	chronic HF) and after initial stabilisation. Secondary objectives are to further assess whether it is safe to start empagliflozin in patients admitted to hospital in this setting.
Trial endpoints	Primary Endpoint: • Clinical benefit, a composite of death, number of heart failure events (HFEs) (including hospitalisations for heart failure (HHFs), urgent heart failure visits and unplanned outpatient visits), time to first HFE and change from baseline in Kansas City Cardiomyopathy Questionnaire - Total Symptom Score (KCCQ-TSS) after 90 days of treatment assessed by the win ratio. Secondary Endpoints: • Improvement in KCCQ-TSS of ≥ 10 points after 90 days of treatment • Change from baseline in KCCQ-TSS after 90 days of treatment • Change from baseline in log-transformed N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) level over 30 days of treatment (area under the curve (AUC)). • Days alive and out of hospital from study drug initiation until 30 days after initial hospital discharge • Days alive and out of hospital from study drug initiation until 90 days after randomisation • Time to first occurrence of cardiovascular (CV) death or HFE until end of trial visit • Occurrence of HHF until 30 days after initial hospital discharge • Occurrence of chronic dialysis or renal transplant or sustained reduction of ≥40% estimated glomerular filtration rate (eGFR) Chronic Kidney Disease Epidemiology Collaboration Equation ((CKD-EPI)cr), or o sustained eGFR (CKD-EPI)cr <15 mL/min/1.73 m^2 for patients with baseline eGFR ≥30 mL/min/1.73 m^2 o sustained eGFR (CKD-EPI)cr <10 mL/min/1.73 m^2 for patients with baseline eGFR <30 mL/min/1.73 m^2 • Diuretic effect as assessed by weight loss per mean daily loop diuretic dose after 15 days of treatment • Diuretic effect as assessed by weight loss per mean daily loop diuretic dose after 30 days of treatment
Trial design	Randomised, double-blind, parallel-group, placebo controlled, multinational and multicentre study
Total number of patients randomised	Approximately 500
Number of patients on each treatment	Approximately 250
Diagnosis	Patients admitted to hospital for treatment of acute HF (de novo or decompensated chronic HF). Patients should be randomised after at least 24 hours and no later than 5 days after hospital admission. Randomisation should occur as soon as the patient is stabilised (see inclusion criterion 7).

[3] Patients who discontinue trial treatment prematurely should undergo the Early Discontinuation Visit as soon as possible and the Follow-up (FUP) Visit 7 days thereafter. Patients should be followed up until Visit 5 (day 90) according to their planned visit schedule.

[4] Written informed consent must be obtained before any other assessment is performed.

[5] Blood pressure and heart rate will be measured with the patient seated and rested for at least 5 minutes. Vital signs at Visit 2a need to be checked before first trial medication intake.

[6] Samples for central lab (including NT-proBNP) at Visit 2a need to be taken before first trial medication intake.

[7] Women of childbearing potential only.

[8] For patient's eligibility, local lab should be used, including a locally performed BNP or NTproBNP result taken during the current hospitalisation or in the 72 hours prior hospital admission. At the time the local BNP or NT-proBNP sample is collected, the baseline rhythm (e.g. sinus rhythm, AF) of the patient must be clarified using ECG or other measures (for example continuous heart monitoring) and documented.

[9] In addition to the scheduled ECGs, ECGs should be done and documented at any time of clinical event (e.g. acute event of arrhythmia, tachy- or bradycardia, angina, or MI).

[10] After the individual patient's end of the trial the investigator should only report any occurrence of cancer, related SAEs and related AESIs of which the investigator may become aware of and only via the SAE form, please see Section 5.2.7.2.1.

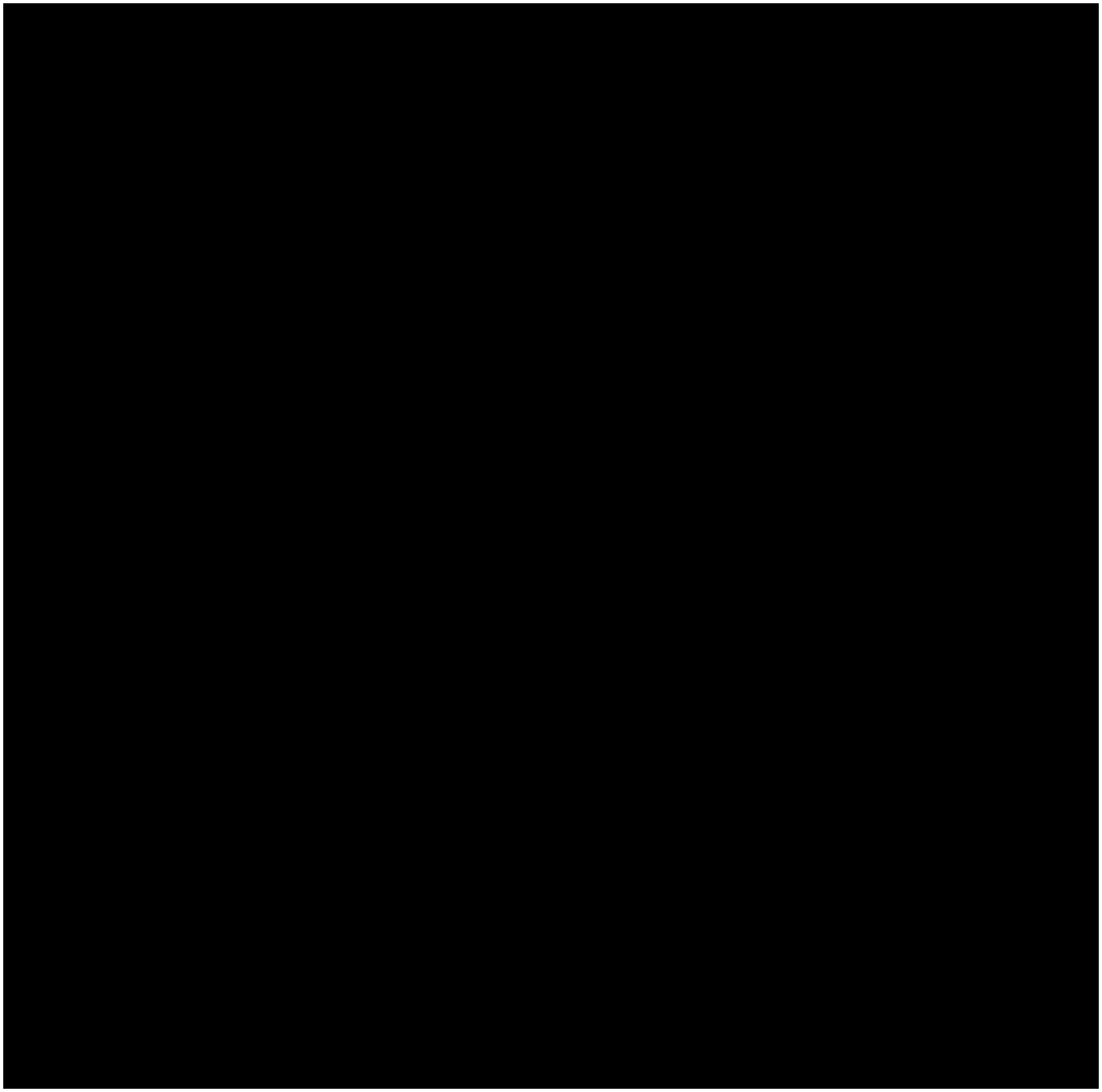
[11] Patients who prematurely discontinue medication are followed up according to protocol, and their visit schedule will end at their scheduled Visit 5.

[12] Urinary pregnancy test and ECG do not need to be repeated if patient prematurely discontinued trial medication and these assessments were done at the Early Discontinuation Visit.

For potential modifications of trial conduct in case of restrictions due to COVID-19, please refer to Sections 4.1.4, 6.1, 8.1 and 10.5.

DMC	Data Monitoring Committee
DBP	Diastolic Blood Pressure
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EF	Ejection Fraction
EOS	End of Study
eGFR	Estimated Glomerular Filtration Rate
EMPA-REG	Empagliflozin – Reducing Excess Glucose
EoT	End of Treatment
EU	European Union
EudraCT	European Clinical Trials Database
ExCom	Executive Committee
FDA	Food and Drug Administration
FUP	Follow-up
γ-GT	Gamma-Glutamyl Transferase
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HA	Health Authority
Hb	Haemoglobin
HbA1c	Glycosylated haemoglobin
HCRU	Health Care Resource Utilisation
HDL	High Density Lipoprotein
HF	Heart Failure
HFE	Heart Failure Event
HFmrEF	Heart Failure with mid-range Ejection Fraction
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HHF	Hospitalisation for Heart Failure
HR	Hazard Ratio
i.v.	intravenous

- Occurrence of chronic dialysis or renal transplant or sustained[1] 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
- Diuretic effect as assessed by weight loss per mean daily loop diuretic dose after 15 days of treatment.
- Diuretic effect as assessed by weight loss per mean daily loop diuretic dose after 30 days of treatment.



The primary endpoint will be assessed at Visit 5.

Patients who prematurely stop medication should have an End of Treatment Visit but be followed up until their planned Visit 5 (Day 90) according to the visit schedule.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

Hospitalisation for HF identifies patients at increased risk of death and re-hospitalisation following discharge. In the EMPEROR trials (see Section 1.1) patients hospitalised for HF were excluded.
Since the long-term mortality and morbidity of empagliflozin in patient with chronic HF will be assessed in EMPEROR trials, the main objective of this study is to assess whether in-hospital administration of empagliflozin leads to an improvement in clinical benefit (a composite of death, number of HFEs, time to first HFE and change from baseline in KCCQ-TSS) in patients hospitalised for acute heart failure (de novo or decompensated chronic) and after initial stabilisation assessed by the win ratio. Secondary objectives are to further assess whether it is safe to start empagliflozin in patients already admitted to hospital in this setting.

Choice of endpoint:

Patient-reported outcomes (PRO) can provide information on a range of patients' health status. Improving patient's symptoms, physical limitations and quality of life is one of the key goals of managing HF, and is endorsed by practice guidelines and the regulators. Health authorities, including US FDA, and major payers such as the Center for Medicare and Medicaid are increasingly interested in PROs [R19-3040, R19-3126]. To better evaluate the effect of empagliflozin on improving health status (symptoms, and physical limitations), the Kansas City Cardiomyopathy Questionnaire (KCCQ) will be used in this trial. The KCCQ is one of the most validated, clinically responsive and widely used HF PRO instruments [R17-2687].

In addition, in DAPA-HF, an outcome trial in over 4700 patients with HFrEF, dapagliflozin showed significant improvement in change in Kansas City Cardiomyopathy Questionnaire - Total Symptom Score (KCCQ-TSS) from baseline at 8 months. A similar improvement in KCCQ overall summary score and KCCQ-TSS was also detected in DEFINE-HF, a study of approximately 260 patients evaluating the effect of dapagliflozin compared to placebo on biomarkers, symptoms, and functional status in patients with HFrEF (both with and without DM) [R19-3125, R19-3124]. KCCQ is a self-administered questionnaire designed and validated to evaluate physical limitations, symptoms (frequency, severity, and changes over time), social limitations, self-efficacy, and quality of life in patients with HF (refer to Appendix 10.1).

In this trial, the KCCQ-TSS will be assessed by the win ratio as part of a composite clinical benefit endpoint including mortality and HF events (see Section 7.2.2).

General safety including parameters relevant to the empagliflozin MOA i.e. hypotension and renal function will be the focus of the safety assessment in this trial. Although it is likely that clinical events like death and hospitalisations will occur in this trial, this study is limited in its

statistical power to conclusively assess the effect on morbidity and mortality outcomes with the planned sample size.

Control group:

Due to its mode of action, empagliflozin has the potential to be efficacious in treating patients' congestion with HF. However, the effect of empagliflozin in patients with acute heart failure (de novo or decompensated chronic) after stabilisation in hospital has not yet been systematically assessed in a randomised clinical trial. Currently, two large clinical outcome trials are ongoing in patients with HFpEF (EMPEROR-preserved) or HFrEF (EMPEROR-reduced) to evaluate empagliflozin for the reduction of cardiovascular death and heart failure hospitalisation in patients outside the hospital setting.

The placebo-controlled design is considered ethically acceptable on the basis of appropriate criteria for patient selection and discontinuation, the ability to change background therapy to maintain, or obtain sufficient levels of haemodynamic and glycaemic control (in patients with T2DM) as defined in relevant local and regional guidelines for optimised standard of care.

Patients should be receiving appropriate care as defined by their physician or practitioner for all cardiovascular conditions according to the prevailing guidelines. In HFrEF patients, this includes, but is not limited to (if indicated and not contraindicated) acetylsalicylic acid, statins, a diuretic, an inhibitor of the renin-angiotensin system with or without neprilysin inhibitor, a beta-blocker and a mineralocorticoid receptor antagonist, each to be given at clinically appropriate doses, and the use of implantable devices like pacemakers or implantable cardioverter defibrillators (ICDs, or cardiac resynchronisation therapies (CRTs)). This therapy should be selected in the context of local or regional guidelines for primary or secondary CV disease prevention.

Duration:

Due to the potential early effect of empagliflozin (see Section 1.1 for mode of action and EMPA-REG-OUTCOME results) empagliflozin is expected to exert its effect within a few days to weeks of administration.

The primary endpoint is clinical benefit, a composite of death, number of HFEs, time to first HFE and change from baseline in KCCQ-TSS at Day 90 assessed by the win ratio.

Thus, a 90 day time point is considered suitable for the assessment of the primary endpoint and evaluation of empagliflozin safety.

3.3 SELECTION OF TRIAL POPULATION

A total number of approximately 500 patients are planned to be randomised in about 13 countries and approximately 125 sites.

consider the requirements for Adverse Event collection reporting (please see Sections 5.2.7.2.1 and 5.2.7.2).

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment, without the need to justify the decision.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- The patient needs to take concomitant medication that interferes with the investigational medicinal product (see Section 4.2.2.1) for restricted medication
- The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events, other diseases, or pregnancy).In case of a temporary reason for treatment discontinuation, trial treatment should be restarted if medically justified, please see Section 4.1.4.

Given the patient's agreement, the patient will undergo the procedures for the Early Discontinuation Visit as soon as possible after treatment discontinuation and the Follow-up Visit as outlined in the Flow Chart and Section 6.2.3.
In addition, if the patient discontinues early, every effort should be made for the patient to attend the regularly scheduled study visits and have all study procedures performed except those pertaining to drug intake. However if this is not possible, then the remaining visits should be conducted by phone. In the rare case that even this is not possible, at least vital status and information about HFEs should be retrieved and documented at the day of the scheduled Visit 5 (Day 90).

If a patient becomes pregnant during the trial, the trial medication will be stopped, the patient will be followed up during the trial and until birth or termination of the pregnancy (see further details in Section 5.2.7.2).

If new efficacy/safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all patients or take any other appropriate action to guarantee the safety of the trial patients.

3.3.4.2 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision.

This will however mean that no further information may be collected for the purpose of the trial and negative implications for the scientific value may be the consequence. Furthermore it may mean that further patient follow up on safety cannot occur.

If a patient wants to withdraw consent, the investigator must be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 3.3.4.1 above.

Table 5.1.3: 1 Clinical congestion score

Signs/Symptoms	**0**	**1**	**2**	**3**
Dyspnoea	None	Seldom	Frequent	Continuous
Orthopnoea	None	Seldom	Frequent	Continuous
Fatigue	None	Seldom	Frequent	Continuous
JVP (cm H2O) (Jugular Venous Pressure[5])	≤6	6< JVP < 10	10≤ JVP <15	≥15
Rales	None	Bases	From base to <50%	From base to >50%
Oedema	Absent/ trace	Slight	Moderate	Marked

The Clinical Congestion Score will be completed according to the Flow Chart. Please refer to Section 6.2.2 for preferred order of completion of assessments.

5.1.4 New York Heart Association classification

The NYHA functional classification will be used to classify the severity of the patients' heart failure. The investigator should place the patients in one of the four categories based on how limited their physical activity are.

Table 5.1.4: 1 New York Heart Association classification

Class	**Patient symptoms**
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath)
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea (shortness of breath)
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases

The classification of patient's physical activity according to NYHA will be performed at Visits 2a, 3, 4, 5 and at early discontinuation.

[5] Jugular venous pressure should be estimated by adding 5 cm H_2O to the vertical distance of the peak jugular venous pulsation from the sternal angle

5.2.7 Assessment of adverse events

5.2.7.1 Definitions of AEs

5.2.7.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following should also be recorded as an AE in the CRF and BI SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions.
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

5.2.7.1.2 Serious adverse event

A serious adverse event (SAE) is defined as any AE, which fulfils at least one of the following criteria:

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

5.2.7.1.3 AEs considered “Always Serious”

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be “serious” even though they may not have met the criteria of an SAE as defined above.

The latest list of "Always Serious AEs" can be found in the eDC system. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.7.2.

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in 5.2.7.2, subsections "AE Collection" and "AE reporting to sponsor and timelines".

5.2.7.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see Section 5.2.7.2.2.

The following are considered as AESIs:

Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- an elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or
- Aminotransferase (ALT, and/or AST) elevations ≥5 fold ULN.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the eDC system.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Decreased renal function

Decreased renal function is defined by a creatinine value showing a ≥ 2 fold increase from baseline and is above the Upper Limit of Normal (ULN).

For the AESI "decreased renal function" patients need to be followed up appropriately based on local clinical guidance.

Ketoacidosis

If metabolic acidosis, ketoacidosis and DKA is suspected further investigations should be done according to the medical judgment and the clinical course until a diagnosis is made and/or the patient is recovered.

Due to its mechanism of action, empagliflozin may potentially modify the clinical presentation of ketoacidosis which may occur at lower plasma glucose levels in patients with DM and potentially also in non-diabetic patient population. The diagnosis of ketoacidosis in these patients can be based on arterial pH ≤7.30, serum bicarbonate levels <15 mmol/L and measurement of serum beta-hydroxybutrate levels. Other diagnostic criteria which can support the diagnosis of ketoacidosis are urine ketones and anion gap >10 mmol/L.

Investigators should note that not all criteria mentioned above need to apply for the diagnosis of ketoacidosis, and clinical judgment should also be taken into consideration.

5.2.7.1.5 Intensity (severity) of AEs

The intensity (severity) of the AE should be judged based on the following:

Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated.
Moderate: Sufficient discomfort to cause interference with usual activity.
Severe: Incapacitating or causing inability to work or to perform usual activities.

5.2.7.1.6 Causal relationship of AEs

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between the adverse event and the given study treatment, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced).

unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable" , or no further information can be obtained.

5.2.7.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Studies (Part B).
The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Studies and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

This study will not analyse pharmacokinetic or pharmacodynamics parameters.

5.4 ASSESSMENT OF BIOMARKER(S)

Established biomarkers of efficacy and safety are described and discussed in Section 5.1 and 5.2.

This study will not analyse exploratory biomarkers.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

5.6.1 Health Care Resource Utilisation (HCRU)

HCRU will be captured via interview with the patient and verified against medical records where available and entered in the eCRF at the visits specified in the Flowchart. Information on utilization of following resources will be collected:

- All-cause hospital admissions (first and recurrent).
- Hospital admission due to worsening of heart failure (first and recurrent).
- All-cause emergency room visits (first and recurrent).
- Emergency room visits due to worsening of heart failure (requiring i.v. diuretic therapy) (first and recurrent).
- Any unscheduled outpatient visits (first and recurrent).
- Unscheduled outpatient visits related to heart failure (first and recurrent).
- Length of hospital stay(s) (initial and recurrent).
- Length of ICU stay during hospital stay (initial and recurrent).
- Intensification of diuretic therapy (adding a new diuretic, increase of dose).

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor safety aspects, and to determine empagliflozin efficacy and safety in an appropriate way.

For more details on NT-proBNP, please refer to Section 3.2.

The scheduled measurements are appropriate to see drug induced changes in vital signs, standard laboratory values, the biomarker NT-proBNP, and in ECG. The primary and secondary endpoints are accepted for evaluation of efficacy, safety and tolerability of an oral HF drug and they are widely used in respective pivotal phase III HF studies.

Health related quality of life questionnaires (specifically the KCCQ) are a necessary part for this phase III trial in order to collect data on patient related outcomes (as part of the primary endpoint).

Therefore, the appropriateness of all measurements applied in this trial is given.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the Flow Chart. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule. The trial medication packs contain sufficient medication to allow for the allowed time windows.

All trial visits should take place at approximately the same time of day and preferably before noon.

During the COVID-19 pandemic, there might be situations when patients might not be able to come to the site for the scheduled visit. This might be e.g. due to restrictions set by authorities or by the investigator site/institution, because the patient is quarantined, or because of any patient specific situation that the investitator judges as being not safe for the patient to come to the site.

For details on potential modifications of the trial conduct related to the COVID-19 pandemic, please refer to Section 10.5.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Please refer to the Flow Chart and Section 5 for details of the procedures performed at each visit.

6.2.1 Screening and run-in period(s)

Due to the short time window when patients can be randomised (between 24 hours after hospitalisation and no later than 5 days), potential study patients should be identified as soon as possible and their improvement followed up accordingly (pre-screening). Potential study patients should be approached to assess their interest in volunteering as a participant in this trial as soon as possible.

Screening Period

The investigations for the main diagnosis for inclusion are to be completed and documented per standard of care as a prerequisite to consideration for study participation. Patients will be included in the study based on local BNP or NT-proBNP and other available laboratory measurements.

Following informed consent, the patient will undergo Visit 1/screening assessments as indicated in the Flow Chart. The assessments must all fall within the acceptable screening visit window but do not need to be performed on the same day. The patient should be registered in IRT as a screened patient.

Re-screening within the same hospitalisation and current episode of acute decompensation is not allowed. Nevertheless, if a patient who failed screening before has another episode of

acute decompensation that leads to a new hospitalisation, patient can be screened again and considered for the study.

Medical History:

Medical History will be documented using pre-specified categories as given in the eDC system. For detailed requirements please see Section 8.3.1.

Baseline Conditions

Ongoing conditions/diagnosis from the Medical History questionnaire will be documented as Baseline Conditions.

If the patient meets the entry criteria, Visit 2a should occur as soon as possible once it has been confirmed that the patient is eligible to continue. If the patient does not meet the entry criteria, (i.e. fail to meet one or more of the inclusion criteria, and/or meet one or more of the exclusion criteria) following Visit 1 procedures, they should be registered as a screen failure in IRT.

6.2.2 Treatment period(s)

After a final check of all in- and exclusion criteria, patients eligible will be randomised at Visit 2a using IRT. Randomisation can occur at the same day as the screening visit. All Visit 2a assessments must be performed before the first dose is taken in hospital. Assessments from Visit 2a will be used as baseline values.

Patients will undergo visit assessments as indicated in the Flow Chart.

Patients will have further visits with a reduced number of assessments two and four days thereafter if they are still hospitalised (Visits 2b and 2c at Day 3 and 5).

The patients will return to the clinic for regularly scheduled Visits 3, 4 and 5 (EoT) on days 15, 30 and 90 respectively after randomisation as specified in the Flow Chart. These on-site visits will assess the occurrence of safety and efficacy endpoints, trial medication compliance (Visit 3, 4 and 5), concomitant therapy or intervention. The assessments at these visits can be performed post-dose. Patients should be instructed to take their medication on the morning of their visits at home like all days. Visits should be routinely scheduled at approximately the same time of day for each visit.

All other medications the patient is receiving should be taken as instructed by the physician. At any time during the treatment period, the HF background therapy is allowed to be adjusted and optimised according to local and international guidelines.
If any additional therapy is considered necessary for the patient's welfare during the treatment period it may be given at the discretion of the Investigator (see also restrictions in Section 4.2.2).

Patient reported outcome measures (first KCCQ, then PGI – Severity – Heart Failure Symptoms questionnaire) should be done first and laboratory samples should be taken at the end of each visit. All other measures should be performed after PGI-S and before laboratory sampling.

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 win ratio is then calculated as the total number of wins in the empagliflozin group (N_W) across all strata divided by the total number of losses (N_L). So the win ratio is = N_W / N_L.

The variance is calculated by the asymptotic normal U statistic approach [R19-3448]

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 7.3.

7.2.3 Secondary endpoint analyses

Secondary endpoints will not be tested in a hierarchical sequence, and no adjustment for multiple comparisons is planned.

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.

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 [R19-3044]. The linear trapezoidal rule will be used to calculate the AUC after the log-transformation has been applied to each value. Analysis of covariance (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 7.3.

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). 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 [R07-4680] 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.

Other secondary endpoints will be summarised descriptively (including days alive and out of hospital).

Analysis of recurrent events will be described in the TSAP.

[redacted]

7.2.5 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 7 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the residual effect period. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) at the database lock.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

Two Coordinating Investigators are responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

An Executive Committee (ExCom) consisting of independent experts (including the Coordinating Investigators of this trial) and sponsor representatives will be established to support the sponsor in designing the trials and successful execution. The composition of the ExCom will be documented in the Trial Master File (TMF). The tasks and responsibilities will be agreed in contracts between the ExCom members and the Sponsor and also summarised in an ExCom charter. The Executive Committee will assess the baseline characteristics of the patients in an ongoing blinded manner and if needed, may take appropriate steps, which may include restrictions to enrolment for certain subpopulations.

A National Coordinator Committee (NCC) will be established and will consist of the leading expert(s) in each of the participating countries. The NCs will support the Sponsor in the successful execution of the trial. The NCC will have an advisory function in the trial. The tasks and responsibilities will be agreed in contracts between the NCC member and the Sponsor.

A Data Monitoring Committee (DMC) will be established. Members of the DMC are independent of BI, they are physicians experienced in the treatment of the disease under investigation and a statistician. The DMC will evaluate safety data. While DMC members may be unblinded, measures are in place to ensure the blinding for everyone else involved in the trial. Regular DMC meetings will be held at specified intervals. The DMC will recommend continuation, modification or termination of the trial as detailed in the DMC charter. DMC recommendations as well as the final BI decision will be reported to the appropriate Regulatory Authorities (RAs)/ Health Authority (Has), IRBs/ECs, and to investigators as requested by local law. The tasks and responsibilities of the DMC are specified in a charter.

An independent external committee (Clinical Event Committee (CEC)) will be established to adjudicate certain hepatic events and ketoacidosis.

<u>Hepatic External adjudication for hepatic events</u>

Certain hepatic events will be adjudicated by external independent experts for severity and causal relationship with the trial medication; both in a blinded fashion. Events to be reviewed will be defined in a charter.

Events may either be defined by abnormal laboratory values and/or relevant adverse events or both.

For qualifying events, relevant source documents generated from any medical evaluations of these events will be requested including for example laboratory values, histological analysis, reports from ultrasound, computed tomography (CT), magnetic resonance imaging (MRI),

P17-10453 Wanner C, Lachin JM, Inzucchi SE, Fitchett D, Mattheus M, George J, et.al. Empagliflozin and clinical outcomes in patients with type 2 diabetes mellitus, established cardiovascular disease and chronic kidney disease. Circulation. 2018. 137(2): 119-129.

P18-10152 Inzucchi SE, Kosiborod M, Fitchett D, Wanner C, Hehnke U, Kaspers S, et.al. Improvement in cardiovascular outcomes with empagliflozin is independent of glycemic control. Circulation. 2018. 138(17): 1904-1907.

P19-01985 Savarese G, Sattar N, Januzzi J, Verma S, Lund LH, Fitchett D, et.al. Empagliflozin is associated with a lower risk of post-acute heart failure rehospitalization and mortality. Insights from the EMPA-REG OUTCOME trial. Circulation. 2019. 139(11): 1458-1460.

P19-02151 Verma S, McMurray J.J.V. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia. 2018. 61: 2108-2117.

R07-4680 Collett.D, Modelling Survival Data in Medical Research. A CRC Press Company. 2003.

R12-1392 Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF, Feldman HI, et.al. Disease Epidemiology Collaboration (CKD-EPI) A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009. 150(9):604-612.

R16-1528 Owan TE, Redfield MM. Epidemiology of diastolic heart failure. Progress in Cardiovascular Diseases. 2005. 47(5): 320-332.

R16-2217 Cheng RK, Cox M, Neely ML, Heidenreich PA, Bhatt DL, Eapen ZJ, et.al. Outcomes in patients with heart failure with preserved, borderline, and reduced ejection fraction in the Medicare population. Am Heart J. 2014. 168(5): 721 - 730.e3.

R16-4813 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.

R17-1562 Bishu K, Redfield MM. Acute heart failure with preserved ejection fraction: unique patient characteristics and targets for therapy. Curr Heart Fail Rep. 2013. 10(3): 190-197.

R17-2687 Spertus J, Peterson E, Conard MW, Heidenreich PA, Krumholz HM, Jones P, et.al. Cardiovascular Outcomes Research Consortium Monitoring clinical changes in patients with heart failure: a comparison of methods. American Heart Journal. 2005. 150(4): 707-715.

R17-3082 Sauser K, Spertus JA, Pierchala L, Davis E, Pang PS. Quality of life assessment for acute heart failure patients from emergency department presentation through 30 days after discharge: a pilot study with the Kansas City Cardiomyopathy Questionnaire. J Card Fail. 2014. 20(1): 18-22.

R17-3097 Comin-Colet J, Lainscak M, Dickstein K, Filippatos GS, Johnson P, Luescher TF, et.al. The effect of intravenous ferric carboxymaltose on health-related quality of life in patients with chronic heart failure and iron deficiency: a subanalysis of the FAIR-HF study. Eur Heart J. 2013. 34: 30-38.

R19-2911 Gattis WA, O'Connor CM, Gallup DS, Hasselblad V, Gheorghiade M., et.al. Predischarge initiation of carvedilol in patients hospitalised for decompensated heart failure: results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial. J Am Coll Cardiol. 2004. 43(9): 1534–41.

R19-2913 Logeart D, Thabut G, Jourdain P, Chavelas C, et al. Predischarge B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure. J Am Coll Cardiol. 2004. 43(4): 635-641.

R19-2914 Zile MR, Bennett TB, et.al. Transition from Chronic Compensated to Acute Decompensated Heart Failure: Pathophysiological insight from continuous monitoring of intracardiac Pressures. Circulation. 2008. 118. 1433-1441.

R19-2915 Gheorghiade M, Vaduganathan M, et al. Rehospitalisation for heart failure: problems and perspectives. J Am Coll Cardiol. 2013. 61(4): 391-403.

R19-2916 Torre-Amione G, Milo-Cotter O, Kaluski E, Perchenet L, Kobrin I, Frey A, et.al. Early worsening heart failure in patients admitted for acute heart failure: time course, hemodynamic predictors, and outcome. J Card Fail. 2009. 15(8): 639–644.

R19-2917 Heidenreich PA, et al. Forecasting the Impact of Heart Failure in the United States: A Policy Statement From the American Heart Association. Circ Heart Fail. 2013. 6: 606-619.

R19-2918 Blecker S, Paul M, Taksler G, Ogedegbe G, Katz S. Heart failure associated hospitalisations in the United States. J Am Coll Cardiol. 2013. 61(12): 1259-1267.

R19-2919 Butler J, Arbogast PG, Daugherty J, Jain MK, Ray WA, Griffin MR. Outpatient utilization of angiotensin-converting enzyme inhibitors among heart failure patients after hospital discharge. J Am Coll Cardiol. 2004. 43(11): 2036-2043.

R19-2920 Fonarow GC, Gawlinski A, Moughrabi S, Tillisch JH. Improved treatment of coronary heart disease by implementation of a Cardiac Hospitalisation Atherosclerosis Management Program (CHAMP). Am J Cardiol. 2001. 87(7): 819-822.

R19-2921 Grodin JL, Liebo MJ, et.al. Prognostic Implications of Changes in Amino-Terminal Pro-B-Type Natriuretic Peptide in Acute Decompensated Heart Failure: Insights from ASCEND-HF. Journal of Cardiac Failure. 2019. 00(00): 1-9.

R19-2924 Aditi A, Bhagat, et.al. Initiation, Continuation, Switching, and Withdrawal of Heart Failure Medical Therapies During Hospitalisation. JACC:HF. 2019. 7(1): 1-12.

R19-2932 Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, et.al. PIONEER-HF Investigators. Angiotensin-neprilysin inhibition in acute decompensated heart failure. N Engl J Med. 2019. 380(6): 539-548.

R19-3040 Heidenreich PA. Patient-Reported Outcomes: The Future of Heart Failure Care. JACC HF. 2019. 7: 1-3.

R19-3044 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.

R19-3124 Nassif ME, Windsor S, Tang F, Khariton Y, Husain M, Inzucchi S, et.al. Dapagliflozin Effects on Biomarkers, Symptoms, and Functional Status in Patients With Heart Failure With Reduced Ejection Fraction: The DEFINE-HF Trial. Circulation. 2019. 40(140): 1-14.

R19-3125 McMurray JJV, Solomon SD, Inzucchi L, et.al. Dapagliflozin with Patients in Heart Failure and Reduced Ejection Fraction. New England Journal of Medicine. 2019. 1-13.

R19-3126 U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Treatment for Heart Failure: Endpoints for Drug Development Guidance for Industry. June 2019.

R19-3245 Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, et.al. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. Journal of the American College of Cardiology. 2018. 71(9): 1021-34.

R19-3448 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.

9.2 UNPUBLISHED REFERENCES

c02695839-01 [redacted]. Clinical Trial Report: Empagliflozin (BI 10773). The EMPA-REG OUTCOME® Trial 1245.25.

c01678844 Investigators Brochure. Empagliflozin. Current Version.

c11963611-01 [redacted] Clinical Trial Report: Jardiance® (empagliflozin). An open-label, mechanistic study to examine the effect of oral empagliflozin (25 mg q.d.) on kinetics of renal glucose reabsorption in patients with type 2 diabetes mellitus and healthy controls. Trial 1245.66.

c26554599-01 [redacted] Clinical Trial Report: A phase III randomised, double-blind trial to evaluate the effect of 12 weeks treatment of once daily EMPagliflozin 10 mg compared with placebo on ExeRcise ability and heart failure symptoms, In patients with chronic HeArt FaiLure with preserved Ejection Fraction (HFpEF) (EMPERIAL – preserved). Trial 1245-0167

c26554767-01 [redacted] Clinical Trial Report: A phase III randomised, double-blind trial to evaluate the effect of 12 weeks treatment of once daily EMPagliflozin 10 mg compared with placebo on ExeRcise ability and heart failure symptoms, In patients with chronic HeArt FaiLure with reduced Ejection Fraction (HFrEF) (EMPERIAL – reduced). Trial 1245-0168

10. APPENDICES

10.1 KCCQ (KANSAS CITY CARDIOMYOPATHY QUESTIONNAIRE)

THE KANSAS CITY CARDIOMYOPATHY QUESTIONNAIRE:

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Place an **X** in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Dressing yourself	❑	❑	❑	❑	❑	❑
Showering/Bathing	❑	❑	❑	❑	❑	❑
Walking 1 block on level ground	❑	❑	❑	❑	❑	❑
Doing yardwork, housework or carrying groceries	❑	❑	❑	❑	❑	❑
Climbing a flight of stairs without stopping	❑	❑	❑	❑	❑	❑
Hurrying or jogging (as if to catch a bus)	❑	❑	❑	❑	❑	❑

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (shortness of breath, fatigue or ankle swelling) changed?
My symptoms of **heart failure** have become . . .

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
❑	❑	❑	❑	❑	❑

3. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1–2 times a week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you?
It has been . . .

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no swelling**
❑	❑	❑	❑	❑	❑

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you want?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1–2 times per week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑	❑	❑

6. Over the past 2 weeks, how much has your **fatigue** bothered you?
It has been . . .

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no fatigue**
❑	❑	❑	❑	❑	❑

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1–2 times per week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑	❑	❑

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you?
It has been . . .

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no shortness of breath**
❑	❑	❑	❑	❑	❑

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week, but not every day	1–2 times a week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Somewhat** sure	**Mostly** sure	**Completely** sure
❑	❑	❑	❑	❑

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse? (for example, weighing yourself, eating a low salt diet, etc.)

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
❑	❑	❑	❑	❑

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
❑	❑	❑	❑	❑

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
❑	❑	❑	❑	❑

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

I felt that way **all of the time**	I felt that way **most of the time**	I **occasionally** felt that way	I **rarely** felt that way	I **never** felt that way
❑	❑	❑	❑	❑

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

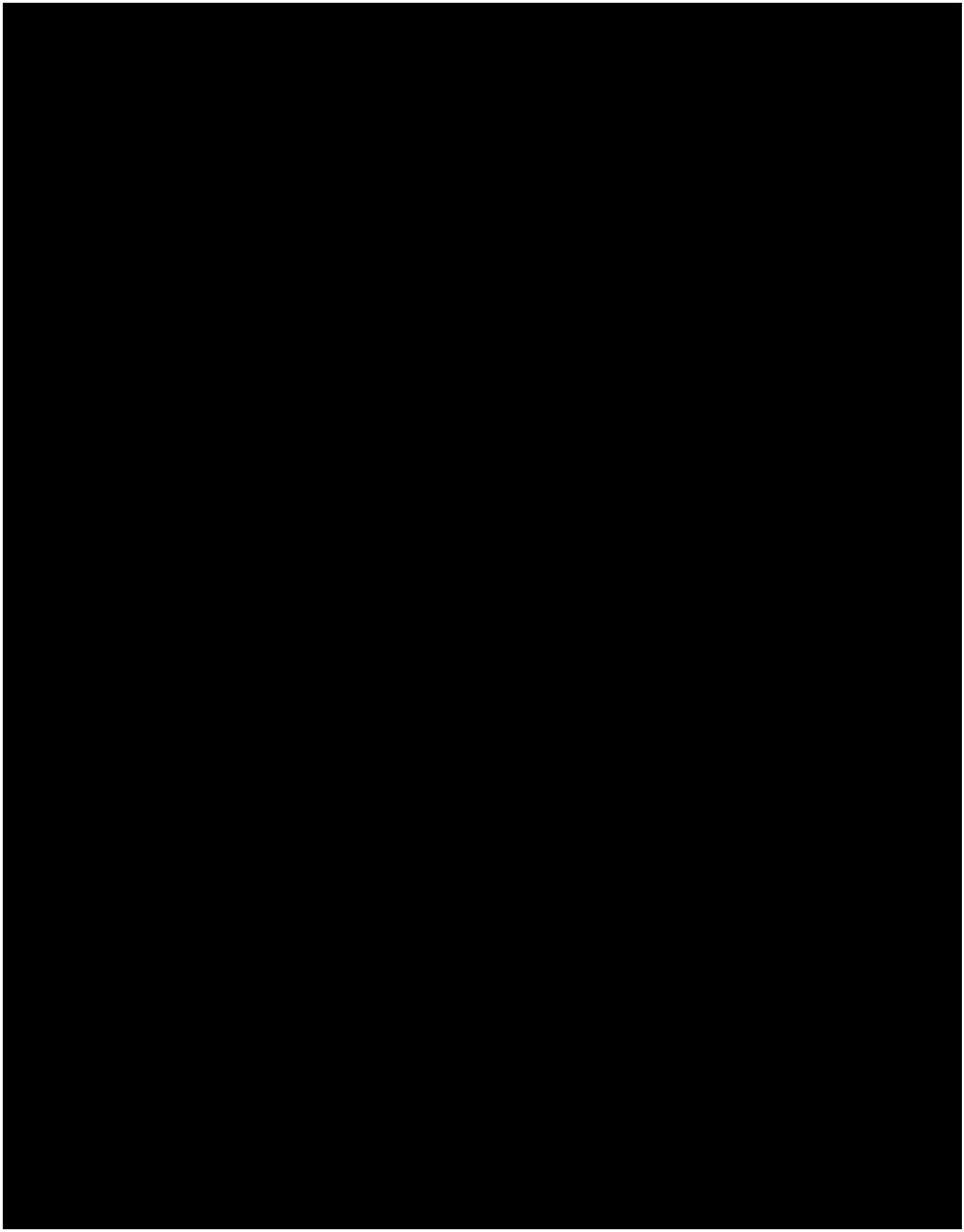
Please place an X in one box on each line

Activity	**Severely** limited	Limited **quite a bit**	**Moderately** limited	**Slightly** limited	**Did not** limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	❑	❑	❑	❑	❑	❑
Working or doing household chores	❑	❑	❑	❑	❑	❑
Visiting family or friends out of your home	❑	❑	❑	❑	❑	❑
Intimate relationships with loved ones	❑	❑	❑	❑	❑	❑

Main in- and exclusion criteria	Main Inclusion Criteria: • Currently hospitalised for the primary diagnosis of acute heart failure (de novo or decompensated chronic HF), regardless of ejection fraction (EF). Patients with a diagnosis of hospitalised heart failure must have HF symptoms at the time of hospital admission • Evidence of left ventricular ejection fraction (LVEF, either reduced or preserved EF) as per local reading preferably measured during current hospitalisation or in the 12 months prior to randomisation • Patients must be randomised after at least 24 hours and no later than 5 days after admission, as early as possible after stabilisation and while still in hospital • Patients must fulfil the following stabilisation criteria (while in the hospital): - SBP ≥100mm Hg and no symptoms of hypotension in the preceding 6 hours, - no increase in i.v. diuretic dose for 6 hours prior to randomisation, - no i.v. vasodilators including nitrates within the last 6 hours prior to randomisation - no i.v. inotropic drugs for 24 hours prior to randomisation. • Elevated NT-proBNP ≥ 1600pg/mL or BNP ≥400 pg/mL according to the local lab, for patients without atrial fibrillation (AF); or elevated NT-proBNP ≥ 2400pg/mL or BNP ≥600 pg/mL for patients with AF, measured during the current hospitalisation or in the 72 hours prior to hospital admission,. For patients treated with an angiotensin receptor neprilysin inhibitor (ARNI) in the previous 4 weeks prior to randomisation, only NT-proBNP values should be used • HF episode leading to hospitalisation must have been treated with a minimum dose of 40 mg of i.v. furosemide (or equivalent i.v. loop diuretic defined as 20 mg of torasemide or 1 mg of bumetanide) Main Exclusion Criteria: • Cardiogenic shock • Current hospitalisation for acute heart failure primarily triggered by pulmonary embolism, cerebrovascular accident, or acute myocardial infarction (AMI) • Current hospitalisation for acute heart failure not caused primarily by intravascular volume overload; • Below interventions in the past 30 days prior to randomisation or planned during the study: - Major cardiac surgery, or TAVI (Transcatheter Aortic Valve Implantation), or PCI, or Mitraclip - All other surgeries that are considered major according to

TABLE OF CONTENTS

IABP	Intra-Aortic Balloon Pump
IB	Investigator's Brochure
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ITT	Intention To Treat
JVP	Jugular Venous Pressure
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-CSS	Kansas City Cardiomyopathy Questionnaire - Clinical Summary Score
KCCQ-TSS	Kansas City Cardiomyopathy Questionnaire - Total Symptom Score
LDL	Low-Density Lipoprotein
LPLT	Last Patient Last Treatment
LVAD	Left Ventricular Assist Device
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiovascular Events
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed Model Repeated Measure
MOA	Mode of Action
MRI	Magnetic Resonance Imaging
NCC	National Coordinator Committee
NT-proBNP	N-Terminal Pro-Brain Natriuretic Peptide
NYHA	New York Heart Association
OPU	Operative Unit
PCI	Percutaneous coronary intervention
PGI-S	Patient Global Impression of Severity of Heart Failure Symptoms
PPS	Per Protocol Set
PRO	Patient Reported Outcome
PV	Pharmacovigilance



The study is planned to be conducted in the US/North America and in Europe and may be expanded to additional countries (e.g. in Asia, South America or Eastern Europe) and more sites based on patient availability.

Screening of patients for this trial is competitive, i.e. screening for the trial will stop at all sites at the same time once a sufficient number of patients has been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the Investigator Site File (ISF) irrespective of whether they have been treated with investigational drug or not.
If a patient is enrolled in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment), the sponsor should be contacted immediately.

3.3.1 Main diagnosis for trial entry

Patients admitted to the hospital for treatment of acute HF (de novo or decompensated chronic HF). Patients should be randomised after at least 24 hours and no later than 5 days after hospital admission. Randomisation should occur as soon as the patient is stabilised (see inclusion criterion 7).

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. Of full age of consent (according to local legislation, at least ≥ 18 years) at screening.

2. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.

3. Male or female patients. Women of childbearing potential (WOCBP)[3] must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information.

4. Currently hospitalised for the primary diagnosis of acute heart failure (de novo or decompensated chronic HF), regardless of EF. Patients with a diagnosis of hospitalised heart failure must have the following HF signs and symptoms at the time of hospital admission:

[3] A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Tubal ligation is NOT a method of permanent sterilisation. A woman who underwent tubal ligation is still considered as WOCBP. However tubal ligation is considered as a method of highly effective birth control.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial.
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

Further follow up of patients affected will occur as described in Section 3.3.4.1.
The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

5.1.5 Patient Global Impression of Severity of Heart Failure Symptoms

Patient Global Impression of Severity of Heart Failure Symptoms (PGI-S) is a 1-item questionnaire to assess patient's impression of symptoms severity, specifically: shortness of breath, fatigue and swelling.

The PGI-S asks the patient to choose one response that best describes how his/her Heart Failure Symptoms, specifically: shortness of breath, fatigue and swelling are now on a 5-point scale:

- Not at all (1)
- Mild (2)
- Moderate (3)
- Severe (4)
- Very severe (5)

Please refer to Section 6.2.2 for order of completion of patient reported outcome measure and Appendix 10.3.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the Flow Chart. Complete physical examination will include general appearance as well as evaluation of organ systems including an assessment of the cardiovascular system.

The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the Flow Chart, prior to blood sampling. This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest.

The preferred method for blood pressure measurement is by a standard mercury sphygmomanometer. If a standard mercury sphygmomanometer is not available, alternative devices recommended by website www.dableducational.org may be used or devices approved for use by the appropriate national agency/ies.

At visit 2a, after the patient has rested quietly in the seated position for five minutes, blood pressure should be taken in both arms. If the pressures differ by more than 10 mmHg (as for example in the presence of a subclavian steal syndrome), the pressure from the arm with the higher pressure (systolic or diastolic) should be entered in the eCRF and this arm should be used for subsequent measurements. The same method and, if possible, the same device should be used throughout the trial for a patient.

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.7.2 Adverse event collection and reporting

5.2.7.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.

The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of trial participation (End of Study (EOS)):
  all AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of trial:
  the investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.7.2.2), but not on the CRF.

For some types of AEs additional information will be collected in the eCRF due to the nature of the event and mechanisms of action of the trial medication. These listed AEs are distinct from AESI. The list of types of AEs for which additional information will be collected may change during the trial based on potential new knowledge about the safety profile of empagliflozin:

- Hypoglycaemic event
- Bone fracture
- Hypotension

5.2.7.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form immediately (within 24 hours) to the sponsor's

Allocation of medication kit number(s) will be managed through the IRT. Patients will be assigned medication at Visit 2a, starting treatment in hospital and will receive their trial mediation kit at discharge to take home. This kit contains sufficient medication until Visit 4. At this visit patients should return the medication and compliance check will be done. At Visit 4 new medication kits will be dispensed. Visit 5 (EoT) is the last day of treatment and the patient should return all remaining medication during this visit.

Early permanent trial medication discontinuation is only justified when any contraindications arise, or when the patient requests to stop trial medication. See Section 3.3.4.1 for details on how to handle trial medication discontinuations. An Early Discontinuation Visit should be performed with the procedures indicated in the Flow Chart.

6.2.3 Follow-up period and trial completion

A Follow-up Visit will be performed 7 days (+7 day window) after the last dose of trial medication. The assessments to be performed at the Follow-up Visit are indicated in the Flow Chart. The Follow-up Visit marks the completion of the study for the individual patient who completed the study on trial medication.

As a standard, Follow-up Visit should be performed as phone call. If considered necessary e.g. for safety reasons requiring personal follow-up, the visit can be done as a site visit.

See Section 3.3.4.1 for procedures to be followed in case a patient prematurely discontinues trial treatment.

For patients who early discontinued trial medication but followed up according to the visit schedule, Visit 5 (EoT) marks the completion of the study for the individual patient.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

Reasons for discontinuation and use of post-baseline concomitant medications will be tabulated.

The details of the analysis will be specified in the TSAP.

7.2.6 Interim Analyses

No interim analysis is planned but a Data Monitoring Committee (DMC) will be in place with tasks as described in Section 8.7.

7.3 HANDLING OF MISSING DATA

Missing data for KCCQ-TSS and NT-proBNP will be estimated using multiple imputation, according to whether patients are on-treatment or off-treatment.

Further details on multiple imputation and rules for handling missing data for other secondary and further endpoints will be specified in the TSAP.

7.4 RANDOMISATION

The trial will be performed as a double-blind design with respect to placebo and empagliflozin. Patients will be randomised to the trial treatments in a 1:1 ratio. Patients will be stratified by HF status (de novo or decompensated chronic HF).

Patients will be randomised in blocks to double-blind treatment via an IRT system.

Approximately equal numbers of patients will be randomised to each treatment group.

BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented.

7.5 DETERMINATION OF SAMPLE SIZE

Powers for superiority in were estimated by simulation using a shared frailty approach. Initially a frailty value was simulated for each patient using a gamma distribution. Deaths were assumed to have constant hazard for any given patient dependent upon the frailty term, leading to a marginal Lomax distribution. HFEs were assumed to have a Poisson distribution within patients, again depending on the frailty parameter, leading to a marginal negative binomial distribution. The number of HFEs per patient was nominally capped at 7 per patient over the 90 day period. For KCCQ-TSS, the frailty terms were directly transformed into a capped normal distribution (values below 0 or above 100 set to 0 and 100 respectively). High frailties corresponded to low KCCQ-TSS scores and vice versa. The use of a shared frailty

scintigraphy, hospital discharge letters, and medical reports from other physicians. All evaluations will be performed in a blinded fashion. The assessments will be analysed based on empagliflozin data combined from multiple trials (i.e. on project level).

Adjudication of ketoacidosis

Events suspected to be metabolic acidosis, ketoacidosis and DKA will be adjudicated by independent external experts in a blinded fashion. Events to be reviewed will be defined in a charter.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI clinical trial portal (Clinergize) to facilitate document exchange.

BI has appointed a Clinical Trial Leader (CT Leader), responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of CT Managers, CRAs, and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.
A central laboratory service and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.

10.2 INCLUSION OF ILLITERATE PATIENTS - KCCQ

In the event of recruiting an illiterate patient, the following process should be followed with respect to completion of the self-reported PRO:

- At each visit where the administration of the Patient Reported Outcome form is required, the trial coordinator or designated site personnel will read each of the items on the questionnaire to the patient, word for word, and without any accompanying explanation.

- The questionnaires will be provided to patients in the language or local dialect that is understood by the patient using the different language versions of the questionnaire that are part of the eCRF for the trial.

- The patient will choose the most appropriate response to the question, and indicate the response on the questionnaire by him/herself. If this is not possible, the trial coordinator or designated site personnel or patient's caregiver will indicate the response on the questionnaire based on the patient's feedback.

In the same way as for all other patients, the completion of the questionnaires should be performed in a quiet area where the patient can consider his/her responses.

10.3 PATIENT GLOBAL IMPRESSION OF SEVERITY OF HEART FAILURE SYMPTOMS: SHORTNESS OF BREATH, FATIGUE AND SWELLING

Please choose one response below that best describes your most recent experience of Heart Failure Symptoms: shortness of breath, fatigue and swelling:

- ☐ Not at all
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

10.4 ACCEPTED FORMS OF CONTRACEPTION FOR PATIENTS IN ITALY

Acceptable methods include consistent and correct use of hormone containing implants and injection contraceptives, combined oral contraceptives, transdermal patches, hormone containing intrauterine devices or systems, bilateral tubal occlusion, complete sexual abstinence, and vasectomy. No other methods will be accepted.

10.5 POTENTIAL MODIFICATION OF TRIAL CONDUCT IN CASE OF RESTRICTIONS DUE TO COVID-19

As mentioned in Section 6.1, in case of any restrictions during the COVID-19 pandemic, study conduct may need to be adjusted. The following contingency measures have been introduced to ensure patient safety and appropriate trial continuation based on a thorough