TRIAL STATISTICAL ANALYSIS PLAN

c32295612-01

BI Trial No.:	1245-0204
Title:	A multicentre, randomised, double-blind, 90-day superiority trial to evaluate the effect on clinical benefit, safety and tolerability of once daily oral **EMP**agliflozin 10 mg compared to placebo, initiated in patients hospitalised for ac**U**te heart fai**L**ure (de novo or decompensated chronic HF) who have been **S**tabilis**E**d (**EMPULSE**) Including Protocol Amendment 1 1245-0204-protocol-amendment-1 [c28603082-02]
Investigational Product(s):	Jardiance®, empagliflozin
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: N/A
Date of statistical analysis plan:	11-MAR-2021 SIGNED
Version:	FINAL

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ACE	Angiotensin Converting Enzyme
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor blocker-Neprilysin Inhibitor
ASA	Acetylsalicylic acid
AST	Aspartate transaminase
ATC	Anatomical-Therapeutic-Chemical
AUC	Area under the curve
BI	Boehringer Ingelheim
BIcMQ	Boehringer Ingelheim customized MedDRA Query
BMI	Body mass index
BP	Blood pressure
bpm	beats per minute
CEC	Clinical Event Committee
CIF	Cumulative Incidence Function
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRT	Cardiac resynchronisation therapy
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Cardiovascular
DAOH	Days alive and out of hospital
DBL	Data base lock
DBP	Diastolic Blood Pressure
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EF	Ejection Fraction

Term	Definition / description
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EoT	End-Of-Text
EOT	End of treatment
EudraCT	European Clinical Trials Database
GI	Gastrointestinal
HbA_{1c}	Glycosylated haemoglobin
HF	Heart failure
HFE	Heart failure event
HLT	High level term
HR	Hazard ratio
IC	Informed consent
ICD	Implantable Cardioverter Defibrillator
ICH	International Conference on Harmonisation
iPD	Important protocol deviation
IRT	Interactive Response Technology
ITT	Intention-to-treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-TSS	Kansas City Cardiomyopathy Questionnaire Total Symptom Score
kg	kilogram
LLT	Low level term
LVEF	Left ventricular ejection fraction
MAR	Missing at random
Max	Maximum
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mg/dL	Milligram per decilitre
MI	Myocardial infarction
Min	Minimum
MMRM	Mixed models repeated measures
MNAR	Missing not at random

Term	Definition / description
MRA	Mineralocorticoid Receptor Antagonist
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association Classification
OC-AD	Observed Case including data After Discontinuation
OC-OT	Observed Case On Treatment
PPS	Per Protocol Set
PT	Preferred term
Q1	Lower quartile
Q3	Upper quartile
RS	Randomised set
SAE	Serious adverse event
SAS	Statistical Analysis System
SBP	Systolic blood pressure
SCR	Screened set
SD	Standard deviation
SE	Standard error
SGLT-1	Sodium-glucose co-transporter 1
SGLT-2	Sodium-glucose co-transporter 2
SI	Système international d'unités
SLR	Sequential linear regression
SMQ	Standardized MedDRA query
SOC	System organ class
TBILI	Total bilirubin
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
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 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, randomisation.

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

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

In the CTP, a stratified win ratio is described, but the weighting method for each stratum is not mentioned. Therefore, the weighting method to be used has been described here in Section 7.4.1.

In the logistic regression models used for the binary endpoint variables (e.g. improvement in KCCQ-TSS of ≥ 10 points after 90 days of treatment), an additional continuous covariate (baseline KCCQ-TSS score) is included (see Section 7.5.2).

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

The primary endpoint is specified in the CTP Section 2.1.2.

An HFE is:
- A hospitalization/ER visit OR
- An urgent care visit OR
- An Outpatient visit

With all of the following:
- The question "Was visit related to the primary diagnosis or worsening of heart failure in the opinion of the treating physician?" is answered yes
- At least one symptom of
  - dyspnea,
  - decreased exercise tolerance,
  - fatigue,
  - edema
  - other symptoms of worsened end-organ perfusion or volume overload
- At least two physical examination findings OR (one physical examination finding and at least one laboratory criterion).
  - Physical examination are
    - peripheral edema,
    - increased abdominal distention or ascites,
    - pulmonary rates/crackles/crepitations,
    - Increased jugular venous pressure and/or hepatojugular reflux,
    - S3 gallop,
    - Clinically significant or rapid weight gain thought to be related to fluid distention,
    - other
  - Laboratory criteria are:
    - Increased BNP or NT-proBNP,
    - radiological *or ultrasonographic* evidence of pulmonary congestions,

- non-invasive diagnostic evidence of clinically significant elevated ventr. filling pressure or low cardiac output
- invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure >=18 mmHG, central venous pressure >=12 mmHg or cardiac index <2.2 L/min/m²
- Other

- Intensification of therapy (significant augmentation of oral diuretics, IV diuretics´, vasoactive agent, or mechanical or surgical intervention)

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

Not applicable.

5.2.2 Secondary endpoints

Secondary endpoints are specified in the CTP Section 2.1.3. Regarding the CV death endpoint, adverse events on the eCRF death event form where the primary cause of death is CV death or unknown cause of death, will be classed as CV death.

Regarding the secondary endpoint "occurrence of HHF until 30 days after initial hospital discharge", HHFs are defined as the subset of HFEs where the investigator has checked the hospitalisation tick box.

Regarding the secondary endpoint "occurrence of chronic dialysis or renal transplant or sustained reduction of ≥40% eGFR Chronic Kidney Disease Epidemiology Collaboration Equation ((CKD-EPI)cr), or

- sustained eGFR (CKD-EPI)cr <15 mL/min/1.73 m^2 for patients with baseline eGFR ≥30 mL/min/1.73 m^2
- sustained eGFR (CKD-EPI)cr <10 mL/min/1.73 m^2 for patients with baseline eGFR <30 mL/min/1.73 m^2",

the following applies: an eGFR (CKD-EPI)cr reduction is considered sustained, if it is determined by two or more consecutive post-baseline central laboratory measurements separated by at least 30 days (first to last of the consecutive eGFR values). Chronic dialysis is regarded as chronic if the frequency of dialysis is twice or more per week for at least 90 days. Chronic dialysis and renal transplant will be confirmed by medical review of data from the concomitant non-drug therapy eCRF page.

[redacted]

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

There will be three basic treatment phases in this trial: screening, study treatment phase (with either empagliflozin 10mg or matching placebo) and post-treatment. However, during the study treatment phase, patients are allowed to go off-treatment and subsequently re-start treatment. This may happen not at all or repeatedly for a given patient.

The purpose of the definitions below is to describe all the different study/treatment intervals, in which a patient can participate in during the course of the trial. Note that the term "treatment regimen" also covers the “off-treatment” time periods.

Table 6.1: 1 Treatment regimens / study intervals

Label	**Interval**	**Start date**
Screening	Screening	Date of informed consent
Placebo/ Empagliflozin 10mg	Treatment	Date of first administration of study medication
Off-treatment (if applicable)	During treatment interval, but not on treatment	Date of last administration of study medication before temporary discontinuation + 1 day
Placebo/ Empagliflozin 10mg (if applicable)	During treatment interval, after restart of study medication	Date study medication re-started
Post-treatment	Post-treatment	Date of last administration of study medication + 1 day

Details on the definition of the on-treatment period for different endpoints are listed in Table 6.1:2. 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 also assign patients to the treatment group as randomised.

If a patient erroneously receives the wrong trial drug, all subsequent medication packs dispensed to the patient will still be for the treatment group to which the patient was randomised. Therefore, the adverse events will be analysed as per randomised treatment, which is expected to reflect the prevailing treatment.

In the exceptional case that a patient took the wrong treatment, adverse events may occur while being on the wrong treatment. Analyses of this data are described in Section 7.8.1.6.

Table 6.1: 2 Endpoint specific assignment to the on-treatment phase

Endpoint	Last day of assignment to the on-treatment phase (days after last intake of study medication)
Adverse events	7
Safety laboratory measurements	3
Heart rate	1
Glycosylated haemoglobin (HbA_{1c})	7
Glucose	1
Body weight	1
Creatinine and estimated glomerular filtration rate (eGFR)	1
N-terminal pro B-type natriuretic peptide (NT-proBNP)	1
Blood pressure (BP)	1
Patient reported outcome	7

6.2 IMPORTANT PROTOCOL DEVIATIONS

A protocol deviation is important, if it affects the rights or safety of the patients or if it 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.

The important protocol deviations (iPDs) will be described in the clinical trial report (CTR). A listing of patients with medication code broken at the trial sites will be provided.

Table 6.2: 1 Important protocol deviations

Category / Code		Description	Requirements	Excluded from
A		**Entrance criteria not met**		
A1		**Target indication not met**		
	A1.07	Conditions on ejection fraction (EF) not met	Inclusion criterion #5 not met	None
	A1.08	Conditions on NT-proBNP not met	Inclusion criterion #8 not met	None
A2 /3		**Eligibility criteria not met**		

Table 6.2: 1 Important protocol deviations (cont.)

Category / Code		Description	Requirements	Excluded from
	A2.04	eGFR out of range	Exclusion criterion #15 met	None
	A3.51	Type 1 diabetes	Exclusion criterion #16 met	None
	A3.55	Not currently hospitalised for the primary diagnosis of acute heart failure (de novo or decompensated chronic HF), regardless of EF	Inclusion criterion #4 not met	None
	A3.56	Randomisation outside of window	Inclusion criterion #6 not met	None
	A3.57	Patient not hemodynamically stabilised	Inclusion criterion #7 not met	None
	A3.58	HF episode leading to hospitalisation not sufficiently treated	Inclusion criterion #9 not met	None
	A3.60	Cardiogenic shock	Exclusion criterion #1 met	None
	A3.61	Primary diagnosis is not acute heart failure	Exclusion criterion #2 met	None
	A3.62	Primary diagnosis is acute heart failure not triggered by volume overload	Exclusion criterion #3 met	None
B		**Informed consent**		
	B1	Informed consent not available	Informed consent date missing	All
	B2	Informed consent too late	Informed consent date was after Visit 1	None
C		**Trial medication and randomisation**		
	C1.02	Incorrect trial medication taken	Wrong medication taken for more than 20% of the overall treatment duration Can only be finally judged after data base lock (DBL), since unblinding information is required.	None
	C3.01	Non-compliance with study drug intake	Compliance <80% or >120%	None
	C4.01[1]	Medication code broken inappropriately	Medication code was broken for no valid reason. Final decision at the DBL meeting based on medical judgement.	None
D		**Concomitant medication**		
	D2.02	Use of prohibited medication	Review of eCRF for prohibited medication. Final decision at the DBL meeting based on medical judgement.	None
G		**Study-specific analysis**		
	G3.50[1]	Assessment order not followed that could influence PRO at baseline or Day 90	PRO measurements not before any other assessment at baseline or Day 90	None
I		**Other safety-related deviations**		
	I2.01	Pregnancy		None

[1] needs to be checked at site by Local Clinical Monitors (CMLs) / Clinical Research Associates (CRAs) as these cannot be checked programmatically

6.3 SUBJECT SETS ANALYSED

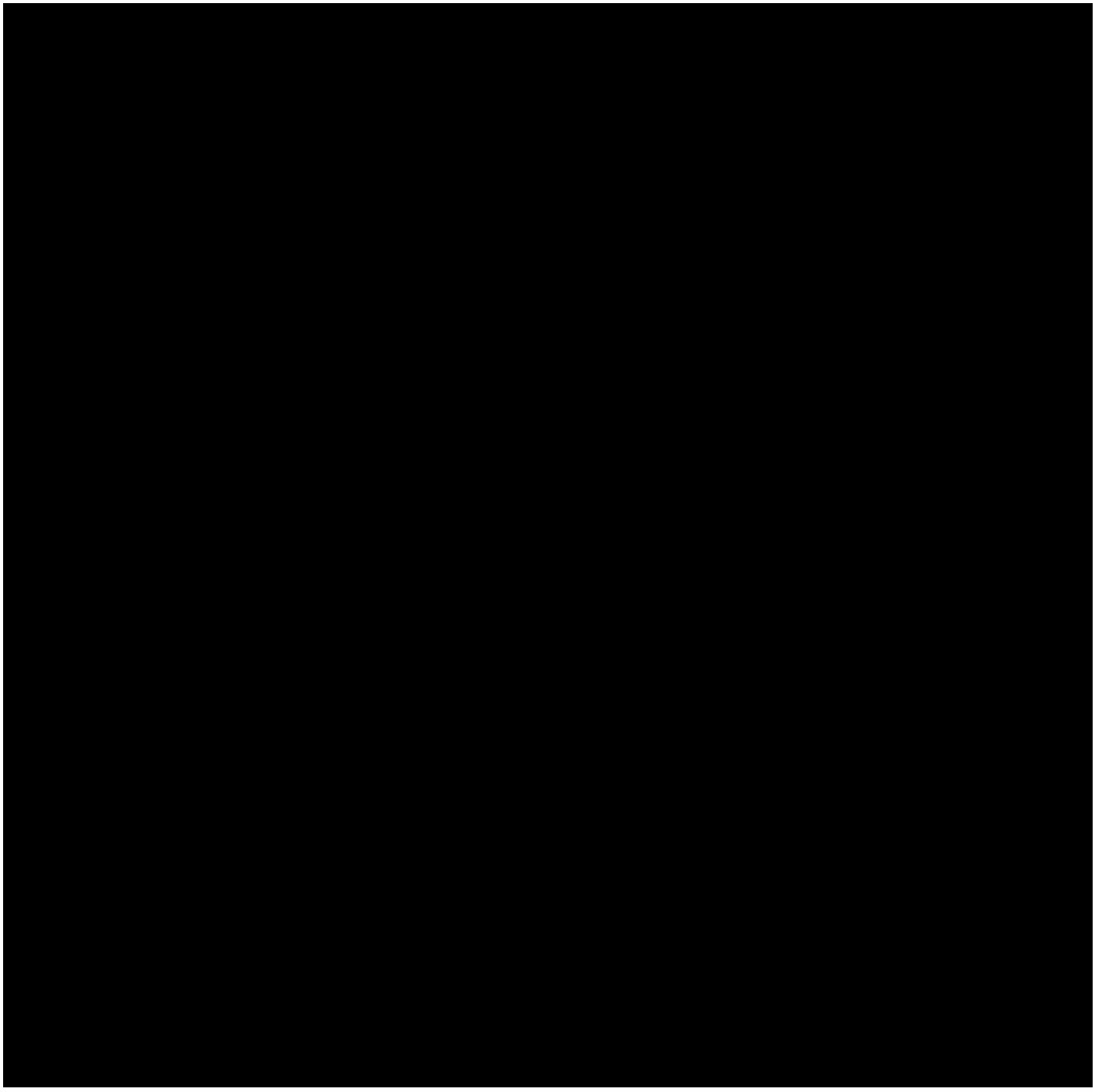
The following patient sets are defined:

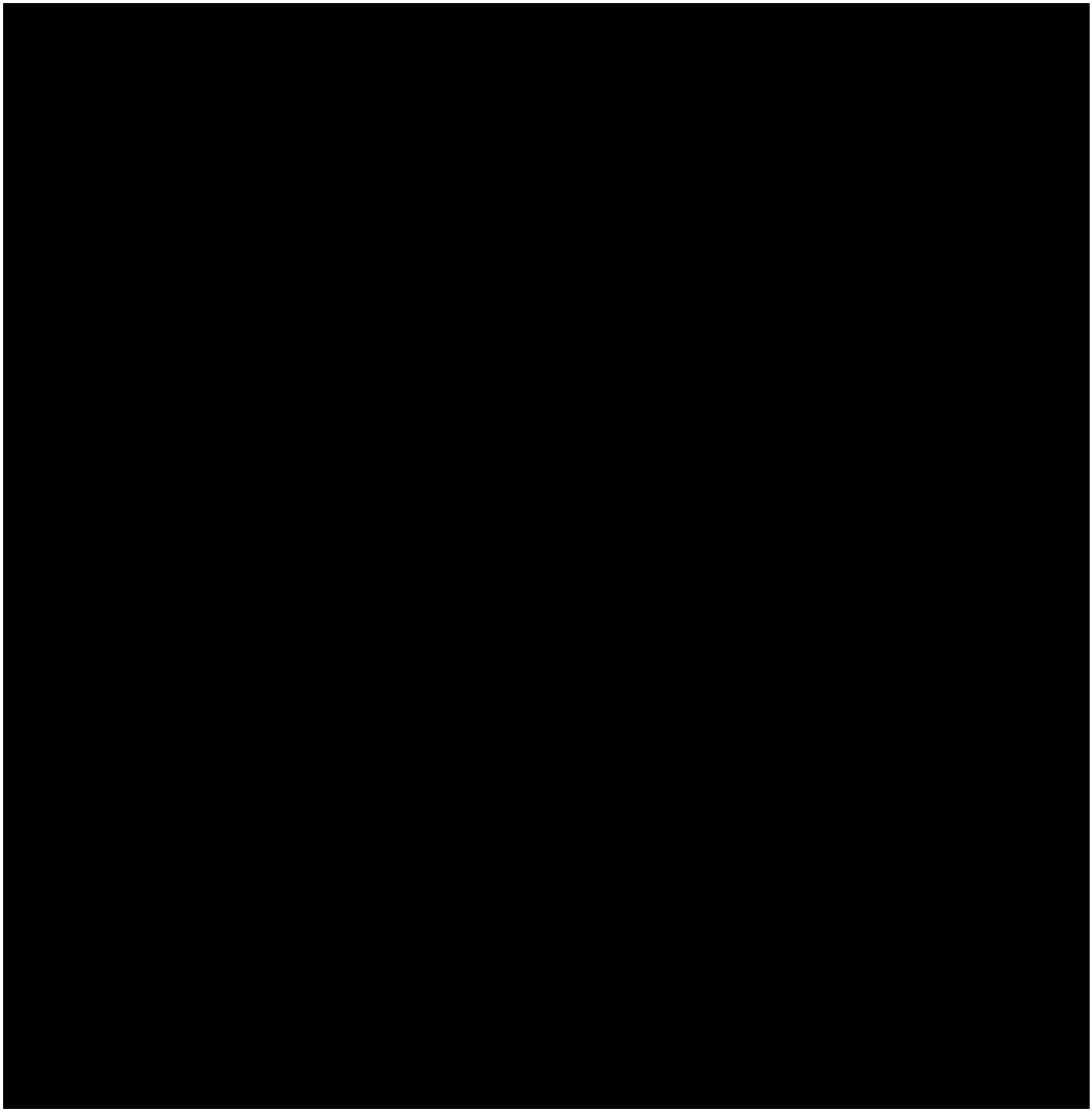
- Screened Set (SCR)
  Consists of all patients screened for the trial, with informed consent given and who completed at least one screening procedure at Visit 1.

- 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 study medication and were documented to have taken at least one dose of investigational treatment.

A Per Protocol Set (PPS) will not be specified for this trial.





6.5 POOLING OF CENTRES

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

6.6 HANDLING OF MISSING DATA AND OUTLIERS

6.6.1 Imputation methods

There will be no imputation of data for safety analyses.

For patients who discontinue the trial treatment prematurely, all efforts will be made to follow patients for survival and for any other endpoints including the primary and secondary endpoints until the end of the trial.

Multiple imputations:
Missing data for the Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS), as part of the stratified win ratio and NT-proBNP (log-transformed values) will be estimated using multiple imputation, according to whether patients are on-treatment or off-treatment.

Values measured after premature discontinuation of study drug will be included in the analyses. All available on- and off-treatment data up to the planned measurement at Day 90 will be included.

There will be different types of missing data to be considered for the imputation.

Table 6.6.1: 1 Adjusted multiple imputation "jump-to-placebo" approach – the missing data imputation method

Missing data imputation (Assumption of missingness)	Non-monotone	Monotone
On-treatment data	MCMC-MI[1] (MAR[3])	SLR-MI[2] (MAR)
Off-treatment[4] data	Jump-to-Placebo (MNAR[5])	Jump-to-Placebo (MNAR)

[1] Markov Chain Monte Carlo – Multiple imputation (MCMC-MI)
[2] Sequential linear regression – Multiple imputation (SLR-MI)
[3] Missing at random (MAR)
[4] Any instance of a patient discontinuing treatment will lead to all future measurements being considered as off-treatment.
[5] Missing not at random (MNAR)

As the first step, the non-monotone on-treatment missing data will be imputed using Markov Chain Monte Carlo (MCMC) simulation and standard techniques; MI will be performed separately by treatment with baseline value as a continuous variable and HF status as a binary variable (de novo or decompensated chronic HF). One hundred imputations will be performed to ensure adequate efficiency and stability of the estimation for missing data. This step will be referred to as 'MCMC-MI'.

For the monotone missing on-treatment data, a sequential linear regression MI approach will be used and referred to as 'SLR-MI'. The MI will be performed on a data set only including on treatment data and once per imputation from the previous step. This procedure will impute values for all missing time points both on- and off-treatment, so imputations for off-treatment values will then be deleted. The regression models will be fitted separately by treatment and

include the baseline value as a continuous covariate, HF status as a class covariate and the values at previous time points as separate continuous covariates.

To impute the missing off-treatment data, a residual-based approach will be used to enact the 'jump-to-placebo'. Throughout this imputation, all observed off-treatment data will be temporarily removed and added back at the end. A covariate-adjusted difference between the relevant treatment arm and placebo (i.e. 0 for those in the placebo arm) will be calculated at each visit using ANCOVA (with HF status and treatment as categorical covariates and baseline value as a continuous covariate). Next, the relevant estimated treatment difference will be deducted from all observed data in the active treatment groups. Note that the adjustments are for the duration of the imputation only and the original values for the observed data will be in the final imputed data set.

SLR-MI will then be performed once per imputation upon this modified data but only including patients either with missing values and/or those in the placebo arm, ensuring imputations are performed using the placebo distribution. The models will include baseline value as a continuous covariate, HF status as a class covariate and the values at previous time points as separate continuous covariates. All missing data will therefore follow the distribution of the placebo arm, jumping from one arm's distribution to the placebo's at the point of missingness, while still accounting for past within-treatment performance (the residuals). After this imputation, all the original observed values (i.e. off-treatment values) will be restored.

For NT-proBNP, the AUC of change from baseline in log-transformed NT-proBNP level will be calculated using these imputed data sets (imputation performed on the log-transformed data first before AUC values are calculated). Then an ANCOVA model will be applied (see Section 7.5.2). Rubin's rules (13) will be used to combine treatment estimates across the 100 imputations. Missing values at Visits 2b and 2c will not be imputed, but observed values at these visits will be used.

For KCCQ-TSS, the stratified win ratio will be calculated using these imputed data sets, by combining with the non-imputed death and HFE data. Because the stratified win ratio is log-normally distributed (10), Rubin's rules (13) can be used on the log-transformed win ratios to combine treatment estimates across the 100 imputations.

The implicit assumption underlying the imputations and analyses is that unobserved off treatment patient measurements will lose any treatment effect immediately post-treatment discontinuation.

A more technical description of the method can be found in Appendix 9.2.

6.6.2 Missing data

Adverse event data
Missing or partial date information for AEs will be replaced according to general Boehringer Ingelheim (BI) rules described in the BI guidance for handling of missing and incomplete AE dates (2).

Death date
For patients with a record of death captured on the electronic case report form (eCRF) with missing or only partial death date from all available sources, the death date will be derived. The latest date of any of the following dates will be used: event onset and end dates from either the AE page, or CEC adjudicated onset dates, by using also imputed AE dates, last day known to be alive + 1 day, range of possible days based on partial death date and date of trial completion.

Missing information on the date of first administration of trial drug
If the date of first drug administration is missing but the patient was randomised, the date of the first drug administration will be set to the date of randomisation. If the date of first administration is partially missing with the month and year present, the day will be set to the date of randomisation, if randomisation was in the same month. If randomisation was in the month prior to the first drug administration, the missing day will be imputed as the first day of the month.

Missing information on the date of trial medication stop

If the date is partially or completely missing, use the minimum of the following dates:

- end of treatment visit date, if available
- date of death
- trial completion (last contact date)
- longest extrapolated treatment duration (assuming 1 tablet/day)

In case of a partially missing date, if the imputed date is before the first day of the month/year given as the partial date, the first day of the month/year will be used.
All other cases need to be assessed by the trial team on an individual patient basis, using the points above as guidance.

Missing information on concomitant therapy or non-medication therapy dates
For incomplete date information, generally 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.
If this leads to contradictions for the start or end date of a concomitant therapy (e.g. imputed end date before documented start date), a partial end date will be imputed as the end of the interval or a partial start date will be imputed as the start of the interval in the database to resolve this contradiction.

If it is unclear from the partial date, whether a therapy was before or after date of baseline, then it will be assumed, that the therapy started after baseline (similar to worst case rules applied for adverse events).
All other cases or conflicting cases resulting from these imputation rules need to be assessed by the trial team on an individual patient basis.

Missing measurement to confirm “sustained” decrease
An eGFR (Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)cr) reduction is

considered sustained, if it is determined by two or more consecutive post-baseline central laboratory measurements separated by at least 30 days (first to last of the consecutive eGFR values). If there is no additional measurement >= 30 days after the eGFR reduction is observed and the patient dies within 60 days of this measurement, then the eGFR reduction is also considered sustained.

Hospital discharge date
Missing hospital discharge dates will be replaced with the date of the last follow-up.

6.6.3 Longitudinal Analyses

There will be different methods of analysing continuous longitudinal data.

Observed case on-treatment (OC-OT):
Only the available data that were observed while patients were on study medication (defined as time from first drug intake until last permanent treatment stop date plus the endpoint specific follow-up time (as defined in Table 6.1: 2)) are considered.
Measurements are assigned to planned weeks according to Table 6.7: 1
Imputed records are not included.

Observed case including data after treatment discontinuation (OC-AD):
All available data are considered, including values obtained on treatment or post-treatment.
Imputed records are not included.
Measurements are assigned to planned weeks according to Table 6.7: 1.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline will be defined as the last available measurement before start of randomised trial medication for all endpoints. For laboratory data (e.g. NT-proBNP), baseline will use central laboratory data.

Since the protocol specifies that all measurements are taken at Visit 2a before any intake of trial medication, all measurements at the first day of drug intake are assumed to qualify as baseline assessments.

For randomised patients without any treatment intake: Baseline will be defined as the last available measurement before or on the day of randomisation.

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

Efficacy and safety measurements will be assigned to visits based on time windows around the planned visit dates. These time windows are defined based on the planned number of days after the date of first administration of study drug.

The time window for the first visit after randomisation starts on the day after the first intake of study drug. The midpoint between two on-treatment visits defines the end of a time window, with the midpoint being included in the time window of the preceding visit.

Table 6.7: 1 Time windows

			Time window (days after baseline)	
Visit number	Visit label	Planned days	Start	End
Endpoints assessed at each on-site visit (e.g. creatinine / eGFR)				
2a	Baseline [1]	1	NA	1
2b	Day 3	3	2	4
2c	Day 5	5	5	10
3	Day 15	15	11	22
4	Day 30	30	23	60
5	Day 90	90	61	Trt stop + x* days
Endpoints that are not assessed on Visit 2b and 2c (e.g. weight)				
2a	Baseline [1]	1	NA	1
3	Day 15	15	2	22
4	Day 30	30	23	60
5	Day 90	90	61	Trt stop + x* days

[1] Only values taken prior to the start of treatment with randomised study drug can be considered baseline values. Time windows will be used for assignment of measurements to scheduled visits.
* See Table 6.1: 2

Only one observation per time window will be selected for analysis at an on-treatment visit – the non-missing value will be selected which is closest to the protocol planned visit day. If there are two observations which have the same difference in days to the planned day or if there are two observations on the same day, the first value will be used.

Baseline definition for concomitant therapies

Concomitant medication taken at baseline is any medication with start date ‘continued’ or before date of first study medication intake (randomisation date will be used for patients not treated) and end date continued on or after date of first study medication intake (randomisation date will be used for patients not treated).

6.8 CALCULATION OF TIME TO EVENT

This section describes the calculation of the time to event and the time that patients without an event are in the study (under risk).

Consistent with that approach, the respective time intervals determine the start and end for the derivation of occurrence of a specific event.

For those patients with an event, the time to event is calculated as:

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

For those patients without an event, the time at risk is calculated as:

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

6.8.1 Start date

In general, the time to event will be derived from the date of randomisation.

For the following endpoints (analysed as occurrence or time to first event), the date of first drug intake will be used as the start date:

- AE analyses according to Section 7.8.1
- Endpoints purely based on laboratory measurements or concomitant medications, that include a relation to baseline (such as decrease from baseline >= 40%, doubling vs baseline, etc.)

Please note, that for composite endpoints, that include component(s) using randomisation date and other component(s) using first drug intake date as start date, the time at risk for the composite will start with date of randomisation (which may be earlier). For the individual components, the component specific start date will be used.

6.8.2 Date of event

For time-to-death endpoints, the respective death date will be used rather than time to the first onset of the fatal AE.

For composite outcomes, e.g. time to first occurrence of cardiovascular (CV) death or HFE until end of trial visit, the earliest onset date of the corresponding components will be used.

The time to first occurrence type of endpoints based on laboratory data including endpoints which have the requirement of a “sustained” measurement are determined by the date of the first measurement that fulfils this condition.

For events with multiple possible episodes, such as HFE or all-cause hospitalisation, the admission date of the first hospitalisation will be used, unless noted otherwise. The same applies to time-to-AE analysis, where the onset date of the first episode will be used.

6.8.3 Censoring

The underlying principle is that the censoring date should be the last date a patient was known to be free of an endpoint event (e.g. free of each component of CV death and HFE).

For all endpoints except all-cause mortality and cause-specific death, patients without occurrence of a specific endpoint (composite endpoint or individual components) will be considered censored at the individual day of end-of-study.

The individual day of trial completion will be the latest of:

- last onset of an AE or date of death
- onset dates of adjudicated events
- end of treatment
- last visit date (NYHA class, KCCQ, pregnancy test, vital signs, ECG, or central laboratory)

Censoring is considered independent from study drug intake.

<u>All-cause mortality</u>

A patient without the event will be censored at the latest of:

- individual day of trial completion (without the restrictions defined above for patients with withdrawn consent or lost to follow-up)
- last date known alive from the vital status page

<u>Endpoints of any cause-specific death, e.g. CV death</u>

The same censoring rule as for all-cause mortality applies, and in addition, date of death if died from other causes than the one specified in the endpoint.

<u>Endpoints based on laboratory data only</u>

Patients who already fulfil the respective condition at baseline are not considered in the number of patients at risk for this endpoint.

If a baseline laboratory measurement is not available for the parameter of interest, it is assumed that the patient did not experience the condition corresponding to the endpoint at baseline and the patient is included in the patients at risk for this endpoint. Patients without an event and available post-baseline laboratory measurement will be considered censored at the date of last laboratory sampling of the corresponding parameter. Patients with a missing baseline laboratory value required to derive a change from baseline and patients without laboratory data following the baseline measurement will be censored on the date of randomisation.

Composite endpoints (analysed using a time-to-event approach)

Only patients that are included in the analyses for all components of the composite endpoint will be included in the analysis of the composite.

Of those, a patient with at least one event in any of the components of the composite will be considered to have an event and the date of the first event will be used for the composite endpoint. A patient without an event will be considered censored at the earliest of all censoring dates of the component endpoints.

7. PLANNED ANALYSIS

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / Standard Deviation (SD) / Standard Error (SE) / Minimum (Min) / lower quartile (Q1)/ Median / upper quartile (Q3)/ Maximum (Max). The 1st and 99th percentiles might be substituting minimum and maximum in tables with open-ended values to safeguard against implausible extremes.

Geometric means and ranges will be added to the presentation or replace the presentation of mean and standard deviation for parameters that follow a log-normal distribution rather than a normal distribution.

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

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

Disposition of the patient population participating in the trial will be analysed by treatment groups, and stratum and presented in the clinical trial report as a frequency-distribution.

Disposition as required for reporting for the trial in European Clinical Trials Database (EudraCT) will be provided. Enrolment will be summarised by country and by age group for reporting in EudraCT.

The reason for not randomising screened patients will be summarized descriptively.

The frequency of patients with iPDs will be presented by treatment group for the randomised set (RS). The frequency of patients in different analysis sets will also be presented for each treatment group.

Descriptive statistics on the impact of COVID-19 on study visits as well as study medication intake will be provided.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be analysed based on the RS. Demographics will be repeated on the TS if the analysis sets differ by more than 1%. Standard descriptive analysis and summary tables will be presented.

Descriptive analysis of the following variables measured at baseline will be presented: Age, BMI, time since diagnosis, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, weight, eGFR, NT-proBNP, LVEF, KCCQ-TSS and hematocrit.

A summary of the number of patients in each randomisation stratum (de novo or decompensated chronic HF) per treatment will also be shown. The information will be based upon the data received from the IRT provider.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report using the RS. Concomitant medication use will be summarised by Anatomical-Therapeutic-Chemical classification level 3 (ATC3) and preferred name. Summaries will be presented for concomitant therapies taken before initial hospitalisation, taken at baseline and separately for concomitant medications. Separate summaries of use of heart failure-related drugs (e.g. ARNi, beta-blockers, ivabradine, diuretics, ACE-inhibitors, ARBs, MRAs, cardiac glycosides), anticoagulants, acetylsalicylic acid (ASA), or lipid lowering drugs will be presented. Use of devices and other non-medication therapy taken before initial hospitalisation and separately for those newly introduced after initial hospitalisation will also be summarised.

Concomitant diseases will be summarised by system organ class and preferred term. Relevant medical history by treatment group will also be presented.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report. The number and percentage of patients with overall compliance will be reported. Overall compliance will be calculated as a weighted average of reported compliance. The sum of all reported compliance over the planned visits will be divided by the total duration. The TS will be considered.

7.4 PRIMARY ENDPOINT

The efficacy analysis will be based on the RS, including all randomised patients. Analyses will be performed according to the intention-to-treat principle, with the use of all available data (on and off-treatment) through the trial period. This equates to a treatment-policy style estimand. Treatment will be evaluated as randomised.
The primary endpoint is clinical benefit (4 and 5) assessed using a stratified win ratio approach. The statistical model will be a non-parametric generalised pairwise comparison within HF status strata. The variance of the stratified win ratio will be calculated using the asymptotic normal U statistics approach (5).

Superiority of empagliflozin vs. placebo will be evaluated with one-sided tests, at a significance level of 0.025.

7.4.1 Primary analysis of the primary endpoint

The primary endpoint is clinical benefit, a composite of death, number of HFEs, time to first HFE and change from baseline in KCCQ-TSS after 90 days of treatment. This will be assessed using a stratified win ratio approach.

All patients randomised to empagliflozin are compared to all patients randomised to placebo within their stratum.

For any two patients, a patient will win, i.e. achieve a better clinical outcome, as determined by assessing the following criteria sequentially, stopping when an advantage for either patient is shown:

1. Death within common follow-up time
   - death is worse than no death
   - earlier death is worse
   - tied, if not possible to determine

2. Number of HFEs within common follow-up time
   - more HFEs is worse
   - tied, if same number of HFEs

3. Time to first HFE within common follow-up time
   - earlier HFE is worse
   - tied, if not possible to determine

4. KCCQ-TSS change from baseline at Day 90
   - more positive change from baseline is better
   - the threshold for the difference is >= 5 for a win
   - tied, if difference < 5

Note, priority is therefore given to death over HFE, and both of these over changes in KCCQ-TSS. Below are some examples:

1. Death, e.g.:
   - Patient A dies 30 days after randomisation (loses)
   - Patient B dies 40 days after randomisation (wins)

2. If no winner based on death, number of HFEs within common follow-up time, e.g.:
   - Patient A had two HFEs (loses)
   - Patient B had one HFE (wins)

3. If no winner based on number of HFEs, time to first HFE, e.g.:
   - Patient A had an HFE 30 days after randomisation (loses)
   - Patient B had an HFE 50 days after randomisation (wins)

4. If no winner based on time to first HFE, KCCQ-TSS change from baseline at Day 90, e.g.:
   - Patient A: KCCQ-TSS change from baseline at Day 90 is 5 (loses)
   - Patient B: KCCQ-TSS change from baseline at Day 90 is 11 (wins)

The implemented generalised pairwise comparisons approach compares all patients in one treatment group to all other patients within their strata in the other treatment group. The stratified win ratio is then calculated as the total number of wins in the empagliflozin group across all strata divided by the total number of losses.

Applying weights that are analogous to a Mantel-Haenszel approach (10), the stratified win ratio is:

$$WR = \frac{\sum_{m=1}^{2} n_e^{(m)}/N^{(m)}}{\sum_{m=1}^{2} n_p^{(m)}/N^{(m)}}$$

where m is the stratum number (m = 1, 2), $n_e^{(m)}$ is the number of wins in the empagliflozin group in the mth stratum, $n_p^{(m)}$ is the number of wins in the placebo group in the mth stratum and $N^{(m)}$ is the total number of patients in the mth stratum.

The variance is calculated by the asymptotic normal U statistic approach (5)

Separate summaries for each component of this endpoint will also be presented.

The method of handling missing KCCQ-TSS values for this analysis is described in Section 6.6.1.

7.5 SECONDARY ENDPOINTS

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 endpoints

Other secondary endpoints are exploratory. No correction for multiple hypotheses testing will be made.

Change from baseline in continuous endpoints, such as KCCQ-TSS, will be analysed using restricted maximum likelihood estimation based on a mixed-effect model for repeated measures (MMRM) analysis to obtain adjusted means for the treatment effects. This model will include discrete fixed effects for treatment group (empagliflozin or placebo) and HF status (de novo or decompensated chronic HF) at each visit and continuous fixed effects for baseline value at each visit. Missing data caused by patient withdrawal or other reasons will be handled implicitly by the MMRM approach. An unstructured covariance structure will be used to model the within-patient errors.

Area under the curve (AUC) of change from baseline in log-transformed NT-proBNP level over 30 days of treatment will be analysed by an analysis of covariance (ANCOVA). Based on literature reviews, NT-proBNP level is regarded as log-normally distributed, therefore values will be log-transformed prior to analysis (6). The linear trapezoidal rule will be used to calculate the AUC after the log-transformation has been applied to each value.

ANCOVA with a discrete fixed effect for HF status (de novo or decompensated chronic HF) and a continuous fixed effect for baseline NT-proBNP level (log-transformed) will be used to compare treatment groups. The method of handling missing NT-proBNP levels for this analysis is described in Section 6.6.1.

Comparisons between treatment groups regarding the binary endpoint variable (improvement in KCCQ-TSS of ≥ 10 points after 90 days of treatment) will be performed using a logistic regression model adjusting for the binary covariate HF status (de novo or decompensated chronic HF) and continuous covariate baseline KCCQ-TSS score. The likelihood-ratio test will be used to test for a difference between treatments. Adjusted odds ratios together with 1-sided 97.5% confidence limits will be used to quantify the effect of treatment, comparing empagliflozin to placebo as the reference.

Time to event endpoints will be analysed using the Cox proportional hazards model (7) with HF status (de novo or decompensated chronic HF) as a covariate. Hazard ratios (HRs) and their associated one-sided 97.5% confidence limits will be estimated for evaluating the superiority of empagliflozin to placebo. All time-to-event endpoints will be reported in days.

Other secondary endpoints will be summarised descriptively [including days alive and out of hospital (DAOH)]. DAOH will be summarised as a percentage (12).

The follow-up time for DAOH analyses is defined as the minimum of 90 days after randomisation, or time between randomisation and date of censoring for non-fatal events except for patients who died within the first 90 days, where 90 days is considered as the DAOH follow-up time. Days alive and out of hospital (DAOH) for each patient is calculated as follow-up time subtracted by the number of days in hospital during the 90 days after randomisation as well as the number of days being dead within the first 90 days. Percentage DAOH is defined as DAOH divided by the DAOH follow-up time of each patient multiplied by 100.

Additionally, a negative binomial model (including HF status [de novo or decompensated chronic HF] as a factor) will be fitted to the data of recurrent HFE. The rate ratio and confidence interval will be reported.

The endpoints "diuretic effect as assessed by weight loss per mean daily loop diuretic dose after 15 days of treatment" and "diuretic effect as assessed by weight loss per mean daily loop diuretic dose after 30 days of treatment" will be defined as follows:

$$\frac{\text{Change in weight (kg) from baseline to Day T}}{\frac{\text{Mean daily i. v. dose}}{\text{40 mg}} \text{ or } \frac{\text{mean daily oral dose}}{\text{80 mg}} \text{ furosemide\# up to Day T}}$$

 # or equivalent loop diuretic dose

where the mean daily dose is defined as:

$$\frac{\sum_{x=1}^{X} N_x \; x \; d_x}{\text{T}}$$

and N = number of days on dose level x, d = dose level and T = day of the weight measurement.

The equivalent loop diuretic dose to a single dose of 40 mg of furosemide is defined as 20 mg of torasemide or 1 mg of bumetanide.

The dose level will be counted as 0 mg, if patients do not take loop diuretics for part of the time period. Patients not taking loop diuretics at all will be excluded from the calculation. Missing data will be handled according to the rules set out in Section 6.6.2.

7.7 EXTENT OF EXPOSURE

There will be three methods of calculating exposure:

a. First intake to last intake of study drug, including off-treatment periods
b. First intake to last intake of study drug, excluding off-treatment periods
c. Overall observational period (randomisation until end of follow-up for primary endpoint, see censoring for non-fatal events in Section 6.8.3)

Descriptive statistics tables with mean, SD, median and range of the number of days a patient was on treatment will be provided. These tables will also provide the sum-total of the time (in years) that all patients were on treatment.

Frequency tables of number and percentage of patients belonging to categorical ranges of exposure weeks will be provided as well. Following are the categories of exposure-ranges (in days): >= 0 days, >= 30 days, >= 60 days, >= 83 days.

7.8 SAFETY ANALYSIS

The safety analysis will be based on the TS. Treatment will be evaluated as randomised.

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

7.8.1 Adverse Events

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

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

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

For analysis of multiple AE occurrences, data from the eCRF will be collapsed into an AE provided that all of the following applies:

- All AE attributes are identical (including Lowest Level Term (LLT), intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest and also additional information of specific AEs or AESIs such as whether a bone fracture is traumatic.
- 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).

For further details on summarisation of AE data, please refer to (8).

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. That means that all adverse events occurring between first drug intake until 7 days after last drug intake will be assigned to the randomised treatment. All adverse events occurring before first drug intake will be assigned to 'pre-treatment' and all adverse events occurring after last drug intake + 7 days will be assigned to 'follow-up', except if otherwise specified.

In Section 15.3 of the CTR, general AE analysis tables will present only on-treatment AEs (applying the rule of 7 days for assignment as on-treatment) for the treatment groups.

Appendix 16.1.13.1 of the CTR will include an analysis (overall summary table, frequency of AEs by SOC / PT, frequency of SAEs by SOC/PT) where AEs and SAEs are assigned to the following phases: Screening, each treatment group, post-treatment for each treatment group.

For listings, AEs will be assigned to one of the following treatment phases: Screening, Placebo, Empa 10, Post Placebo, Post Empa, off-treatment.

7.8.1.2 AE summaries

An overall summary of adverse events will be presented.

The frequency of patients with adverse events will be summarised by treatment, primary system organ class and preferred term. Incidence rates as defined in Section 7.8.1.7 will generally be included.

AEs will also be reported by intensity (without incidence rates). Separate tables will be provided for:

- for patients with serious adverse events,
- for patients with drug related serious AEs,
- for patients with AEs leading to discontinuation,

- for patients with drug-related AEs.

AEs leading to death will be listed.

The system organ classes, and preferred terms will be sorted by frequency (within system organ class).

Additionally, the following analyses will be reported in Appendix 16.1.13.1 of the CTR for disclosure on EudraCT and clinicaltrials.gov:

- Frequency [N (%)] of patients with non-serious adverse events occurring with incidence in preferred term greater than 5% by treatment,
- Adverse events per arm for disclosure on EudraCT by treatment
- Non-serious adverse events for disclosure on EudraCT by treatment
- Serious adverse events for disclosure on EudraCT by treatment

7.8.1.3 Adverse events of special interest (AESIs)

Hepatic injury

A frequency table of patients with hepatic injury as defined by the investigator on the eCRF tick box by treatment, primary system organ class and preferred term will be provided.

Hepatic injury AEs will be summarised based on a Standardised MedDRA Query (SMQ) based definition. From 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 preferred term will be provided. Hepatic injury SAEs based on the above SMQ definition will be presented.

Patients with hepatic injury will be listed.

For presentations on adjudicated hepatic events, refer to Section 7.8.1.5.

Acute renal failure

A frequency table of patients with acute renal failure as defined by the investigator on the eCRF tick box by treatment, primary system organ class and preferred term will be provided.

A frequency table of patients with AEs related to acute renal failure by treatment, primary SOC and preferred term will be provided based on the narrow SMQ Acute renal failure (20000003).

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

In addition, frequency tables will be produced for patients with elevated creatinine ≥ 2 x baseline and > 1 x upper limit of normal (ULN).

Patients with acute renal failure will be listed.

Ketoacidosis

A frequency table of patients with AEs related to ketoacidosis will be presented by treatment, primary SOC and preferred term for investigator reported cases and for the narrow and broad BIcMQ definition of diabetic ketoacidosis (DKA).

For presentations on adjudicated events, refer to Section 7.8.1.5.

Patients with DKA based on the broad BIcMQ (30000019) or investigator reported ketoacidosis will be listed.

7.8.1.4 Specific AEs

Hypoglycaemic events

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

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

Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a plasma glucose concentration ≤ 70 mg/dL or required assistance.

Different tables will be shown for (i) patients with investigator-defined hypoglycaemia, and (ii) patients with confirmed hypoglycaemic adverse events, i.e. hypoglycaemic adverse events that had a plasma glucose concentration ≤ 70 mg/dL or required assistance.

In addition, the number of patients with hypoglycaemia according to SMQ (20000226) will be presented.

Patients with hypoglycaemic events will be listed.

Urinary tract infections (UTI) and genital infections

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

- Genital infections (BIcMQ narrow subsearch 1.1 "Genital tract infections predisposed to by glucosuria" (30000038))
- UTI (BIcMQ narrow subsearch 2.1 "UTI predisposed by glucosuria" (30000041))

Complicated urinary tract infections defined as serious adverse events of BIcMQ Infection narrow, subsearch 2.1 "UTI predisposed by glucosuria" (30000041), all events of subsearch 2.1.1 'Renal infections predisposed by glucosuria' (30000042), all events of PT Urosepsis will be presented.

Complicated genital infection: defined as all serious events using the BIcMQ Infection narrow subsearch 1.1 'Genital tract infections predisposed to by glucosuria' (30000038) and all event of the subsearch 'Complicated genital tract infections predisposed to by glucosuria' (30000129) will also be presented.

Patients with UTIs or genital infections will be listed.

Bone fracture events

Frequency tables of patients with bone fracture by treatment, primary system organ class (SOC) and preferred term will be provided (based on the narrow BIcMQ "Bone fractures" (30000008) and investigator reporting).

Investigator reported fractures will be reported overall and separately for each type of fracture (traumatic and non-traumatic).

Patients with bone fractures will be listed.

Urinary tract malignancy events

Urinary tract malignancy will be shown based on the BIcMQ – broad sub-search 14.1 'Urinary bladder and tract malignancies' (30000057) and broad sub-search 14.2 'Renal malignancies' (30000103):

Presentation of frequency will be done by treatment, high level term and preferred term.

Patients with urinary tract malignancy will be listed.

Volume depletion

Volume depletion will be based on the BIcMQ 'Volume depletion of non-haemorrhagic cause and subsequent hypotension'– narrow subsearch 2 'Volume depletion and hypotension due to dehydration' (30000090).

A frequency table of patients with volume depletion by treatment, primary SOC and preferred term will be provided.

A separate table for serious volume depletion events will be presented.

Patients with volume depletion will be listed.

Hypotension

Frequency tables of patients with symptomatic hypotension as defined by the investigator on the eCRF tick box by treatment, primary system organ class and preferred term will be provided.

Symptomatic hypotension episodes will be presented by whether the intensity of diuretic medication was reduced and by whether the intensity of non-diuretic antihypertensive therapy was reduced.

A separate table for symptomatic hypotension events, which are serious, will be presented.

Additionally, hypotension by treatment, primary system organ class and preferred term will be provided. Hypotension is defined as preferred terms of the BIcMQ 'Volume depletion of non-haemorrhagic cause and subsequent hypotension' – narrow sub-search 2 'Volume depletion and hypotension due to dehydration' (30000090) but excluding terms of the narrow subsearch 1 'Volume depletion due to dehydration'(30000089).

A separate table for hypotension events, which are serious, will be presented.

Patients with hypotension events will be listed.

7.8.1.5 Events qualifying for external adjudication by the adjudication committee

An independent external CEC regularly reviews 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 the separate CEC Charter.

Adjudication assessments will be incorporated into the database.

Details of the adjudication process are described in the CEC charter.

Hepatic adverse events
Frequency tables summarising the relatedness and severity will be provided, including a listing showing the trigger events and adjudication results. This will include all adjudicated events up to 30 days after treatment stop.

Ketoacidosis
Frequency tables showing adjudicated certain ketoacidosis will be provided, including a listing showing the trigger events and adjudication results. This will include all adjudicated events up to 7 days after treatment stop.

7.8.1.6 AEs while patients taking wrong medication

A listing will be provided for AEs that occurred while a patient was taking the wrong study medication. If such a patient is identified, an additional adverse event table that assigns the adverse events to the actual treatment taken will be presented. A patient who took both the assigned treatment and at least one tablet of the wrong treatment, will be counted as at risk in both treatment groups for the respective relevant time. The table will include all adverse events by SOC and PT.

7.8.1.7 Adverse event incidence rates

For AE tables showing patients with events, in addition to the frequency tabulations, time-adjusted adverse event analyses will be performed for all AEs, investigator defined drug-related AEs, AEs leading to discontinuation, serious AEs, and adverse events of special interest by SOC and PT or High-Level Term (HLT) and PT, respectively.

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

Patients with AE:
time at risk (AE) in days = date of start of AE with specified PT/SOC/HLT – study treatment start date + 1

Patients without AE:
time at risk (AE) in days = end date of time at risk – study treatment start date + 1, where end date of time at risk is the minimum of date of last study drug intake + x days and date of death, if applicable.

The standard approach will be x=7 days, but for certain AESIs in addition other approaches will 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 summarised in this row; e.g. for patients with an AE in a specified SOC, time at risk = date of start of AE with specified PT in this SOC – start of study treatment + 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].

In a similar way, the time at risk and incidence rate for the post-treatment period is derived. Here the start date is the start date of the post-treatment phase instead of the study treatment start date.

For some specific outputs showing number of episodes, event rates will be defined as number of episodes divided by time at risk. Time at risk will be the end date of time at risk – study treatment start date + 1, where the end date of time at risk is the minimum of date of last study drug intake + 7 days and date of death, if applicable.

7.8.1.8 COVID-19 related analyses

The subgroup of patients with SARS-COV-2 infection will be analysed. SARS-COV-2 infections will be defined by the narrow BIcMQ SARS-COV-2 infection. All analyses will be repeated using the broad instead of the narrow BIcMQ.

An overview of adverse events will be presented for this subgroup of patients. Additionally, the number of patients with adverse events, the number of serious AEs and AEs leading to discontinuation of study treatment will be presented by treatment, primary SOC and preferred term.

A listing will be prepared presenting all SARS-COV-2 infections.

7.8.2 Laboratory data

Standard safety tables will not include eGFR or creatinine. Analyses for eGFR and creatinine will be done separately.

For continuous safety laboratory parameters, normalised values will be derived, as well as the differences to baseline. The process of normalisation as well as standard analyses for safety laboratory data are described in the BI guidance for the Display and Analysis of Laboratory Data (9). All analyses considering multiples of upper limits of normal (ULN) will be based on original and not normalised data.

Laboratory parameters will be shown in conventional units. Where conventional units differ from SI units, analyses will be repeated on SI units.

Laboratory measurements (not mentioned in Table 6.1: 2) taken up to 3 days after the last administration of randomised study drug will be considered as on-treatment. Default settings will be used for repeated values (using closest and then worst value).

Laboratory values will be compared to their reference ranges and frequency tables will be provided for the number of patients within and outside the reference range at baseline and the last measurement on treatment. Descriptive statistics will be provided by treatment group for baseline, last value on-treatment and for changes from baseline to last value on treatment. For semi-quantitative or categorical laboratory values, shift tables for baseline and last value on treatment will also be provided. Frequency tables will summarise the number of patients with potentially clinically significant abnormalities.

Additionally, for urine ketones. a shift table of baseline vs value at each visit will be shown.

For the table of potentially clinically significant abnormalities, only patients with at least one available on-treatment value will be included in the analysis of an individual laboratory parameter. Other tables are comparing baseline to on-treatment values and will only include patients with a baseline value and at least one available on-treatment value. All individual data will be presented in listings.

To support analyses of liver-related adverse drug effects, patients with Aspartate transaminase (AST) and/or Alanine transaminase (ALT) ≥3xULN with concomitant or subsequent Total Bilirubin (TBILI) ≥2xULN in a 30 day period after AST/ALT elevation are of special interest. In addition, of these cases, it will be considered whether the alkaline phosphatase (AP) is less than 2 x ULN (maximum value in a 30 day period after AST/ALT elevation) or not. The start of the 30-day time span is triggered by each liver enzyme elevation above the defined thresholds. Patients who fulfil one or two of the criteria for ALT/AST or total bilirubin elevations above and have no information available for the remaining parameter(s) within the 30 day time window will not be listed under “ALT and/or AST ≥ 3xULN with TBILI ≥ 2xULN”.

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

- ALT/AST ≥ 3 x ULN
- ALT/AST ≥ 5 x ULN
- ALT/AST ≥ 10 x ULN
- ALT/AST ≥ 20 x ULN

All liver enzyme elevations within 30 days of treatment discontinuation will be shown.

Frequency tables of patients with elevated liver enzymes defined by ALT and/or AST, total bilirubin and AP combinations will be provided. Details on patients with elevated liver enzymes will be listed.

For the following parameters:

- eGFR,

- haemoglobin,
- haematocrit,
- creatinine (only descriptive),

the time course of changes will be assessed. The analysis will be performed by applying MMRM models to the TS (on-treatment data) and the RS (all data). No imputation will be applied. The MMRM models that will be used are specified in Section 7.5.2. These analyses will be conducted on data before any normalisation. The MMRM analyses will also be shown graphically.

To support analysis of renal function, eGFR throughout the trial will be categorised according to the following Chronic Kidney Disease (CKD) staging (Table 7.8.2: 1): All calculations for the staging of renal function will be based on the originally measured laboratory values, not on normalised values with BI standard reference ranges.

Table 7.8.2: 1 CKD staging

Stage	eGFR (mL/min/1.73m²)	Description	Label for displays	Additional labels
1	≥90	Normal or high	≥90	≥90 (CKD 1)
2	60 to <90	Mildly decreased	60 to <90	60 to <90 (CKD 2)
3A	45 to <60	Mildly to moderately decreased	45 to <60	45 to <60 (CKD 3a)
3B	30 to <45	Moderately to severely decreased	30 to <45	30 to <45 (CKD 3b)
4	15 to <30	Severely decreased	15 to <30	15 to <30 (CKD 4)
5	<15	Kidney failure	<15	<15 (CKD 5)

A shift table from baseline to last value on treatment and to minimum value on treatment for eGFR (CKD-EPI)cr will be provided.

7.8.3 Vital signs

Heart rate and blood pressure (diastolic and systolic) over time will be summarised descriptively based on the RS (all data). Descriptive statistics will also be shown graphically.

7.8.4 ECG

Clinically relevant abnormalities found at physical examination will be considered to have already existed prior to signing of informed consent and therefore should be considered baseline conditions instead of adverse events, unless there is good reason to assume that they first appeared after signing of consent.

Outcomes of ECGs will be part of the reporting of medical history or AE reporting. Categorical findings as collected in the eCRF will also be summarised descriptively.

7.8.5 Others

Not applicable.

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.	*BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED.
3.	*BI-KMED-BDS-HTG-0045*: "Standards for Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.
4.	Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J. 2012. 33: 176-182
5.	Dong G, Li D, Ballerstedt S, Vandemeulebroecke M. A generalized analytic solution to the win ratio to analyze a composite endpoint considering the clinical importance order among components. Pharm Stat. 2016. 15: 430-437
6.	Schou M, Gustafsson F, Kjaer A, Hildebrandt PM. Long-term clinical variation of NT-proBNP in stable chronic heart failure patients. European Heart Journal. 2007. 28(2): 177-182
7.	Collett.D, Modelling Survival Data in Medical Research. A CRC Press Company. 2003
8.	*BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED.
9.	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.
10.	Dong G, Qiu J, Wang D, Vandemeulebroecke M. The stratified win ratio. Journal of Biopharmaceutical Statistics 2018;28:778–96
11.	Carpenter JR, Roger JH, Kenward MG. Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. J Biopharm Stat 2013;23(6):1352-1371
12.	Ariti CA, Cleland JG, Pocock SJ, et al. Days alive and out of hospital and the patient journey in patients with heart failure: Insights from the candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM) program. Am Heart J. 2011;162(5):900-906. doi:10.1016/j.ahj.2011.08.003
13.	Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley and Sons; 2004

9. ADDITIONAL SECTIONS

9.1 DERIVATION OF KCCQ DOMAINS

The following algorithm will be used to score the KCCQ.

9.1.1 Kansas City Cardiomyopathy Questionnaire (KCCQ)

There are 10 summary scores within the KCCQ, which are calculated as follows:

1. Physical Limitation

Code responses to each of Questions 1a-f as follows:

- Extremely limited = 1
- Quite a bit limited = 2
- Moderately limited = 3
- Slightly limited = 4
- Not at all limited = 5
- Limited for other reasons or did not do = <missing value>

If at least three of Questions 1a-f are not missing, then the Physical Limitation Score is calculated as follows:

Physical Limitation Score = 100*[(mean of Questions 1a-f actually answered) – 1]/4

2. Symptom Stability

Code the response to Question 2 as follows:

- Much worse = 1
- Slightly worse = 2
- Not changed = 3
- Slightly better = 4
- Much better = 5
- I've had no symptoms over the last 2 weeks = 3

If Question 2 is not missing, then the Symptom Stability Score is calculated as follows:

Symptom Stability Score = 100*[(Question 2) – 1]/4

3. Symptom Frequency

Code responses to Questions 3, 5, 7 and 9 as follows:

Question 3

- Every morning = 1
- 3 or more times a week but not every day = 2
- 1-2 times a week = 3
- Less than once a week = 4
- Never over the past 2 weeks = 5

Questions 5 and 7

- All of the time = 1
- Several times a day = 2
- At least once a day = 3
- 3 or more times a week but not every day = 4
- 1-2 times a week = 5
- Less than once a week = 6
- Never over the past 2 weeks = 7

Question 9

- Every night = 1
- 3 or more times a week but not every day = 2
- 1-2 times a week = 3
- Less than once a week = 4
- Never over the past 2 weeks = 5

If at least two of Questions 3, 5, 7 and 9 are not missing, then the Symptom Frequency Score is calculated as follows:

S3 = [(Question 3) – 1]/4

S5 = [(Question 5) – 1]/6

S7 = [(Question 7) – 1]/6

S9 = [(Question 9) – 1]/4

Symptom Frequency Score = 100*(mean of S3, S5, S7 and S9)

4. Symptom Burden

Code responses to each of Questions 4, 6 and 8 as follows:

- Extremely bothersome = 1
- Quite a bit bothersome = 2
- Moderately bothersome = 3
- Slightly bothersome = 4
- Not at all bothersome = 5
- I've had no swelling/fatigue/shortness of breath = 5

If at least one of Questions 4, 6 and 8 is not missing, then the Symptom Burden Score is defined as follows:

Symptom Burden Score = 100*[(mean of Questions 4, 6 and 8 actually answered) – 1]/4

5. Total Symptom Score

The Total Symptom Score is defined as the mean of the following available summary scores:

Symptom Frequency Score and Symptom Burden Score

6. Self-Efficacy

Code responses to Questions 10 and 11 as follows:

Question 10

- Not at all sure = 1
- Not very sure = 2
- Somewhat sure = 3
- Mostly sure = 4
- Completely sure = 5

Question 11

- Do not understand at all = 1
- Do not understand very well = 2
- Somewhat understand = 3
- Mostly understand = 4
- Completely understand = 5

If at least one of Questions 10 and 11 is not missing, then the Self-Efficacy Score is calculated as:

Self-Efficacy Score = 100*[(mean of Questions 10 and 11 actually answered) – 1]/4

7. Quality of Life

Code responses to Questions 12, 13 and 14 as follows:

Question 12

- It has extremely limited my enjoyment of life = 1
- It has limited my enjoyment of life quite a bit = 2
- It has moderately limited my enjoyment of life = 3
- It has slightly limited my enjoyment of life = 4
- It has not limited my enjoyment of life at all = 5

Question 13

- Not at all satisfied = 1
- Mostly dissatisfied = 2
- Somewhat satisfied = 3
- Mostly satisfied = 4
- Completely satisfied = 5

Question 14

- I felt that way all of the time = 1
- I felt that way most of the time = 2
- I occasionally felt that way = 3

- I rarely felt that way = 4
- I never felt that way = 5

If at least one of Questions 12, 13 and 14 is not missing, then the Quality of Life Score is calculated as:

Quality of Life Score = 100*[(mean of Questions 12, 13 and 14 actually answered) – 1]/4

8. Social Limitation

Code responses to each of Questions 15a-d as follows:

- Severely limited = 1
- Limited quite a bit = 2
- Moderately limited = 3
- Slightly limited = 4
- Did not limit at all = 5
- Does not apply or did not do for other reasons = <missing value>

If at least two of Questions 15a-d are not missing, then the Social Limitation Score is calculated as:

Social Limitation Score = 100*[(mean of Questions 15a-d actually answered) – 1]/4

9. Overall Summary Score

The Overall Summary Score is defined as the mean of the following available summary scores:

Physical Limitation Score, Total Symptom Score, Quality of Life Score and Social Limitation Score

10. Clinical Summary Score

The Clinical Summary Score is defined as the mean of the following available summary scores:

Physical Limitation Score and Total Symptom Score

Note: references to “means of questions actually answered” imply the following.

If there are n questions in a scale, and the subject must answer m to score the scale, but the subject answers only n-i, where n-i >= m, calculate the mean of those questions as

(sum of the responses to those n-i questions) / (n-i)

not

(sum of the responses to those n-i questions) / n

The change from baseline to Day 90 in KCCQ-TSS will be calculated as the difference of the score at Day 90 and at baseline.

9.2 ALGORITHM FOR IMPUTATION ACCORDING TO JUMP-TO-PLACEBO METHOD

This algorithm imputes missing on-treatment data as MAR, and then imputes missing off-treatment data as MNAR by a jump-to-placebo method.

The conceptual approach is described by Carpenter et. al. (11). The implementation is planned as follows:

1. Remove any off-treatment data from dataset

2. Non-monotone missing data is imputed under MAR to create a monotone pattern
    a. 100 imputations are performed by MCMC-MI, stratified by treatment, with the following parameters:
        i. Baseline value included as a continuous variable, HF status as a binary variable (de novo or decompensated chronic HF)
        ii. Multiple chains with 200 burn-in iterations per chain
        iii. Jeffrey's prior

3. SLR-MI is used to impute missing monotone on-treatment data:
    a. All data is imputed using SLR-MI, separately by treatment, with the following parameters:
        i. Baseline (continuous), HF status (de novo or decompensated HF) included as covariates
    b. All imputed data for patients at an off-treatment time point is deleted

4. On-treatment group means are calculated for each imputation at each visit
    a. ANCOVA used to calculate adjusted means with the following parameters:
        i. Baseline (continuous), HF status (de novo or decompensated chronic HF), and treatment included as covariates
        ii. Restricted Maximum Likelihood and Kenward-Rogers methods
        iii. Least Square Means used

5. Placebo group on-treatment means at each visit are subtracted from all group on-treatment means at the same visit, to give treatment differences

   a. Note that these will be 0 for the placebo group

6. Individual data is 'temporarily saved' at this point, excluding available off-treatment data

7. Treatment differences are subtracted from the respective (by visit and treatment) data values
   a. Results are the 'residuals' after removal of treatment effect(s)
   b. This is referred to as the residual data

8. Subset of the residual data is created with all patients in placebo group and all patients with missing values at first visit requiring imputation. Note that these missing values will all be off-treatment.

9. Multiple imputation is performed on the first visit requiring imputation
   a. Linear regression models are used to derive the distributional parameters;
      i. One imputation per existing imputation
      ii. Residual subset used
      iii. Baseline (continuous), HF status (de novo or decompensated chronic HF), all previous visits (continuous) included as model covariates

10. Imputed off-treatment values from subset merged with residual data sets.

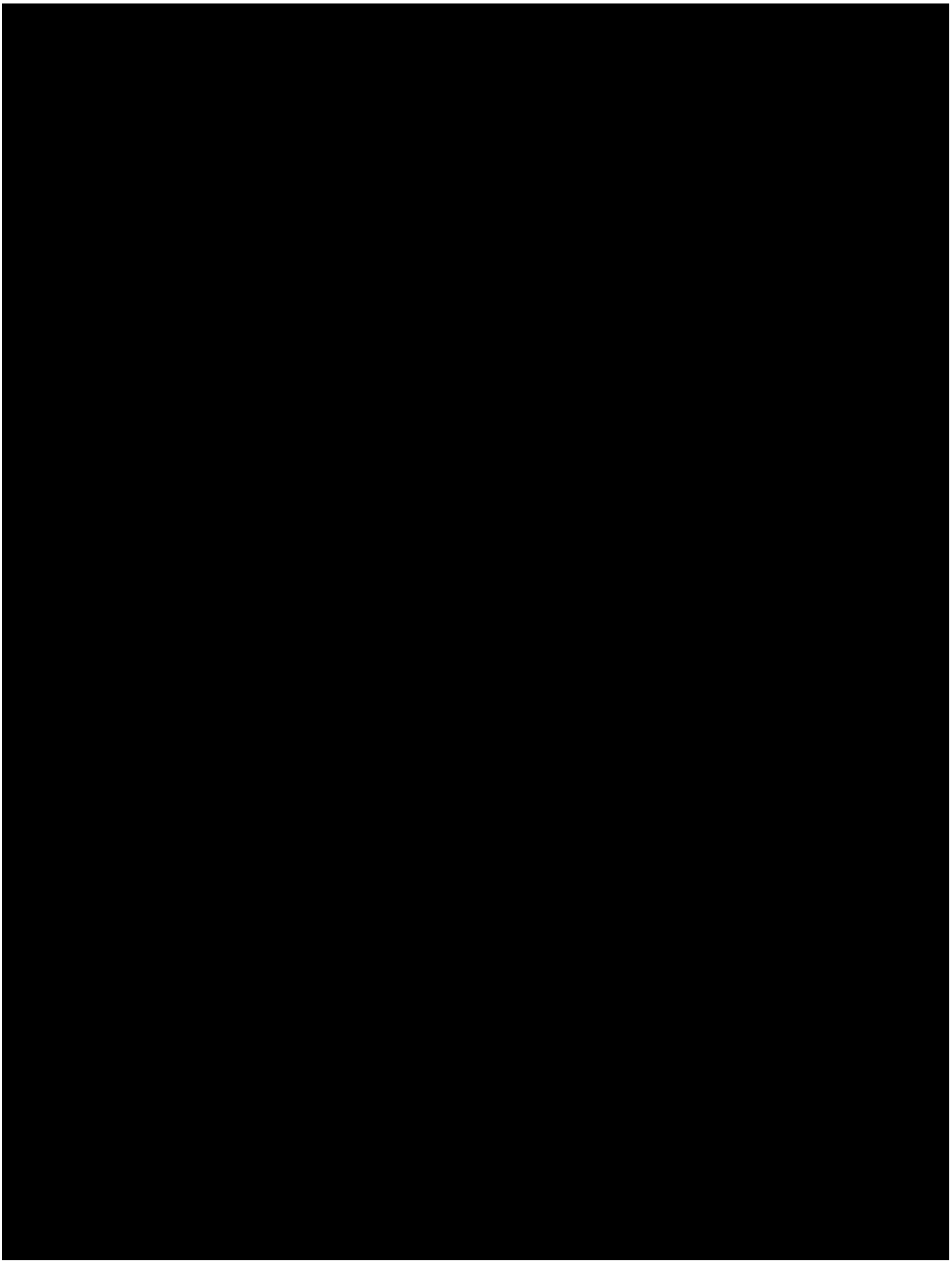
11. If visits that require imputation remain, go to step 8, else proceed to next step

12. Original data set, saved data sets and residual data sets are merged so that all missing values in the saved data set are filled with observed off-treatment measurements where available, otherwise the values from corresponding residual data sets are used.

13. The next step depends on the data being imputed:

    a. For NT-proBNP, the AUC of change from baseline in log-transformed NT-proBNP level will be calculated for these imputed data sets. Then an ANCOVA model will be applied (see Section 7.5.2).
    b. For KCCQ-TSS, the stratified win ratio will be calculated using these imputed data sets, by combining with the non-imputed death and HFE data (see Section 7.4.1). Then take logs of the stratified win ratios.

14. Estimates and variances are combined using Rubin's rules (13) to give a single estimate and variance for each parameter of interest across all imputations.



10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**11-Mar-2021**	[redacted]	None	This is the final TSAP without any modification

APPROVAL / SIGNATURE PAGE

Document Number: c32295612 **Technical Version Number:1.0**

Document Name: 8-01-tsap

Title: A multicentre, randomised, double-blind, 90-day superiority trial to evaluate the effect on clinical benefit, safety and tolerability of once daily oral EMPagliflozin 10 mg compared to placebo, initiated in patients hospitalised for acUte heart faiLure (de novo or decompensated chronic HF) who have been StabilisEd (EMPULSE)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician	[redacted]	12 Mar 2021 10:27 CET
Approval-Medical Writer		12 Mar 2021 10:33 CET
Approval-Clinical Trial Leader		12 Mar 2021 12:19 CET
Approval-Project Statistician		13 Mar 2021 12:04 CET
Approval-Team Member Medicine		16 Mar 2021 19:36 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed