Name of company:		**Boehringer Ingelheim**	
Name of finished product:		**Jardiance**	
Name of active ingredient:		**Empagliflozin**	
Protocol date: **10 NOV 2016**	**Trial number:** **1245.121**		**Revision date:** **20 Nov 2019**

	treatment group.
Diagnosis :	Heart failure (HF) with reduced ejection fraction (EF).
Main criteria for inclusion:	• Patients with chronic HF diagnosed for at least 3 months before Visit 1, and currently in NYHA HF class II-IV • Chronic HF with reduced EF defined as LVEF ≤ 40% per local reading (obtained under stable condition by echocardiography, radionuclide ventriculography, invasive angiography, MRI or CT). A historical LVEF may be used if it was measured within 6 months prior to visit 1 or the LVEF may be measured after study consent has been obtained. The LVEF must be documented in an official report prior to randomization. • In addition to LVEF ≤ 40%, patient must have at least one of the following evidence of HF: - If EF ≥36 to ≤40: Elevated NT-proBNP at Visit 1 ≥2500 pg/ml for patients without AF, OR ≥5000 pg/ml for patients with AF, analysed at the Central Laboratory, - If EF ≥31 to ≤35: Elevated NT-proBNP at Visit 1 ≥1000 pg/ml for patients without AF, OR ≥2000 pg/ml for patients with AF, analysed at the Central Laboratory, - If EF≤30%: Elevated NT-proBNP at Visit 1 ≥600 pg/ml for patients without AF, OR ≥1200 pg/ml for patients with AF, analysed at the Central Laboratory - For EF ≤ 40% and documented HHF within 12 months prior to visit 1, and an elevated NT-proBNP at Visit 1 ≥ 600 pg/ml for patients without AF and ≥ 1200 pg/ml for patients with AF, analysed at the Central Laboratory. • Appropriate dose of medical therapy for HF (such as ACEi, ARB, β-blocker, oral diuretics, MRA, ARNI, ivabradine) and appropriate device therapy, consistent with prevailing CV guidelines, stable for at least 1 week prior to Visit 1(screening) and during screening period until Visit 2 (Randomisation) with the exception of diuretics stable for only one week prior to Visit 2 to control symptoms. The investigator must document the reason why patient not on target dose per local guidelines. • Appropriate use of medical devices such as cardioverter defibrillator (ICD) or a cardiac resynchronization therapy (CRT) consistent with prevailing local or international CV guidelines (refer to exclusion #29)

Trial Period	**Screening[1]**	**Randomised Treatment Period [2]**															**Follow Up Period [3]**		**Relevant CTP section**
Visit	**1**	**2**	**3**	**4**	**5 Phone call**	**6**	**7 Phone call**	**8**	**9 Phone call**	**10**	**11 Phone call**	**12**	**13 Phone call**	**14**	**15 Phone call**	**16**	**EOT Visit**	**FU Visit [3]**	
Trial week	**-3**	**1**	**4**	**12**	**22**	**32**	**42**	**52**	**64**	**76**	**88**	**100**	**112**	**124**	**136**	**148**	**EOT Visit**	**EOT + 30 days**	
Days from Randomisation Visit window [4]	**-28 to -4**	**1**	**29±7**	**85 ±7**	**155 ±7**	**225 ±7**	**295 ±7**	**365 ±7**	**449 ±7**	**533 ±7**	**617 ±7**	**701 ±7**	**785 ±7**	**869 ±7**	**953 ±7**	**1037 ±7**	**---**	**--- ±7**	
Fasting status [5]	**NF**	**F**	**NF**	**NF**	**-**	**NF**	**-**	**NF**	**-**	**NF**	**-**	**NF**	**-**	**NF**	**-**	**NF**	**F**	**F**	
Weight	X	X	X	X		X		X		X		X		X		X	X	X	5.2.5
Concomitant Therapy	X	X	X	X		X		X		X		X		X		X	X	X	4.2
Assessment of Endpoints [10,11]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2, 5.3,
12-lead-ECG [10, 12]	X																X		5.3.5
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.3.7
KCCQ		X		X		X		X									X	X	5.2.1
EQ-5D		X		X		X		X				X				X	X	X	5.6.1
HCRU		X	X	X		X		X		X		X		X		X	X		5.6.2
Urine Pregnancy test[13]	X	X	X	X		X		X		X		X		X		X	X		5.3.4.2
Safety lab test	X[14]	X	X	X		X		X		X		X		X		X	X	X	5.3.4
NT-proBNP	X	X	X	X				X									X	X	5.5
High-sensitivity Troponin T		X																	5.5
HbA1c [15]	X	X		X		X		X		X		X		X		X	X		
Lipid profile panel		X						X				X					X	X	5.3.4

GCP	Good Clinical Practice
HbA1c	Glycated Haemoglobin
HCRU	Health Care Resource Utilisation
HDL	High Density Lipoprotein
HF	Chronic Heart Failure
HgB	Haemoglobin
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HHF	Hospitalisation for Heart Failure
HR	Heart Rate
HRQOL	Health-related quality of life
IB	Investigator's Brochure
ICD	Implantable Cardioverter Defibrillator
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
i.v.	intravenous
KCCQ	Kansas City Cardiomyopathy Questionnaire
LDL	Low Density Lipoprotein
LVAD	Left Ventricular Assist Device
LVEF	Left Ventricular Ejection Fraction
LPDD	Last Patient Drug Discontinuation
LPO	Last patient out
MACE	Major Adverse Cardiovascular Events
MedDRA	Medical Dictionary for Drug Regulatory Activities
MI	Myocardial Infarction
MMRM	Mixed Model Repeated Measures
MRA	Mineralocorticoid Receptor Antagonist
MRI	Magnetic Resonance Imaging
MRS	Modified Rankin Scale
NCC	National Coordinator Committee
NT-proBNP	N-terminal of the prohormone brain natriuretic peptide
NYHA	New York Heart Association
PK	Pharmacokinetics
PSA	Prostate Specific Antigen
p.o.	per os (oral)
q.d.	quaque die (once a day)
RBC	Red Blood Cells
REP	Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
RS	Randomised Set
SAE	Serious Adverse Event
SBP	Systolic blood Pressure
SEC	Scientific Excellence Committee

empagliflozin was well tolerated and in patients with CKD3 led to statistically significant reduction of HbA1c and clinically meaningful improvement in body weight and BP compared to placebo at Week 24, these results were sustained for up to 52 weeks [P14-01211]. In patients with CKD4 renal impairment, while there was not change in the glycaemic response, the reduction in BP and renal hemodynamic changes (similar to what was observed in the EMPA-REG OUTCOME trial) were preserved. In the EMPA-REG OUTCOME trial a similar reduction in CV risk was observed in the subgroup of patients with different degree of renal impairment, including patients with eGFR between >45-60 and >30-45 mL/min/1.73 m^2.

2 RATIONALE, OBJECTIVES, AND BENEFIT-RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Heart failure is an important public health problem, and one of the leading causes of hospitalisation in the Western countries. With the increasingly aging population and increasing incidence of obesity, the scope and cost to society associated with this condition will progressively rise. There is an unmet medical need in treatment of patients with HF, despite available therapies for HFrEF, outcomes remain suboptimal with increase rate of rehospitalisation and high mortality rate [P16-03760]. HF also significantly decreases health-related quality of life (HRQOL) and pharmacological therapies have not shown consistent improvement in HRQOL.

Empagliflozin improves survival in patients with high cardiovascular risk by mechanisms which go beyond the blood glucose lowering effect. There was no heterogeneity by baseline HbA1c categories in HHF or “CV death and HHF” risk reduction in the EMPA-REG OUTCOME trial. Empagliflozin exerts its glucose lowering effect by preventing sodium and glucose reabsorption. The initial natriuresis will be compensated within days of drug administration through changes in tubulo-glomerular feedback. However, the glucosuria lasts as long as the medication is used. This leads to consequent hemodynamic changes associated with a modest osmotic diuresis, blood pressure lowering effect, improvement in arterial stiffness, reduction in oxidative stress, and decrease in heart rate(HR) x Pressure product, a measure of myocardial oxygen consumption, with no increase in HR and no effect on sympathetic nerve activity [P15-00589, P15-09541]. Of note, the effect of empagliflozin on improving CV outcomes is evident even at low urinary glucose excretion demonstrated in those with low HbA1c as well as in those with reduced renal function (i.e. eGFR < 60 mL/min/1.73 m^2). Subgroup analysis of the EMPA-REG OUTCOME trial showed no difference in patients with baseline HbA1c <7%, 7 to 8%, 8 to 9%, or >9% for CV death or HHF risk reduction. In addition, patients who had no HbA1c change or only modest change up to 0.2% throughout the trial have shown to have a similar risk reduction of HHF as the patients with at least 0.3% or higher reduction in HbA1c. Also as noted changes in BP reduction and hemodynamic changes were preserved in patients with CKD4, despite loss of glycaemic efficacy. Lack of correlation between CV outcome improvement and blood glucose levels provides supporting evidence that the benefit of empagliflozin in HHF or CV death risk reduction should also be expected in patients without diabetes [P16-01253, c09670340, c11764168]. The beneficial CV effects of empagliflozin cannot be explained by the modest glucose control achieved in the EMPA-REG OUTCOME trial. Other outcome

trials with the goal of tight glycaemic control (ADVANCE, ACCORD, and VADT) have failed to show significant CV benefit [R16-1560] and decrease in incident HF or mortality [R16-0736].

It should be noted that in a mechanistic trial non-diabetic subjects showed metabolic changes such as glucosuria, increase in endogenous glucose production, and substrate shift from glucose to lipid oxidation similar to those observed in patients with T2DM after one dose and up to 4 weeks of daily administration of empagliflozin [P16-01830]. Furthermore, in a trial of healthy volunteers, empagliflozin 10 mg resulted in approximately 50 g glucosuria per day [P13-04190]. This amount of glucose excretion is similar to what had been observed in patients with eGFR between 30-60 mL/min 1.73 m2 (CKD3) which was close to 55 g glucosuria per day. In the EMPA-REG OUTCOME trial, patients with CKD3 showed a trend for the CV death or HHF risk reduction very similar to the risk reduction in the main cohort and in patients with CKD2 and 1. While the higher level of glucosuria is associated with a higher HbA1c reduction and better glycaemic control, this correlation is lacking for the CV benefits associated with empagliflozin, and in fact a lower glucose excretion similar to what has been observed in patients with CKD3 or in healthy volunteers seems to be sufficient to improve the CV outcomes. Therefore, the expected benefit of empagliflozin such as BP reduction, weight loss, improvement in arterial stiffness, and hemodynamic changes, as well as CV benefits seen in patients with T2DM is also speculated to be seen in HF patients without DM and in patients with CKD3 and 4. These findings further support the rationale of exploring the effect of empagliflozin beyond DM. Although the type of HF was not assessed entering the EMPA-REG OUTCOME trial, it is highly likely in this trial both patients with preserved and reduced ejection fraction were included, considering the high prevalence of both HFrEF and HFpEF in patients with DM [R16-1529].

The modes of action described above, and beneficial effect in patients with history of HF in the EMPA-REG OUTCOME trial, further supports the scientific rationale of performing this trial to explore the effect of empagliflozin in patients with HFrEF.

2.2 TRIAL OBJECTIVES

The objective of this event-driven trial is to demonstrate superiority of empagliflozin 10 mg versus placebo on top of guideline-directed medical therapy in patients with symptomatic, chronic HF and reduced ejection fraction (LVEF ≤ 40%).

For further description of trial endpoints and statistical analysis, please refer to Section 5 and 7.

This trial is part of an investigational clinical trial program of empagliflozin in patients with chronic HF. A trial to investigate the efficacy and safety in patients with preserved EF (LVEF > 40%) is ongoing in parallel.

2.3 BENEFIT-RISK ASSESSMENT

The overall benefits and safe profile of empagliflozin have been outlined in previous sections. A pharmacologic rationale for the use of empagliflozin in HF can be found in Section 1.1.

In this trial, the effect of empagliflozin will be evaluated in HF patients. DM is known to be a frequent and clinically important co-morbidity in HF patients. To evaluate this important co-

morbidity, HF patients across the DM spectrum (i.e. T1DM, T2DM, pre-diabetes) as well as HF patients who do not have DM, will be included in this trial.

Special safety considerations are required for patients with T1DM, and several safety monitoring strategies will be employed, including training of investigators and education of patients on the risk and prevention strategies for ketoacidosis, diabetic ketoacidosis (DKA). Since an SGLT-2 inhibitor may alter the typical presentation of this condition, T1DM patients will receive a home monitoring device to measure blood ketones and a diary for patients to record their blood glucose, ketone values and insulin intake. Patients with T1DM will also be required to carry a trial information card which includes information about the possible altered presentation of ketoacidosis to be presented to health care professionals should the patient be seen in an urgent care setting. For further details refer to Section 4.2.1.

As outlined above, inclusion of patients who do not have diabetes is also allowed in this trial. It has been shown in healthy volunteers dosing with empagliflozin results in glycosuria summing up to about 2/3 the average glucosuria in patients with T2DM. This is similar to the amount of glucose lost in T2DM subjects with moderate renal impairment. Because in the EMPA REG Outcome study no difference in CV benefit was detected for patients with renal impairment vs the overall population, it is hypothesized that this amount of glucosuria is not the main factor to obtain CV effects with empagliflozin.

There are no long-term safety data for empagliflozin in patients without diabetes. Data in non-diabetic subjects is limited to healthy volunteers, without significant co-morbidities or concomitant medications. Exposure in healthy volunteers is from single dose and multiple dose studies with exposure up to 28 days. However, while limited, such data does include over 500 healthy volunteers exposed to empagliflozin during the clinical development for treatment of T2DM. No specific safety concern was identified and no occurance of symptomatic hypoglycaemia was detected [U12-2707-01]. It is noted that in patients with T2DM, the risk of hypoglycaemia was only increased with empagliflozin compared to the placebo group in patients who were concomitantly treated with insulin or a sulfonylurea. Further, in a mechanistic study [c11963611-01], subjects without DM were shown to increase endogenous glucose production in response to glucosuria after administration with empagliflozin. As a result, blood glucose levels remained in the normal range for these individuals [P16-01830]. Therefore it is scientifically reasonable to hypothesize that in non-diabetic patients, with no medical indication for insulin or sulfonylurea treatment that the risk of hypoglycaemia associated with empagliflozin treatment would be lower than in patients with T2DM.

Because of the mode of action, blockade of the SGLT-2 with consequent glucosuria, is the same in patients with and without diabetes, although to different degree, it is considered likely that the tolerability of empagliflozin in non-diabetic patients may be no less favourable in patients with T2DM.

There is also currently limited therapeutic experience with empagliflozin in patient aged 85 years and older. The prevalence of chronic heart failure increases with age and the therapeutic options in the elderly above 85 years are limited. The inclusion of this population

number of patients with an adjudication confirmed primary endpoint event will be reached within a given timeframe, the trial team will initiate required actions to stop the trial. From this time point on, all patients are expected to perform their last visit (EOT visit) with the proposed time schedule communicated via an investigator letter (see also Section 6.2.3).

*based on an 18 months recruitment and event rate as outlined in Section 7.7.

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI). The operational aspects (trial management and monitoring) of the trial and Data Management will be outsourced globally to a Contract Research Organisation (CRO).

A Coordinating Investigator is responsible to coordinate Investigators at different centres participating in this multicentre and multinational trial. Tasks and responsibilities are defined in a contract stored in the electronic Trial Master File (eTMF) at the CRO.

An ExSC and a Scientific Excellence Committee (SEC) consisting of independent experts and Sponsor representatives will be established to support the Sponsor in designing the trials and successful execution. The ExSC and SEC will have a scientific and advisory function in the trial. The ExSC will be involved with the detailed trial design, discussions and decision making, while the SEC has wide representation of different scientific disciplines and will be consulted on topics requiring broader consensus. The composition of the ExSC and the SEC will be documented in the eTMF. The tasks and responsibilities will be agreed in contracts between the ExSC and the SEC and the Sponsor, and also summarised in an ExSC- and SC-charter filed in the eTMF.

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), independent of the Sponsor and CRO will assess the progress of the trial, including an unblinded safety and efficacy assessment at specified intervals, and to recommend to the Sponsor whether to continue, modify, or stop the trial. Measures are in place to ensure blinding of the ExSC, SEC, NCC, Sponsor, CRO and all other trial participants. The tasks and responsibilities of the DMC will be specified in a charter. The DMC will maintain written records of all its meetings.

Relevant documentation on the participating (Principal) Investigators and other important participants, including their curricula vitae, will be filed in the Investigator Site File (ISF).

BI has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to;

- manage the trial in accordance with applicable regulations and applicable BI and CRO Standard Operating Procedures (SOPs),
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,

3.1.1.3 Adjudication of ketoacidosis

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

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

A variety of medications have been tested in patients with HFrEF with beneficial effect in morbidity and mortality. The aim of this trial is to recruit patients with HFrEF on various HF background therapies to evaluate the long term effect of empagliflozin on CV death and HHF in a real life clinical setting.
Due to its mode of action empagliflozin should be efficacious in treating patients with HF and could provide additional efficacy in combination with any given background therapy.

The placebo-controlled design is considered ethically acceptable on the basis of appropriate criteria for patient discontinuation, ability to change background therapy to maintain, or obtain, sufficient level of hemodynamic control as defined in relevant local and regional guidelines for optimised standard of care.

The double-blind treatment period is planned until the necessary number of events is observed to evaluate efficacy of empagliflozin compared to standard of care. The 30 days follow-up period is considered to be sufficient for assessment of adverse events and efficacy outcomes after stopping trial medication.

Patients should be receiving appropriate care as defined by their physician or practitioner for all cardiovascular conditions according to the prevailing guidelines. This includes, but is not limited to, (if indicated and not contraindicated) aspirin, statins, a diuretic, an inhibitor of the renin-angiotensin system, a beta-blocker and a mineralocorticoid receptor antagonist, each to be given at clinically appropriate doses, and the use of implantable devices like ICD and CRT. This should be conducted in the context of local or regional guidance for primary or secondary CV prevention.

The rationale for dose and dose-interval selection is described in Section 4.1.2.

3.3 SELECTION OF TRIAL POPULATION

An appropriate number of patients will be screened for the trial in approximately 15 countries. Approximately 480 trial centres will participate to ensure that the estimated 2850 patients are randomised to trial medication and complete the trial. Investigators who fail to randomise at least one patient in the first 12 weeks from site initiation may be excluded from further participation. If enrolment is delayed, additional centres may be initiated. The total number of randomised patients may be adapted based on assessment of the blinded event rate. If the accumulated blinded data suggests a slower accrual of primary outcome events over calendar time than originally projected, then the number of patients randomised may be increased up to 4000. Operationally, the recruitment period would be extended and could continue up to 6 months before the target number of events is expected to be achieved. The number of primary outcome events required is not affected by this consideration. For further details refer to Section 7.7.

Clinical trials contribute toward reducing health disparities through improved knowledge about treatment among diverse populations. Greater diversity in clinical trial samples allows for broader generalisation of trial results, increased minority access to trials, improved standards of care, decreased disparities in disease treatment and outcomes, and improved external validity supported by a more representative sample. Greater number of African-Americans as an example suffer from HF and all efforts must be made to have adequate representation of this minority population from the USA [P15-10667]. Each Investigator should develop a recruitment strategy that ensures the recruitment of a representative patient population and takes into consideration gender, race and ethnicity.

According to previous heart failure trials and registries the prevalence of DM amongst patients with HF varies from 25% to 40%. Prevalence of pre-DM is not clearly understood but it is estimated to vary from 15% to 50% [R16-2384, R16-2382]. In a recent large HF outcome trial, 35% of the patients reported to have diabetes and another 15% found to have undiagnosed diabetes and around 27% had pre-diabetes [R16-2383].

Since there is a chance that empagliflozin, as a diabetes drug, when used in CV outcome trials recruits more patients with T2DM, capping on trial level will be used to aim for a similar distribution of patients with DM, pre-DM or no DM as it is expected in the population of patients with the chronic heart failure in real life.

Via IRT it will be ensured that approximately a minimum of 35% of the trial population will be diabetic patients, a minimum of 15% will be prediabetic patients and a minimum of 20% will be non-diabetic patients.

Additionally recruitment to the three categories of DM, pre-DM or no DM will be monitored on regional level. Capping on regional level may be applied to achieve a contribution of each region to each category of diabetes status. DM in this context is defined as screening HbA1c ≥6.5%, active treatment with antidiabetic medication (for indication of DM) or history of DM. Pre-DM is defined as screening HbA1c ≥5.7% and <6.5% without the intake of antidiabetic medication (unless taken for a non-DM indication) and no history of DM. Patients with no DM is defined as screening HbA1c < 5.7 % without any intake of antidiabetic medication (unless taken for a non-DM indication) and no history of DM [R16-2261].

Screening of patients for this trial is competitive, i.e. screening for the trial will stop at all centres when a sufficient number of patients have been randomised to trial treatment. Investigators will be notified when screening is complete and will not be allowed to recruit additional patients thereafter. Patients who have completed visit 1 procedures prior to notification of the termination of recruitment will be allowed to be randomised in the trial, if they meet all eligibility criteria. Patient eligibility will be based upon a complete medical history including a physical examination and clinical laboratory tests. Judgment of the clinical relevance of a concomitant disease is at the discretion of the Investigator.

Re-screening and/or re-testing (of assessments) is permitted if approved by Local Clinical Monitor (CML)/Clinical Lead (CL) or delegate. Whilst the information provided below is not

outcome events and vital status. If possible, other AE's and concomitant therapy changes since last visit must be recorded.

Every attempt must be made by the investigator to ensure patients continue participating in the trial during trial medication interruptions and after discontinuation of trial medication. Patients who prematurely discontinue trial medication are allowed to restart treatment, at any time if appropriate in the opinion of the Investigator. At every visit following trial medication discontinuation Investigators must consider if trial medication can be re-started.

Patients that are not actively taking trial medication may be less motivated to adhere to the scheduled trial visits. Investigators and site staff should work to detect early signs of losing interest and readily present such patients (not actively taking trial medication) with the following options to encourage continued participation:

Option 1	Continue to attend regularly scheduled trial visits at the centre until the trial ends
Option 2	Conduct all remaining trial visits over the phone
Option 3	Discontinue participation in remaining trial activities but permit collection of vital status and CV outcome events at the end of the trial through the patient or alternative person designated by the patient (e.g., family, spouse, partner, legal representative, or physician) even if only by telephone. If possible, other AE's and concomitant therapy changes to be recorded. Sites should encourage the patient to return to the clinic for the final study visit.
Option 4	Discontinue participation in remaining trial activities but permit collection of vital status at the end of the trial through the patient, alternative person designated by the patient, or through review of patient's medical information from alternative sources (e.g., doctor's notes, hospital records, etc.)

Patients will be asked to choose the most rigorous form of follow-up that they are willing to comply with.

A patient could be instructed to permanently stop the trial medication only after discussion with Investigator, if eligibility criteria are being violated, or if the patient fails to comply with the protocol (e.g. non-attendance at trial assessments).

Withdrawal of informed consent
A patient has the right to withdraw informed consent for participation at any time for any reason. However, withdrawal of consent from trial participation should be very rare and unusual. Because of this, the Investigator must be involved in the discussions with the patient regarding a withdrawal of consent. Additionally, the Investigator must discuss the withdrawal of consent with the Sponsor's/CRO's representative prior to stopping trial participation.

Early discontinuation of trial medication is not a criterion for withdrawal of consent for participation in the trial.

5.1.3 Further endpoints

- Time from first to second adjudicated HHF
- Time to first all-cause hospitalisation
- Occurrence of adjudicated HHF within 30 days after first adjudicated HHF
- Occurrence of adjudicated HHF and CV death. This endpoint will account for clinical hierarchies in composite outcomes, i.e. CV death is ascribed greater importance than HHF (see win ratio in Section 7.3.3)
- New onset of atrial fibrillation
- Adjudicated MI (fatal or non-fatal)
- Adjudicated stroke (fatal or non-fatal)
- Adjudicated TIA
- Composite of time to first event of all-cause mortality and all-cause hospitalisation
- Composite of adjudicated CV death or adjudicated non-fatal MI
- Composite of adjudicated CV death or adjudicated non-fatal stroke
- Adjudicated CV death, adjudicated non-fatal MI, adjudicated non-fatal stroke (3-point MACE)
- Progression to macro albuminuria (defined as UACR >300 mg/g) from baseline for patients with baseline UACR ≤ 300 mg/g
- Time to first new onset of sustained normo- or micro-albuminuria (UACR ≤ 300 mg/g) in patients with macro albuminuria at baseline
- Time to first new onset of sustained normo-albuminuria (UACR < 30 mg/g) in patients with micro- or macro-albuminuria at baseline
- eGFR $(CKD\text{-}EPI)_{cr}$ change from baseline to 30 days after treatment stop
- Composite of sustained reduction of ≥40% eGFR $(CKD\text{-}EPI)_{cr}$ or sustained eGFR$(CKD\text{-}EPI)_{cr}$ <15 mL/min/1.73 m^2 (< 10 mL/min/1.73 m^2 for patients with eGFR $(CKD\text{-}EPI)_{cr}$ <30 mL/min/1.73 m2 at baseline) or adjudicated CV death
- Composite of sustained reduction of ≥40% eGFR $(CKD\text{-}EPI)_{cr}$ or sustained eGFR$(CKD\text{-}EPI)_{cr}$ <15 mL/min/1.73 m^2 (< 10 mL/min/1.73 m^2 for patients with eGFR $(CKD\text{-}EPI)_{cr}$ <30 mL/min/1.73 m2 at baseline) or all-cause mortality
- Composite of sustained reduction of ≥40% eGFR $(CKD\text{-}EPI)_{cr}$ or sustained eGFR $(CKD\text{-}EPI)_{cr}$ <15 mL/min/1.73 m^2 (< 10 mL/min/1.73 m^2 for patients with eGFR $(CKD\text{-}EPI)_{cr}$ < 30mL/min/1.73 m2 at baseline), adjudicated CV death, or adjudicated HHF
- Change from baseline in KCCQ overall summary score at week 52
- Change from baseline in KCCQ total symptom score at week 52
- Change from baseline in KCCQ individual domains at week 52

- Change from baseline in KCCQ based on patient-preferred outcome at week 52
- Change in NYHA class from baseline at week 52
- Change from baseline in Health-related quality of life measured by EQ-5D
- Health economic analysis by Health Care Resource Utilisation (HCRU)
- Changes in NT-proBNP from baseline over time
- Time to achievement of NT-proBNP < 1000 pg/ml
- Change in albuminuria from baseline over time
- Change in albuminuria from baseline over time by baseline Urine Albumin Creatinine Ratio (UACR) categories (<30 mg/g, ≥30mg/g to ≤300mg/g, >300 mg/g)
- Incidence of acute renal failure (based on narrow SMQ)
- Time to first acute kidney injury (based on preferred term)
- Change from baseline in body weight over time
- Change from baseline in Systolic Blood Pressure (SBP) over time
- Change from baseline in Diastolic Blood Pressure (DBP) over time
- Change from baseline in pulse rate over time
- Change from baseline in HbA1c over time in the overall population and in 3 subgroups (non-DM, pre-DM, and DM)

Refer to the trial statistical analysis plan (TSAP) for the complete set of further endpoints.

5.2 ASSESSMENT OF EFFICACY

The CEC is responsible for the adjudication of all relevant CV events, which could potentially fulfil the criteria for the primary, secondary and further endpoints. The CEC charter is available in the ISF for details regarding adjudication. Please also refer to Section 3.1.1.1 for information on the CEC.

5.2.1 Kansas City Cardiomyopathy Questionnaire

KCCQ is a 23-item self-administered questionnaire designed to evaluate physical limitations, symptoms (frequency, severity, and changes over time), social limitations, self-efficacy, and quality of life in patients with HF.

The paper-and-pen version in the required native language of the patient is to be used. If the required language is not available then the patient is not required to complete the questionnaire.

The questionnaire takes about 5-8 minutes to complete and will be distributed according to the Flow Chart.

The Investigator (or designated site-personnel) should ensure that the patient has access to a quiet area at the site where he/she can be left alone to record her/his response in the

questionnaire. In instances where a patient cannot give or decide upon a response, no response should be recorded. The Investigator (or designated site-personnel) should check that all items have been completed by the patient, but the response to each item should not be scrutinised. Instructions to patients are included in the questionnaire. The respective procedure for illiterate patients (if included) is described in the Appendix 10.1.

To assess the further endpoint of change from baseline in KCCQ based on patient-preferred outcome at week 52, the investigator or designee will be required to ask the patient one additional question about which domain is the most difficult for the patient to cope with. The response to this question will be recorded in the eCRF.

5.2.2 New York Heart Association classification

The New York Heart Association (NYHA) functional classification will be used to classify the severity of the patients' heart failure (ref. Appendix 10.3). The investigator should place the patients in one of the four categories based on how limited their physical activity are. Candidates for screening are required to have a NYHA functional class II, III or IV.

The classification of patient's physical activity according to NYHA will be performed at all on-site until end of the trial. If a visit is designated as an on-site visit but is conducted by phone, the NYHA functional classification must be performed.

5.2.3 NT-proBNP

Refer to Section 5.5 Assessment of biomarkers.

5.2.4 Blood pressure

SBP and DBP as well as pulse rate (electronically or by palpation, count for 1 minute) will be measured after 5 minutes of rest in the seated position according to the Flow Chart. At visit 1, after the patient has rested quietly, in the seated position for five minutes, three blood pressure measurements will be taken and recorded in the eCRF. The mean of these 3 blood pressure values will be used to determine eligibility. At subsequent visits, blood pressure recordings should be measured using a similar type of and validated certified blood pressure recording instrument on the same arm when possible.

5.2.5 Body weight

BMI (kg/m2) will be calculated for determination of eligibility at Visit 1.

Body weight will be measured at all on-site visits

- after the urine sampling (weight after bladder voiding),
- shoes and coat/jackets should be taken off, and
- pockets should be emptied of heavy objects (i.e. keys, coins etc.).

this condition has to be documented as medical history or baseline condition in the eCRF, respectively.

For documentation of symptomatic acute UTI during trial conduct, a urine culture sample has to be taken and sent to central lab for confirmation of the diagnosis.

5.3.4.5 Ketone monitoring in patients with type 1 diabetes (T1DM) only

Patients with T1DM will be provided an electronic device to determine their ketone concentration (i.e. a blood glucose monitoring device/meter that is also capable of measuring blood ketones).

Patients should measure their ketones at least once daily, ideally after fasting for at least 6 hours, throughout the treatment period, and for 5 days after empagliflozin / placebo treatment has been stopped. Patients should be reminded to test their ketones in case of any symptoms of ketoacidosis, e.g. nausea, vomiting, and abdominal pain. Patients must be reminded about the signs and symptoms of ketoacidosis, on the interpretation of ketone values measured via the meter, and on appropriate action to take in the event of increased ketone levels (see below). In the same way as during routine clinical care, patients should also be reminded to test for ketones in case of repeatedly elevated blood glucose levels (e.g. >11.1 mmol/L (> 200 mg/dL)) which cannot be explained.

Patients will be instructed that in the event of increased ketones, they are to either follow the rules given by their treating physician (e.g. increased fluid intake and/or insulin bolus) or contact their trial site. Blood glucose and ketone levels should be checked every 1-2 hours until they are back in a range considered to be normal. Patients are to be instructed to immediately refer themselves to hospital and/or the Investigator, or to contact an emergency physician in case of a blood ketone concentration > 1.5 mmol/L (as indicated in the meter manual). In case of a suspected ketoacidosis a blood gas test (pH, bicarbonate) should be performed locally at the earliest opportunity and the patient treated according to local medical judgement. The results of the blood gas test will be collected on the relevant page of the eCRF.

Patients not adhering to the instructions given by the Investigator should be retrained at the earliest possible opportunity. The risk benefit for the patient continuing on study treatment should be considered.

5.3.5 Electrocardiogram

ECGs will be performed at visits as indicated in the Flow Chart. Printed paper traces from 12-lead ECGs (I, II, III, aVR, aVL, aVF, V1-V6) will be collected. They should be evaluated, signed, dated and commented upon by the treating physician/Investigator or appropriately qualified designee and stored locally. The diagnosis and results from the ECG report should be collected in the eCRF.

In the event of any cardiac symptoms (i.e. suspicion of heart rhythm disorders or cardiac ischaemia) during the course of the trial, if an additional ECG is recorded at time of event, or later at the next regular visit, they will be evaluated, signed, dated and commented upon by

- results in death,
- is life-threatening, this 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,
  or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment 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.

For Japan only: The following events will be handled as "deemed serious for any other reason": AEs which possibly lead to disability will be reported as SAEs.

AEs considered "Always Serious"
In accordance with the European Medicines Agency initiative on Important Medical Events, BI 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 given above.

The latest list of "Always serious AEs" can be found in the ISF. These events should always be reported as SAEs as described above.

Note: Cancers of new histology and exacerbations of existing cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

Adverse events of Special Interest (AESIs)
The term AESI relates to any specific AE that has been identified at the substance 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/CRO's Pharmacovigilance Department within the same timeframe that applies to SAE, see Section 5.3.7.2.

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 and/or ALT $\geq$3 fold ULN combined with an elevation of total bilirubin $\geq$2 fold ULN measured in the same blood draw sample, and/or
- Marked peak aminotransferase (ALT, and/or AST) elevations $\geq$ 5 fold ULN

Events which occurred after the REP will be considered as post treatment events.

AE reporting to the Sponsor/CRO and timelines
The Investigator must report all non-exempted 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 unique entry point (contact details provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the investigator could inform the Sponsor/CRO upfront via telephone. This does not replace the requirement to complete and fax 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.

Information required
For each AE, the Investigator should provide the information requested on the appropriate eCRF pages and the paper SAE form, if applicable. The Investigator should determine the causal relationship to the trial medication.

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

- Worsening of the underlying disease or of other pre-existing conditions. Exemptions are specified in "Exemptions to SAE reporting" and must be adhered to as described in that chapter.
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the Investigator. If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.

All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been sufficiently characterised, or no further information can be obtained.

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:

- Hypoglycaemic event
- Genital infection
- Acute pyelonephritis
- Sepsis
- Urinary tract infection
- Bone fracture

Pregnancy
In rare cases pregnancy may occur in a clinical trial. Once a patient has been enrolled into this clinical trial and has taken trial medication, the Investigator must report any drug

5.4.3 Analytical determinations

Empagliflozin concentrations in plasma samples will be determined by a validated HPLC-MS/MS assay (high performance liquid chromatography, tandem mass spectrometry). In order to identify samples from patients taking placebo, the bioanalyst will be un-blinded so that samples from patients receiving placebo will not be analysed for empagliflozin.

5.5 ASSESSMENT OF BIOMARKER(S)

Samples for NT-proBNP will be collected at Visit 1 (Screening) to determine whether the patient is eligible for the trial. Further samples for NT-proBNP will be collected at later time points in the trial (see Flow Chart)) to investigate a potential effect of the trial medication. Samples for NT-proBNP will be analysed at the Central Laboratory.

Samples for the determination of high-sensitivity cardiac troponin T will be collected at Visit 2 (Randomisation) and analysed at the Central Laboratory.

5.5.1 Biobanking (optional)

Participation in sampling for biobanking (including DNA) is voluntary and not a prerequisite for participation in the trial. Biobanking samples will be taken only after separate ICF has been given in accordance with local ethical and regulatory requirements. Banked samples may be analysed in the future for scientific evaluations or to further, for example, the mechanistic understanding of drug effects and/or to identify genetic or other factors associated with response to therapy or the risk of adverse drug reactions.

Measures are in place to comply with the applicable rules for the collection, biobanking and future use of biological samples and clinical data, in particular

- Sample and data usage has to be in accordance with the separate biobanking ICF.
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials.
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data
- Samples and/or data may be transferred to third parties and other countries as specified in the biobanking ICF

5.5.1.1 Methods and timing of sample collection

Sampling will be performed at the time points specified in the Flow Chart

DNA banking

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.

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

Health related quality of life questionnaires are a necessary part for this phase III trial in order to collect data for a health economic evaluation.

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

6 INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All trial visits, except for screening visit and telephone visits should preferably take place before noon. The patients should be fasting (no food or liquid except water the last 10-16 hours) at Visit 2 (Randomisation), EOT Visit and Follow Up Visit.

If a patient mistakenly takes trial medication on the morning of Visit 4 before attending the clinic, or comes in non-fasted where a fasting condition is required (ref. Flow Chart), the visit should be rescheduled for another day as soon as possible reminding the patients about expected time of dosing. The rescheduled visit must take place in a short enough time-frame so that the patient has sufficient trial medication available.

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 these time windows.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The Flow Chart summarises the investigational procedures to be done at each visit, and trial procedures should be performed before intake of any trial medication. The procedures are further described below.

6.2.1 Screening (Visit 1)

No trial procedures should be done unless the patient has consented to taking part in the trial. Preferably the patient should also be informed about biobanking (including DNA) sampling already at this visit.

Patients who have been diagnosed with T1DM are to be provided with the consent form that contains information relevant for patients with T1DM.

Once the patient has consented to trial participation, he/she is considered to be enrolled in the trial and have started screening. The patient should be registered in the enrolment log and in the IRT as a screened patient. Patients will continue taking background medication for heart failure and treatment for their concomitant disorders if applicable. The screening visit may be conducted over multiple days, at the discretion of the investigator, as long as all screening procedures are performed and resulted within the allowable visit window in the flow chart. For example, a site may obtain written informed consent followed by collection of samples for the safety lab analysis and ECG. Remaining procedures may be performed on a separate day, once it is confirmed that the patient's laboratory values, including NTproBNP value, are not exclusionary.

Background medical therapy for HF should be stable for at least 1 week prior to Visit 1 and during screening period until Visit 2 (Randomisation) with the exception of diuretics which should be stable for only one week prior to Visit 2 to control symptoms.

If the patient meets the entry criteria, Visit 2 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, the site may make a phone contact to inform the patient that he/she is no longer required to return to the clinic for Visit 2.

Patients who fail screening (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 should be registered as a screen failure in IRT.

6.2.2 Treatment period

Randomisation will occur at Visit 2 using IRT. The patients will return to the clinic for regularly scheduled visits 4, 12, 32 and 52 weeks after randomisation during the first year of trial participation, and every 24 weeks thereafter for the duration of the trial, as specified in the Flow Chart. These on-site visits will assess the occurrence of safety and efficacy endpoints, trial medication compliance, concomitant therapy or intervention.

Telephone follow-up calls will be scheduled 10-12 weeks after every on-site visit starting after Visit 4 and continuing throughout the trial (see Flow Chart). The telephone contacts will focus on safety (e.g. hospitalisations or occurrence of AEs), changes in concomitant therapy and trial medication compliance.

The patients should be fasting at the Randomisation Visit (Visit 2).

Consenting patients with T1DM should be provided with the ketone monitoring device, the patient diary and Trial information card. The site staff are to provide instruction to the patient on how to properly use the ketone monitoring device and the importance of recording their glucose, ketone and insulin intake throughout the trial. At all subsequent visits, site staff are required to review the patient's diary with the patient to ensure that the diary is properly completed. Patients with T1DM should be provided with ketone monitoring supplies as necessary.

The optional blood sample for DNA will preferably be collected at the Randomisation Visit for all patients eligible for randomisation, but could also be taken at any later visit after the separate consent is signed.

At any time during the treatment period the Investigator is allowed to adjust and optimise HF background therapy 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 sites selected to participate in collection of samples for PK analysis, please refer to Section 5.4 and the Lab Manual for details.

Patients will be dispensed medication at each on-site visit and allocation of new kit number(s) will be managed through the IRT. Trial medication administration should be done after physical and laboratory assessments.

In the final analysis after the evaluation of recurrent HHF, alpha will be split into 0.001 to be used for the analysis of eGFR slope, and the rest will be transferred to the meta-analyses.

In case the trial is finished early at the time of interim analysis, using $\alpha_{interim}$ for the primary and key-secondary endpoints in the testing hierarchy according to the α-spending function in Section 7.4, the following α-split will be used for eGFR slope analysis and the meta-analyses:

0.1 * $\alpha_{interim}$ will be used for the eGFR slope analysis and
0.9 * $\alpha_{interim}$ will be transferred to the meta-analyses

In both the interim and final analyses, if the slope analysis is successful, the alpha of this branch will then be transferred to the meta-analyses.

The testing hierarchy is summarised in Figure 7.2: 1 showing the alpha-spending at the final analysis.

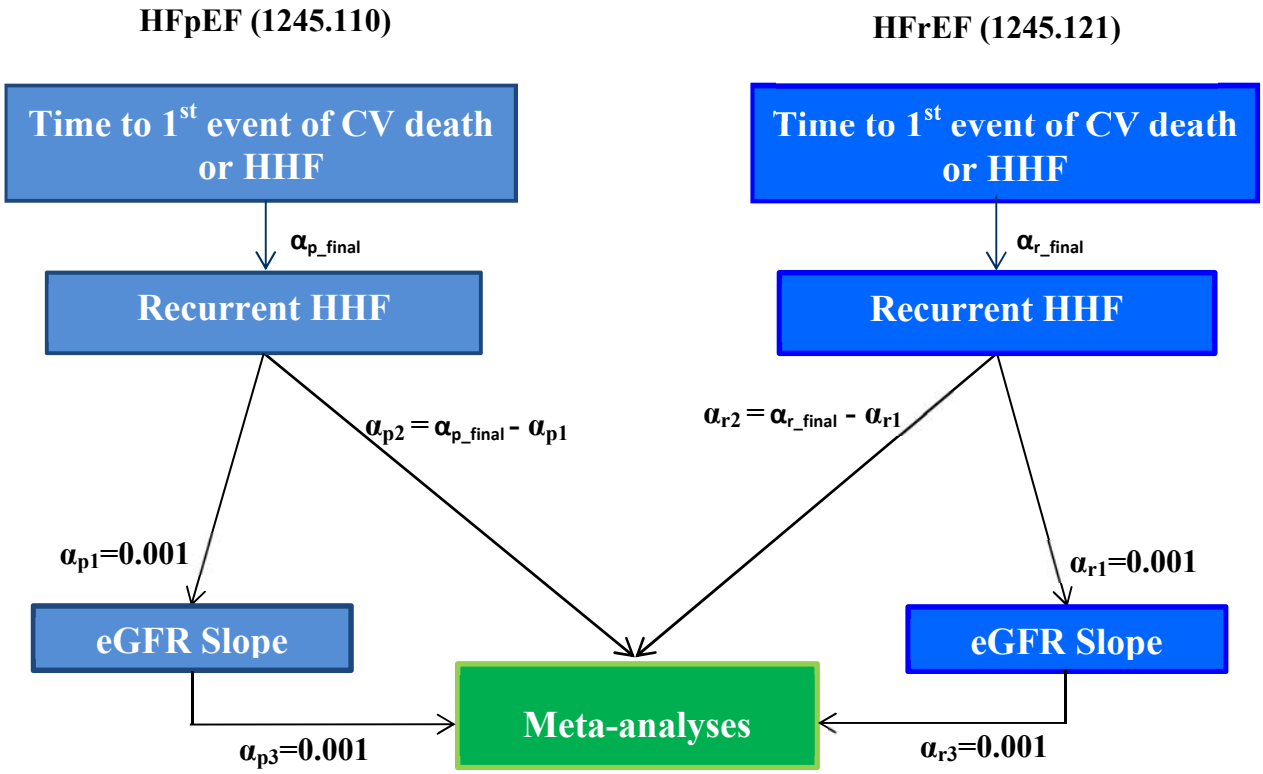

Figure 7.2: 1 Hierarchical analysis of trial in HFrEF (1245.121) and the parallel trial in HFpEF(1245.110) showing the alpha-spending at the final analysis

The other secondary endpoints will be evaluated in an exploratory manner.

7.3 PLANNED ANALYSES

The primary efficacy analysis will be based on the randomised set (RS), including all randomised patients.

7.3.2 Secondary endpoint analyses

The key secondary endpoint occurrence of adjudicated HHF (first and recurrent) will be modelled using a joint frailty model together with adjudicated CV death in order to take into account the dependence between the endpoints. The joint frailty model will be adjusted for the same covariates as the primary analysis.

The joint frailty model therefore models the hazards in the following way:

$r_i(t \mid \omega_i, Z_i) = \omega_i \exp\{\beta'_1 Z_i\} r_0(t)$

$\lambda_i(t \mid \omega_i, Z_i) = \omega_i^{\alpha} \exp\{\beta'_2 Z_i\} \lambda_0(t)$

where $r_i(t)$ is the hazard of the recurrent HHF for the ith patient, proportional to the baseline intensity function r_0. The hazard function of CV death for the ith patient is λ_i proportional to the baseline hazard λ_0. β_1 and β_2 are vectors of the regression coefficients of the covariate vectors Z_i including treatment, age (continuous), gender, history of DM, geographical region, LVEF (continuous) and eGFR $(CKD\text{-}EPI)_{cr}$ at baseline (continuous). Patient specific independent random effects are denoted by ω_i, with α giving the relation between HHF and CV death. Patient specific independent random effects denoted by ωi and are assumed to follow a gamma distribution with mean 1.

The resulting likelihood function can be solved assuming piecewise constant hazards.

Slope in change from baseline of eGFR $(CKD\text{-}EPI)_{cr}$ will be analysed by a random coefficient model allowing for random intercept and random slope per patient. The model will include the factors treatment, gender, geographical region, baseline LVEF, and status of DM as fixed effects and eGFR $(CKD\text{-}EPI)_{cr}$ at baseline (continuous), age (continuous), time, interaction of treatment by time, and interaction of eGFR $(CKD\text{-}EPI)_{cr}$ at baseline (continuous) by time as linear covariates and allow for randomly varying slope and intercept between patients. The model will include all on-treatment change from baseline data.

Since the slope is run on the change from baseline data, the intercept will model the acute drop, whereas the long-term effect is modelled by the slope.

Change from baseline in clinical summary score for HF symptoms and physical limitations domains of the KCCQ at week 52 will be evaluated by a mixed model for repeated measures data including age (continuous) and eGFR $(CKD\text{-}EPI)_{cr}$ at baseline (continuous) as linear covariates and baseline score by visit, visit by treatment, gender, geographical region, baseline LVEF, and status of DM at baseline as fixed effects. All on-treatment data up to week 52 will be included.

Occurrence of all-cause hospitalisation (first and recurrent) will be evaluated by a similar joint frailty model for adjudicated HHF, and will be modelled together with all-cause mortality.

The other time-to-event type of secondary endpoints will be analysed using the same Cox proportional hazards model as the primary analysis. This also applies for time to adjudicated CV death and all-cause mortality, rather than using the joint frailty model described above.

7.3.3 Further endpoint analyses

Further time-to-event endpoints will be analysed in the same Cox proportional hazards model as the primary analysis.

Change from baseline to 30 days after treatment stop of eGFR $(CKD\text{-}EPI)_{cr}$ will be evaluated by an ANCOVA model, including treatment group, gender, geographical region, baseline LVEF, and history of DM as fixed effects and baseline eGFR $(CKD\text{-}EPI)_{cr}$ (continuous) and age (continuous) as linear covariates.

An unmatched win ratio considering adjudicated CV death and adjudicated HHF will be analysed based on unmatched pairs. All patients randomised to empagliflozin will be compared to all patients randomised to placebo. Only common follow-up time will be considered for the comparison. Patients on empagliflozin are considered to have "won" the comparison if either the other patient has died while the patient on empagliflozin was still alive, or if both patients did not die, then if the other patient had more occurrences of HHF, or if the number of occurrences of HHF is the same but the time to the first occurrence of HHF is longer. The number of comparisons won is noted as N_W. Patients on empagliflozin are considered to have "lost" the comparison if the empagliflozin patient died while the patient on placebo was still alive, or if both patients did not die, then if the patient on empagliflozin had more occurrences of HHF, or if the number of occurrences of HHF is the same but the time to the first occurrence of HHF is shorter. The number of comparisons lost is noted as N_L. The win ratio is N_W / N_L.

The rules for winning and losing follow a modified Rogers 2014 [R16-4909] approach also considering the time to the first HHF event in case of a tie on the number of HHF events. The analysis of the unmatched win ratio will be conducted as described in Pocock 2012 [R16-4813].

Further longitudinal continuous endpoints will be analysed in a mixed model with repeated measures (MMRM), including age and eGFR $(CKD\text{-}EPI)_{cr}$ at baseline as linear covariates and visit by treatment interaction, baseline by visit interaction, geographical region, gender, baseline LVEF, and baseline history of DM as fixed effects.

The details of analyses will be defined in the TSAP prior to unblinding.

7.3.4 Safety analyses

In general, safety analyses will be descriptive in nature and will be based on BI standards. Standard BI summary tables and listings will be produced. No hypothesis testing is planned. Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the REP will be considered 'treatment-emergent'. The REP is defined as 7 days after last dose intake. 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).

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 highlighted in the listings. 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.

Vital signs (blood pressure, pulse rate), 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.

7.3.5 Pharmacokinetic analyses

Individual concentration-time data with descriptive statistics for empagliflozin trough concentrations will be presented in the clinical trial report.

7.3.6 Prespecified meta-analyses

On project level, meta-analyses are pre-specified. Data from this trial and a parallel trial in HFpEF patients (1245.110) will be pooled.

The statistical model will include trial as a covariate. More details are specified in the meta-analysis plans.

7.4 INTERIM ANALYSES

The safety and conduct of the trial will be monitored by an independent DMC. Details on this process are outlined in the DMC charter.

There will be one unblinded interim analysis to be conducted by the DMC. At the time of the interim analysis, the ExSC, SEC, Sponsor, CRO and all trial/site personnel will stay blinded to the interim results. For blinding, please also refer to Section 4.1.5.1.

After approximately 500 primary adjudicated outcome events have been accrued (approximately 60% of information is available) an interim analysis will be performed.

The following Hwang, Shih and De Cani α-spending function for the analysis at information fraction t_k (planned to be approximately 60%) with parameter γ = -8 will be used:

$$\alpha^*(\gamma, t_k) = \min\left\{\alpha, \quad \alpha\frac{1-e^{-\gamma t_k}}{1-e^{-\gamma}}\right\} = \min\left\{0.025, \quad 0.025\frac{1-e^{8t_k}}{1-e^{8}}\right\}$$

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook. Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the Sponsor's representatives or delegates, by the IRB / IEC and the regulatory authorities.

8.6 TRIAL MILESTONES

The start of the trial is defined as the date of the enrolment of the first patient in the whole trial (FPI).

The end of the trial is defined as the date of the last visit of the last patient in the whole trial (LPO).

The "Last Patient Drug Discontinuation" (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual Investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPDD at their site.

Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the Sponsor/CRO with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.

The Sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

For Japan only: When the trial is completed, the Investigator should inform the head of the trial site of the completion in writing, and the head of the trial site should promptly inform the IRB and Sponsor/CRO of the completion in writing.

8.7 PROTOCOL VIOLATIONS

For Japan only: The investigator should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to trial subjects or for other medically compelling reason, the principal investigator

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impartial witness (if the patient returns on another day). If a different impartial witness is present, the entire ICF process must be repeated.

- Participating patients will provide a thumb impression or make a mark (or signature if the patient is able to sign him/herself) on the signature section of the ICF forms.

- The date of the patient's signature will be left blank as the patient is illiterate. However, if the patient is able, he/she will date the mark/signature personally.

- The impartial witness or the site designated personnel may write the name of the patient on the ICFs.

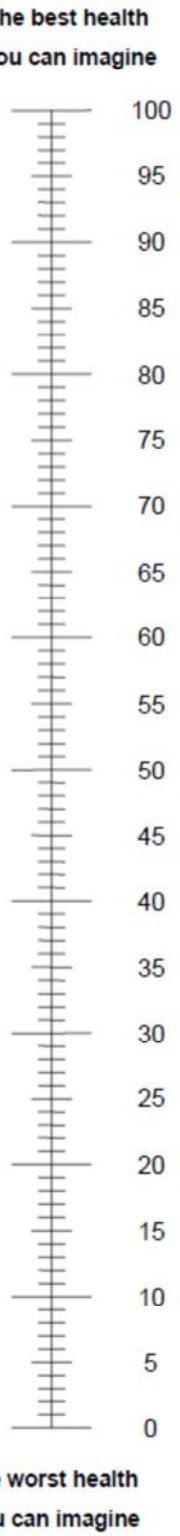
- The impartial witness should enter his/her name, sign and personally date the witness section of the ICFs. In countries where local data protection regulation permits it, the address or identification number of the impartial witness should also be entered. The signature then attests that the content of the patient information sheet ICF was accurately explained to the patient, who apparently understood and freely gave consent to participate in the trial.

- The designated site personnel also signs and personally dates the ICF.

- The same process as outlined above will be followed for obtaining consent for the optional sampling for biobanking (including DNA).

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

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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	❑	❑	❑	❑	❑	❑

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		**Jardiance**	
Name of active ingredient:		**Empagliflozin**	
Protocol date: **10 NOV 2016**	**Trial number:** **1245.121**		**Revision date:** **20 Nov 2019**

	• eGFR ≥ 20 mL/min/1.73m2 at Visit 1
Test product(s):	Empagliflozin
dose:	10 mg q.d
mode of administration:	p.o.
Comparator products:	Placebo
dose:	NA
mode of administration:	p.o.
Duration of treatment:	• 4-28 days screening period • The study was designed based on an assumption of 18 months recruitment and an event rate of 15%. The actual length of the recruitment period may be extended beyond 18 months and the follow-up period may be adjusted to achieve the 841 confirmed primary outcome events. The estimated total trial duration and length of the double-blind treatment for each patient will vary accordingly. • Follow-up visit 30 days after end of treatment The trial will continue until the required number of adjudicated primary endpoint events have occurred to be able to comply with the objective of the trial.
Endpoints	Primary endpoint; The composite primary endpoint for this trial is the time to first event of adjudicated CV death or adjudicated HHF in patients with HFrEF. Key secondary endpoints which are part of the testing strategy, are the following; • Occurrence of adjudicated HHF (first and recurrent) • eGFR $(CKD\text{-}EPI)_{cr}$ slope of change from baseline Other secondary endpoints are: • Time to first occurrence of chronic dialysis or renal transplant or sustained reduction of ≥40% eGFR $(CKD\text{-}EPI)_{cr}$ or o sustained eGFR $(CKD\text{-}EPI)_{cr}$ <15 mL/min/1.73 m^2 for patients with baseline eGFR ≥30 mL/min/1.73 m^2 o sustained eGFR $(CKD\text{-}EPI)_{cr}$ <10 mL/min/1.73 m^2 for patients with baseline eGFR <30 mL/min/1.73 m^2

Trial Period	**Screening[1]**	**Randomised Treatment Period [2]**															**Follow Up Period [3]**		**Relevant CTP section**
Visit	**1**	**2**	**3**	**4**	**5 Phone call**	**6**	**7 Phone call**	**8**	**9 Phone call**	**10**	**11 Phone call**	**12**	**13 Phone call**	**14**	**15 Phone call**	**16**	**EOT Visit**	**FU Visit [3]**	
Trial week	**-3**	**1**	**4**	**12**	**22**	**32**	**42**	**52**	**64**	**76**	**88**	**100**	**112**	**124**	**136**	**148**	**EOT Visit**	**EOT + 30 days**	
Days from Randomisation Visit window [4]	**-28 to -4**	**1**	**29±7**	**85 ±7**	**155 ±7**	**225 ±7**	**295 ±7**	**365 ±7**	**449 ±7**	**533 ±7**	**617 ±7**	**701 ±7**	**785 ±7**	**869 ±7**	**953 ±7**	**1037 ±7**	**---**	**--- ±7**	
Fasting status [5]	**NF**	**F**	**NF**	**NF**	**-**	**NF**	**-**	**NF**	**-**	**NF**	**-**	**NF**	**-**	**NF**	**-**	**NF**	**F**	**F**	
eGFR (CKD-EPI$_{cr}$ formula)	X	X	X	X		X		X		X		X		X		X	X	X	5.3.4.1
UACR	X	X	X	X		X		X		X		X		X		X	X	X	5.3.4.1
PK sampling (substudy) [16]				X															5.4.1
Sampling for biobanking of serum/plasma/urine/ DNA (optional, requires separate informed consent) [17]		X[18]		X				X											5.5.1
Dispense trial medication [19]		X	X	X		X		X		X		X		X		X			4.1.4, 6.2.2
Return Medication/ medication compliance check			X	X		X		X		X		X		X		X	X		4.3

SGLT-1	Sodium-glucose co-transporter 1
SGLT-2	Sodium-glucose co-transporter 2
SMQ	Standardised MedDRA Query
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TDMAP	Trial Data Management and Analysis Plan
TIA	Transient Ischaemic Attack
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
UACR	Urine Albumin Creatinine Ratio
ULN	Upper limit of normal
UTI	Urinary Tract Infection
VAS	Visual Analogue Scale
WBC	White Blood Cells
WOCBP	Women of childbearing potential

in the clinical trial setting will help support the assessment of benefit-risk of empagliflozin for patients over 85 years. Special caution should be used in these patients, who may be at increased risk of adverse consequences attributed to empagliflozin- related volume depletion.

Many patients with chronic HF have renal impairment, and to ensure that the trial results reflect this population, patients with eGFR ≥ 20 ml/min/1.73m^2 can be included. In the EMPA-REG Outcome trial, the cardiovascular benefits of empagliflozin were not driven by its pharmacological effect of lowering blood glucose and were consistently noted in patients with different degrees of renal impairment, including patients with eGFR between > 30 and < 45 ml/min/1.73m^2. In previous trials in patients with T2DM, the safety profile in moderate and severe renal impairment was comparable to the overall trial population [P17-10453]. Renal safety will be closely monitored throughout the trial. Refer to Sections 5.3.4.1 and 5.3.7.1.

The overall tolerability and safety profile outlined in Section 1.2, and the current IB, supports chronic administration of empagliflozin 10 mg in human studies.

Investigators will be encouraged to treat participants to best standard of care in compliance with the local guidelines and recommendations for HF, and diabetes if present. Based on the putative mechanism of actions (reviewed in Section 2.1) and the result of the EMPA-REG OUTCOME trial it is assumed that patients with HFrEF should benefit from empagliflozin treatment on top of guideline-directed therapies. The safety profile of empagliflozin in these patients should follow a similar trend which was previously observed in over 10000 patients with T2DM treated with empagliflozin, including patients with high CV risk. Safety will be ensured by close monitoring of the subjects for AEs both clinically and by laboratory testing.

To continue the assessment of the long-term safety of empagliflozin, adjudication of cardiovascular events, certain hepatic events, and ketoacidosis will be performed in this trial. The progress of the trial will also be assessed at regular intervals by an independent Data Monitoring Committee (DMC). For further details please refer to Section 3.1.1.

One interim analysis is planned after approximately 500 primary events have been accrued. If the prespecified criteria for stopping for success at the interim analysis has been reached, the Executive Steering Committee (ExSC) and the Sponsor will be informed. The final decision whether to stop the trial will be made by Sponsor. For further details refer to Section 7. 4.

As with all drugs, the potential for hypersensitivity and allergic reactions has to be taken into consideration when empagliflozin is administered. Other risks to the patients are the risks inherent to any investigational medicinal product used in a clinical trial setting, such as unexpected adverse clinical or laboratory events.

Empagliflozin causes intravascular volume contraction. In patients with volume depletion, correcting this condition prior to initiation of empagliflozin is recommended.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by the Sponsor and regulators. Therefore, this trial requires timely detection, evaluation, and

- ensure appropriate oversight of vendors.

Statistical Evaluation will be done by BI according to BI SOPs and Data Management will be done by the CRO in accordance with CRO SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial will be defined according to BI and CRO SOPs and the applicable SOPs will be listed in the contract with the CRO.A list of responsible persons and relevant local information can be found in the ISF.

A central laboratory service and an Interactive Voice/Web-based Response System (IRT) - vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in ISF.

3.1.1.1 Clinical Event Committee

An independent external committee (Clinical Event Committee, [CEC]) will be established to adjudicate centrally and in a blinded fashion whether pre-specified criteria for adjudication endpoints are met.

For any events that qualify for adjudication, trial sites will be required to provide in a timely manner clinical documentation such as (but not limited to) electrocardiograms (ECGs), laboratory values, angiography reports, echocardiography reports, Computed Tomography (CT) and/or Magnetic Resonance Imaging (MRI reports), discharge summaries, and autopsy reports to support the external event adjudication. If the CEC requests more data, all efforts must be made by the site to collect all available data to support adjudication.

For reporting of events and exemption from expedited reporting refer to Section 5.3.7.2.

The tasks and responsibilities of the CEC, and the pre-specified criteria for adjudication will be specified in a charter. The CEC will maintain the adjudication results in writing.

3.1.1.2 Hepatic external adjudication

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 hepatic 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 laboratory values, histological analysis, reports from ultrasound, CT, MRI, 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).

an exhaustive list, it provides some guidance as to when such re-screening and/or re-testing would be considered appropriate.

Re-testing:

Re-testing for eligibility criteria is only to be performed once for a laboratory result which is obviously received beyond stability at the central laboratory or thought to be a spurious result based on previously available laboratory results. The re-test should be carried out as soon as possible so the laboratory test results will be received within the next planned visit windows in order to avoid protocol window violations.

Re-screening:

- Re-screening of the same patient is only allowed once.
- The patient should be declared a screening failure in the electronic Case Report Form (eCRF) and IRT with their original patient number.
- Upon re-screening, the IRT system will allocate a new screening number for the patient
- The patient must be re-consented using the current approved version of the information sheet and consent form.

A log of all patients enrolled into the trial (i.e. who have signed ICF) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for trial entry

The trial will be performed in patients with chronic heart failure with an ejection fraction ≤ 40%.

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. Age ≥ 18 years at screening. For Japan only: Age ≥ 20 years at screening
2. Male or female patients. WOCBP[a] must be ready and able to use highly effective methods of birth control per ICH M3 (R2) [R09-1400] 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
3. Patients with chronic HF diagnosed for at least 3 months before Visit 1, and currently in HF NYHA class II-IV
4. Chronic HF with reduced EF defined as LVEF ≤ 40% per local reading (obtained under stable[b] condition by echocardiography, radionuclide ventriculography, invasive angiography, MRI or CT). A historical LVEF may be used if it was measured within 6 months prior to visit 1 or the LVEF may be measured after study consent has been

The right to withdraw informed consent at any time for any reason also applies to the optional informed consent to biobanking (including DNA sampling), which is separate from the consent for trial participation.

If the patient withdraws informed consent for participation in the trial, the trial will end for that patient. The patient should stop taking trial medication and should be asked to complete the end of treatment (EOT) visit and follow-up procedures as described in the Flow Chart. Completing these procedures is strongly recommended for the patient's safety. Patients that withdraw informed consent will not be replaced.

Vital status must be collected at the end of trial for patients that withdraw consent from trial participation, if allowed by local regulations.

Patients lost to follow-up
If a patient is lost, every effort will be made by the Investigator and site staff to contact and locate the patient before the patient is declared lost to follow-up. Investigators and site staff must use every possible allowable means, according to local regulations, to locate patients who have missed visits. Efforts to contact the patient may include but are not limited to:

- Calling all numbers for patient and listed contacts (including in the evening and on weekends).
- Calling primary care physician, referring specialist and/or other listed physicians for more recent information, date of last office visit or to determine vital status.
- Sending an email and follow up with mailing certified letters (return receipt requested) to all known patient addresses and all listed contacts (e.g., relatives, friends, neighbours) that were provided by the patient.
- Reviewing patient's records and medical notes for any details of a hospitalisation, doctor's visit or other procedure that may indicate location or status of subject.
- Use Internet to search for possible contact information for the patient.
- Try reverse directory for phone numbers to get possible addresses and/or new contact details.
- Utilise social networking sites.
- Check local, regional, and national public records to locate the patient or search for vital status in accordance with local law.
- Consider home visit.
- Contact patient finder service.

Pregnancy
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 5.3.4.2).

An excessive withdrawal rate can have a severe negative impact on the scientific value of the trial. The "Intention To Treat" analysis requires that all randomised patients be followed until trial end even if the trial medication was temporarily interrupted, discontinued or never started. Every effort should be made to keep the patients in the trial as scheduled. This includes careful patient selection and appropriate explanation of the trial requirements and

5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

A complete physical examination will be performed by the Investigator according to the Flow Chart. Documentation of, and findings from the physical examination, must be part of the source documents available at the site.

5.3.2 Clinical routine examination

During the course of the trial the patient may undergo examinations that are not trial specific but a part of the clinical routine such as:

- ECG
- Echocardiography, radionuclide ventriculography, invasive angiography, MRI or CT.

In order to capture arrhythmias and significant changes in ECG, and LVEF measurements in echocardiography (or similar), the Investigator will be asked to enter the results from these examinations in the eCRF.

If the patient has an ICD the Investigator will be asked to enter information gathered from interrogations of the ICD in the eCRF

5.3.3 Vital signs

Vital signs to be measured are SBP, DBP and pulse rate.

5.3.4 Safety laboratory parameters

All safety laboratory samples will be collected as described in the Flow Chart.

All parameters that will be determined during the trial conduct are listed in Table 5.3.4: 1. The analysis will be performed by a central laboratory. The respective reference range and details about sample handling and shipment will be provided in the ISF (Lab Manual).

the treating physician/Investigator and stored locally. Any clinically relevant new changes in the ECG (regardless of patients' symptoms) should be reported as AEs and followed up and/or treated locally until normal or stable condition. ECG associated with cardiovascular endpoints must be submitted to the adjudication committee, together with the baseline ECG.

Each ECG tracing stored locally should be labelled with trial and patient number, patient initials and date.

5.3.6 Other safety assessments

5.3.6.1 Outcome of non-fatal stroke

For patients experiencing a non-fatal stroke the Modified Rankin Scale (MRS) should be used to assess stroke outcome (Appendix 10.4). The scale is widely used in clinical practice and consists of grades, from 0 to 6, with 0 corresponding to no symptoms and 6 corresponding to dead. Investigators will measure and score the MRS based on an interview with the patient at the next regular on-site visit after the onset of the stroke. In those cases where MRS assessment occurred within 90 days after the stroke, a repeat MRS-assessment should be performed at the next on-site visit. For patients who experience a non-fatal stroke less than 90 days prior to the study closure date, the final MRS assessment will occur at the final study visit for that patient. Detailed information on the stroke (date and time of onset, type, symptoms, method of detection, outcome) will be collected in the eCRF.

5.3.6.2 Hepatic events

For assessment of hepatic events please refer to Section 3.1.1.2.

5.3.7 Assessment of adverse events

5.3.7.1 Definitions of AEs

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.

Adverse reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A serious adverse event (SAE) is defined as any AE which:

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF.

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 ULN.

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

The Investigator should refer to follow-up schedule for renal endpoint events described in Section 5.3.4.1.

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 and measurement of serum beta-hydroxybutrate levels. Other diagnostic criteria which can support the diagnosis of ketoacidosis are urine ketones and anion gap >10.

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.

Events leading to lower limb amputation
Any event leading to a lower limb procedure of amputation, auto-amputation or disarticulation as defined below is considered as an AESI.

"Amputation is a resection of a limb through a bone. Disarticulation is a resection of a limb through a joint. Auto-amputation is a spontaneous separation of non-viable portion of the lower limb.

Not included in this definition are debridement (removal of callus or dead tissue), procedures on a stump (like stump revision, drainage of an abscess, wound revision etc.) and other procedures (e.g., nail resection or removal) without a concomitant resection of a limb (amputation or disarticulation)." (International Working Group of Diabetic Foot, 2015).

exposure during pregnancy (DEDP) immediately (within 24 hours) to the Sponsor's /CRO's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the Sponsor's/CRO's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (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 Trials 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.

Exemptions to SAE reporting
A list of adverse events that commonly occur in the trial population or which are components of trial endpoints are exempted from reporting on the SAE form, if the event onset is after randomization and the event does not qualify as AESI. These events are known consequences of the underlying disease and it is not possible, based on a single case, to conclude that there is a reasonable possibility that the investigational drug caused these events. Pulmonary complications of heart failure are added to the exemption list, since patients with HF commonly experience such complications. Thus these events could be reported as pulmonary events, although the underlying aetiology was attributed to HF.

Regardless of relationship to trial medication, these events will not be reported by the Sponsor to regulatory agencies or ethics committees in an expedited manner unless they qualify as an AESI (for definition of AESI, see 5.3.7.1) with fulfilment of expedited regulatory safety reporting requirements.

These events include:

Cardiovascular (CV) related death. The CV related death also includes death due to undetermined cause, and death due to pulmonary events that may be secondary to complications of heart failure such as pulmonary oedema, pulmonary vascular disease secondary to heart disease.

HF hospitalisation

Non-fatal MI

Non-fatal stroke and Transient ischemic attack (TIA)

CV hospitalisation events

Pneumonia (fatal and non-fatal)

New or exacerbated COPD (fatal and non-fatal)

Approx. 8.5 mL blood will be drawn into a PAXgene Blood DNA Tube, preferably at Visit 2. In Korea, a 6 ml K2 EDTA tube will be used.

Plasma banking
Approx. 10 mL blood will be drawn into an EDTA blood collection tube.

Serum banking
Approx. 8.5mL blood will be drawn into a serum separation tube.

Urine banking
Approx. 10 mL urine (preferably morning mid-stream urine) will be collected.

For all biological samples collected, detailed instructions on sampling, preparation, processing, shipment and storage are provided in the laboratory manual. Plasma, serum and urine samples will be stored at an external biobanking facility contracted by the Sponsor; DNA, extracted from the original whole blood sample, will be stored at the Sponsor except for samples collected in China. These samples will be stored at an external biobanking facility contracted by the Sponsor.

5.6 OTHER ASSESSMENTS

5.6.1 EQ-5D

Health related quality of life will be assessed using the EQ-5D-5L version (refer Appendix 10.2.1) according to the Flow Chart. EQ-5D is a standardised instrument for use as a measure of health outcome. It is designed for self-completion by patients.

The EQ-5D self-report questionnaire (EQ-5D) essentially consists of 2 pages comprising:

- the descriptive system (five dimensions of health; namely mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension comprises five levels (no problems, slight problems, moderate problems, severe problems, extreme problems/unable to perform activity).
- the EQ-VAS (visual analogue scale) which records the patient's self-rated health status on a vertical graduated (0 – 100) VAS.

For further description on completion of the questionnaire refer to the last part of Section 5.2.1.

5.6.2 Health Care Resource Utilisation (HCRU)

HCRU data will be used for health economic analysis (i.e. cost-effectiveness analysis) required for reimbursement decisions. Resource use will be captured via interview with the patient and entered in the eCRF at all on-site visits during the complete trial period and will allow calculation of direct and indirect costs. Main components to be collected are unscheduled outpatient visits and hospitalisations.

This is an event driven trial. Patients will remain in the treatment period until the necessary number of events is reached.

Permanent trial medication discontinuation is only justified when clear persistent contraindications arise, or when the patient requests to stop trial medication. See Section 6.2.4 for details on how to handle trial medication discontinuations, and Section 3.3.4 for when discontinuation from trial is justified.

6.2.3 End of Treatment, Follow Up Period and Trial Completion

Patients on treatment at the time when required number of outcome events are reached (see Section 7.7), will be asked to return to the clinic for the EOT visit with the proposed time schedule communicated via an investigator letter, followed by the Follow Up Visit 30 days later. If a patient has permanently discontinued the trial medication and is not willing to return to the clinic for predefined trial visits, a telephone call at the end will be required, to document the occurrence of outcome events and vital status. If possible, other AE's and concomitant therapy changes to be recorded. Sites should encourage the patient to return to the clinic for the final study visit (ref. Section 3.3.4.1).

During the EOT Visit all trial medication will be collected and compliance calculated, occurrence of safety and efficacy endpoints will be assessed and complete physical examination, laboratory assessments, and ECG will be performed (ref. Flow Chart).

The Follow Up Visit should also be a clinic visit for all patients, and the following examinations should be performed (ref. Flow Chart):

- Concomitant Therapy
- Vital signs and body weight
- NYHA classification
- Documentation of any adverse events and endpoints
- Vital status
- Blood and urinary sampling
- KCCQ and EQ-5D
- Modified Rankin Scale (only in case of suspected stroke within last 90 days)

The patients should be fasting at the EOT and Follow Up Visit.

6.2.4 Early discontinuation of trial medication and trial termination

The EOT activities will be performed when a patient discontinues trial medication treatment permanently.

Note: The EOT activities should not be used for temporary interruptions of trial medication.

All patients will have a follow up visit 30 days following discontinuation of trial medication, irrespective whether they complete the treatment period or prematurely discontinue trial medication.

The safety analysis will be based on the treated set (TS), which consists of all patients treated with at least one dose of the trial medication.

For both efficacy and safety analyses, treatment will be evaluated as randomised.

For serum creatinine and values based on upon this measurement such as eGFR, baseline will be defined as the mean of all available measurements from the screening visit until start of randomised trial medication.

Baseline status of DM is defined as:

- DM: any pre-treatment HbA1c above 6.5 or history of DM as entered in the eCRF on the medical history page
- Pre-DM: no history of DM and no HbA1c >=6.5 before treatment and a pre-treatment HbA1c value of >= 5.7 and <6.5
- Non-DM: not meeting criteria of DM or pre-DM above

For all other endpoints, baseline will be defined as the last available measurement before start of randomised trial medication.

7.3.1 Primary endpoint analyses

The primary endpoint will be analysed using a Cox proportional hazards model with age (continuous), gender, treatment, geographical region, baseline status of diabetes (DM, pre-DM, no DM), baseline LVEF (≤30%, >30% to ≤35%, > 35%) and eGFR $(CKD\text{-}EPI)_{cr}$ at baseline (continuous) as covariates.

The time to the event of interest will be calculated by (event date − randomisation date) +1. All events observed after randomisation until completion of the planned treatment phase will be included in the analysis. Patients who do not have an event during the trial period will be censored at the individual end of the planned treatment phase or the last day that the patient was known to be free of the event, whichever is earlier. Time to censoring will be calculated by (individual end of the planned treatment phase or the last day known to be free of the event – randomisation date) + 1. For patients who have more than one primary endpoint event during the trial, the time to the first occurrence of the primary endpoint event will be considered for the primary analysis. Only the adjudicated and confirmed events are included in the primary analysis.

To detect any heterogeneity in the treatment effect among diabetic patients, pre-diabetic patients and non-diabetic patients, a subgroup analysis will be performed by including diabetic status by treatment interaction term into the Cox model.

Standard subgroup analyses of the primary endpoint include geographical region, sex, BMI, renal function, prognostic factors, age, ethnicity, race and different background therapies etc. More details will be specified in the TSAP.

A sensitivity analysis will be provided based on the treated set but only including any events up to 30 days after treatment discontinuation.

The chosen alpha-spending function spends an alpha-level of 0.001 at the time of approximately 60% of information for the interim analysis.

If the p-value for the primary endpoint and the p-value for CV-death (from the primary Cox proportional hazards model) are lower than the cut-off to be evaluated from the alpha spending function (planned at 0.001 one-sided), the trial will be stopped for overwhelming efficacy. In this case, the hierarchy will be tested as specified in Section 7.2. Otherwise the trial will be continued.

The final alpha level is therefore planned at a one-sided alpha-level of 0.0248 which translates in a two-sided alpha of 0.0496.

The event rate will be assessed by the trial team in a blinded manner only during trial recruitment and before the unblinded interim analysis (see Section 7.7).

7.5 HANDLING OF MISSING DATA

There will be no imputation for safety data or for time-to-event type of endpoints. For patients who discontinue the trial treatment prematurely, all efforts will be made to follow the patients for survival and any other endpoints, including the primary and key secondary endpoints, until the end of the trial.

For the slope analysis of eGFR $(CKD\text{-}EPI)_{cr}$, all available on-treatment change from baseline data will be used. Patients without on-treatment data after randomisation will not be included in this analysis.

For the analysis of change from baseline to 30 days after treatment stop, only available data will be used. Only patients with post-treatment data will be used in this analysis.

For other longitudinal efficacy endpoints such as KCCQ scores, MMRM methodology will be used. Models will be run on both all observed data and all observed on-treatment data. Details of the imputation rule will be given in the statistical analysis plan.

An eGFR (CDK-EPI) reduction is considered sustained, if it is determined by two consecutive post-baseline central laboratory measurements separated by $\geq$ 30 days. If only one post-baseline value is available and the patient dies within 60 days of this measurement without second measurement $\geq$ 30 days after the first, then the eGFR reduction is also considered sustained.

7.6 RANDOMISATION

The trial will be performed as a double-blind design with respect to placebo and empagliflozin. Subjects will be randomised to the trial treatments in a 1:1 ratio. The randomisation will be stratified by the following factors:

- Geographical region (North America, Latin America, Europe, Asia, Other)
- Status of DM at screening :

should prepare and submit the records explaining the reasons thereof to the Sponsor/CRO, and retain a copy of the records.

8.8 COMPENSATION AVAILABLE TO THE PATIENT IN THE EVENT OF TRIAL RELATED INJURY

For Japan only: In the event of health injury associated with this trial, the Sponsor is responsible for compensation based on the contract signed by the trial site.

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10.2 PATIENT REPORTED OUTCOMES

10.2.1 EQ-5D

Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY
- I have no problems walking ❑
- I have slight problems walking ❑
- I have moderate problems walking ❑
- I have severe problems walking ❑
- I am unable to walk ❑

SELF-CARE
- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*
- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION
- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

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10.2.2 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**
❑	❑	❑	❑	❑	❑

10.3 NYHA FUNCTIONAL CLASSIFICATION

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

10.4 MODIFIED RANKIN SCALE

Scale	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead