interest and the TS analyses will use data from the OC-OT period of interest. For the OC-OT analyses any REP after the final follow-up visit will not be considered for the trial-specific endpoints but will be considered for BI/project standard analyses of routine safety data. One exception will be for BI/project standard analyses of routine safety data that are based purely on adjudicated terms, these will also not consider the REP after the final follow-up visit, as adjudication is not planned for events with an onset after the final follow-up visit.

While tables will generally display results by randomised treatment, listings will reflect whether a measurement/AE occurred on- or off-treatment.

In addition to the summaries below, standard tables required for the clinical trials disclosure process (ClinicalTrials.gov and EudraCT) will be produced (15).

7.8.1 Adverse Events

As the safety profile of empagliflozin has been well studied in previous trials collection of safety data has been streamlined. Only pre-specified non-serious AEs are planned to be collected along with all SAEs. The exception to this will be for patients entered in Japanese sites, where all AEs (non-serious AEs and SAEs) will be recorded. The pre-specified non-serious AEs are:

- Leading to study drug discontinuation
- Bone fracture
- Severe hypoglycaemia
- Gout
- Symptomatic dehydration
- AESIs (ketoacidosis, lower limb amputation and liver injury)
- Could lead to amputation

Unless stated otherwise the AE analyses detailed below will only be based on the pre-specified non-serious AEs and SAEs.

The focus of the AE evaluation will be based on the adjudicated terms, and these will take precedence over investigator-reported terms for all of the analyses and summaries described below. Summaries will be provided to show the results of adjudication in particular summarising any changes in investigator-reported AE PTs.

AEs will be coded using MedDRA 20.1.

7.8.1.1 Analysis of trial-specific AE endpoints

The time to first occurrence of the trial-specific AE endpoints detailed in Section 5.4 will be analysed using the same methodology as for the primary efficacy endpoint (Section 7.4.1).

The main analysis of these endpoints will be based on the RS using all available data from follow-up period (OC-AD). Additional analyses on the TS using all on-treatment data (OC-OT) will also be performed.

[redacted]

No formal hypothesis testing or adjustment for multiple testing will be performed for these endpoints, any p-values presented will be for information only.

7.8.1.2 Standard analyses of AEs

Unless otherwise specified, the analyses of AEs in this section will be descriptive in nature and based on the TS using data from the OC-OT period of interest. All analyses of AEs will be based on the number of patients with AEs and not on the number of AEs.

For further details on the summarisation of AE data, please refer to (16) and (17).

The on-treatment analysis of AEs will be based on the concept of treatment emergent AEs, whereby all AEs occurring between first drug intake (randomisation date) up to 7 days (REP) after last drug intake will be assigned to the randomised treatment. All AEs occurring before first drug intake will be assigned to 'screening' and all AEs occurring after the REP will be assigned to 'post-treatment'. For details on the treatment definition, see Section 6.1.

In general, AE summaries will present only on-treatment AEs (applying the 7-day REP rule); though there are some additional summaries described below where longer periods after discontinuing study treatment are considered.

7.8.1.2.1 General AE summaries

An overall summary of AEs will be presented.

The frequency of patients with AEs will be summarised by treatment, primary SOC and PT. Incidence rates as defined in Section 7.8.1.2.5 will generally be included. Separate tables will be provided for patients, for each of the following:

- All AEs
- Study drug-related AEs
- SAEs
- Study drug-related SAEs
- AESIs (ketoacidosis, lower limb amputations and liver injury) 'as adjudicated'
- AEs leading to study drug discontinuation
- AEs with a fatal outcome

[redacted]

The summary of AEs with a fatal outcome will be repeated including all AEs experienced up to the end of the trial.

The SOCs and PTs within SOC will be sorted by frequency, based on maximum percentage within either treatment group.

The overall summary of AEs, all AEs and study drug-related AEs by SOC and PT will be repeated for patients from Japanese sites included all AEs, i.e. with the inclusion of non-serious AEs not pre-specified in the CTP.

7.8.1.2.2 Adverse Events of Special Interest

The focus of the AESI summaries will be on adjudicated terms with investigator-reported term summaries considered as supportive. Further details on the adjudication process refer to Standard Operating Procedure (SOP) 9b: EMPA-KIDNEY: Adjudication Procedures (4). Note as adjudication is not performed on events with an onset after the final follow-up visit, the REP after the final follow-up visit is not included in the summaries below.

Liver injury

Liver injury has a biochemical definition as per the CTP, if evidence of a liver injury is confirmed or unrefuted via adjudication an AE will be recorded with a PT of 'Liver injury'. Adjudication will also provide an additional 'offspring' AE detailing the aetiology.

Frequency tables of patients with an adjudicated PT of 'Liver injury' along with the aetiology will be provided, using both the '7-day on-treatment approach' and a '30-day on-treatment approach'. These will be repeated for SAEs. The [redacted]

Ketoacidosis

A frequency table of patients with ketoacidosis events 'as adjudicated' will be produced by primary SOC and PT (according to the adjudicated primary aetiology), this will be repeated for SAEs. [redacted]

A frequency table of the adjudicated events will be produced in order to display the full results of the adjudication.

Lower limb amputations

Frequency tables of patients with lower limb amputation events 'as adjudicated' will be produced by PT and adjudicated level of amputation. In addition to the '7-day on-treatment approach' the table will be repeated for all patients with adjudicated lower limb amputations that occurred between first study drug intake up to trial completion will be presented. SAEs and AEs leading to study drug discontinuation will also be presented.

[redacted]

A frequency table of the adjudicated events will be produced in order to display the full results of the adjudication.

7.8.1.2.3 Other Adjudicated AEs

Adjudication outside of the AESIs will be limited to all deaths and events initially reported as HHF, MI, stroke and acute kidney injury. Further details on the adjudication process refer to Standard Operating Procedure (SOP) 9b: EMPA-KIDNEY: Adjudication Procedures (4). Note as adjudication is not performed on events with an onset after the final follow-up visit, the REP after the final follow-up visit is not included in the summaries below.

Where appropriate listings will be provided showing the trigger events and the result of adjudication.

Fatal AEs

Frequency tables of 'as adjudicated' cause of death by primary SOC and PT will be produced, along with a summary by the protocol-specified categorisation [tabulated in (4)]. In addition to the '7-day on-treatment approach' all 'as adjudicated' causes of death that occurred between first study drug intake up to final follow-up visit will be presented.

Hospitalisation due to heart failure

Frequency tables of patients with a HHF event 'as adjudicated' will be produced by adjudicated primary SOC and PT.

Myocardial infarction

Frequency tables of patients with a MI event 'as adjudicated' will be produced by adjudicated primary SOC and PT.

Stroke

Frequency tables of patients a stroke event 'as adjudicated' will be produced by adjudicated primary SOC and PT.

Serious acute kidney injury

Frequency tables of patients with a serious acute kidney event 'as adjudicated' will be produced by adjudicated stage, aetiology, primary SOC and PT.

[redacted]

Serious genital infections

Frequency tables of patients with a serious genital infection event 'as adjudicated' will be produced by adjudicated primary SOC and PT. [redacted]

7.8.1.2.4 Specific AEs

Hepatic events

Patients with hepatic AEs (whether associated with liver injury or not) will be summarised based on a Standardised MedDRA Query (SMQ) based definition. From the SMQ 'Drug related hepatic disorders (20000006)' the following narrow sub-SMQs will be used:

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

A table with frequencies of patients with these AEs by treatment, primary SOC and PT will be provided. [redacted]. SAEs and AEs leading to study drug discontinuation based on the above SMQ definition will also be presented.

In addition to the '7-day on-treatment approach', a '30-day on-treatment approach' will be presented for all AEs based on the SMQ definition.

Events indicative of ketoacidosis

A frequency table of patients with an AE indicative of ketoacidosis will be presented by treatment, primary SOC and PT for terms within the narrow BI customised MedDRA Queries (BIcMQ) definition of diabetic ketoacidosis (DKA). For these terms, patients with SAEs and AEs leading to study drug discontinuation [redacted] will be presented.

Hypoglycaemic events

Patients with AEs of severe hypoglycaemia, defined as low blood sugar causing severe cognitive impairment, which requires assistance from another person for recovery, will be summarised. The summary will include the number of episodes, serious episodes and whether any led to study drug discontinuation. [redacted]

In addition, the number of patients with an AE in the SMQ 'Hypoglycaemia (20000226)' (narrow) will be presented by primary SOC and PT. This will be repeated for SAEs and AEs leading to study drug discontinuation.

[redacted]

UTI and genital infection events

Genital infection AEs will be identified as those belonging to the BIcMQ 'Infections' with the narrow sub-search of 'Genital tract infections predisposed by glucosuria'.

UTI AEs will be identified as those belonging to the BIcMQ 'Infections' with the narrow sub-search of 'UTI predisposed by glucosuria'.

For each of the above the number of patients with an SAE will be presented by primary SOC and PT. This table will be repeated for AEs leading to study drug discontinuation. T[redacted]

Pyelonephritis or urosepsis events

Pyelonephritis or urosepsis AEs will be identified as those belonging to the BIcMQ 'Infections' with the narrow sub-search of 'Renal infections predisposed by glucosuria' or the PT of 'Urosepsis'.

The number of patients with an SAE will be presented by primary SOC and PT. This table will be repeated for AEs leading to study drug discontinuation. [redacted]

Bone fracture events

A summary of the number of patients with an investigator-identified bone fracture AE, SAE and AE leading to study drug discontinuation will be presented by primary SOC and PT. The summary of all AEs will also be produced by site (long bones or non-long bones) and cause (high impact trauma, low impact trauma or other causes). Similar summaries will be produced for patients with an AE belonging to the narrow BIcMQ 'Bone fractures'.

[redacted]

In addition to the '7-day on-treatment approach' used above, patients with an AE based on the BIcMQ that occurred between first study drug intake up to trial completion will be presented.

Urinary tract malignancy events

Urinary tract malignancy AEs will be identified as those belonging to the BIcMQ 'Malignancies' either in the broad sub-search 'Urinary bladder and tract malignancies' or broad sub-search 'Renal malignancies'.

A summary of patients with such an AE will be produced by high level term and PT will be produced. In addition to this '7-day on-treatment approach' a similar summary used above, patients with an AE based on the BIcMQ that occurred between first study drug intake up to trial completion will be presented.

Volume depletion events

A summary of the number of patients with a symptomatic dehydration AE, SAE and AE leading to study drug discontinuation will be presented by primary SOC and PT.

For volume depletion events, similar summaries to those above will be produced for patients with an AE belonging to the BIcMQ 'Volume depletion of non-haemorrhagic cause and subsequent hypotension' narrow sub-search 2 'Volume depletion and hypotension due to dehydration'.

For hypotension events, similar summaries will be produced for patients with an AE belonging to the BIcMQ 'Volume depletion of non-haemorrhagic cause and subsequent hypotension' narrow sub-search 2 'Volume depletion and hypotension due to dehydration' but excluding terms of the narrow sub-search 1 'Volume depletion due to dehydration'.

[redacted]

Acute kidney injury events

The number of patients with an SAE in the SMQ 'Acute renal failure (20000003)' (narrow) will be presented by primary SOC and PT. This will be repeated for AEs leading to study drug discontinuation.

[redacted]

Gout

A summary of the number of patients with an investigator-identified gout AE (defined as MedDRA PTs of 'Gout', 'Gouty arthritis' or 'Gouty tophus'), SAE and AE leading to study drug discontinuation will be presented by primary SOC and PT.

Hyperkalaemia

A summary of the number of patients with an investigator-identified hyperkalaemia (defined as MedDRA PTs of 'Blood potassium increased' or 'Hyperkalaemia') SAE and AE leading to study drug discontinuation will be presented by primary SOC and PT.

COVID-19 events

The MedDRA 20.1 dictionary used for the trial has no coded terms available for recording COVID-19 AEs. Additional terms were therefore made available to sites, whereby the terms 'Coronavirus test positive', 'COVID-19' or 'Coronavirus pneumonia' could be used.

The subgroup of patients with an on-treatment COVID-19 AE (SAEs and pre-specified non-serious AEs) will be analysed. For these patients an overall summary of AEs will be presented with additional tables for all AEs, SAEs and AEs leading to study drug discontinuation presented by treatment, primary SOC and PT. For these summaries only AEs with an onset

date 7 days prior to a patient's first COVID-19 AE until the end of the on-treatment period will be used.

A listing will be prepared presenting details of all COVID-19 AEs.

7.8.1.2.5 AE incidence rates

In addition to the frequency tabulations, time-adjusted AE analyses will be performed for all applicable summaries.

The time at risk in patient years for the on-treatment period is derived as follows:

Patients with AE:

Time at risk (AE) in days = date of start of AE – randomisation date + 1

Patients without AE:

Time at risk (AE) in days = end date of time at risk – randomisation date + 1, where end date of time at risk is the minimum of date of last study drug intake + x days or date of death, if applicable.

The standard approach will be x=7 days, but x=30 days and 'up to trial completion' approaches will also be used.

Total AE-specific time at risk per treatment group is then derived as:

Time at risk (AE) [years] = Sum of time at risk [days] over all patients in a treatment group/365.25

For 'each row of a table' (e.g. displaying an SOC), time at risk is calculated using start of first AE summarized for the row; e.g. for patient with AE in a specified SOC, time at risk = date of start of AE with specified PT in this SOC – date of randomisation + 1.

The AE incidence rate per 100 patient years will then be calculated as follows:

Incidence rate per 100 patient years (pt-yrs) = 100 * number of patients with AE / time at risk (AE) [years].

7.8.2 Laboratory data

Safety tables will not include central or local assessments of eGFR, UACR or HbA1c as these data are summarised in the efficacy section.

7.8.2.1 Analysis of trial-specific laboratory endpoints

The main analysis of these endpoints be based on the RS of patients using all available data from follow-up period (OC-AD). Additional analyses on the TS of patients using all on-treatment data (OC-OT) will also be performed.

Potassium

Changes from baseline in locally assessed potassium will be evaluated using a MMRM following the same methodology as detailed in Section 7.6.2.

Liver transaminases

A categorical summary by treatment group for each of the following categories will be produced:

- ALT or AST ≥5 x ULN
- ALT or AST ≥3 x ULN with bilirubin ≥2 x ULN, in the same blood sample

The effect of allocated treatment on each of the above categories will be compared using a chi-squared test. If any of the expected cell counts in the 2x2 contingency table are less than 5, the Fisher's exact test will be used instead of the chi-squared test.

Haematocrit, haemoglobin, sodium, calcium and phosphate

These parameters are only measured and collected for the UK subset of patients; haematocrit and haemoglobin are measured at baseline and 18 months and sodium, calcium and phosphate at 18 month only.

Changes from baseline to 18 months in haematocrit and haemoglobin will be compared between the two treatments using ANCOVA with baseline fitted as a covariate. Mean values at 18 months for sodium, calcium and phosphate will be compared between the two treatments using t-tests.

7.8.2.2 Standard analyses of laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (18).

Before summarising, laboratory data will be converted to conventional units. Where conventional units differ from the International System of Units (SI), summaries will be repeated.

Standard descriptive summaries will be provided by treatment group for baseline, last value on-treatment and changes from baseline to last value on treatment. These summaries will be based on converted values.

Laboratory values will be compared to their reference ranges (where available) via frequency tables showing the number of patients within and outside the reference range at baseline and for the last value on treatment. Frequency tables will also summarise the number of patients with potentially clinically significant abnormalities, as defined using standard BI criteria. These summaries will be based on converted values.

To support the analyses of liver related AEs, frequency tables showing the number of patients falling into each of the following categories will be produced:

- ALT and/or AST ≥3 x ULN, ≥5 x ULN, ≥10 x ULN and ≥20 x ULN
- ALT and/or AST ≥3 x ULN with bilirubin ≥2 x ULN (in the same blood sample or within 30 days of the elevated liver enzyme)

A graphical display (eDISH plot) of ALT and bilirubin will also be produced. For the TS OC-OT summaries, all liver enzyme elevations up to 30 days after study treatment discontinuation will be considered.

7.8.3 Vital signs

A MMRM analysis of changes in weight, SBP and DBP will performed using the methodology detailed in Section 7.6.2.

A descriptive summary of changes in hip and waist circumference will also be produced.

7.8.4 ECG

Not applicable for this trial.

7.8.5 Others

The effect of allocated treatment on discontinuation of study treatment, both overall and by reason of discontinuation [SAEs (overall and by SOC), non-serious AEs (overall and by SOC) and other reasons], will be compared using a chi-squared test. If any of the expected cell counts in the 2x2 contingency table are less than 5, the Fisher's exact test will be used instead of the chi-squared test.

8. REFERENCES

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5.	KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease, Kidney Int. 2020; 98(4) (Suppl) [P20-09106]
6.	*BI-KMED-BDS-HTG-0045:* "How to Guide: Standards for Reporting of Clinical Trials and Project Summaries"
7.	Beyersmann J, Allignol A, Schumacher M "Competing risks and multistate models with R", New York: Springer (2012) [R16-3839]
8.	Jackson D, et al. "Relaxing the independent censoring assumption in the Cox proportional hazards model using multiple imputation", Stats Med 33, 4681-4694 (2014) [R21-2797]
9.	Burkoff N, et al. "Gamma imputation tutorial (Jackson 2014)", vignette for InformativeCensoring R library, July 2020 [R21-2798]
10.	Rogers JK, et al. "Analysis of recurrent events with an associated dropout time: application of the joint frailty model", Stat Med 13, 2195-2205 (2016) [R16-2229]
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14.	Vonesh, et al. "Mixed-effects models for slope-based endpoints in clinical trials of chronic kidney disease", Stats Med 38, 4218-4239 (2019) [R19-4093]
15.	*BI-KMED-BDS-QRG-0010:* "Quick Reference Guide: Preparation of tables for results disclosure"
16.	*BI-KMED-BDS-HTG-0035:* "How to Guide: Handling of Missing and Incomplete AE dates"

17.	*BI-KMED-BDS-HTG-0041:* "How to Guide: Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template"
18.	*BI-KMED-BDS-HTG-0042:* "How to Guide: Handling, Display and Analysis of Laboratory Data"

9.2 INTERIM ANALYSIS

A formal interim analysis may be performed by the DMC when a minimum of 150 first ESKD events have occurred. If based on the results of the interim analysis, pre-defined stopping criteria are met and the DMC recommend stopping the trial for efficacy, substantial further data will be collected as patients will attend their final follow-up visits and provide latest information on their renal status and blood for central creatinine analysis. All formal hypothesis testing will be based on the results of the analyses from the final database including data from the final follow-up visits. Note the information fraction used in the alpha-spending functions for the primary and key secondary endpoints will be based on the number of primary outcome events observed at the time of the DMC interim analysis, as a proportion of the anticipated number at the scheduled end of the trial. Formal statistical testing of the key secondary endpoints will be performed via the Hochberg procedure controlling the overall type I error rate, refer to Section 7.5.1.

Agreement may be sought from the Steering Committee to delay or cancel the planned interim analysis in the following circumstances:

- If predictive models based on available blinded data indicate an expected period of less than or equal to 3 months between the accrual of 150 first ESKD events and of 1070 first primary outcome events. In this instance the interim analysis would not be conducted.

- If unforeseen circumstances (e.g. a significant worsening of the COVID-19 pandemic) make the conduct of the interim analysis operationally not feasible. In this instance the interim analysis would be delayed and potentially not conducted if the delay led to the above bullet being met.

If a formal interim efficacy analysis is not conducted the primary endpoint will be formally assessed without adjustment for multiplicity and the key secondary endpoints controlled at the familywise error rate of 5.0%.

[redacted]

9.4 WORST DIRECTION APPROACH

For situations where we have two observations recorded on the same day a worst direction approach will be used as shown in Table 9.4: 1. For parameters with a '1' the highest value will be chosen, for those with a '-1' the lowest value and for those with a '0' the value furthest away from the midpoint of the BI standard reference range.

Table 9.4: 1 Worst direction definitions

Laboratory test	Worst Direction
Alkaline Phosphatase	1
Corrected Calcium	0
Creatinine	1
eGFR	-1
HbA1c	1
Haematocrit	-1
Haemoglobin	-1
Potassium	1
Sodium	0
NT-proBNP	1
Phosphate	0
AST	1
ALT	1
Bilirubin	1
Albumin/Creatinine (Urine)	1
Albumin (Urine)	1
Creatinine (Urine)	-1
Protein/Creatinine (Urine)	1
Protein (Urine)	1

9.5 SAMPLE CODE FOR SEMI-PARAMETRIC JOINT FRAILTY MODEL

The following sample of code will be used, the input dataset includes an observation for each hospitalisation (first and recurrent) and either an observation for death or for censoring:

```
proc nlmixed data = <input data> gconv=1E-18 fconv=2.2E-18 qpoints=50;
  parms / data= <param>; *-- dataset of initial parameter values from optimisation step --*;

  *-- r = bounds for recurrent events, h = bounds for death events --*;
  bounds r01 r02 r03 r04 r05 h01 h02 h03 h04 h05 theta >= 0;

  base_haz_r = r01*event_r1+r02*event_r2+r03*event_r3+r04*event_r4+r05*event_r5;
  cum_base_haz_r = r01*dur_r1+r02*dur_r2+r03*dur_r3+r04*dur_r4+r05*dur_r5;

  base_haz_d = h01*event_d1+h02*event_d2+h03*event_d3+h04*event_d4+h05*event_d5;
  cum_base_haz_d = h01*dur_d1+h02*dur_d2+h03*dur_d3+h04*dur_d4+h05*dur_d5;

  logofloggammadens = (1/theta)*nu-(1/theta)*exp(nu)-lgamma(1/theta)-(1/theta)*log(theta);
  logofstandardnormal = -(nu**2)/2;

  linpred1= beta11*TRT + <beta1x*covariatex> +nu;
  linpred2= beta21*TRT + <beta2x*covariatex> +gamma*nu;

  loglik1=-exp(linpred1) * cum_base_haz_r;
  loglik2=-exp(linpred2) * cum_base_haz_d;

  *-- log likelihood for recurrent events --*;
  if cnsr = 1 then loglik=log(base_haz_r)+linpred1;

  *-- log likelihood for deaths --*;
  if cnsr = 2 then loglik=loglik1+log(base_haz_d)+linpred2+loglik2+logofloggammadens-
logofstandardnormal;

  *-- log likelihood for censoring --*;
  if cnsr = 0 then loglik=loglik1 + loglik2 + logofloggammadens - logofstandardnormal;

  model timevar ~ general(loglik);
  random nu ~ normal(0,1) subject=usubjid;
run;

** End of Code **;
```

9.6 DEFINING SUSTAINED EGFR DECLINES AND USE OF LOCAL DATA

The following rules provide further detail on the derivation rules for defining sustained eGFR declines and the use of local data:

- Select only one value per visit window to be used in the derivation of events, plus the final follow-up visit sample if not already selected. Results after the final follow-up visit are not used.

- Events are derived from the central and local laboratory data separately. Local laboratory values cannot confirm a central laboratory value (or vice versa), with respect to being 'sustained'.

- An event cannot be obtained from a local laboratory value at a visit if a central laboratory value is also available at that visit.

- When determining if a value is sustained due to a second measurement the second measurement meeting the criteria must be from the next planned visit in the protocol defined schedule and be at least 30 days later. If a visit is missing before the next value meeting the criteria, then this is not considered sustained, e.g., meeting the criteria at 6 months and 18 months with no measurements at 12 months does not qualify as an event.

- A value may also be considered sustained if it is the latest result at the last visit window. Last visit window is defined separately for central and local laboratory data so may be defined as two different visit windows in a patient.

- For central laboratory data it is defined as the last visit window that contains either a central laboratory measurement or a direct visit, i.e., a visit in person.

- For local laboratory data it is defined as the last visit window that contains either a local laboratory measurement or a direct visit, i.e., a visit in person.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**01-MAR-20**	[redacted]	None	This is the final TSAP without any modification.
2	**01-OCT-21**	[redacted]	3	Inclusion of R as analysis software.
			4	Definition of start date of COVID-19 impacting on the trial.
			[redacted]	
			6.1, 7.8	Clarification of REP and its inclusion/exclusion after the final follow-up visit.
			[redacted]	
			6.6	Additional detail on the handling of missing eGFR data.
			6.7	Further clarifications.
			7.3	Compliance summary added before and after COVID-19 disruption.
			7.4.1	Detail provided on methodology for checking proportional hazards assumption.
			7.4.2, 7.5.1.2	[redacted]
			7.5.1.1	Further detail provided on all-cause hospitalisation analysis with additional references.
			[redacted]	
			7.8.1.2.4	Additional summaries of COVID-19 events defined.
			8	Further references included.
			9.2	Further detail on planned interim analysis.

Table 10: 1 History table (cont.)

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
3	**07-FEB-22**	[redacted]	5.1	Further detail on ESKD definition provided.
			[redacted]	
			6.6	Further detail on the handling of missing central laboratory eGFR values and hospital discharge dates.
			6.7	Detail of handling of data recorded on the same day.
			6.8.1	Clarifying definition of overlapping hospitalisations.
			7	Defining a pre-defined number of events required for a subgroup to be analysed.
			7.5.1.1	Revision to step 1 for calculation of starting values to improve model convergence.
			[redacted]	
			[redacted]	[redacted]
			7.8.1.2	Removal of AE collapsing rules and change to sorting order of AEs. Removal of level and history of amputation tables. [redacted] SMQ narrow term clarified. Bone fracture AE tables by site and cause added. Gout and hyperkalaemia tables added.
			[redacted]	[redacted]
			9.4	Section added to define worst direction approach.
			9.5	Sample code added for semi-parametric JFM.

Table 10: 1 History table (cont.)

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
4	**15-JUL-22**	[redacted]	4	[redacted] Explanation of minimisation error and change to fitting of region factor.
			[redacted]	
			6.6	Details on handling of too low/high to quantify laboratory data added.
			6.7	Definition of time window for 4-week post final follow-up data.
			6.8.2	Censoring rules made consistent for all endpoints
			7.4.1	Confirmation of the change in the fitting of the region randomisation factor.
			7.4.2	[redacted]
			[redacted]	

Table 10: 1 History table (cont.)

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
4	**15-JUL-22**	[redacted]	[redacted]	
			7.8	Removal of the REP after the final follow-up visit for summaries based purely on adjudicated terms.
			7.8.1.2.2	SAE summaries added for liver injury and ketoacidosis summaries. Removal of lower limb amputation summaries by investigator term.
			7.8.1.2.4	Confirmation acute kidney injury events summary to be based on narrow terms. PTs for hyperkalaemia added
			9.1	[redacted]
			9.6	New section providing further detail on the derivation of sustained eGFR declines and the use of local laboratory data.

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Project Statistician	[redacted]	15 Jul 2022 15:48 CEST
Approval-Clinical Trial Leader		15 Jul 2022 16:01 CEST
Approval-Medical Writer		19 Jul 2022 09:31 CEST
Approval		19 Jul 2022 10:04 CEST
Author-Trial Statistician		19 Jul 2022 10:39 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed