TRIAL STATISTICAL ANALYSIS PLAN

c38811533-02

BI Trial No.:	1245-0202
Title:	EMPACT-MI: A streamlined, multicentre, randomised, parallel group, double-blind placebo-controlled superiority trial to evaluate the effect of **EMPA**gliflozin on hospitalisation for heart failure and mortality in patients with a**C**u**T**e **M**yocardial **I**nfarction Including Protocol Amendment 1 <1245-0202>-protocol-version-02 [c31546238-02]
Investigational Product(s):	Jardiance®, empagliflozin
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2. LIST OF ABBREVIATIONS

Term	Definition / description
ANCOVA	Analysis of Covariance
BNP	Brain Natriuretic Peptide
CABG	Coronary artery bypass grafting
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Equation
COVID-19	Coronavirus-Disease 2019
CRT-D	Cardiac resynchronization therapy with defibrillator
CRT-P	Cardiac resynchronization therapy without defibrillator
CV	Cardiovascular
DAOH	Days alive and out of hospital
eGFR	Estimated Glomerular Filtration Rate
HbA1c	Glycosylated haemoglobin
HHF	Hospitalisation for Heart Failure
ICD	Implantable cardioversion defibrillator
LDL	Low-Density Lipoprotein
LVEF	Left Ventricular Ejection Fraction
MI	Myocardial infarction
NSTEMI	Non-ST Elevation Myocardial Infarction
NT-proBNP	N-Terminal Pro-Brain Natriuretic Peptide
OC-AD	Observed Cases including data after treatment discontinuation
OC-OT	Observed Cases on-treatment
PCI	Percutaneous coronary intervention
RS	Randomised Set
SCR	Screened Set
SGLT-2	Sodium Glucose Co-Transporter 2
STEMI	ST Elevation Myocardial Infarction
T2D	Type 2 Diabetes
TS	Treated Set

3. INTRODUCTION

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

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

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

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

None.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoint is specified in the CTP section 2.1.2 as the composite of time to first heart failure hospitalisation (HHF) or all-cause mortality, calculated from date of randomisation.

For detailed specifications refer to the 'Event review charter and guidance for EMPACT-MI' (1). Further programming specifications are given in Section 10.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Key secondary endpoints are specified in the CTP section 2.1.3. as

- Total number of HHF or all-cause mortality
- Total number of non-elective cardiovascular (CV) hospitalisations or all-cause mortality
- Total number of non-elective all-cause hospitalisations or all-cause mortality
- Total number of hospitalisations for myocardial infarction (MI) or all-cause mortality

For detailed specifications refer to the 'Event review charter and guidance for EMPACT-MI' (1). Further programming specifications are given in Section 10.

5.2.2 Secondary endpoint(s)

One other secondary endpoint is specified in the CTP section 2.1.3 as time to CV mortality.

For further clarification:

- CV death includes death with unknown cause.

5.3 FURTHER ENDPOINT(S)

Further endpoints are specified in the CTP section 2.2.2.

For further clarification:

- Time to first revascularisation will be derived from the eCRF page 'concomitant targeted non-drug therapies' and includes percutaneous coronary intervention (PCI) or coronary bypass artery grafting (CABG) not pre-planned at randomisation

- Time to first renal replacement therapy or renal transplantation will be derived from the eCRF page 'concomitant targeted non-drug therapies' and includes chronic renal replacement therapies only, defined by a renal replacement therapy lasting for at least 90 days.

- For the endpoint 30-day all-cause hospitalisation, patients who died within the 30 days will be counted as an event.

Further endpoints added include:

- Time to first HHF or CV death
- Time to first implantable cardioversion defibrillator (ICD) or cardiac resynchronization therapy with defibrillator (CRT-D) or cardiac resynchronization therapy without defibrillator (CRT-P) for patients without any of ICD, CRT-D or CRT-P at baseline. ICD/CRT at baseline will be derived via the tick boxes on the eCRF medical history page
- Time to first chronic renal replacement therapy or renal transplantation or renal death (renal death defined as a death event with primary AE leading to death in narrow SMQ 'Acute Renal Failure')
- Time to first hospitalisation for MI or fatal MI (fatal MI based on CV death sub-category 'Acute myocardial infarction' according to event review charter)
- Total number of hospitalisations for MI or death due to MI

5.4 OTHER VARIABLE(S)

Treatment exposure

Treatment exposure is defined as time from first intake to last intake of study drug, including off-treatment periods.

Overall observational period

The overall observational period (until vital status follow-up) is defined as time from randomization until end of follow-up for vital status, see censoring for all-cause mortality in Section 6.8.3.

The observational period (until individual day of trial completion) is defined as time from randomization until individual day of trial completion, see Section 6.8.3.

Treatment compliance

Treatment compliance will be defined per scheduled visit as a binary variable. If there is more than one reported visit in the visit window as defined in Section 6.7, the patient will be

defined as being compliant with study drug if the duration within the visit window for which the patient reported to be compliant with study drug is >=50%. If the duration within the visit window for which the patient has missing data for study drug compliance is >50%, the study treatment compliance will be missing. For a given time window, only the period up until the earliest of date of permanent treatment stop and date of last compliance report will be used. The TS will be used for analysis.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

There will be four basic treatment phases in this trial: screening, study treatment phase (with either empagliflozin 10mg or matching placebo), post-treatment and post-study. 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. Temporary discontinuations and following re-starts will not be collected in the eCRF. The treatment phase is defined from first study drug intake to last study drug intake.

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.

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
Post-treatment	Post-treatment	Date of last administration of study medication + 1 day
Post study	Post study	Date of trial completion +1 day

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.

The on-treatment phase which will be used e.g. in analyses of adverse events (see Section 7.8) starts at first study drug intake and includes the time up to 7 days after the last intake of study medication (the residual effect period).

If a patient erroneously receives the wrong trial drug, all subsequent medication packs dispensed to the patient will correspond to 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 7.8.1.5.

6.2 IMPORTANT PROTOCOL DEVIATIONS

An important protocol deviation (iPD) is a protocol deviation that may significantly impact the completeness, accuracy, and/or reliability of the trial data or that may significantly affect a subject's right, safety, or well-being. Refer to the Protocol Deviations Management Plan for documentation of iPD categories and management of important PDs (iPDs), see (2) and (3).

Handling of iPDs in analysis is included in the DV domain specifications and stored within the TMF in EDMS. iPDs will be presented based on the randomised set (definition of randomised set see Section 6.3).

6.3 SUBJECT SETS ANALYSED

The following subject sets are defined:

- Screened Set (SCR)
  Consists of all patients screened for the trial, with informed consent given

- Randomised set (RS)
  This patient set includes all randomised patients, whether treated or not. A patient randomised in error after death (i.e. a mis-randomization) will be excluded.

- 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

Table 6.3: 1 Subject sets analysed

	Subject set		
Class of endpoint	SCR	RS	TS
Primary and key secondary endpoints		primary analysis	on-treatment analysis (incl. data up to treatment stop + 7 days)
(other) Secondary and further endpoints		X	
Safety endpoints & treatment exposure			X
Demographic/baseline endpoints		X	(X)
Disposition	X		

(X) An additional TS presentation of the demographic/baseline endpoints may be provided in the End of Text (EoT) section, if subject numbers for RS and TS are clearly different (see Section 7.1).

6.4 SUBGROUPS

Subgroups to be considered in the analyses are provided below in Table 6.4:1. Missing categories for subgroup variables will not be considered in the respective analysis, except for descriptive analyses of adverse events.

If there is missing information for any of the subgroups, where data is also collected in the Interactive Response Technology (IRT) system, then the information as transferred from IRT will be used to assign a patient to a certain category. This applies to potential capping criteria ‘time of randomization’.

For the stratification factor T2D, the updated information from IRT will be used for all analyses.

For subgroup analyses of variables with ordered categories, the interaction p-values will be calculated using trend tests, taking into account that the subgroup categorizations are ordered. Assuming the difference between the adjacent subgroup is the same, each subgroup is coded as numeric value ordinally and fitted into the model as numeric covariate. The model also includes terms of subgroup variable and subgroup-by-treatment interaction.

Table 6.4: 1 Categories of baseline covariates for subgroup analyses

Variable	Categorization	Efficacy endpoints[1]	Safety[2]
T2D	T2D, no T2D	X	X
Age [years]	< 65 ≥ 65	X	
	<50 50-<65 65-<75 >=75	X	X
Sex	Male Female	X	X
Region[3]	North America Latin America Europe Asia	X	X
Ethnicity	Hispanic/ Latino Not Hispanic/ Latino	X	X
Race	White Black/ African-American Asian Other including mixed race	X	X
eGFR at baseline (CKD-EPI), in [mL/min/1.73m^2]	>=90 60 to <90 45 to <60 30 to <45 <30	X	X
	>=60 <60	X	
Baseline Systolic Blood Pressure	<110 mmHg 110- <130 mmHg >=130 mmHg	X	
Baseline Left Ventricular Ejection Fraction (LVEF) before randomisation	>=35% <35%	X	
History of MI	Yes No	X	
Time from index MI diagnosis to randomisation	<= median > median	X	

Table 6.4: 1 Categories of baseline covariates for subgroup analyses (cont.)

Variable	Categorization	Efficacy endpoints1	Safety2
Signs, symptoms of HF that required treatment during index hospitalisation	Yes No	X	
Lowest LVEF during index hospitalisation	<45% >=45%	X	
ACE/ARB/ARNI use at baseline	Yes No	X	
MRA use at baseline	Yes No	X	
Loop or high ceiling diuretic use at baseline	Yes No	X	
Betablocker use at baseline	Yes No	X	
Type of index MI	STEMI NSTEMI	X	

[1] Subgroups planned for the primary and key secondary endpoints as well as for time to first HHF or CV death.
[2] X means subgroups planned for overall Adverse Event (AE) summaries, SAEs by System Organ Class (SOC) and Preferred Term (PT), and AEs leading to treatment discontinuation.
[3] Region categorisation: see Table 10.4:1

6.5 POOLING OF CENTRES

This section is not applicable because centre/country is not included in the statistical model. For country-specific or regional analyses, please see Section 10.3.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

6.6.1 Imputation methods

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.

Imputation of missing covariates in multivariate Cox regression models, for total events (i.e. first plus recurrent) analyses and other statistical analysis models (including MMRM models, ANCOVA models and logistic regression analysis)
To avoid excluding patients from Cox regression analyses, models and for total events (i.e. first plus recurrent) analyses or other statistical models due to missing covariates the following steps will be followed. If there is missing information on covariates for Cox regression analyses, models and for total events (i.e. first plus recurrent) analyses or other statistical models, the overall population (randomised set) median of the corresponding variable will be imputed for continuous covariates and the most frequent category, based on

the randomised set, will be imputed for categorical covariates. For subgroup analyses, only patients with available data (either from eCRF or, if missing in eCRF, from IRT) for the subgroup variable will be included in the subgroup analysis. For the evaluation of eGFR changes, baseline eGFR will not be imputed.

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 (4).

Missing admission dates for hospitalisations after the index hospitalisation
The index hospital admission date is mandatory for a patient to be randomised and will not be missing. Hence, the below rules apply to all hospital admission dates excluding the index hospitalisation. If a non-index hospital admission date is missing or partially given then define a range of possible admission dates:

- The lower bound is the maximum of:
    - Randomisation
    - The earliest possible date from the partial admission date, if not missing
    - The latest complete discharge date from hospitalisations that are definitively before the hospitalisation, i.e. either the index hospitalisation or with admission dates prior to the earliest possible admission date
- The upper bound is the minimum of:
    - Last non-fatal follow-up
    - The latest possible date from the partial admission date, if not missing
    - The latest possible discharge date of the hospitalisation, if not missing

If there is a linked adverse event onset date and it is between the upper and lower bound then this is used as the admission date.
If the linked adverse event onset date is after the upper bound, then the upper bound is used.
Otherwise in all other cases the lower bound is used as the admission date.

Missing information on discharge date for index hospitalisation
If an index hospitalisation discharge date is missing or partially given then define a range of possible discharge dates:

- The lower bound is the maximum of:
    - Index hospitalisation admission date
    - The earliest possible date from the partial discharge date, if not missing
    - Randomisation date, if IRT indicates discharge was not prior to randomisation
- The upper bound is the minimum of:
    - Randomisation date-1, if IRT indicates discharge was prior to randomisation
    - Last non-fatal follow-up
    - The latest possible date from the partial discharge date, if not missing
    - Any admission date after the index hospitalisation
    - Visit 2b visit date

Take the maximum of the upper and lower bounds

Missing information on discharge dates for hospitalisations after the index hospitalisation
If a non-index hospitalisation discharge date is missing or partially given then define a range of possible discharge dates:

- The lower bound is the maximum of:
  - The admission date on the same hospitalisation
  - The earliest possible date from the partial discharge date, if not missing
- The upper bound is the minimum of:
  - Last non-fatal follow-up
  - The latest possible date from the partial discharge date, if not missing
  - Any admission date from later hospitalisations, i.e. those with later admission dates

If there is a linked adverse event end date and it is between the upper and lower bound then this is used as the discharge date. Otherwise take the maximum of the upper and lower bounds.

Missing or partial start dates for concomitant targeted non-drug therapy after randomisation (from eCRF page 'concomitant targeted non-drug therapies)

Missing or partial date information for start dates will be replaced according to general Boehringer Ingelheim (BI) rules described in the BI guidance for handling of missing and incomplete AE dates (4).

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, the hospitalisation page, by using also imputed AE and hospitalisation dates, individual day of trial completion, last date known to be alive+1day. In case of a partially missing date, if the subsequently derived date is before the first day (or after the last day) of the month/year given as a partial date, the first day (or last day) of the month/year will be used.

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. For cases where only the month or month and year is given, take the earliest possible date in line with the month or month and year of the partial date given that is not prior to the randomisation date.

Missing information on the date of trial medication stop
If the date is partially or completely missing, use the minimum of the following dates:

- Date of death
- Trial completion (End of Study Participation Date)
- Longest extrapolated treatment duration (assuming 1 tablet/day)
- (in case of a partially missing date) last day of the year/month given as the partial date.

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.

Missing information on concomitant therapy dates (not for concomitant targeted non-drug therapies)
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 the medication is reported as not started before index hospital admission, and the imputed start date contradicts this then the start date is imputed to the day of index hospital admission if this is in the range of possible dates and can resolve the contradiction.
If prior steps lead 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.

Missing information on reference ranges for local laboratory values
Missing information on reference ranges for local laboratory values will be imputed according to (5).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For all covariates used for adjustment in all analysis models, except for analyses based on endpoints derived from eGFR over time, baseline will be defined as the last available measurement before randomization, including measurements at the day of randomization.

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

For NT-proBNP, BNP and uric acid, the CTP specifies that the highest value during index hospitalisation before randomisation will be collected in the eCRF. These will be used as baseline values.

For all other variables and all subgroup definitions given in Table 6.4:1, baseline will be defined as the last available measurement before start of study drug.

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 (7 days for AE analyses and 1 day for creatinine) 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.

The time windows for the visits after randomisation start relative to the day of first study drug administration. These time windows are defined based on the planned number of days after the date of first administration of study drug. The midpoint between two post-baseline visits

defines the end of a time window, with the midpoint being included in the time window of the preceding visit. These windows will be used in the analysis of treatment compliance over time and in regional analyses of eGFR over time (see Section 10).

Table 6.7: 1 Time windows

			Time window (days from first study drug intake)	
Visit number	Visit label	Planned days	Start	End
Treatment compliance				
3	Week 2	15	2	98
4	Month 6/ Week 26	181	99	271
5	Month 12/ Week 52	361	272	451
6	Month 18/ Week 78	541	452	631
7	Month 24/ Week 104	721	632	811
8	…			

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 for patients not treated) and end date continued on or after date of first study medication intake (randomisation 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, e.g. for defining the primary endpoint, the time to first event will be derived from the date of randomisation.

If study drug administration happened before calling IRT, the date of first drug administration will be used as start date.

For AE analyses according to Section 7.8.1, the date of first study drug intake will be used as the start date.

6.8.2 Date of event

For time-to-event endpoints including hospitalisations, the investigator-reported hospital admission date will be used for hospitalisation components.

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

For composite outcomes, e.g. time to first occurrence of all-cause mortality or HHF, the earliest date of the corresponding components will be used.

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

The primary analysis includes all events up to individual day of trial completion including the period after the End of Study (EoS) visit (if available).

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 all-cause mortality and HHF).

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 trial completion.

The individual day of trial completion will be the latest of

- the last date the patient could be followed up for all non-fatal events as documented in the eCRF
- last onset of an AE or death date
- last hospital admission or discharge date
- end of treatment date

- last visit date (excluding visits with type ‘medical records review only’ and excluding End of Study visit)

- End of study participation date (excluding visits with type ‘medical records review only’)

Censoring is considered independent from study drug intake.

All-cause mortality

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

- Individual day of trial completion

- last date known to be alive from the vital status page (for patients still alive after start of study closure) or last known alive date from End of Study page (for patients with unknown vital status after start of study closure)

Endpoints of any cause-specific death, e.g. CV death

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.

Composite endpoints

Of those, only patients that are included in the analyses for all components of the composite endpoint will be included in the analysis of the composite.

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.

Censoring for analyses up to treatment stop + x days

For any analyses until a certain number of x days after treatment discontinuation (e.g. sensitivity analyses until 7 days after treatment discontinuation), censoring time will be the minimum of the censoring time as described above and treatment discontinuation + x days. Patients with an event after treatment discontinuation + x days will be censored at treatment discontinuation + x days.

6.8.4 Time at risk for count variables

The time at risk for count variables (e.g. the key secondary endpoints of total number of HHF and death) will be calculated from the date of randomization up until individual day of trial completion.

If study drug administration happened before calling IRT, the date of first drug administration will be used as start date.

7. PLANNED ANALYSIS

For End-Of-Text 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” (6).

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 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 (7).

Number of patients lost to follow up (no information on vital status after start of study closure) and number of patients lost to follow up for the primary endpoint (no information on primary endpoint after start of study closure) will be summarised.

The disposition table will be repeated by subgroup of patients from Ukrainian sites vs non-Ukrainian sites. 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.

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. These summary tables will include description of subgroup variables detailed in Table 6.4:1 and variables collected on screening and randomization visit. Descriptive analysis of the following variables measured at baseline will be presented: Age, BMI, time from index admission to randomization, systolic blood pressure , diastolic blood pressure, pulse rate, weight, eGFR, LVEF, NT-pro-BNP, BNP, uric acid, haemoglobin, potassium, HbA1c and LDL cholesterol. HbA_{1c} will be presented for patients

with diabetes at baseline. Descriptive analysis of variables from index hospitalization will be presented, as well as a cross-table for lowest LVEF from index hospitalization (before randomization) by treatment required for HF signs/symptoms.
A summary of the number of patients in each randomisation stratum per treatment will also be shown. The information will be based upon the data received from the IRT provider.

The covariate and subgroup analysis variable 'History of MI' will be derived including data from two eCRF pages, the enrichment criteria page and the medical history page. The variable will be set to 'Yes' if any of the two pages indicates a history of MI.

The covariate 'peripheral artery disease (PAD) at baseline' will be derived including data from two eCRF pages, the enrichment criteria page and the medical history page. The variable will be set to 'Yes' if any of the two pages indicate PAD.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report using the RS by treatment group. 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 at baseline and separately for those at the day of discharge. In addition, a table showing all concomitant medications taken at the day of the 6-months visit and one table showing all concomitant medications cumulative from baseline or introduced up until the 6-months visit. Separate summaries of lipid-lowering drugs, anti-thrombotic drugs, anti-coagulant drugs (with subcategories) and thrombolytic drugs at baseline, at day of discharge and at day of the 6-months visit will be presented, as well as a table showing medication cumulative from baseline or newly introduced until the 6-months visit. The frequency of patients starting any non-study drug SGLT-2 inhibitor during study will be displayed, as well as time-to first start of any non-study drug SGLT-2 inhibitor using cumulative incidence functions adjusting for the competing risk of death.

In the RS, medical history by treatment group will be presented, and relevant baseline conditions will be presented by SOC and PT. In addition, descriptive statistics are planned for concomitant non-drug procedures starting after randomisation by treatment group and by type of procedure.

For regional analyses on concomitant medication use please see Section 10.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report. The number and percentage of patients reporting compliance will be reported per scheduled visit as defined in Section 5.4. The TS will be used for analysis.

The analysis on compliance with study drug will be repeated by subgroup of patients from Ukrainian sites vs non-Ukrainian sites.

7.4 PRIMARY ENDPOINT(S)

The primary estimand of this trial is the treatment-policy estimand.

7.4.1 Primary analysis of the primary endpoint(s)

The primary analysis will be based on RS, using all data available until individual day of trial completion, including the data after end of treatment for patients not completing the treatment phase as planned and including data up until a follow-up visit, if available. This equates a treatment-policy estimand. Please see Section 10.1 for detailed definition of the primary endpoint derivation.

The primary endpoint will be analysed using a Cox proportional hazards model with treatment, T2D at baseline (yes vs no), geographical region (North America, Latin America, Europe, Asia), age at baseline (continuous), eGFR (CKD-EPI) at baseline (<45 vs 45-<60 vs 60-<90 vs >=90 ml/min/1.73m2), LVEF at baseline (<35% vs ≥35%), persistent or permanent atrial fibrillation at baseline (yes vs no), prior MI at baseline (yes vs no), peripheral artery disease (PAD) at baseline (yes vs no) and smoking at baseline (current vs non-current) as covariates. Since the stratification factors are included in the model as covariates, no stratified Cox regression will be used. eGFR will be derived from serum creatinine at baseline according to Section 7.8.2. Breslow's method for dealing with ties will be used.

The hazard ratio for the effect of treatment (empagliflozin versus placebo) and its two-sided 95% Wald confidence limits will be estimated and presented with the two-sided p-value for the null hypothesis of equality based on the Wald chi-squared statistic. A hazard ratio of less than one will favour empagliflozin.

The proportional hazard assumption will be checked. In case the proportionality assumption is violated for treatment, an attempt will be undertaken to identify groups of patients for which the proportionality assumption holds and a stratified Cox regression will be performed. In addition a piecewise Cox model assuming proportional hazards in a series of consecutive time intervals as proposed by Collett (8) might be investigated.

The probability of the primary endpoint event over time will be displayed by treatment using Kaplan Meier estimates, which includes the presentation of certain quantiles of the failure times (e.g. 5%, 7.5%, 10%, 15% quantiles) and Kaplan-Meier rates after specific number of days.

Centre is not included in the statistical model due to the large number of centres involved in this trial (approximately 400 planned centres).

A hierarchical testing procedure will be followed for the assessment of the primary and key secondary endpoints as described in the CTP section 7.1.

A hierarchical testing procedure will be applied from the primary endpoint to the set of key secondary endpoints 1 and 2. If, and only if, the primary endpoint is significant at α=5% (two-sided) and shows superiority of empagliflozin versus placebo, then a Hochberg step-up procedure [R20-0113] will be applied to test the family of two key secondary endpoints of

- Total number of HHF or all-cause mortality

- Total number of non-elective CV hospitalisations or all-cause mortality

at α=5% (two-sided).

The Hochberg step-up procedure will be applied as follows: If the largest p-value of the two key secondary endpoints is below or equal to 5%, both null hypotheses of the key secondary endpoints listed above will be rejected. If both show superiority for empagliflozin over placebo, confirmatory testing of the two remaining key secondary endpoints will follow via a hierarchical testing approach at α=5% (two-sided). Otherwise, if the smaller p-value of the two key secondary endpoints listed above is below or equal to 2.5% only the corresponding null hypothesis can be rejected. In this case, the null hypotheses of the two remaining key secondary endpoints will be tested in an exploratory manner only.

7.4.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the primary endpoint(s)

Sensitivity analyses

The following sensitivity analyses will be conducted:

- To investigate the influence of actual treatment intake, a Cox regression analysis (model as specified above) including only on-treatment data, i.e. only data up to treatment stop + 7 days and using the TS
- To investigate the influence of start of prohibited medication, a Cox regression analysis (model as specified above) including only data up to first start of any non-study drug SGLT-2 inhibitor (alone or in combination)
- To investigate the influence of covariate adjustment, a Cox regression analysis with model including only treatment and stratification factors (region and T2D status) as covariate, not adjusting for any other covariates
- To investigate the influence of investigator-based collection of HHF events, a Cox regression analysis (model as specified above) on the composite of time to first investigator-reported broad HHF or all-cause mortality, using the definition of HHF as in Section 10.1 and additionally including hospitalisations with criteria outlined in Section 10.1 but:
    a) irrespective of electivity of the corresponding hospitalisation
    b) irrespective of the presence of signs, symptoms or laboratory findings
    c) irrespective of treatment for HF
    d) irrespective of all of electivity, presence of signs, symptoms and laboratory findings and treatment for HF (combination of a, b and c)
- To investigate the influence of Covid-19, a Cox regression analysis excluding all Covid-19 related deaths (any fatal AE in narrow BIcMQ of Sars-Cov-2 infection) from the primary endpoint
- To investigate the treatment effect if the conflict in Ukraine did not occur (hypothetical estimand): Using a Cox regression analysis (model as specified in primary analysis) applied to all patients from the RS and in which for patients from Ukrainian sites only data up until the last day before the start of conflict in Ukraine (intercurrent event) will be included (date: 23rd February 2022).

A forest plot will be presented with the estimated HR and the two-sided 95% CI for each sensitivity analysis. The Kaplan Meier curves (or cumulative incidence functions with

competing event for Covid-19 related death for the sensitivity analysis excluding Covid-19 related deaths) will also be presented for each sensitivity analysis.

A Kaplan-Meier curve of time to censoring for primary endpoint will be presented in order to assess whether there was differential censoring between treatment groups. For this analysis, a primary endpoint event will be counted as censoring and a censoring for the primary outcome will be counted as an event.

Patients with a hospitalization with primary cause heart failure will be listed.

Subgroup analyses

Subgroup variables will be explored as described in Section 6.4 for the primary endpoint. The HR between the two treatments along with 95% CI and the p-value for test of treatment equality within each category of the subgroup as well as the p-value for the subgroup-by treatment interaction will be estimated by the Cox proportional hazard model including the same covariates as in the primary analysis of the primary endpoint, the subgroup variable, if not part of the covariates of the primary analysis model, and subgroup-by-treatment interaction. If the subgroup variable is another categorization of a covariate, this covariate will be dropped from the subgroup model. A forest plot will be presented with the estimated HR and the two-sided 95% CI for each subgroup category. The Kaplan Meier curves will also be presented for each subgroup category.

If there are less than 14 patients with event in one subgroup (or overall), then this subgroup will not be included in the model (for overall <14 patients with event, the model will not be applied). If this leaves only one subgroup, the subgroup analysis will not be conducted. Subgroups without any event in one or both treatment groups may be combined with other subgroups. For subgroup variables with ordered categories, if there are <14 patients with event in one subgroup, the subgroup may be combined with a neighboring one

For the continuous covariates, baseline eGFR and age, the treatment effect will also be investigated on a continuous scale for the covariate. For this purpose the continuous covariate will be added to the model, if not already included, the categorized variable will be dropped from the model and the interaction term of the continuous covariate and treatment will additionally be included into the model. The hazard ratio depending on the continuous covariate will be plotted and the interaction p-value will be reported.

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

Key secondary endpoints will be analysed using the RS.

7.5.1.1 Primary analysis of the key secondary endpoint(s)

Comparisons between treatment groups regarding the count endpoint variable of total number of HHF or all-cause mortality will be performed using a negative binomial regression model adjusting for all covariates as specified in the analysis model for the primary endpoint, and using log(observation time) as an offset variable. Observation time for the negative binomial

regression model is based on the individual day of trial completion (as defined in Section 6.8). Differences in least squares means will be calculated and corresponding p-value used for hypothesis testing. Regression coefficients together with 95% confidence intervals will be used to quantify the effect of treatment, comparing empagliflozin to placebo as the reference.

For clarification, the negative binomial regression model will use an exponential baseline intensity function.

In the event that this analysis fails to converge, the model will be repeated including only treatment, region, T2D and the offset variable.

The key secondary endpoints of total number of non-elective CV hospitalisations or all-cause mortality, total number of non-elective all-cause hospitalisations or all-cause mortality and total number of hospitalisations for MI or all-cause mortality will be analysed in the same way as the total number of HHF or all-cause mortality.

The negative binomial model assumptions will be checked. In case the model fit is inappropriate in that the deviance value is much larger than the degrees of freedom, a model using the Sandwich-type estimator for the standard error will be performed.

Non-parametric mean cumulative function curves will be used for graphical presentation for all key secondary endpoints.

7.5.1.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the key secondary endpoint(s)

Sensitivity analyses

The following sensitivity analyses will be conducted, always including the same covariates as in the primary analysis unless stated otherwise:

- To investigate the influence of actual treatment intake, a negative binomial model including only on-treatment data, i.e. only data up to treatment stop + 7 days and using the TS
- To investigate the influence of start of prohibited medication, a negative binomial model including only data up to first start of any non-study drug SGLT-2 inhibitor (alone or in combination)
- To investigate the influence of covariate adjustment, a negative binomial model including only treatment and stratification factors (region and T2D status) as covariate, not adjusting for any other covariates
- Only for endpoint ‘total number of HHF or all-cause mortality’: To investigate the influence of investigator-based collection of HHF events, a negative binomial regression model (model as specified above) on the composite total number of investigator-reported broad HHF or all-cause mortality, using the definition of HHF as in Section 10.1 and additionally including hospitalisations with criteria outlined in Section 10.1 but:
    - irrespective of electivity of the corresponding hospitalisation
    - irrespective of the presence of signs, symptoms or laboratory findings
    - irrespective of treatment

  - irrespective of electivity, presence of signs, symptoms and laboratory findings and treatment (combination of a, b and c)
- To investigate the influence of Covid-19, a negative binomial model excluding all Covid-19 related deaths from the key secondary endpoints
- To investigate the treatment effect if the conflict in Ukraine did not occur (hypothetical estimand): Using a negative binomial model applied to all patients from the RS and in which for patients from Ukrainian sites only data up until the last day before the start of conflict in Ukraine (intercurrent event) will be included (date: 23rd February 2022).

A forest plot will be presented with the estimated rate ratio and the two-sided 95% CI for each sensitivity analysis. Non-parametric mean cumulative function curves will also be presented for each sensitivity analysis.

Subgroup analyses

Subgroups will be explored as outlined in Section 6.4 for all key secondary endpoints. For subgroup analyses the term of subgroup (if not already part of the model) and subgroup by treatment interaction will be added to the model. If the subgroup variable is another categorization of a covariate, this covariate will be dropped from the subgroup model.

If there is <5 events, <5 patients or <90 days at risk in any treatment group of a subgroup (or overall), then this subgroup will not be included in the model (for <5events, <5 patients or <90 days at risk overall, the model will not be applied). If this leaves only one subgroup, the subgroup analysis will not be conducted. Subgroups without any events in one or both treatment groups may be combined with other subgroups. For subgroup variables with ordered categories, if there are <5 events, <5 patients or <90 days at risk in any treatment group of a subgroup, the subgroup may be combined with a neighboring one.

7.5.2 (Other) Secondary endpoint(s)

Other secondary endpoints will be analysed using the RS and are exploratory. No correction for multiple hypotheses testing will be made.

Time to CV mortality will be analysed using a Cox proportional hazards model with the same covariate adjustment as for the primary endpoint. Cumulative incidence functions with competing event of non-CV death will be used for graphical presentation. A frequency table of the subcategories of CV death will be given.

7.6 FURTHER ENDPOINT(S)

Further endpoints will be analysed using the RS.

For clarification, to derive the endpoints ’30-day all-cause hospitalisation’ and ‘Days alive and out of hospital’ all hospitalisations will be included (i.e. non-elective and elective hospitalisations), except for elective hospitalisations that had been pre-planned at randomisation. Please also refer to Section 10.2.

Comparisons between treatment groups regarding the binary endpoint variable ‘30-day all cause hospitalisation’ (calculated from date of discharge or randomisation, whatever comes

latest) will be performed using a logistic regression model adjusting for the same covariates as in the primary analysis model. Patients who died within the 30 days will be counted as an event. Only patients with at least 30-day observation time for all-cause hospitalisation and death will be analysed (i.e. patients with observation time <30 days due to withdrawal or lost-to-follow-up will be excluded from this analysis). Patients with discharge date of the index hospital admission being equal to the day of death will be excluded in this analysis. The likelihood-ratio test will be used to test for the difference between treatments. Adjusted odds ratios together with 95% confidence intervals will be used to quantify the effect of treatment, comparing empagliflozin with placebo as the reference.

The continuous endpoint days alive and out of hospital until day 90 after randomisation will be analysed descriptively. Days alive and out of hospital until 6 months, 9 months and 12 months after randomisation will be analysed using the same approach. 6 months is considered 180 days, 9 months is considered 270 days and 12 months is considered 365.25 days.

Days alive and out of hospital (DAOH) will be summarised as a percentage (9) as follows:

The follow-up time for analyses of DAOH until day 90 after randomisation is defined as the minimum of 90 days after randomisation, or time between randomisation and individual day of trial completion 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 until day 90 is defined as DAOH until day 90 divided by the DAOH follow-up time of each patient multiplied by 100. The same approach will be taken for DAOH until 6 months, 9 months and 12 months.

Time-to first event endpoints will be analysed in the same way as the primary endpoint primary model. Kaplan Meier curves will be presented for visualisation. If the time-to-event endpoint does not include all-cause mortality, cumulative incidence curves will be used instead.

For time to first HHF or CV death subgroup analyses as defined in Section 6.4 will be performed.

For the two endpoints time to CV death and time to first HHF or CV death, sensitivity analyses will be done to investigate the influence of the conflict in Ukraine on the results. In these sensitivity analyses, a Cox regression will be applied in which for patients from Ukrainian sites only data up until the last day before the conflict in Ukraine started will be included (date: 23rd February 2022). In addition, categories of death will be shown by subgroup of Ukrainian sites vs non-Ukrainian sites.

7.7 EXTENT OF EXPOSURE

Extent of exposure will be analysed on the TS. Extent of exposure is defined in Section 5.4. Descriptive statistics tables with mean, SD, median and range of the number of days/months/years 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 weeks): <12 weeks, ≥12 to <26 weeks, ≥26 to <52 weeks, ≥52 to <78 weeks, ≥78 to <104 weeks, ≥104 weeks. Categorical ranges may be adapted based on the actual duration of the study.

The analysis on extent of exposure will be repeated by subgroup of patients from Ukrainian sites vs non-Ukrainian sites. Overall observational time (until vital status follow-up) and overall observation time (until individual day of trial completion) as defined in Section 5.4 will be analysed on the RS using the same descriptive statistics.

7.8 SAFETY ANALYSIS

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

The AE analysis will include all adverse events (including outcome events as reported by the investigator).

While tables will generally display results by randomised treatment, listings will reflect whether an AE occurred during on-treatment or post-treatment phase.

7.8.1 Adverse Events

Unless otherwise specified, the analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of subjects 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 further details on summary of AE data, please refer to (4), (10).

For a subset of adverse events exempted from expedited reporting and AESIs auto-coding is applied, because these are collected via tick-boxes in the eCRF. Please see Table 7.8.1:1 for auto-coding applied.

Table 7.8.1: 1 Auto-coding for exempted AEs and AESIs

Exempted event or AESI from CTP	Derived preferred term from auto-coding
Heart Failure	Cardiac failure
Myocardial infarction	Myocardial infarction
Non-cardiac chest pain	Non-cardiac chest pain
Post-procedural heamorrhage	Post procedural heamorrhage
GI bleeding	Gastrointestinal haemorrhage
Haematuria	Haematuria
Respiratory tract infection (not COVID-19)	Respiratory tract infection
Pneunomia (not COVID 19)	Pneumonia
Syncope	Syncope
Contrast induced acute kidney injury	Nephropathy toxic
Ketoacidosis	Ketoacidosis
Hepatic Injury	Liver injury

7.8.1.1 Assignment of AEs to treatment

The analysis of AEs will be based on the concept of treatment-emergent AEs. That means that all AEs occurring between first drug intake till 7 days 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 last drug intake + 7 days will be assigned to ‘post treatment’, except if otherwise specified. For details on the treatment definition, see Section 6.1.

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, unless otherwise defined. In section 15.3, only SAEs, AEs leading to study drug discontinuation of at least 7 days or AESIs will be displayed.

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 these tables, all AEs which were collected will be displayed (including non-serious AEs that neither led to study drug discontinuation nor qualified as AESI).

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

Please refer to Section 7.8.1.3 on certain AESIs with additional definitions for the duration of the ‘on-treatment’ phase.

7.8.1.2 AE summaries

An overall summary of patients with at least one AE expected to be reported in this trial will be presented: This will include any serious adverse events, AEs leading to study drug discontinuation of at least 7 days or AESIs.

The frequency of patients with AEs will be summarised by treatment, primary system organ class and preferred term. Incidence rates as defined in Section 7.8.1.6 will generally be included.

Separate tables based on AEs expected to be reported in this trial will be provided for:

- for patients with serious adverse events,
- for patients with drug-related serious AEs,
- for patients with AEs leading to permanent treatment discontinuation,
- for patients with fatal AEs,
- for patients with drug-related AEs,
- for patients with an AE of special interest (AESI), separately for each AESI category

The frequency of patients with adverse events to be reported in this trial occurring with incidence in preferred term greater than 2% by treatment will also be presented. Overall AE summaries, AEs by SOC and PT, SAEs and AEs leading to discontinuation will additionally be investigated by subgroups as outlined in Table 6.4:1.

In addition, AEs leading to death will be listed and a summary table for all fatal AEs up to individual day of trial completion will be given. Patients with AEs leading to permanent treatment discontinuation will also be listed.

The system organ classes and PTs will be sorted by decreasing frequency (within SOC). Customized sorting orders may also be used based on trial needs, e.g. SOC sorted by frequency.

Sensitivity analyses will be performed to investigate the influence of the conflict in Ukraine on the results. The overall AE summary table, tables showing patients with AEs by SOC/PT, SAEs by SOC/PT and fatal AEs will be repeated in which for patients from Ukrainian sites only data up until the last day before the conflict in Ukraine started will be included (date: 23rd February 2022).

Additionally, the following analyses will be reported in Appendix 16.1.13.1 of the CTR for disclosure on EudraCT and clinicaltrials.gov (see (7) for further details), based on AEs to be reported in this trial:

- Frequency [N (%)] of patients with non-serious AEs occurring with incidence in preferred term greater than 5% by treatment,

- AEs per arm for disclosure on EudraCT by treatment
- Non-serious AEs for disclosure on EudraCT by treatment
- Serious AEs for disclosure on EudraCT by treatment

Refer to Section 10.3 for regional analyses.

7.8.1.3 Adverse events of special interest (AESIs)

Hepatic injury

Adverse events reported as AEs of special interest relating to hepatic injury as specified in the protocol will be summarised.

A table with frequencies of patients with these AEs by treatment, primary SOC and preferred term will be provided. This presentation will be repeated by DM status at baseline (DM vs no DM). Hepatic injury SAEs and hepatic injury AEs leading to permanent treatment discontinuation will be presented separately.

In addition to the '7-day-on-treatment approach', a '30-day-on-treatment approach' will be presented for the overall hepatic injury adverse events.

Patients with hepatic injury 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 separately for the narrow BIcMQ definition of diabetic ketoacidosis. The presentation of investigator-reported cases will be repeated by T2DM status at baseline (T2DM vs no T2DM).

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

Adverse events leading to lower limb amputation

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

For events leading to lower limb amputations in addition to the' 7 -day-on-treatment approach' all AEs that occurred between first study drug intake up to individual day of trial completion will be presented (following censoring rules like non-fatal outcome events).

Adverse event leading to lower limb amputations (up to individual day of trial completion) will additionally be summarised by level of first amputation and reason for first amputation.

Patients with adverse events leading to lower limb amputation will be listed.

Contrast induced acute kidney injury

A frequency table of patients with AEs of contrast induced acute kidney injury as identified by the investigator by treatment, primary SOC and preferred term will be provided. Based on number of patients with events, subgroup analyses by eGFR at baseline may be performed. Separate tables for contrast induced acute kidney injury events, which are serious and those which are leading to discontinuation will be presented.

Patients with contrast induced acute kidney injury will be listed including their baseline eGFR.

Additional analyses on AESIs

Appendix 16.1.13.1 of the CTR will include subgroup analyses for selected AESI concepts. AESI concepts to be analysed include ketoacidosis (narrow BIcMQ 'Ketoacidosis' (30000019)), hepatic injury (investigator-defined) and AEs leading to lower limb amputation (investigator defined). The following subgroups will be considered: sex (male vs female), race (White vs Black or African American vs Asian vs Other incl. mixed race), age (<50 vs 50-<65 vs 65-<75 vs >=75), eGFR (<30 vs 30-<45 vs 45-<60 vs 60-<90 vs >=90) and T2D (yes vs no). For these analyses, only AEs to be reported in this trial will be included (i.e. SAEs, AEs leading to treatment discontinuation of at least 7 days or AESIs). The Treated Set will be used and analyses include AEs occurring between first drug intake till 7 days after last drug intake.

7.8.1.4 Specific AEs

Serious hypoglycaemia or hypoglycaemia leading to study drug discontinuation of at least 7 days

The number of patients with hypoglycaemia according to narrow SMQ (20000226) will be presented, including only SAEs and AEs leading to study drug discontinuation.

Subgroup analyses on events with respect to T2D status at baseline (yes vs no) will be performed. Separate tables for hypoglycemia events, which are serious and those which are leading to permanent treatment discontinuation will be presented.

Patients with such events will be listed.

Serious hypotension or hypotension leading to study drug discontinuation of at least 7 days

Hypotension by treatment, primary system organ class and preferred term will be provided, including only SAEs and AEs leading to study drug discontinuation. Hypotension is defined as preferred terms of the BIcMQ 'Volume depletion and hypotension due to dehydration' (30000090) but excluding preferred terms of dehydration and hypovolaemia.

Separate tables for hypotension events, which are serious and those which are leading to permanent treatment discontinuation will be presented.

Patients with such events will be listed.

Serious volume depletion or volume depletion leading to study drug discontinuation of at least 7 days

Volume depletion will be based on the BIcMQ '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 including only SAEs and AEs leading to study drug discontinuation.

Separate tables for volume depletion events, which are serious and those which are leading to permanent treatment discontinuation will be presented.

Patients with such events will be listed.

Serious acute renal failure or acute renal failure leading to study drug discontinuation of at least 7 days

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), including only SAEs and AEs leading to permanent study drug discontinuation. Subgroup analyses by eGFR at baseline will be performed. Separate tables for acute renal failure events, which are serious and those which are leading to permanent treatment discontinuation will be presented.

Patients with such events will be listed.

Sensitivity analyses will be performed to investigate the influence of the conflict in Ukraine on the results. Frequency tables on patients with AESIs or specific AEs will be repeated in which for patients from Ukrainian sites only data up until the last day before the conflict in Ukraine started will be included (date: 23rd February 2022). In addition, for AEs leading to lower limb amputation the frequency table showing all AEs up until trial completion will be repeated using this censoring approach for Ukrainian patients.

7.8.1.5 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 expected to be reported in this trial (SAEs, AEs leading to study drug discontinuation and AESIs) by SOC and PT.

7.8.1.6 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.

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 first 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 individual day of trial completion, 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 for patients with AE 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 first 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.

7.8.2 Laboratory data

No safety laboratory parameter will be collected after randomization as per global CTP.

For laboratory parameters, including serum creatinine, standardized values will be analysed. Laboratory parameters will be shown in conventional units. Where conventional units differ from SI units, analyses will be repeated on SI units. Normalized values of baseline laboratory data will be presented in Appendix 16.1.13.1. The process of standardization and normalization is described in the BI guidance for the Display and Analysis of Laboratory Data (11).

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. Descriptive statistics will be provided by treatment group for baseline values.

For regional analyses, please see Section 10.3.

7.8.3 Vital signs

Heart rate and blood pressure (diastolic and systolic) at baseline will be summarised descriptively based on the RS as part of the baseline characteristics.

7.8.4 ECG

Not applicable.

7.8.5 Others

Frequency of pregnancies and pregnancy outcomes will be listed by treatment.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be released to unblind the trial database after the last patient has completed their End-of-Study/Follow-up visit and all data has been entered and cleaned as defined in the “Data Ready to be Unblinded and/or Final Trial Closure Notification” (RUN) form.

9. REFERENCES

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2.	c38770729: Protocol Deviation Management Plan
3.	c35802484-01: Integrated Quality Risk Management Plan
4.	*BI-KMED-BDS-HTG-0035*: “Handling of Missing and Incomplete AE Dates”, current version; Veeva Vault.
5.	*BI-KMED-BDS-MAN-0025*: “Handling of incomplete reference ranges”, current version; Veeva Vault.
6.	*BI-KMED-BDS-HTG-0045*: "Standards for Reporting of Clinical Trials and Project Summaries", current version; Veeva Vault.
7.	*BI-KMED-BDS-QRG-0010*: “Preparation of tables for results disclosure", current version; Veeva Vault.
8.	Collett D. Modelling survival data in medical research. Chapman and Hall/CRC 2003 [R07-4680]
9.	R22-1038: 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
10.	*BI-KMED-BDS-HTG-0066*: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; Veeva Vault.
11.	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; Veeva Vault.
12.	*BI-KMED-COPS-BUP-0007:* “Clinical Bridging Study Waiver (BSW) and Subgroup Analysis (SGA) Reports for Asian countries”, current version; Veeva Vault.
13.	*001-MCS-40-113:* "Clinical Trial Report (CTR) Phase I - IV, Interim Reports and Other Associated Regulatory Documents”, current version; Veeva Vault.

10. ADDITIONAL SECTIONS

10.1 DETAILED DESCRIPTION OF PRIMARY ENDPOINT

Only the events satisfying HHF criteria of "Event review charter and guidance for EMPACT-MI", will be included into the analysis:

- eCRF documents that the hospitalisation was non-elective (this includes hospitalisations with unknown attribute of urgency)

- eCRF documents that the date of hospital discharge is at least one day after hospital admission (only non-missing admission and discharge dates will be used, the discharge date must be after the admission date based on the lowest level of information available in those dates)

- The primary cause for hospitalisation in eCRF is documented as "Heart Failure" which is supported by documented in eCRF evidences of signs or symptoms of heart failure (lab and imaging findings are considered as signs) that required treatment:

    - 'Did the patient have new or worsening symptoms, signs or laboratory findings of heart failure?' = Yes AND
    - 'Was therapy for heart failure initiated or intensified?'=Yes
    - For clarification:
        - If the response to 'Did the patient have new or worsening symptoms, signs or laboratory findings of heart failure?' is Yes, but all single symptoms, all single signs and all single lab findings are=No, this criterion is not seen as fulfilled
        - If the response to 'Was therapy for heart failure initiated or intensified' =Yes, but all single therapies = No, this criterion is not seen as fulfilled

The date of the HHF is defined as the date of the corresponding hospital admission.

10.2 DETAILED DESCRIPTION OF (KEY) SECONDARY ENDPOINTS AND FURTHER ENDPOINTS

- According to the 'Event review charter and guidance for EMPACT-MI' and for further clarification: A hospitalisation will be analysed as a hospitalisation if the date of hospital discharge is at least one day after the date of hospital admission (only non-missing admission and discharge dates will be used, the discharge date must be after the admission date based on the lowest level of information available in those dates)

- For clarification: For the key secondary endpoint 'Total number of HHF or all-cause mortality' a hospitalisation will be included in the analysis if it satisfies the criteria for an HHF as defined in Section 10.1

- Non-elective hospitalisations always include hospitalisations with unknown attribute of urgency

- CV hospitalizations include

- hospitalisations with primary reason heart failure
- hospitalisations with primary reason MI
- hospitalisations with primary reason any other CV causes

- Given the acute nature of an MI, a hospitalisation with primary reason MI will always be analysed as a non-elective hospitalisation

10.3 ADDITIONAL ANALYSES FOR REGIONAL SUBMISSIONS

Appendix 16.1.13.2 of the CTR will include the below regional analyses.

Disposition and demographics of the subpopulation for patients from USA and subgroup analyses for patient from the USA vs non-USA will be performed. Efficacy endpoints evaluated will be primary endpoint and key secondary endpoints. Safety will be summarized for patients from the USA.

Additional country or region-specific analyses will be conducted for patients of Asian race from East-Asia (China, Japan and Korea), China, Japan and India and included into the country-specific submission documents as also outlined in (12) and (13). The primary endpoint, all key secondary endpoints, secondary and further endpoints will be presented. Main adverse event overviews, disposition, demographics will be presented.

For East-Asia and Japan, the region-specific analyses include subgroup analyses for the primary, key secondary endpoints and main AE tables for subgroups defined in Section 6.4, except region, ethnicity and race within the local population. Analyses for the primary endpoint will be done using Cox regression and for key secondary endpoints via negative binomial regression models. The rules for not applying these models in subgroup analyses as described above still apply (i.e. for the primary endpoint see Section 7.4.2: if there are less than 14 patients with event; for key secondary endpoints see Section 7.5.1.2: if there are <5 events, <5 patients or <90 days at risk in any treatment group of a subgroup).

10.3.1 Time windows

Patients from Bulgaria, Germany, Hungary and Serbia only:

Patients from these countries have an additional visit 3b and regional visit windows are specified in Table 10.3.1:1 below. These windows will be used in the additional regional analysis of compliance over time and eGFR over time.

Table 10.3.1:1 Time windows for regional analyses

			Time window (days after first study drug intake)	
Visit number	Visit label	Planned days	Start	End
Creatinine/eGFR and treatment compliance				
2a	Baseline [1]	1	NA	1
3	Week 2	15	2	53
3b	Month 3/ Week 13	91	54	136
4	Month 6/ Week 26	181	137	271
5	Month 12/ Week 52	361	272	451
6	Month 18/ Week 78	541	452	631
7	Month 24/ Week 104	721	632	811
8	…			

[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.

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 residual effect period) are considered. For eGFR (lab value), all measurements taken up to 1 day after last permanent treatment stop date are considered on-treatment.

Observed case including data after treatment discontinuation (OC-AD):
All available data are considered, including values obtained on treatment or post-treatment.

On-treatment (for OC-OT analysis) or all post-randomisation (for OC-AD analysis) eGFR and compliance (for compliance, only OC-OT analysis) measurements will be assigned to visits based on time windows around the planned visit dates (see Table 10.3.1:1). These time windows are defined based on the planned number of days after the date of first study drug intake.

For eGFR, only one observation per time window will be selected for a 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.

eGFR over time will be listed as well as clinically significant abnormalities based on eGFR over time.

10.3.2 Treatment Compliance

Including patients from Bulgaria, Germany, Hungary and Serbia only:

Treatment compliance will be summarised as per Section 5.4, but using the regional visit windows as per Table 10.3.1:1.

10.3.3 Concomitant diseases and medication

Including patients from Bulgaria, Germany, Hungary and Serbia only:

Concomitant medication use will be summarised by Anatomical-Therapeutic-Chemical classification level 3 (ATC3) and preferred name. Summaries will be presented for concomitant therapies newly introduced after baseline until study end. Separate summaries of lipid-lowering drugs, anti-thrombotic drugs, anti-coagulant drug (with subcategories) and thrombolytic drugs newly introduced after baseline until study end will be presented, as well as a table showing medication at baseline or newly introduced after baseline (including after visit 4).

Including patients from Japan only:

Concomitant medication use at the End of Study visit will be summarised by Anatomical-Therapeutic-Chemical classification level 3 (ATC3) and preferred name. Separate summaries of lipid-lowering drugs, anti-thrombotic drugs, anti-coagulant drug (with subcategories) and thrombolytic drugs will be presented.

10.3.4 Further endpoints

Including patients from Bulgaria, Germany, Hungary and Serbia only:

eGFR will be calculated based on standardized serum creatinine. Change in eGFR (CKD-EPI) from baseline over time (at 2 weeks, 3 months/13 weeks and 6 months/26 weeks) will be analysed in a mixed model with repeated measures (MMRM). The analysis will include baseline age as linear covariate, the fixed categorical effects of treatment at each visit, geographical region, T2D at baseline, gender, LVEF at baseline (<35% vs ≥35%), persistent or permanent atrial fibrillation at baseline (yes vs no), prior MI at baseline (yes vs no), peripheral artery disease (PAD) at baseline (yes vs no), smoking at baseline (current vs non-current) and the fixed continuous effects of baseline eGFR at each visit. The MMRM analyses will be performed using on-treatment data only (OC-OT) and will be repeated on all data including measurements after treatment stop (OC-AD).

An unstructured covariance structure will be used to model the within-patient errors.

Change in eGFR (CKD-EPI) from baseline to last value on treatment (or last value in study) will be evaluated by an ANCOVA model, including eGFR at baseline and age as linear covariates and treatment group, geographical region, T2D at baseline, gender, LVEF at baseline (<35% vs ≥35%), persistent or permanent atrial fibrillation at baseline (yes vs no), prior MI at baseline (yes vs no), peripheral artery disease (PAD) at baseline (yes vs no) and smoking at baseline (current vs non-current) as covariates.

For MMRM and ANCOVA analysis on eGFR (OC-AD) the randomised set will be used, while for the on-treatment analysis (OC-OT) the treated set will be used. Descriptive statistics will be calculated for the value at the scheduled visit and change from baseline based on OC-AD on the randomised set and OC-OT on the treated set.

10.3.5 Safety Analyses

Including patients from Germany and Serbia only:
The frequency of patients with AEs will be summarised by treatment, primary SOC and PT. Separate tables will be given for all SAEs, AEs leading to discontinuation and separately for each AESIs.

Including all patients, as a specific request from PMDA:

A frequency table of patients with AEs related to 'in-stent thrombosis' by treatment, primary SOC and preferred term will be provided based on the broad BITS 'Device related thrombosis associated with MI'. Patients with device related thrombosis associated with MI will be listed.

10.4 REGIONS AND COUNTRIES

Countries will be assigned to regions following the assignment of the IRT system, which is outlined in Table 10.4:1. Listed countries include currently planned backup countries.

Table 10.4:1 Regions and countries

Region	Country
North America	USA
	Canada
Latin America	Argentina
	Brazil
Europe	Australia
	Bulgaria
	Denmark
	France
	Germany
	Hungary
	Israel
	Netherlands
	Poland
	Romania
	Russia
	Serbia
	Spain
	Ukraine
Asia	China
	India
	Japan
	Korea

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**10 MAY 2022**	[redacted]	None	This is the final TSAP
Revised	**26 MAY 2023**		5.3	Clarification of derivation of baseline ICD/CRT at added.
			6.4	Subgroups Atrial fibrillation at baseline and revascularization for index MI deleted. Endpoint 'Time to first HHF or CV death' added for subgroup analyses.
			6.6.1	Clarification about using imputation for covariates for other statistical models added.
			6.8.3	Date a patient switched to option 5 excluded from censoring as date is included in visit dates already.
			7.1	Clarification about derivation of covariate and subgroup variable 'history of MI' added. Clarification about derivation of covariate 'PAD at baseline' added.
			7.4.2	Clarification added for subgroup analyses if the subgroup is another categorization of a covariate.
			7.5.1.1	Clarification added, including for when the Sandwich type estimator will be used.
			7.5.1.2	Clarification added for subgroup analyses if the subgroup is another categorization of a covariate.
			7.6	Added subgroup analyses for time to first HHF or CV death. Clarification about derivation of 30-day-all-cause hospitalisation and DAOH added.
			7.8.1.3	Analysis of ketoacidosis by T2D added Analyses on AESI concepts by subgroup added.
			7.8.1.4	Update of naming of the BIcMQs related to hypotension.
			7.8.2	Clarification that laboratory values will be standardized, while normalized laboratory values will be shown in appendix 16.1.13.1.
			10.1	Correction of typo: Discharge date must be after admission date instead of the other way round.
			10.2	Correction of typo: Discharge date must be after admission date instead of the other way round. Clarification that details apply in the same way for further endpoints. Clarification that for endpoint 'Total number of HHF or all-cause mortality' a hospitalisation will be included if it fulfils criteria of a an HHF as defined for the primary endpoint component.
			10.3	Clarification of subgroup analyses within regional Japanese / East-Asian population added.
			10.3.1	Listings of eGFR to be included for specified countries.
			10.3.4	Clarification added for eGFR calculation