Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. DOI: 10.1056/NEJMoa2107038

This supplement contains the following items:

CLINICAL TRIAL PROTOCOL

	Document Number:	c03946327-01
EudraCT No.:	2016-002278-11	
BI Trial No.:	1245.110	
BI Investigational Product(s):	Empagliflozin	
Title:	A phase III randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic **H**eart **F**ailure with **p**reserved **E**jection **F**raction (**HFpEF**).	
Lay title:	**EMP**agliflozin outcom**E** t**R**ial in patients with chr**O**nic hea**R**t failure EMPEROR-Preserved	
Clinical Phase:	III	
Trial Clinical Monitor:	[redacted]	
Coordinating Investigators	[redacted]	
Status	Final Protocol	
Version and Date:	**Version: 1.0**	**Date: 09 NOV 2016**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		**Jardiance**	
Name of active ingredient:		Empagliflozin	
Protocol date **09 NOV 2016**	**Trial number:** **1245.110**		**Revision date:**

Title of trial:	A phase III randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic Heart Failure with preserved Ejection Fraction (HFpEF)
Coordinating Investigator:	[redacted]
Trial site(s):	Multicentre trial in approximately 22 countries.
Clinical phase:	III
Objective(s):	The objective of this event-driven trial is to demonstrate superiority of empagliflozin 10 mg versus placebo in patients with symptomatic, chronic HF and preserved ejection fraction (LVEF > 40%) under stable treatment of HF symptoms
Methodology:	Randomised, double blind, placebo controlled, parallel group trial.
No. of patients: **total entered:**	Approximately 4126 randomised Based on blinded assessment of the event rate of the primary endpoint, which is performed during recruitment before any interim

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	unblinding, the number of patients randomised may be increased up to 6000. The number of primary outcome events required is not affected by this consideration.
each treatment:	Approximately 2063 (2 treatment groups)
Diagnosis :	Heart failure (HF) with preserved ejection fraction (EF).
Main criteria for inclusion:	• Patients with chronic HF diagnosed for at least 3 months before Visit 1 and currently in HF NYHA class II-IV • Chronic HF with preserved EF defined as LVEF > 40 % per local reading (obtained by echocardiography, radionuclide ventriculography, invasive angiography, MRI or CT), and no prior measurement of LVEF ≤ 40% under stable conditions. The EF must have been obtained and documented at Visit 1 or within 6 months prior to Visit 1, and more than 90 days after any Myocardial Infarction. • Elevated NT-proBNP > 300 pg/ml for patients without AF, OR > 900 pg/ml for patients with AF, analysed at the Central laboratory at Visit 1 • Patients must have at least one of the following evidence of HF: a) Structural heart disease (left atrial enlargement and/or left ventricular hypertrophy) documented by echocardiogram at Visit 1, OR b) Documented hospitalisation for HF (HHF) within 12 months prior to Visit 1 • Oral diuretics, if prescribed to patient according to local guideline and discretion of the Investigator, should be stable for at least 1 week prior to Visit 2 (Randomisation) • eGFR $(CKD\text{-}EPI)_{cr} \geq 20$ mL/min/1.73m^2 at Visit 1

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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:	• 4-21 days screening period • Approximately 20-38 months double-blind treatment until the required number of adjudicated primary events is reached with empagliflozin or placebo • Follow-up visit 30 days after end of treatment The trial will continue until required number of adjudicated primary endpoint events have occurred to be able to comply with the objective of the trial.
Endpoints	<u>Primary endpoint;</u> The composite primary endpoint for this trial is the time to first event of adjudicated CV death or adjudicated HHF in patients with HFpEF. <u>Key secondary endpoints;</u> The 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 sustained reduction of ≥40% eGFR $(CKD\text{-}EPI)_{cr}$ or

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	○ 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 ○ 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 · Time to first adjudicated HHF · Time to adjudicated CV death · Time to all-cause mortality · Time to onset of diabetes mellitus (DM) in patients with pre-DM · Change from baseline in clinical summary score (HF symptoms and physical limitations domains) of the KCCQ at week 52 · Occurrence of all-cause hospitalisation (first and recurrent)
Safety criteria:	· Adverse events (AE) · AE of special interest (AESI) · Incidence and intensity of AE including serious AE (SAE) · Withdrawal from trial medication due to AE · Clinically relevant new finding or worsening of existing condition on physical examination · Clinically relevant changes in laboratory measurements from baseline · Assessment of vital status
Statistical methods:	The overall type one error rate will be preserved at a level of 0.05 (2-sided). The primary and the key secondary endpoints will be analysed in the following testing hierarchy: 1. Time to first event of adjudicated CV death or adjudicated HHF 2. Occurrence of adjudicated HHF (first and recurrent) 3. eGFR $(CKD\text{-}EPI)_{cr}$ slope of change from baseline At 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 analysis, and the rest will be transferred to the meta-analyses which will

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	include this trial and the trial conducted in parallel in patients with HFrEF (1245.121). For the primary analysis of the primary endpoint a Cox proportional hazards regression model of time to first event of adjudicated CV death or adjudicated HHF with covariates of age (continuous), gender treatment, geographical regions, history of DM (DM, Pre-DM, No DM), LVEF (continuous) and eGFR $(CKD\text{-}EPI)_{cr}$ at baseline (continuous) will be used. The primary analysis will be performed on the randomised (intention to treat) set. Approximately 4126 patients will be randomised to accumulate approximately 841 confirmed primary events within 18 months accrual and approximately 20 additional months follow-up period to achieve a power of ~90%. The number of patients randomised may be increased up to 6000 patients based on a blinded assessment of the event rate, which is performed during recruitment before any interim unblinding. The number of 841 confirmed primary outcome events is not affected by this consideration. One interim analysis is planned after approximately 500 primary adjudicated events have been accrued. If the pre-specified 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 on whether to stop the trial will be made by the Sponsor. Safety will be evaluated descriptively on the treated set.		

FLOW CHART

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]	**-21 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**	
Informed Consent [6]	X																		3, 8
In-/exclusion criteria	X	X																	3.3
Medical History/ Concomitant diagnoses	X																		8.3.1
Screening (register in IRT)	X																		6.2.1
Randomisation (via IRT)		X																	6.2.2
Demographics[7]	X																		-
NYHA classification	X	X	X	X		X		X		X		X		X		X	X	X	5.2.2 10.3
Physical exam		X				X		X		X		X		X		X	X		5.3.1
Clinical routine exam[8]		X	X	X		X		X		X		X		X		X	X		5.3.2
Vital signs [9]	X	X	X	X		X		X		X		X		X		X	X	X	5.3.3
Height	X																		-

Trial Period	**Screening[1]**	**Randomised Treatment Period[2]**															**Follow Up Period [3]**		**Relevant CTP section**
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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	5.2.4
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 [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 Tests	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	X	5.5
High-sensitivity TroponinT		X																	5.5
HbA1c [15]	X	X		X		X		X		X		X		X		X	X		-

Trial Period	**Screening[1]**	**Randomised Treatment Period[2]**															**Follow Up Period[3]**		**Relevant CTP section**
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Lipid profile panel		X						X				X					X	X	5.3.4
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
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

1. The screening procedures can be done on different days within the time window
2. From Visit 8 and onwards, on-site visits will be scheduled every 24 weeks until end of trial.
   Patients who prematurely discontinue trial medication will perform EOT visit and Follow Up visit, and then continue with scheduled visits until the trial is stopped.
   For patients not willing to attend scheduled visits, telephone calls must be made regularly (ref. Section 3.3.4.1) to document any occurrence of outcome events and vital status.
   If the trial continues beyond 148 weeks, visits are to be repeated with same intervals as from week 64 and onwards.
3. Timepoint for the EOT will be communicated via an Investigator letter when the Sponsor is confident that required number of events will be reached within a reasonable timeframe (ref. Section 3.1 and 6.2.3). All patients will have a follow up visit 30 days following regular or premature completion of the treatment period.
4. Visit dates are determined per the date of randomisation. If a visit is missed, the patient should be returned to the original visit schedule at the next visit.
5. NF = non fasting, F=fasting. Fasting means no food or liquid intake except for water the last 10-16 hours
6. Informed consent may be obtained prior to visit 1 in order to give time to collect medical records. Visit 1 should be performed within 30 days of signing the informed consent form (ICF).
7. If accepted by local authorities or ethic committees, demographics to be collected in this trial are gender, year of birth, ethnicity and race.
8. The Investigator will be asked to record results from clinical routine examinations like ECG, echocardiography or similar procedures (MRI, CT-scan, etc.), and if applicable information gathered from interrogations of the ICD in the eCRF.
9. Vital signs measurements in this trial are blood pressure and pulse rate.
10. Protocol specified outcome events should be collected on the appropriate eCRF page only. The outcome events which are exempted from SAE reporting are listed in Section 5.3.6.
11. For patients with non-fatal stroke the Modified Rankin Scale (MRS) should be scored by the investigator based on an interview 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..
12. For the 12-lead ECG done at the baseline and EOT visit, the interpretation of the tracing must be made locally by a qualified physician and documented on the ECG section of the eCRF. In case of any cardiac symptoms (indicating rhythm disorders or cardiac ischaemia), additional 12-lead ECG(s) should be done to document a potential outcome event.
13. For female patients of child-bearing potential, local urine pregnancy test should be performed according to the Flow Chart. More frequent testing should be performed if required by local regulations/authorities.
14. For the screening Visit 1, the safety laboratory is limited to liver transaminases, alkaline phosphatase, serum creatinine and urinalysis. Patients do not have to be fasting.
15. HbA1c to be analysed in all patients, e.g. diabetics and non-diabetics.
16. For PK analysis, one blood sample will be collected prior to the next scheduled dose of trial medication at Visit 4 and between 22 to 26 h after the most recent drug intake.
17. Collection of biobanking samples (plasma, serum, urine, DNA) is optional. Participating patients are required to give informed consent specifically for biobanking. Samples will be stored at a biobanking facility for future research.
18. DNA biobanking requires only one blood sample to be taken, preferably at Visit 2 (Randomisation). However, collection at later visits is permitted as long as the informed consent for biobanking remains valid.
19. At all visits; the respective kit number has to be allocated to the patient via IRT. Trial medication should be taken after all trial related procedures are completed at an on-site visit.

TABLE OF CONTENTS

ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
ACR	Albumin Creatinine Ratio
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine-Aminotransferase
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor blocker-Neprilysin Inhibitor
AST	Aspertate-Aminotransaminase
BI	Boehringer Ingelheim
BMI	Body Mass Index
BNP	B-type Natriuretic Peptide
CA	Competent Authority
CEC	Clinical Event Committee
CHF	Congestive Heart Failure
CI	Confidence Interval
CK	Creatine Kinase
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Equation
CL	Clinical Lead (title refers to CRO's Project Leader on national/regional level)
CML	Local Clinical Monitor (title refers to Sponsor's Project Leader on national/regional level)
CRA	Clinical Research Associate
CRO	Clinical Research Organisation
CRT	Cardiac Resynchronisation Therapy
CT	Computed Tomography
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DILI	Drug Induced Liver Injury
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
EDC	Electronic Data Capture
ExSC	Executive Steering Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
EOT	End of treatment
EQ5D	EuroQol 5 dimensions
eTMF	Electronic Trial Master File

EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GI	Gastrointestinal
HbA1c	Glycated Haemoglobin
HCRU	Health Care Resource Utilisation
HDL	High Density Lipoprotein
HF	Chronic Heart Failure
HHF	Hospitalisation for Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HR	Heart Rate
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
LA	Left Atrial
LDL	Low Density Lipoprotein
LPDD	Last Patient Drug Discontinuation
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiovascular Event
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
NT-proBNP	N-terminal of the prohormone brain natriuretic peptide
NYHA	New York Heart Association Classification
PK	Pharmacokinetics
p.o.	per os (oral)
PSA	Prostate-Specific Antigen
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
RI	Renal Impairment
RS	Randomisation Set
SAE	Serious Adverse Event
SBP	Systolic blood Pressure
SEC	Scientific Excellence Committee
SGLT-1	Sodium-glucose co-transporter 1

SGLT-2	Sodium-glucose co-transporter 2
SMQ	Standardised MedDRA Query
SOP	Standard Operating Procedure
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
UGE	Urine Glucose Excretion
ULN	Upper limit of normal
UTI	Urinary Tract Infection
VAS	Visual Analogue Scale
WBC	White Blood Cells
WOCBP	Women of childbearing potential

1 INTRODUCTION

1.1 MEDICAL BACKGROUND

Chronic heart failure (HF) is a progressive syndrome characterised by the inability of the heart to provide adequate blood supply to meet the metabolic demand of different tissues or do it at the expense of elevated left ventricle filling pressure. HF is a prevalent disease affecting an estimated 26 million people worldwide. In the United States alone the prevalence is 5.7 million, and there are 670,000 new cases per year [R16-1527]. HF is associated with premature mortality and frequent hospitalisation. Approximately 50% of patients who develop HF die within 5 years after diagnosis [P16-03952]. Annually, more than 1 million patients are hospitalised with a primary diagnosis of HF. HF is the most common cause of hospitalisation among individuals above 65 years of age in the western countries [P16-03760]. Two types of HF have been defined mainly based on the LV ejection fraction (EF) and also other structural changes in heart muscle. They consist of heart failure with reduced EF (HFrEF) <40% and heart failure with preserved EF (HFpEF) ≥40%. Relative prevalence of HFpEF among HF patients is approximately 50% [R16-1528]. Amongst patients with HF who require hospitalisation, the proportion of HFpEF is rising. Analysis of a large HF registry showed that the proportion of patients hospitalised with HF (HHF) who had HFpEF increased from 33% in 2005 to 39% in 2010 [R16-1529]. The rate of rehospitalisation among patients with HFrEF is close to 29% within 60-90 days of hospitalisation discharge which is equal to HFpEF [R16-1527].

Despite advances in therapy and management, HF remains a deadly clinical syndrome. After HHF, the one year mortality rate is high and not different between patients with preserved or reduced left ventricular ejection fraction (LVEF) [R16-2217], underscoring a high unmet medical need in this population.

About 25 to 45% of patients with HF have concomitant type 2 diabetes mellitus (T2DM), and nearly 15-25% have borderline DM (pre-diabetes), indicating a potential link between the HF syndromes and glucometabolic disturbances [R16-2382, R16-2384].

Despite the current standard of care for treatment of HFrEF such as medical therapy [angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), beta blockers, mineralocorticoid receptor antagonists (MRA), ivabradine and angiotensin receptor blocker-neprilysin inhibitor (ARNI)] or device therapy, the mortality and morbidity remains high. For HFpEF, however, control of congestive symptoms during acute episodes is the mainstay of management of these patients and no class of drugs have shown to increase survival or reduce HHF [P16-03760, P16-05920].

Empagliflozin is an orally available inhibitor of the renal dependent glucose co-transporter 2 (SGLT-2) indicated for, reduction of blood glucose in patients with T2DM by promoting urinary glucose excretion. It also reduces blood pressure, arterial stiffness and measures of the myocardial workload, likely through various mechanisms, as well as improving other CV risk factors (uric acid, visceral fat mass, albuminuria) [P15-00589, P15-09541].

In 2010 Boehringer Ingelheim (BI) initiated the EMPA-REG OUTCOME trial to explore CV benefit of the drug as well as to establish the safety profile of empagliflozin [P15-09840]. This trial completed in 2015 and showed empagliflozin, when given in addition to standard care treatment in high CV risk patients with T2DM, reduces the risk of 3-point MACE by 14% mostly driven by a 38% reduction in CV death. Furthermore this trial demonstrated reduction in the prespecified and adjudicated composite outcome of "CV death or HHF" and HHF by 34%.

Consistent with the main results of the EMPA-REG OUTCOME trial, in approximately 10% of the trial population who had investigator-reported heart failure at baseline, empagliflozin showed significant reduction in CV death, HHF, and composite of "HHF or CV death" [P16-01253].

1.2 DRUG PROFILE

Empagliflozin is an orally available, potent, and selective inhibitor of the renal SGLT-2. Its selective inhibition reduces renal reabsorption of sodium and glucose. This leads to both increased urinary sodium and glucose excretion. While the urinary sodium excretion returns to normal within few days of empagliflozin administration, the effect on urinary glucose continues.

Empagliflozin has been developed for the treatment of T2DM, and has received marketing approval in various regions including the European Union, Latin America, USA and Japan where it is marketed under the brand name Jardiance®.

For a more detailed description of the drug profile please refer to the current Investigator's Brochure (IB) [c01678844-06] and local prescribing information for empagliflozin.

1.2.1 Non-clinical assessment of safety

For further information regarding pre-clinical evaluation, please refer to the current version of the IB for empagliflozin.

1.2.2 Clinical pharmacokinetics

In humans, empagliflozin predominantly showed linear pharmacokinetic (PK). Empagliflozin reaches peak levels at approximately 1.5 hours and showed a biphasic decline with the terminal elimination half-life of 12.4 hours ranging from 10 to 19 hours.

Empagliflozin exposure increases with renal or hepatic impairment; however, no dose adjustment is recommended as the observed changes in exposure were not clinically meaningful. No clinically relevant PK interactions were observed with other oral antidiabetics, warfarin, verapamil, ramipril, simvastatin, digoxin, hydrochlorothiazide, torasemide, emfibrozil, rifampicin, probenecid and oral contraceptives (Microgynon®). For further details refer to the current version of the IB for empagliflozin.

1.2.3 Clinical efficacy and safety

Approximately 550 healthy volunteers were exposed to empagliflozin (up to 800 mg single dose and up to 50 mg multiple dosing). Approximately 8500 patients with T2DM have been treated with empagliflozin in research studies, of which approximately 4400 have been

treated for more than 52 weeks. Also, empagliflozin was tested in over 4600 patients with T2DM and high CV risk for median treatment duration of 2.6 years.

The EMPA-REG OUTCOME trial was a randomised, placebo-controlled trial of empagliflozin 10 and 25 mg in 7020 patients with T2DM and high CV risk. It ended in 2015 after accruing the minimum prespecified 691 major adverse CV events. Empagliflozin was associated with significant risk reduction of all-cause mortality by 32% (HR 0.68; 95% CI 0.57, 0.82 p<0.0001) and CV death by 38% (HR 0.62; 95% CI 0.49, 0.77, p value <0.0001). In addition, the EMPA-REG OUTCOME trial showed reduction in the prespecified and adjudicated composite outcome of "CV death or HHF" by 34% (HR 0.66; 95% CI 0.55, 0.79, p value <0.0001). This result was consistent across various predefined sensitivity analysis and internal consistency was confirmed by showing overall homogeneity over a wide range of subgroups, including patients with and without history of HF at baseline. There was no significant difference in improving CV outcomes between the 10 and 25 mg dose.

The Phase III studies in T2DM showed that treatment with empagliflozin 10 mg or 25 mg once daily for up to 24 weeks results in a reduction of HbA1c up to 1%, body weight reduction between 2-3 kg, and a decrease in systolic blood pressure (SBP) between 3-5 mmHg compared with placebo. This was consistently observed with empagliflozin as monotherapy, add on to metformin, metformin and sulphonylurea, pioglitazone with or without metformin, and to basal insulin with metformin and/or sulphonylurea. Phase III studies up to 104 weeks in T2DM support the sustained effect of empagliflozin.

In clinical studies, empagliflozin was well tolerated in both healthy volunteers and patients with T2DM including patients with high CV risk up to a median duration of 2.6 years. The frequency of overall Adverse Events (AEs), AEs leading to discontinuation and Serious AE (SAEs) were comparable to placebo. There was no significant increase in frequency of hypoglycaemia with empagliflozin compared to placebo except when used in combination with a sulphonylurea or basal insulin. In general there was a small increase in frequency of urinary tract infection (UTI) compared to placebo. There was an increase in frequency of genital infections with the use of empagliflozin. There was a small increase in total cholesterol, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol and no significant changes in triglycerides. No changes in electrolytes were observed with empagliflozin.

In the EMPA-REG OUTCOME trial renal function over time, as measured by the eGFR, is shown in Figure 1.2.3:1 [P16-06807]. After the initial decrease, eGFR remained steady in the empagliflozin group and was reversed after the cessation of the trial medication (Figure 1.2.3:2). At the follow-up visit, the adjusted mean difference from placebo in the change from baseline in the eGFR with each of the two doses of empagliflozin was 4.7 ml per minute per 1.73 m2 (95% confidence interval, 4.0 to 5.5; P<0.001 for both comparisons) (Figure 1.2.3:2). The data indicated that the initial drop in eGFR after administration of empagliflozin is reversible and most likely due to hemodynamic carnages. This is very similar to what have been observed with ACEi and ARBs. The EMPA-REG OUTCOME trial also generated the hypothesis that the expected deterioration in renal function in patients with T2DM slowed down after using empagliflozin, and this will be further tested in the HF trials using the eGFR slope analysis and composite renal endpoints (see Section 5.1.2 and 5.1.3).

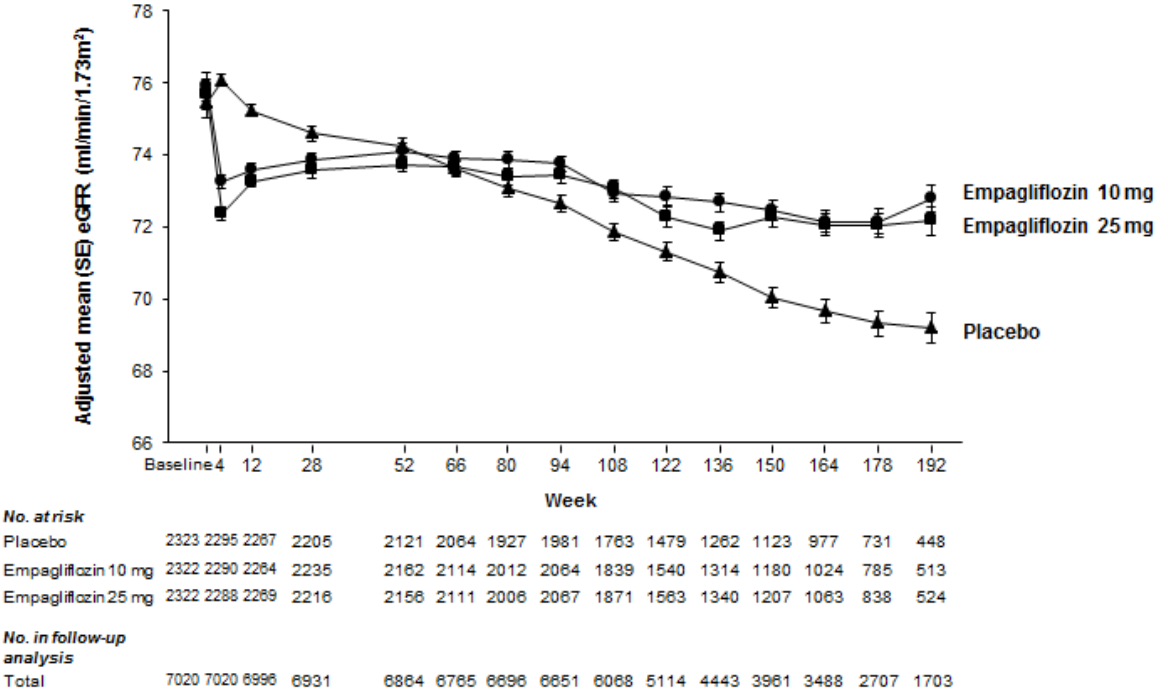

Figure 1.2.3:1 Change in eGFR over192 weeks in the EMPA-REG OUTCOME trial.

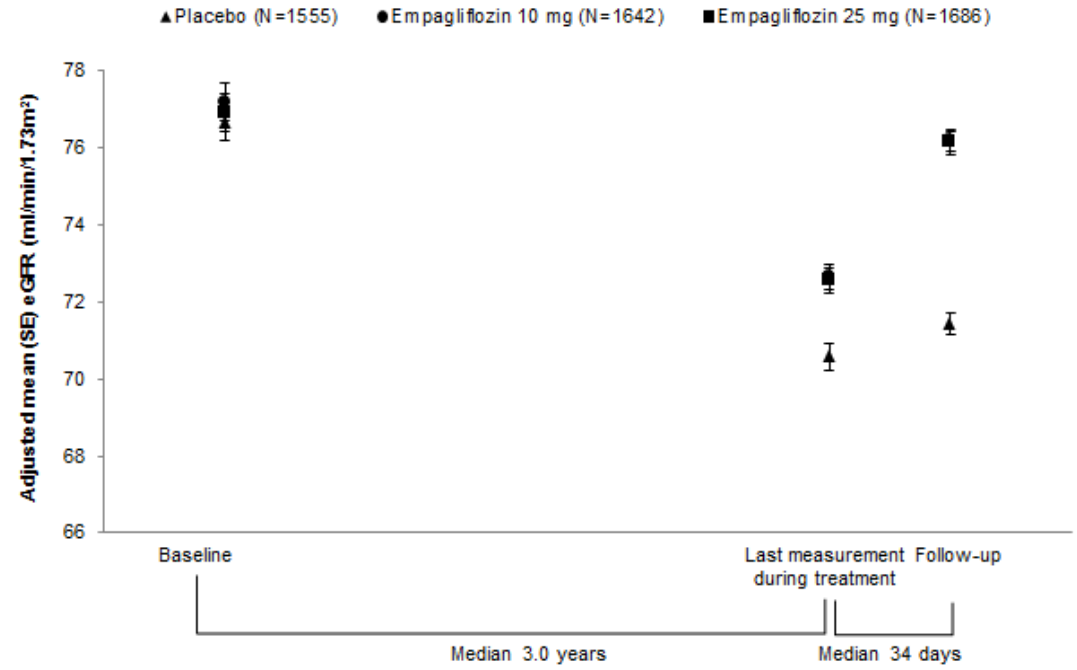

Figure 1.2.3:2 Change in eGFR from baseline to last measurement during treatment and follow-up in the EMPA-REG OUTCOME trial.

In a dedicated trial in patients with moderate and severe RI (eGFR between 15-60 mL/min/1.73 m^2 [Chronic Kidney Disease (CKD3 and CKD4)]) treatment with 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 RI, 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 HFpEF. Despite advances in the management of HF, no new therapies have been found to improve outcomes by reducing mortality or morbidity (i.e. CV death or HHF) in these patients [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 DM [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 study, non-DM subjects showed metabolic changes such as, 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 m^2 (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 HFpEF.

2.2 TRIAL OBJECTIVES

The objective of this event-driven trial is to demonstrate superiority of empagliflozin 10 mg versus placebo in patients with symptomatic, chronic HF and preserved ejection fraction (LVEF > 40%) under stable treatment of HF symptoms.

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 reduced 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. 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 DM 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 HFpEF 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. Special attention will be paid to prevent metabolic acidosis, ketoacidosis and diabetic ketoacidosis (DKA). For further details refer to Section 4.2.1.

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 follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety, see also Section 5.3.6.1.

Based on the findings in the nonclinical trials conducted to date and in accordance with international regulatory guidelines, the inclusion of women of childbearing potential (WOCBP) in this trial is justified. To minimise the risk of unintentional exposure of an embryo or foetus to the investigational drug, WOCBP must agree to the requirements for pregnancy testing and contraceptive methods described in this protocol.

3 DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This randomised, double-blind, multi-national, parallel group trial compares empagliflozin 10 mg once daily to placebo as add-on to standard of care treatment in patients with HFpEF.

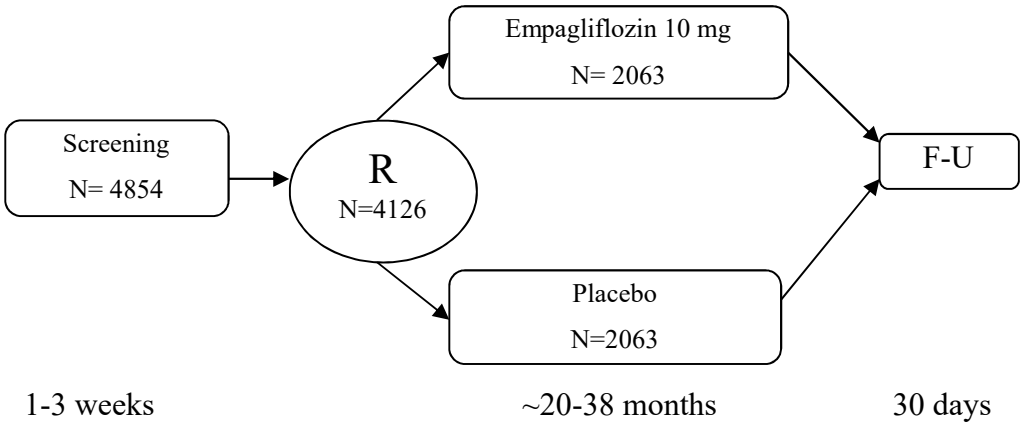

Figure 3.1: 1 Trial design

Patients are included in the trial once they have signed the informed consent form (ICF). All patients suitable after screening and who still meet the inclusion/exclusion criteria when returning for Visit 2 approximately 1-3 weeks later will be randomised into one of the treatment groups in a 1:1 manner.

Randomisation will be stratified with respect to geographical region (North America, Latin America, Europe, Asia and "Other", history of DM (DM, pre-DM, no DM), LVEF (<50%, ≥50%) and eGFR $(CKD\text{-}EPI)_{cr}$ (<60 mL/min/1.73 m², ≥60mL/min/1.73 m²) at screening.

The trial is event-driven and all randomised patients will remain in the trial until the defined number of adjudicated primary endpoint events has been reached. Estimated trial duration is 38 months with a recruitment period of approximately 18 months. The estimated length of the double-blind treatment will vary from approximately 20 to 38 months for each patient. The trial duration may be prolonged in case the number of patients and/or primary endpoint events is not reached within the planned timelines. The total number of randomised patients may be adapted based on assessment of the blinded event rate. For further details refer to Section 7.7.

The number of confirmed adjudicated primary endpoint events will be continuously monitored during the trial. As soon as the available data reliably suggests that the total 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.

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 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 the 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 SEC-charter filed in the eTMF.

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 Sponsor, ExSC, SEC, 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,
- 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, 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).

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 HFpEF without showing benefit in morbidity and mortality. The aim of this trial is to recruit patients with HFpEF 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 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 22 countries. Approximately 500 trial centres will participate to ensure that the estimated 4126 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 centre 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. 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% [R16-2382, R16-2384]. In a recent large HF outcome trial, 35% of the patients reported to have DM, another 15% found to have undiagnosed DM and around 27% had pre-DM [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 patients with DM, a minimum of 15 % will be patients with pre -DM 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 active treatment with antidiabetic medication (for indication of DM) or screening HbA1c ⩾6.5% 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, and 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].

IRT will be used to aim for a trial population consisting of approximately 35% to 50% with an LVEF ≥50%. To ensure adequate enrolment of patients the final decision on capping will be based on the recommendation from the ExSC during the recruitment period.

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 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 preserved EF defined as LVEF > 40 % per local reading (obtained by echocardiography, radionuclide ventriculography, invasive angiography, MRI or CT), and no prior measurement of LVEF ≤ 40% under stable conditions[b]. The EF must have been obtained and documented at Visit 1 or within 6 months prior to Visit 1, and more than 90 days after any myocardial infarction (as defined in exclusion criterion No. 1)
5. Elevated NT-proBNP > 300 pg/ml for patients without AF, OR > 900 pg/ml for patients with AF, analysed at the Central laboratory at Visit 1

[a] Women of childbearing potential are defined as:
- having experienced menarche and
- not postmenopausal (12 months with no menses without an alternative medical cause) and
- not permanently sterilised (e.g., tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

[b] In the Investigator's opinion

6. Patients must have at least one of the following evidence of HF:
    a. Structural heart disease[c] (left atrial enlargement and/or left ventricular hypertrophy) documented by echocardiogram at Visit 1 or within 6 months prior to Visit 1, OR
    b. Documented HHF[d] within 12 months prior to Visit 1
7. Oral diuretics, if prescribed to patient according to local guidelines and discretion of the Investigator, should be stable for at least 1 week prior to Visit 2 (Randomisation)
8. Body Mass Index (BMI) < 45 kg/m2 at Visit 1
9. Signed and dated written ICF in accordance with GCP and local legislation prior to admission to the trial

3.3.3 Exclusion criteria

1. Myocardial infarction (increase in cardiac enzymes in combination with symptoms of ischaemia or newly developed ischaemic ECG changes), coronary artery bypass graft surgery or other major cardiovascular surgery, stroke or TIA in past 90 days prior to Visit 1
2. Heart transplant recipient or listed for heart transplant
3. Implantation of cardioverter defibrillator (ICD) within 3 months prior to Visit 1
4. Implanted cardiac resynchronisation therapy (CRT)
5. Cardiomyopathy based on infiltrative diseases (e.g. amyloidosis), accumulation diseases (e.g. haemochromatosis, Fabry disease), muscular dystrophies, cardiomyopathy with reversible causes (e.g. stress cardiomyopathy), hypertrophic obstructive cardiomyopathy or known pericardial constriction
6. Any severe (obstructive or regurgitant) valvular heart disease expected to lead to surgery during the trial in the Investigator's opinion
7. Acute decompensated HF (exacerbation of chronic HF) requiring intravenous (i.v.) diuretics, i.v. inotropes or i.v. vasodilators, or left ventricular assist device within 1 week from discharge to Visit 1, and during screening period until Visit 2 (Randomisation)
8. Atrial fibrillation or atrial flutter with a resting heart rate > 110 bpm documented by ECG at Visit 2 (Randomisation)
9. Systolic blood pressure (SBP) ≥ 180 mmHg at Visit 2. If SBP >150 mmHg and <180 mmHg at Visit 2, the patient should be receiving at least 3 antihypertensive drugs
10. Symptomatic hypotension and/or a SBP < 100 mmHg at Visit 1 or Visit 2

[c] Structural heart disease is further defined in Appendix 10.5
[d] The main reason for HHF must be HF. Documentation for HHF must be provided in the source documents

11. Chronic pulmonary disease requiring home oxygen, oral steroid therapy or hospitalisation for exacerbation within 12 months, or significant chronic pulmonary disease in the Investigator's opinion, or primary pulmonary arterial hypertension
12. Indication of liver disease, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatase above 3 x upper limit of normal (ULN) as determined at Visit 1
13. Impaired renal function, defined as eGFR < 20 mL/min/1.73 m2 $(CKD\text{-}EPI)_{cr}$ or requiring dialysis, as determined at Visit 1
14. Haemoglobin < 9 g/dl at Visit 1
15. History of ketoacidosis
16. Major surgery (major according to the investigator's assessment) performed within 90 days prior to Visit 1, or scheduled major elective surgery (e.g. hip replacement) within 90 days after visit 1
17. Gastrointestinal (GI) surgery or GI disorder that could interfere with absorption of trial medication in the investigator's opinion
18. Any documented active or suspected malignancy or history of malignancy within 2 years prior to screening, except appropriately treated basal cell carcinoma of the skin, in situ carcinoma of uterine cervix or low risk prostate cancer (patients with pre-treatment PSA < 10 ng/mL and biopsy Gleason score of ≤ 6 and clinical stage T1c or T2a)
19. Presence of any other disease than heart failure with a life expectancy of <1 year in the investigator's opinion
20. Patients who must or wish to continue the intake of restricted medications (see Section 4.2.2) or any drug considered likely to interfere with the safe conduct of the trial
21. Treatment with any SGLT-2 inhibitor or combined SGLT-1 and 2 inhibitor within 1 week prior to Visit 1 or during screening period until Visit 2 (Randomisation)
22. Currently enrolled in another investigational device or drug trial, or less than 30 days since ending another investigational device or drug trial(s), or receiving other investigational treatment(s). Patients participating in a purely observational trial will not be excluded
23. Known allergy or hypersensitivity to empagliflozin or other SGLT-2 inhibitors
24. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable trial subject or unlikely to complete the trial
25. Women who are pregnant, nursing, or who plan to become pregnant while in the trial
26. Any other clinical condition that would jeopardise patients safety while participating in this trial, or may prevent the subject from adhering to the trial protocol

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

This is a long-term outcome trial and every effort should be made by the site staff to encourage patients to remain in the trial and on trial medication unless medical condition substantially changes to alter the safety profile. If a patient is withdrawn from the trial the ExSC and the Sponsor should be informed immediately about each individual case.

Prematurely discontinuation of trial medication
For patients who prematurely discontinue trial medication all efforts should be made to observe these patients and ask them to continue to attend the scheduled visits until the end of trial. It is expected that all efforts are made to follow up on the collection of all adverse events, outcome events and concomitant therapy, and to have a complete dataset without missing data.

If a patient who prematurely discontinued trial medication is not willing to return to the predefined trial visits, at minimum a telephone call every 24 weeks (preferably every 12 weeks) and a telephone call at trial end will be required, to document the occurrence of 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
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.

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 procedures prior to enrolment as well as an explanation of the consequences of premature withdrawal.

3.3.4.2 Discontinuation of the trial by the Sponsor

BI reserves the right to discontinue the trial overall or at a particular trial centre at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial centre
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial (see also Section 3.1.1).
3. Violation of GCP, the Clinical Trial Protocol (CTP), or the contract disturbing the appropriate conduct of the trial

The Investigator / the trial centre will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4 TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The trial medication will be provided by BI.

4.1.1 Identity of the investigational Medicinal product and comparator

The characteristics of test products are below:

Substance:	empagliflozin
Pharmaceutical formulation:	film-coated tablet
Source:	Boehringer Ingelheim
Unit strength:	10 mg
Posology:	1 tablet once daily
Rout of administration:	oral

Substance:	placebo matching empagliflozin
Pharmaceutical formulation:	film-coated tablet
Source:	Boehringer Ingelheim
Unit strength:	-
Posology:	1 tablet once daily
Rout of administration:	oral

4.1.2 Selection of doses in the trial

Empagliflozin 10 mg and 25 mg are approved for the treatment of T2DM.

Empagliflozin exerts its effect by promoting glucosuria and consequent hemodynamic changes associated with diuresis, improvement in arterial stiffness, blood pressure lowering effect with no increase in HR and reduction in HR x Pressure product, an index of myocardial oxygen consumption. These modes of actions support the scientific rationale of using empagliflozin in patients with HF.

In the EMPA-REG-OUTCOME trial both doses were administered to patients with T2DM and showed to be equally effective in reducing CV death, HHF, and composite of HHF or CV death in patients with HF at baseline.

In subgroup analysis empagliflozin improved the main outcome of CV death and HHF with the similar magnitude in patients with low or high levels of HbA1c at baseline. This indicates the risk reduction for HF outcome is independent of the degree of glycaemic control at baseline, suggesting that these benefits can be achieved with the 10 mg dose similar to the 25

mg dose in the non-diabetic population as well. The mechanism of action is supported by studies in healthy volunteers where both doses were associated with about 50g glucosuria.

Given the lower exposure with 10 mg empagliflozin similar general safety, and CV effects similar for both doses, empagliflozin 10 mg once daily has been selected in this trial.

For further details see current version of the IB.

4.1.3 Method of assigning patients to treatment groups

During Visit 2 eligible patients will be randomised to receive empagliflozin 10 mg, or matching placebo, in a 1:1 ratio according to the randomisation plan. The assignment will occur in a blinded fashion via Interactive Response Technology (IRT).

To facilitate the use of the IRT, the Investigator will receive a manual including all necessary instructions for using the system. A copy of the manual will be available in the ISF.

Patient assignment to the treatment group will be determined by a computer generated random sequence. Access to the randomisation code will be controlled and documented - for further details please refer to Section 4.1.5.1. and 4.1.5.2.

Using this procedure, relevant parties will be blinded to the treatment group assignment.

For information on stratification and capping please refer to Section 3.3.

4.1.4 Drug assignment and administration of doses for each patient

Patients who qualify will be randomised to one of the dosages described in Section 4.1.1. Trial medication will be dispensed in a double-blind and single-dummy manner.

Dispensing of kits for the double-blind treatment period will begin at Visit 2 and continue at every visit until end of trial. For further details regarding packaging (e.g. number of tablets per container) please refer to Section 4.1.6.

From the start of the treatment period patients will be instructed to take the trial medication once daily with a glass of water. Empagliflozin can be taken with or without food.

To ensure a dose interval of about 24 hours, the medication should be taken in the morning at approximately the same time every day. If a dose is missed by more than 12 hours, that dose should be skipped and the next dose should be taken as scheduled. On days before the next visit, the dose should be taken 22-26 hours before the planned dose at the visit. No double doses should be taken.

Patients should be instructed not to take their medication on the morning of trial visits as they will be dosed whilst in the clinic. Visits should be routinely scheduled at approximately the same time of day for each visit. The actual date and time of administration of the trial medication at the trial visit will be recorded in the eCRF.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, Investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial, will remain blinded with regard to the randomised treatment assignments until after database lock.

The DMC will be provided with unblinded data in order to allow them to review efficacy and safety and to fulfil their tasks as outlined in the data monitoring committee charter. An independent team, not otherwise involved in the conduct of the trial, will provide the unblinded results to the DMC.

The randomisation code will be kept secret by Clinical Trial Support up to database lock.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the Investigator via the IRT. It must only be used in an emergency situation when the identity of the trial medication must be known to the Investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. Whenever possible and if time allows, the need for unblinding will be discussed with the medical representative from the Sponsor or delegate before the unblinding of trial medication takes place. The reason for unblinding must be documented in the source documents and/or appropriate eCRF page along with the date and the initials of the person who broke the code.

The patient could continue with trial medication after unblinding.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's Pharmacovigilance group to access the randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives and not to be shared further.

For Japan only: In this blinded trial, an emergency code break will be available to the Investigator / the sub-Investigators via the IRT. This code break may only be accessed in emergency situations when the identity of the trial medication must be known to the Investigator /the sub-Investigators in order to provide appropriate medical treatment or if required to assure the safety of trial participants. Each site receives a manual from the IRT provider that contains instructions on how to unblind the treatment of a patient via the IRT (via 24-hour Emergency helpline). If the code break for a patient is accessed, the Sponsor or delegate must be informed immediately. The reason for accessing the code break, together with the date, must be documented on the appropriate eCRF page. In case third party needs to break the code, however, when the Investigator cannot be reached, the code can be opened by calling emergency code manager.

4.1.6 Packaging, labelling and re-supply

The investigational products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice

(GMP). Re-supply to the sites will be managed via the IRT, which will also monitor expiry dates of supplies available at the sites.

For details of packaging and the description of the label, please refer to the ISF.

4.1.7 Storage conditions

Trial medication must be stored under the recommended storage conditions indicated on the label. A temperature log must be maintained by the investigator / pharmacist / investigational drug storage manager to make certain that the drug supplies are stored at the correct temperature. If the storage conditions are found to be outside the specified range, the process outlined in the ISF should be followed.

4.1.8 Drug accountability

The Investigator and/or Pharmacist and/or investigational drug storage manager will receive the investigational drugs delivered by the Sponsor or delegate when the following requirements are fulfilled:

- Approval of the trial protocol by the Institutional Review Board (IRB) / ethics committee
- Availability of a signed and dated clinical trial contract between the Sponsor or delegate and the head of the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the principal Investigator,
- Availability of a signed and dated clinical trial protocol
- Availability of the proof of a medical license for the principal Investigator
- For USA; Availability of Form 1572

The Investigator and/or Pharmacist and/or investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the Sponsor, CRO or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the Sponsor, CRO or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. The Investigator / Pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the Sponsor or delegate. At the time of return to the Sponsor/CRO, the Investigator / Pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the Investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

The use of medication for the treatment of HF will be at the discretion of the Investigator and should be in accordance with local/international guidelines.

All concomitant (additional) medications and other therapies should be recorded on the appropriate pages of the eCRF.

Concomitant antidiabetic medications should be adjusted individually as clinically indicated by the patient's usual diabetes care provider. Restrictions of antidiabetic background therapy are described in Section 4.2.2.

Patients without a diagnosis of DM experiencing repeated or severe symptoms such as nervousness, sweating, intense hunger, trembling, weakness and palpitations should contact the Investigator or other healthcare professional, as these symptoms might be suggestive of hypoglycaemia. In the case of hypoglycaemia, in patients with or without DM, that may put the patient at risk (e.g. repeated symptomatic hypoglycaemia or severe hypoglycaemia), appropriate care should be provided at the discretion of the Investigator.

Special attention must be paid to the prevention of ketoacidosis. All patients must be made aware of this risk and need to be instructed to contact the Investigator or other healthcare professional in case of symptoms of metabolic acidosis, ketoacidosis and DKA. Cases of DKA have been reported in patients treated with empagliflozin, including fatal cases. In a number of reported cases, the presentation of the condition was atypical with only moderately increased blood glucose values; below 14 mmol/l (250 mg/dl).

The risk of DKA must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness.

Patients should be assessed and treated for ketoacidosis immediately according to local guidelines if these symptoms occur, regardless of blood glucose level. If ketoacidosis is suspected, the trial medication should be discontinued, the patient should be evaluated, and prompt treatment should be initiated.

Patients who may be at higher risk of ketoacidosis while taking empagliflozin include patients on a very low carbohydrate diet (as the combination may further increase ketone body production), patients with an acute illness, pancreatic disorders suggesting insulin deficiency (e.g. Type 1 diabetes mellitus (T1DM), history of pancreatitis or pancreatic surgery), insulin dose reduction (including insulin pump failure), alcohol abuse, severe dehydration, and patients with a history of ketoacidosis. Empagliflozin should be used with caution in these patients. In patients requiring insulin, caution should be taken when the dose of insulin is reduced.

In clinical situations known to predispose to ketoacidosis (e.g. prolonged fasting due to acute illness or surgery), the Investigator should consider monitoring for ketoacidosis and temporarily discontinue the trial medication.

There are no trial specific emergency procedures to be followed.

4.2.2 Restrictions

The use of any SGLT-2 inhibitors or combined SGLT-1 and 2 inhibitors except the blinded trial medication is prohibited during the course of the trial. This also includes the 30 days period between the EOT and the Follow Up Visit.

If any restricted treatment is given during the conduct of the trial, the trial medication can be discontinued temporarily, or if needed permanently.

If the patient is in need of any additional treatment during this period, this may be given at the discretion of the Investigator. The patient can still remain on trial medication.

WOCBP must use the contraception methods as described in the patient information.

4.3 TREATMENT COMPLIANCE

Patients are requested to bring all remaining trial medication including empty package material with them when attending visits.

The Investigator or his/her designate will count the number of the returned tablets and calculate the compliance based on the number of tablets taken, divided by the number of tablets that should have been taken since last visit, multiplied by 100. See formula below.

$$\text{Compliance (\%)} = \frac{\text{Number of tablets actually taken since last tablet count x 100}}{\text{Number of tablets which should have been taken in the same period}}$$

Compliance should be between 80% and 120%. Compliance should be emphasised with a goal of at least 80% compliance rate. However, randomised patients will not be discontinued for poor compliance without prior discussion with the monitor or designee.

Patients who are not compliant with their medication should again be carefully interviewed and again re-informed about the purpose and the conduct of the trial.

5 VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL EFFICACY ENDPOINTS

5.1.1 Primary endpoint(s)

The composite primary endpoint for this trial is the time to first event of adjudicated CV death or adjudicated HHF in patients with Heart Failure with preserved Ejection Fraction (HFpEF).

5.1.2 Secondary endpoint(s)

The key secondary endpoints which are part of the testing strategy, are the following:

1. Occurrence of adjudicated HHF (first and recurrent),
2. eGFR $(CKD\text{-}EPI)_{cr}$ slope of change from baseline

Other secondary endpoints (not part of confirmatory testing hierarchy on trial level) are the following:

- Time to first occurrence of sustained* reduction of ≥40% eGFR $(CKD\text{-}EPI)_{cr}$ or
    - 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
    - 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

  *An eGFR $(CDK\text{-}EPI)_{cr}$ reduction is considered sustained, if it is determined by two or more consecutive post-baseline central laboratory measurements separated by at least 30 days (first to last of the consecutive eGFR values).
- Time to first adjudicated HHF
- Time to adjudicated CV death
- Time to all-cause mortality
- Time to onset of DM (defined as HbA1c ≥6.5% or as diagnosed by the Investigator) in patients with pre-DM defined as no history of DM and no HbA1c ≥6.5 before treatment, and a pre-treatment HbA1c value of ≥ 5.7 and <6.5
- Change from baseline in clinical summary score (HF symptoms and physical limitations domains) of the Kansas City Cardiomyopathy Questionnaire (KCCQ) at week 52
- Occurrence of all-cause hospitalisation (first and recurrent)

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 $(CKD\text{-}EPI)_{cr}$ < 30mL/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 $(CKD\text{-}EPI)_{cr}$ < 30mL/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
- Changes in NT-proBNP from baseline over time
- Change in albuminuria from baseline over time
- Change in albuminuria from baseline over time by baseline 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 the 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 KCCQ

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 will 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.

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 and telephone visits until end of the trial.

5.2.3 NT-proBNP

Refer to Section 5.5 Assessment of biomarkers

5.2.4 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.).

5.2.5 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. All recordings should be made using a similar type of and validated certified blood pressure recording instrument on the same arm. Further details on blood pressure measurement procedure are provided in Appendix 10.6.

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).

Table 5.3.4: 1 Safety laboratory parameters – whole blood, serum or plasma

Haematology

- Hematocrit
- Haemoglobin
  - Reticulocyte Count (reflex test if Hb outside normal range)
- Red Blood Cells (RBC) / Erythrocytes
- WBC / Leukocytes
- Platelet Count / Thrombocytes
- Differential Automatic (relative and absolute count):
  Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes

Clinical chemistry

- Albumin
- Alkaline phosphatase
  - γ-GT (gamma-glutamyl transferase) reflex test triggered by elevated alkaline phosphatase on two sequential measures
- ALT (alanine transaminase, SGPT)
- AST (aspartate transaminase, SGOT)
- Bicarbonate
- Bilirubin total, fractionated if increased
- Calcium
- Chloride
- Creatinine
- Creatine kinase (CK)
- Hs Troponin I (reflex tests if CK is elevated)
- Glucose
- Magnesium
- Phosphate
- Potassium
- Protein total
- Sodium
- Urea (BUN)
- Uric acid

Lipids

- Cholesterol (total)
- HDL cholesterol
- Calculated LDL cholesterol
- Triglycerides (reflex test for direct measurement of LDL cholesterol triggered if triglycerides are > 400 mg/dl or 4.52 mmol/l)

5.3.4.1 Renal function

Urine albumin/creatinine ratio (UACR) in spot urine will be determined and calculated at the central laboratory.

The estimated glomerular filtration rate (eGFR) will be derived from serum creatinine values, age, sex and race based on the CKD-EPI equation [R12-1392]:

$GFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black]

where:
Scr is serum creatinine in mg/dL,
κ is 0.7 for females and 0.9 for males,
α is -0.329 for females and -0.411 for males,
min indicates the minimum of Scr /κ or 1, and
max indicates the maximum of Scr /κ or 1.

The race of the patient will be entered because of potential differences due to race. The CKD-EPI equation considers the race as an adjustment factor, therefore the race must be known for accurate estimation.

In case of an eGFR loss of ≥ 40% since baseline, or when the eGFR drops to < 15 mL/min/1.73 m^2 for patients with an eGFR ≥ 30 mL/min/1.73 m^2 at baseline (<10 mL/min/1.73 m^2 for patients with an eGFR < 30 mL/min/1.73 m^2 at baseline); an additional visit between 30 days to preferably 60 days after detection should be scheduled (unless detected at the EOT visit at trial end) to collect a blood sample for repeat central analysis of creatinine for calculation of the eGFR. If a signal of abnormal creatinine or eGFR is reported to the site by others (e.g. treating physicians from local labs), an additional sample should be sent to central lab, and if it is still abnormal, another sample should be sent to central lab between 30 days and preferably 60 days.

Kidney function will be classified as described in the table below (Table 5.3.4.1:1):

Table 5.3.4.1: 1 Classification of kidney function

CKD stage	eGFR
1	≥ 90
2	60-89
3a	45-59
3b	30-44
4	15-29
5	< 15

5.3.4.2 Pregnancy testing

Pregnancy testing (urine) will be performed in female patients of child bearing potential according to the time points indicated in the Flow Chart. Pregnancy kits will be provided by the Central Laboratory. For reporting of pregnancy event refer to Section 5.3.7.2.

5.3.4.3 Criteria for hypoglycaemic events

In DM patients, all symptomatic hypoglycaemia events, or severe hypoglycaemias (e.g. if the patient required assistance of another person), or any hypoglycaemia episode with glucose values < 54 mg/dl (< 3.0 mmol/l), or if the investigator considered the event to be an AE should be documented as an AE "hypoglycaemic event". In non-diabetic or pre-diabetic patients, the investigator should consider and rule out other alternative causes for such symptoms and can perform blood glucose levels to confirm the diagnosis of hypoglycaemia.

5.3.4.4 Urinary tract infections and genital infections

Patients having a history of chronic/recurrent urinary tract infections (UTI) or genital infections or an acute episode of UTI or genital infection at screening will be identified, and

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.

5.3.5 Electrocardiogram

ECGs will be performed at Visit 2, and at the EOT Visit 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 and stored locally. The diagnosis and results from the ECG reports 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 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. 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 adverse event (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:

- 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. Any suspected transmission via a medicinal product of an infectious agent is considered a serious adverse reaction.

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 below.

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

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "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" the patient needs 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).

Each lower limb amputation, disarticulation, or auto-amputation should be reported separately. The SAE report should include the date of the procedure, the level of amputation or disarticulation, the medical condition(s) leading to the procedure and if the patient had some of the known risk factor(s) for lower limb amputation.

Intensity of AEs

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

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

Causal relationship of AEs

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.
Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced

- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

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

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

For Japan only: The reason for the decision on causal relationship for unlisted AEs needs to be provided in the eCRF.

5.3.7.2 Adverse event collection and reporting

AE Collection

The Investigator shall maintain and keep detailed records of all AEs in their patient files. The following must be collected and documented on the appropriate eCRF(s) by the Investigator:

- From signing the ICF onwards through the Residual Effect Period (REP), until individual patient's end of trial participation:
    - all AEs (serious and non-serious), Outcome events and all AESIs.
- After the individual patient’s end of trial:

  The Investigator does not need to actively monitor the patient for AEs, but must report relevant SAEs and relevant AESIs of which the Investigator may become aware of.

The REP (timeframe after last dose of trial medication when measurable drug levels or pharmacodynamic effects are still likely to be present) is defined as 7 days after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment. Please also refer to Section 7.3.4.

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

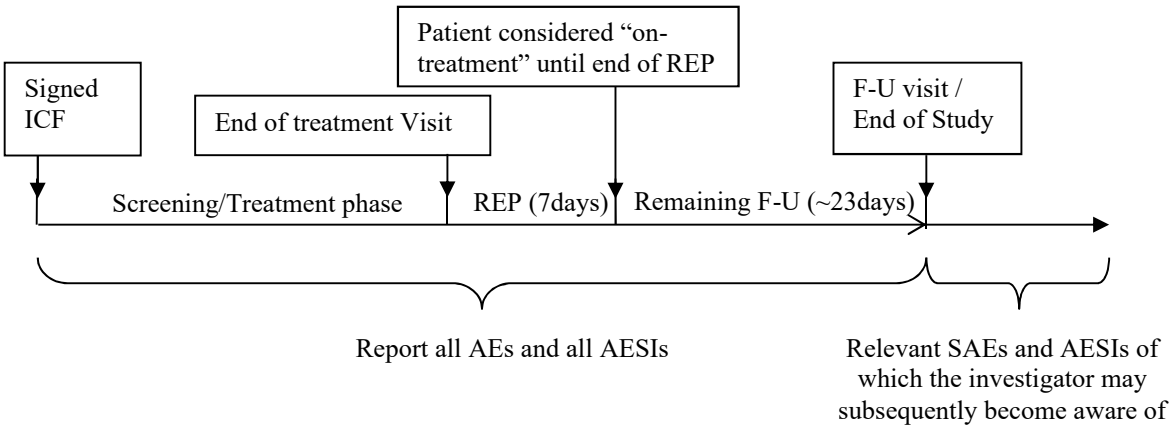

Figure 5.3.7.2: 1 Timelines for adverse event collection

AE reporting to the Sponsor/CRO and timelines

The Investigator must report all non-exempted SAEs, AESI and any non-serious AE relevant for the reported SAE, immediately (within 24 hours) on the BI SAE form. The same timeline applies if follow-up information becomes available.

For Japan only: All SAEs must be reported immediately to the head of the trial site.

Any protocol exempted event that occurs prior to randomisation and fulfils the criteria of an SAE will be reported immediately (within 24 hours) by the Investigator on the BI SAE form via fax immediately (within 24 hours) to the Sponsor's/CRO's unique entry point (country specific contact details will be provided in the ISF); **however, if the patient has been randomised, the exempted events will not be reported as SAEs to the sponsor and no causality assessment will be performed. These events will be entered only on the AE eCRF pages (within 24 hours). The investigator is also required to provide all defined supporting documentation.**

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.

If any exempted event or any other adverse event (serious or non-serious) occurs, the investigator or attending physician has the responsibility and will take direct and appropriate action to provide care for the patient and to decide whether or not the trial medication should be discontinued.

An independent Data Monitoring Committee (DMC) will monitor the safety data in the trial on an ongoing basis. Reported SAEs occurring after randomisation that are protocol exempted events will be collected in the eCRFs and evaluated by the DMC. These events will not be collected on SAE forms for expedited review or reporting.

Aggregate analysis of endpoint data to determine any potential benefit or risk and to ensure patient safety during the clinical trial will be performed on a regular basis by the DMC.

With receipt of any further information to these events, appropriate follow-up forms have 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. The Investigator should determine the causal relationship to the trial medication.

The following should also be recorded as an (S)AE in the CRF 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 CRF 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 immediately (within 24 hours) a potential drug exposure during pregnancy (DEDP) 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 serious adverse events that commonly occur in the trial population or which are components of trial endpoints are exempted from expedited reporting. 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.

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)

Based on the same conclusion that it is not possible to perform a causality assessment on these events based on a single case, the trial investigators are exempted from performing a causality assessment and reporting these serious adverse events on the SAE form to the Sponsor.
All such events will be collected systematically on the eCRF (within 24 hours) from the time of randomisation throughout follow up.

This reporting policy assumes global regulatory agency approval.

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS (SUBSTUDY)

5.4.1 Pharmacokinetic endpoints

The PK sampling will be done from a limited number of randomised patients (approximately 1650 patients) and at pre-selected sites only. The pre-dose blood samples will be collected at visit 4 to determine plasma empagliflozin trough concentrations. These samples will serve to determine steady state trough concentrations of empagliflozin.

The date and exact clock time of trial medication intake the day before this visit will be recorded together with the date and exact clock time of drawing the trough pharmacokinetic sample.

5.4.2 Methods of sample collection

The time interval for blood sample collection relative to the most recent intake of trial medication should be between 22 and 26 h. For quantification of empagliflozin trough plasma concentrations, 3 mL of blood will be drawn from a forearm vein in an EDTA-anticoagulant blood drawing tube at each time-point. Details of sample handling and sample logistics can be found in the ISF (Central lab manual).

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 BIOMARKERS

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 informed consent 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

Approx. 8.5 mL blood will be drawn into a PAXgene Blood DNA Tube, preferably at Visit 2.

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.

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 completing 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.

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 patient 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 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

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.

Once the patient has consented to the trial participation, she/he is considered to be enrolled in the trial and have started screening. The patient should be registered in the enrolment log and be registered in the IRT as a screened patient. Patients will continue to take background medication for heart failure and treatment for their concomitant disorders if applicable.

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 (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.

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).

For 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.

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 (ref. 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.

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.

Patients who discontinue trial medication prematurely should thereafter continue to follow scheduled visits until trial end. For patients reluctant to attend the scheduled visits after prematurely discontinuing trial medication, some trial assessments may be negotiated with exception of collection of adverse events, outcome events and concomitant therapy.

Please refer to Section 3.3.4.1 for detailed procedures to be followed in case a patient wants to stop trial medication.

In case of early trial termination (e.g. based on recommendation by the DMC, a reasonable timeframe to stop the trial (perform last patient visits) will be defined and communicated to the Investigators.

7 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The eligible patients for this trial will be randomised to empagliflozin 10 mg and placebo in 1:1 ratio, stratified by geographical region, status of DM (DM, pre-DM, no DM) , LVEF (<50%, ≥50%) and eGFR $(CKD\text{-}EPI)_{cr}$ (<60 mL/min/1.73 m², >=60 mL/min/1.73 m²) at screening visit.
To ensure the trial population consist of a reasonable combination of non-, pre- and DM patients, and to aim for approximately 35% to 50% of the population or more with an LVEF ≥50% capping will be used on trial level (see also Section 3.3). Capping on regional level may be applied to achieve a contribution of each region to each category of diabetes status.

The composite primary endpoint is the time to first event of adjudicated CV death or adjudicated HHF. The statistical model for the primary analysis is the Cox proportional hazards model. The hazard ratio and its confidence limits will be determined for evaluating the superiority of empagliflozin to placebo for the primary endpoint.

The key secondary endpoints, which are part of the testing strategy, are

- occurrence of adjudicated HHF (first and recurrent), and
- $eGFR\ (CKD\text{-}EPI)_{cr}$ slope of change from baseline

7.2 NULL AND ALTERNATIVE HYPOTHESES

A hierarchical testing procedure will be followed for the assessment of the primary and the key secondary endpoints. For all endpoints, superiority of empagliflozin vs. placebo will be evaluated with a two-sided test in the following structure:

Null hypothesis: There is no difference between the effect of placebo and the effect of empagliflozin in terms of the endpoint in question.

Alternative hypothesis: There is a difference between the effect of placebo and the effect of empagliflozin in terms of the endpoint in question. The tests will be performed in the following hierarchical order:

1. Time to first event of adjudicated CV death or adjudicated HHF
2. Occurrence of adjudicated HHF (first and recurrent)
3. $eGFR\ (CKD\text{-}EPI)_{cr}$ slope of change from baseline

Starting from step 1, if the null hypothesis is rejected, and the result is more favourable for empagliflozin, superiority is concluded in the tested endpoint, and the overall type I error is preserved for the test in the next step. If at any step the null hypothesis is not rejected, subsequent tests are conducted in an exploratory fashion.

The overall type one error rate will be preserved at a level of 0.05 (2-sided). The type one error rate used at the final analysis will be influenced by the pre-planned interim analysis – see Section 7.4.

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.

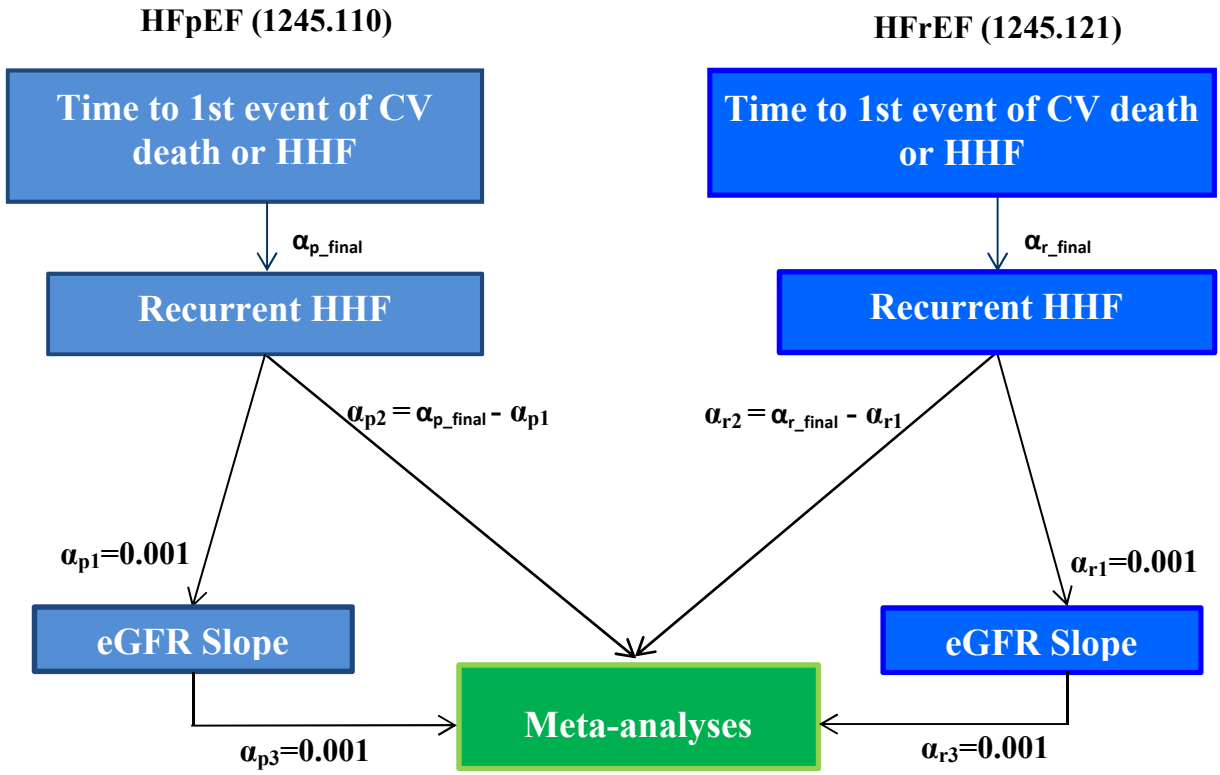

Figure 7.2: 1 Hierarchical analysis of trial in HFpEF (1245.110) and the parallel trial in HFrEF (1245.121) showing the alpha-spending at the final analysis.

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.

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 evaluated on the randomised set using a Cox proportional hazards model with treatment, age (continuous), gender, geographical region, baseline status of DM (DM, pre-DM, no DM), LVEF (continuous) and eGFR $(CKD\text{-}EPI)_{cr}$ at baseline (continuous) as covariates.

The time to the event of interest will be computed as (event date − randomisation date) +1. All events observed after randomisation until trial termination will be included in the analysis. Patients who do not have an event during the trial period will be censored at the individual day of trial completion or the last day that the patient was known to be free of the event, whichever is earlier. The time to censoring will be computed as (individual day of trial completion 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 will be used for 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 the diabetic status by treatment interaction term into the Cox model.

Standard subgroup analyses of the primary endpoint include geographical region, sex, BMI, LVEF, 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 only including any events up to 30 days after treatment discontinuation.

7.3.2 Secondary endpoint analyses

The key secondary endpoints 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, and status of DM as fixed effects and eGFR $(CKD\text{-}EPI)_{cr}$ at baseline (continuous), LVEF (continuous), age (continuous), time and interaction of treatment 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 repeated measures model including baseline score, LVEF (continuous), age (continuous) and eGFR $(CKD\text{-}EPI)_{cr}$ at baseline (continuous) as linear covariates and treatment, visit, baseline score by

visit, visit by treatment, gender, geographical region and status of DM and 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 as adjudicated HHF and will be evaluated with a joint model 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 and history of DM as fixed effect and baseline eGFR $(CKD\text{-}EPI)_{cr}$ (continuous), age (continuous), LVEF (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. 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. 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 Rogers 2014 [R16-4909] and 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 baseline value, age, LVEF and eGFR $(CKD\text{-}EPI)_{cr}$ at baseline as linear covariates and treatment group, visit, visit by treatment interaction, baseline by visit interaction, geographical region, gender 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 residual effect period REP of 7 days will be considered 'treatment-emergent'. 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-analysis

On project level, meta-analyses are pre-specified. Data from this trial and a parallel trial in HFrEF patients, 1245.121, 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 time of interim analysis, the ExSC, the SEC, Sponsor, CRO, and all trial 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:

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

For an interim analysis at the timepoint of approximately 60% of information, the chosen alpha-spending function gives an alpha-level of 0.001 at time of interim.

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 cutoff to be evaluated from the alpha-spending function (planned at 0.001 one-sided), then 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 of data for safety data or for time-to event endpoints. For patients who discontinue the trial treatment prematurely, all efforts will be made to follow patients for survival and for any other endpoints including the primary and 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 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 $(CDK\text{-}EPI)_{cr}$ reduction is considered sustained, if it is determined by two or more consecutive post-baseline central laboratory measurements separated by at least 30 days (first to last of the consecutive eGFR values). If there is no additional measurement after the eGFR reduction is observed and the patient dies within 60 days of this measurement without second measurement >= 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:
  - no DM (HbA1c < 5.7% without the intake of antidiabetic medication, unless taken for a non-DM indication, and no history of DM), or
  - pre-DM (HbA1c >=5.7% and <6.5% without the intake of antidiabetic medication unless taken for a non-DM indication, and no history of DM), or
  - DM (HbA1c >= 6.5% or intake of antidiabetic medication for a DM indication, or a history of DM)
- eGFR $(CKD\text{-}EPI)_{cr}$ at screening
  - <60 mL/min/1.73 m²
  - ≥60 mL/min/1.73 m²
- LVEF
  - LVEF < 50%
  - LVEF ≥ 50%

Patients will be randomised in blocks to double-blind treatment via an IRT system. Approximately equal numbers of patients will be randomised to each treatment group. BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the Clinical Trial Report (CTR). Access to the codes will be controlled and documented.

7.7 DETERMINATION OF SAMPLE SIZE

For the sample size calculation, a yearly event rate in the placebo group of 10% is assumed. The assumption is based on the CHARM-Preserved study and part of the TOPCAT study from the Americas [R07-4374, R16-1458]. The annual event rates in CHARM-Preserved were 8.1% in the candesartan group and 9.1% in the placebo group. The annual rates from the Americas in the TOPCAT study were 10.4 in the spironolactone group and 12.6 in the placebo group.
The trial is designed to achieve a power of 90% for a two sided test at level $\alpha = 0.05$.
The following table presents the number of required events together with the number of to be randomised and treated patients assuming an accrual period of 18 months and a follow-up period of 20 months for different assumed true hazard ratios. However, the follow-up period is not fixed but the trial will continue until the necessary number of events has been observed, which are confirmed by the adjudication committee.

The drop-out rate from the trial is assumed to be low (< 1% per year) and is therefore not further considered for the determination of sample size.

Table 7.7: 1 Sample size calculation – not including interim analyses:

Yearly event rate for HHF+CV Death (Placebo)	Hazard ratio	Number of events for 90% power for HHF+CV Death	Number of patients for 18 months accrual and 20 months follow up
10%/Year	0.70	331	1710
10%/Year	0.75	509	2562
10%/Year	0.80	841	4126
10%/Year	0.85	1601	7656
10%/Year	0.90	3814	17814

A hazard ratio of 0.8 was chosen as a conservative estimate based on the results of the EMPA-REG OUTCOME trial described in Section 1.2.3

Therefore, at least 841 confirmed primary events should be observed and at least 4126 patients should be randomised and treated in order to achieve a power of 90% assuming a true hazard ratio of 0.8.

Including interim analysis with Hwang-Shih-deCani alphaspending with gamma=-8 at 60% of information will diminish the power only slightly to 89.98%.

The event rate will be assessed in a blinded manner during recruitment before any interim unblinding. If the accumulated blinded data suggests a lower event rate based on an assumed hazard ratio of 0.8 between the groups, then the number of randomised patients may be increased to a maximum of 6000 patients. The number of confirmed primary outcome events will not be affected by this consideration and will remain 841 events.

Calculations were performed using ADDPLAN6.1.1 by ADDPLAN Inc.

Based on the abovementioned assumptions, and considering that HHF (first and recurrent) will only be tested if the primary endpoint is successful, the chance of showing significance for HHF (first and recurrent) in a positive trial is at least 70%.

For the integration of a Japanese population in this global phase III trial, and in order to comply with the regulatory requirements for bridging the trial results to this population, the Japanese patients to be randomised will be followed and controlled if necessary. Approximately 145 patients are expected to be randomised to each treatment arm for the Japanese population.

8 INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for GCP, relevant BI SOPs and CRO SOPs, the EU regulation 536/2014, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The Investigator will inform the Sponsor or delegate immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

The BI transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the Investigator and of the Sponsor with regard to publication of the results of this trial are described in the Investigator contract. As a rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

For Japan only: The rights of the investigator / trial site and of the Sponsor or delegate with regard to publication of the results of this trial are described in the investigator contract / trial site's contract. As a general rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

The certificate of insurance cover is made available to the Investigator and the patients, and is stored in the ISF (Investigator Site File).

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH / GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory, and the ICF and any additional patient-information form retained by the Investigator as part of the trial records. A signed copy of the ICF and any additional patient information must be given to each patient or the patient's legally accepted representative.

The Investigator must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible. The patient must be given sufficient time to consider participation in the trial. The Investigator obtains written consent of the patient's own free will with the ICF after confirming that the patient understands the contents. The Investigator

must sign (or place a seal on) and date the ICF. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the ICF.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the Sponsor's or delegate's instructions.

The respective procedure for illiterate patients is described in the Appendix 10.1.

The consent and re-consenting process should be properly documented in the source documentation.

The patient must be informed that his/her personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorised monitors (CML/CL/ Clinical Research Associate (CRA)) or Clinical Quality Assurance auditors appointed by BI, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

In order to achieve a high level of standardised processes, data collection of efficacy and safety endpoints is coordinated centrally:

- central lab analysis of efficacy endpoints, biomarkers and safety lab
- central ECG collection (for clinically relevant ECG changes documented as an AE or suspected clinically relevant ECG changes)
- central IRT for stratification, randomisation and kit allocation at each visit
- central adjudication of HHF and cardiovascular events, and hepatic adjudication.

The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan available in eTMF.

A quality assurance audit/inspection of this trial may be conducted by the Sponsor, Sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the Investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

ECRF for individual patients will be provided by the Sponsor or delegate. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements the Investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and

other data pertinent to the investigation on each trial subject. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail).

Data reported on the eCRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the subject may not be sufficient to confirm eligibility for the trial and the Investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case the Investigator must make three documented attempts to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

Before providing any copy of patients' source documents to the Sponsor or delegate the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted to ensure patient confidentiality.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For the eCRF, data must be derived from source documents, for example:

- Patient identification: gender, date or year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of Patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of Patient's Participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The Sponsor or delegate will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of on-site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

The Investigator / institution will permit trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the eCRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). The CRA and auditor may review all eCRFs and ICFs. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The Sponsor or delegate will also monitor compliance with the protocol and ICH GCP.

An adaptive approach to clinical trial monitoring will be utilised. This is initiated by an assessment of the risk associated with the trial combined with an assessment of critical data and processes. A Risk Assessment Mitigation Plan and Integrated Project Management Plan collectively document the strategies involved with the implementation of onsite, remote and central monitoring activities in order to direct focus to the areas of greatest risk which have the most potential impact to safety patient and data quality. Trial oversight is achieved by regular review of a report of risk which then influences any required changes to the monitoring strategy.

The Investigator /institution will allow on-site trial-related monitoring, audits, IRB/IEC review and regulatory inspections. Direct access should be granted to all source documents (paper and e-records) including progress notes, copies of laboratory and medical test results The CRA and auditor may review all CRFs and ICFs. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1.
The Sponsor/CRO will also monitor compliance with the protocol and ICH GCP.

8.3.3 Storage period of records

Trial site(s):

The trial site(s) must retain the source documents and essential documents (including ISF) according to the national or local requirements (whatever is longer) valid at the time of the end of the trial.
Sponsor:

The Sponsor or delegate must retain the essential documents according to the Sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal regulatory reporting obligation and in accordance to the regulatory requirements. As this trial is primarily intended to evaluate the cardiovascular impact of empagliflozin in patients with chronic heart failure, the Sponsor will not report the SAEs included in the protocol exempted events list of the eCRF as described in

Section 5.3.7.2. Events will be recorded and reported regularly to the DMC. The Sponsor will ensure that all appropriate regulatory agencies confirm that this approach is acceptable to them.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below and in Section 5.5.1. Patient privacy will be ensured by using patient identification code numbers.

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.

The end of the trial is defined as the date of the last visit of the last patient in the whole trial "Last Patient Out").

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 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 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 should prepare and submit the records explaining the reasons thereof to the Sponsor or delegate, 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

9 REFERENCES

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10 APPENDICES

10.1 INCLUSION OF ILLITERATE PATIENTS

10.1.1 Patient reported outcome forms

In the event of recruiting an illiterate patient, the following process should be followed with respect to completion of the EQ-5D self-report questionnaire and the KCCQ:

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

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

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

In the same way as for all other patients, the completion of the EQ-5D questionnaire and the KCCQ should be performed in a quiet area where the patient can consider his/her responses to both the descriptive system and VAS.

10.1.2 Patient information and informed consent (including biobanking)

In the event of recruiting an illiterate patient, the following process should be followed with respect to patient information and informed consent:

- The designated site personnel performing the informed consent process will read the trial approved patient information sheet and ICFs to the patient, and explain the details of the trial, all in the presence of an impartial witness.

- This impartial witness must be literate, and can be the patient's relative or caregiver, or a member of staff employed by the clinic but not part of the immediate trial team. In addition, if there are any further local regulations with respect to the consent of illiterate patients, these should also be followed.

- The requirements of the trial will be explained thoroughly and the patient will be given ample time to ask questions and consider his/her participation. If he/she wishes, the patient can take the patient information sheet and ICFs home for further consideration.

- If patient agrees to take part in the trial, he/she would then return to the clinic for the consent process to be completed. The site designated personnel responsible for this process will confirm that the patient has no further questions in the presence of the

same impartial witness (if the patient returns on another day). If a different impartial witness is present, the entire informed consent 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 ICFs.

- 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 and ICFs 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 ICFs.

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

10.2 PATIENT REPORTED OUTCOMES

10.2.1 EQ-5D

Health Questionnaire

English version for the USA

USA (English) © 2009 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group

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

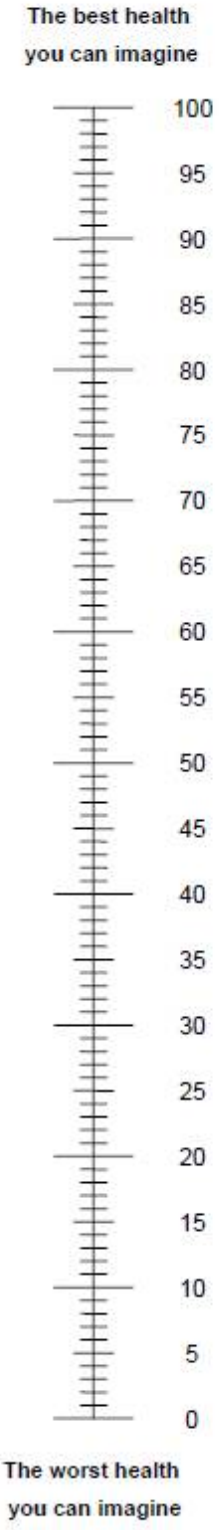
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 ❑

- 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 = ☐



10.2.2 KCCQ

THE KANSAS CITY CARDIOMYOPATHY QUESTIONNAIRE:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Please place an **X** in one box on each line

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

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

10.5 STRUCTURAL HEART DISEASE

Left atrial (LA) enlargement is defined by at least one of the following measurements:

- LA width ≥ 4.0 cm, or
- LA length ≥ 5.0 cm, or
- LA area ≥ 20 cm^2, or
- LA volume ≥ 55 ml, or
- LA volume index ≥ 34 ml/m^2

Left ventricular hypertrophy is defined by at least one of the following measurements:

- Septal thickness or posterior wall thickness ≥ 1.1 cm.
- LV mass index (LVMI) ≥115 g/m2 for males and ≥95 g/m2 for females
- E/e′ (mean septal and lateral) ≥13
- e’ (mean septal and lateral) <9 cm/s

10.6 BLOOD PRESSURE MEASURMENT PROCEDURE

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

At visit 1, blood pressure should be taken 3 times in both arms. If the pressures differ by more than 10 mmHg (as in the presence of a subclavian steal syndrome), the arm with the higher pressure (systolic or diastolic) should be used for subsequent measurements.

After the patient has rested quietly, in the seated position for five minutes, three blood pressure measurements will be taken approximately two minutes apart and all three results must be entered in the eCRF. The seated HR will be taken during one of the two-minute intervals.

Blood pressure measurements should be recorded to the nearest 2 mmHg only when measured with a manual sphygmomanometer; when digital devices are used the value from the device should be rounded to the nearest 1 mmHg.

For calculation of mean values, decimal places should be rounded to integers (e.g. a DBP of 94.5 would be rounded to 95 mmHg and a DBP of 109.4 would be rounded to 109 mmHg).

11 DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

Number of global amendment		
Date of CTP revision		
EudraCT number		
BI Trial number		
BI Investigational Product(s)		
Title of protocol		
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – **IRB / IEC / Competent Authority to be notified of change with request for approval**		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		
Description of change		
Rationale for change		

APPROVAL / SIGNATURE PAGE

Document Number: c03946327 **Technical Version Number:1.0**

Document Name: clinical-trial-protocol-version-1

Title: A phase III randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic Heart Failure with preserved Ejection Fraction (HFpEF).

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor	[redacted]	09 Nov 2016 19:33 CET
Approval-Team Member Medicine		09 Nov 2016 20:37 CET
Author-Trial Statistician		10 Nov 2016 09:17 CET
Approval-Therapeutic Area Head		10 Nov 2016 10:57 CET
Author-Trial Clinical Pharmacokineticist		10 Nov 2016 13:15 CET
Verification-Paper Signature Completion		15 Nov 2016 17:43 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed

Boehringer Ingelheim

CLINICAL TRIAL PROTOCOL

	Document Number:	c03946327-04
EudraCT No.:	2016-002278-11	
BI Trial No.:	1245.110	
BI Investigational Product(s):	Empagliflozin	
Title:	A phase III randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic **H**eart **F**ailure with **p**reserved **E**jection **F**raction (**HFpEF**).	
Lay title:	**EMP**agliflozin outcom**E** t**R**ial in patients with chr**O**nic hea**R**t failure EMPEROR-Preserved	
Clinical Phase:	III	
Trial Clinical Monitor:	[redacted]	
Coordinating Investigators	[redacted]	
Status	Final Protocol (based on Global Amendment 03)	
Version and Date:	**Version: 4.0**	**Date: 20 Nov 2019**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		**Jardiance**	
Name of active ingredient:		Empagliflozin	
Protocol date **09 NOV 2016**	**Trial number:** **1245.110**		**Revision date:** **20 Nov 2019**

Title of trial:	A phase III randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic Heart Failure with preserved Ejection Fraction (HFpEF)
Coordinating Investigator:	[redacted]
Trial site(s):	Multicentre trial in approximately 22 countries.
Clinical phase:	III
Objective(s):	The objective of this event-driven trial is to demonstrate superiority of empagliflozin 10 mg versus placebo in patients with symptomatic, chronic HF and preserved ejection fraction (LVEF > 40%) under stable treatment of HF symptoms
Methodology:	Randomised, double blind, placebo controlled, parallel group trial.
No. of patients: **total entered:**	Approximately 4126 randomised If the accumulated blinded data suggests a slower accrual of primary outcome events over calendar time than was originally projected, then the number of patients randomised may be increased up to 6000. 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. Such a decision would be made during recruitment and before any interim unblinding. The number of primary outcome

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		**Jardiance**	
Name of active ingredient:		Empagliflozin	
Protocol date **09 NOV 2016**	**Trial number:** **1245.110**		**Revision date:** **20 Nov 2019**

	events required is not affected by this consideration.
each treatment:	Approximately 2063 (2 treatment groups) This may be increased up to approximately 3000 per treatment group.
Diagnosis :	Heart failure (HF) with preserved 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 preserved EF defined as LVEF > 40 % per local reading (obtained by echocardiography, radionuclide ventriculography, invasive angiography, MRI or CT), and no prior measurement of LVEF ≤ 40% under stable conditions. A historical LVEF may be used if it was measured within 6 months prior to visit 1, and more than 90 days after any myocardial infarction (as defined in exclusion criterion No.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. • Elevated NT-proBNP > 300 pg/ml for patients without AF, OR > 900 pg/ml for patients with AF, analysed at the Central laboratory at Visit 1 • Patients must have at least one of the following evidence of HF: a) Structural heart disease (left atrial enlargement and/or left ventricular hypertrophy) documented by echocardiogram at Visit 1, OR b) Documented hospitalisation for HF (HHF) within 12 months prior to Visit 1 • Oral diuretics, if prescribed to patient according to local guideline and discretion of the Investigator, should be stable for at least 1 week prior to Visit 2 (Randomisation) • eGFR $(CKD\text{-}EPI)_{cr} \geq 20$ mL/min/1.73m^2 at Visit 1
Test product(s):	Empagliflozin
dose:	10 mg q.d.
mode of administration:	p.o.
Comparator products:	Placebo

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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 10%. 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	<u>Primary endpoint;</u> The composite primary endpoint for this trial is the time to first event of adjudicated CV death or adjudicated HHF in patients with HFpEF. <u>Key secondary endpoints;</u> The 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 · Time to first adjudicated HHF · Time to adjudicated CV death · Time to all-cause mortality · Time to onset of diabetes mellitus (DM) in patients with pre-DM · Change from baseline in clinical summary score (HF symptoms and physical limitations domains) of the KCCQ at week 52

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	· Occurrence of all-cause hospitalisation (first and recurrent)
Safety criteria:	· Adverse events (AE) · AE of special interest (AESI) · Incidence and intensity of AE including serious AE (SAE) · Withdrawal from trial medication due to AE · Clinically relevant new finding or worsening of existing condition on physical examination · Clinically relevant changes in laboratory measurements from baseline · Assessment of vital status
Statistical methods:	The overall type one error rate will be preserved at a level of 0.05 (2-sided). The primary and the key secondary endpoints will be analysed in the following testing hierarchy: 1. Time to first event of adjudicated CV death or adjudicated HHF 2. Occurrence of adjudicated HHF (first and recurrent) 3. eGFR $(CKD\text{-}EPI)_{cr}$ slope of change from baseline At 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 analysis, and the rest will be transferred to the meta-analyses which will include this trial and the trial conducted in parallel in patients with HFrEF (1245.121). For the primary analysis of the primary endpoint a Cox proportional hazards regression model of time to first event of adjudicated CV death or adjudicated HHF with covariates of age (continuous), gender treatment, geographical regions, history of DM (DM, Pre-DM, No DM), LVEF (continuous) and eGFR $(CKD\text{-}EPI)_{cr}$ at baseline (continuous) will be used. The primary analysis will be performed on the randomised (intention to treat) set. Approximately 4126 patients will be randomised to accumulate approximately 841 confirmed primary events within 18 months accrual and approximately 20 additional months follow-up period to achieve a power of ~90%. 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 6000 patients. 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. Such a decision would be made during recruitment before any interim unblinding. The number of 841 confirmed primary outcome events is not affected by this consideration.

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	One interim analysis is planned after approximately 500 primary adjudicated events have been accrued. If the pre-specified 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 on whether to stop the trial will be made by the Sponsor. Safety will be evaluated descriptively on the treated set.		

FLOW CHART

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**	
Informed Consent [6]	X																		3, 8
In-/exclusion criteria	X	X																	3.3
Medical History/ Concomitant diagnoses	X																		8.3.1
Screening (register in IRT)	X																		6.2.1
Randomisation (via IRT)		X																	6.2.2
Demographics[7]	X																		-
NYHA classification	X	X	X	X		X		X		X		X		X		X	X	X	5.2.2 10.3
Physical exam		X				X		X		X		X		X		X	X		5.3.1
Clinical routine exam[8]		X	X	X		X		X		X		X		X		X	X		5.3.2
Vital signs [9]	X	X	X	X		X		X		X		X		X		X	X	X	5.3.3
Height	X																		-

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]**	
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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	5.2.4
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 [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 Tests	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	X	5.5
High-sensitivity TroponinT		X																	5.5
HbA1c [15]	X	X		X		X		X		X		X		X		X	X		-

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]**	
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Fasting status[5]	**NF**	**F**	**NF**	**NF**	**-**	**NF**		**NF**	**-**	**NF**	**-**	**NF**	**-**	**NF**	**-**	**NF**	**F**	**F**	
Lipid profile panel		X						X				X					X	X	5.3.4
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
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

1. The screening procedures can be done on different days within the time window.
2. From Visit 8 and onwards, on-site visits will be scheduled every 24 weeks until end of trial.
   Patients who prematurely discontinue trial medication will perform EOT visit and Follow Up visit, and then continue with scheduled visits until the trial is stopped.
   For patients not willing to attend scheduled visits, telephone calls must be made regularly (ref. Section 3.3.4.1) to document any occurrence of outcome events and vital status.
   If the trial continues beyond 148 weeks, visits are to be repeated with same intervals as from week 64 and onwards.
3. Timepoint for the EOT will be communicated via an Investigator letter when the Sponsor is confident that required number of events will be reached within a reasonable timeframe (ref. Section 3.1 and 6.2.3). All patients will have a follow up visit 30 days following regular or premature completion of the treatment period.
4. Visit dates are determined per the date of randomisation. If a visit is missed, the patient should be returned to the original visit schedule at the next visit.
5. NF = non fasting, F=fasting. Fasting means no food or liquid intake except for water the last 10-16 hours
6. All visit 1 procedures should be performed within 28 days of signing the informed consent form (ICF).
7. If accepted by local authorities or ethic committees, demographics to be collected in this trial are gender, year of birth, ethnicity and race.
8. The Investigator will be asked to record results from clinical routine examinations like ECG, echocardiography or similar procedures (MRI, CT-scan, etc.), and if applicable information gathered from interrogations of the ICD in the eCRF.
9. Vital signs measurements in this trial are blood pressure and pulse rate.
10. Protocol specified outcome events should be collected on the appropriate eCRF page. Exemptions from reporting on the SAE form are specified in Section 5.3.7.
11. For patients with non-fatal stroke the Modified Rankin Scale (MRS) should be scored by the investigator based on an interview 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.
12. For the 12-lead ECG done at screening and EOT visit, the interpretation of the tracing must be made locally by a qualified physician or appropriately qualified designee and documented on the ECG section of the eCRF. In case of any cardiac symptoms (indicating rhythm disorders or cardiac ischaemia), additional 12-lead ECG(s) should be done to document a potential outcome event.
13. For female patients of child-bearing potential, local urine pregnancy test should be performed according to the Flow Chart. More frequent testing should be performed if required by local regulations/authorities.
14. For the screening Visit 1, the safety laboratory is limited to liver transaminases, alkaline phosphatase, serum creatinine and haematology panel. Patients do not have to be fasting.
15. HbA1c to be analysed in all patients, e.g. diabetics and non-diabetics.
16. For PK analysis, one blood sample will be collected prior to the next scheduled dose of trial medication at Visit 4 and between 22 to 26 h after the most recent drug intake.
17. Collection of biobanking samples (plasma, serum, urine, DNA) is optional. Participating patients are required to give informed consent specifically for biobanking. Samples will be stored at a biobanking facility for future research.
18. DNA biobanking requires only one blood sample to be taken, preferably at Visit 2 (Randomisation). However, collection at later visits is permitted as long as the informed consent for biobanking remains valid.
19. At all visits; the respective kit number has to be allocated to the patient via IRT. Trial medication should be taken after all trial related procedures are completed at an on-site visit.

TABLE OF CONTENTS

ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
AE	Adverse Event
AESI	Adverse Event of Special Interest
AF	Atrial fibrillation or Atrial flutter
ALT	Alanine-Aminotransferase
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor blocker-Neprilysin Inhibitor
AST	Aspertate-Aminotransaminase
BI	Boehringer Ingelheim
BMI	Body Mass Index
CA	Competent Authority
CEC	Clinical Event Committee
CI	Confidence Interval
CK	Creatine Kinase
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Equation
CL	Clinical Lead (title refers to CRO's Project Leader on national/regional level)
CML	Local Clinical Monitor (title refers to Sponsor's Project Leader on national/regional level)
CRA	Clinical Research Associate
CRO	Clinical Research Organisation
CRT	Cardiac Resynchronisation Therapy
CT	Computed Tomography
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DILI	Drug Induced Liver Injury
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ExSC	Executive Steering Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
EOT	End of treatment
EQ5D	EuroQol 5 dimensions
eTMF	Electronic Trial Master File
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GI	Gastrointestinal

HbA1c	Glycated Haemoglobin
HCRU	Health Care Resource Utilisation
HDL	High Density Lipoprotein
HF	Chronic Heart Failure
HHF	Hospitalisation for Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
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
KA	Ketoacidosis
KCCQ	Kansas City Cardiomyopathy Questionnaire
LA	Left Atrial
LDL	Low Density Lipoprotein
LPDD	Last Patient Drug Discontinuation
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiovascular Event
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
p.o.	per os (oral)
PSA	Prostate-Specific Antigen
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
RI	Renal Impairment
RS	Randomisation Set
SAE	Serious Adverse Event
SBP	Systolic blood Pressure
SEC	Scientific Excellence Committee
SGLT-1	Sodium-glucose co-transporter 1

SGLT-2	Sodium-glucose co-transporter 2
SMQ	Standardised MedDRA Query
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
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

1 INTRODUCTION

1.1 MEDICAL BACKGROUND

Chronic heart failure (HF) is a progressive syndrome characterised by the inability of the heart to provide adequate blood supply to meet the metabolic demand of different tissues or to be able to do so only at the expense of elevated left ventricle filling pressure. HF is a prevalent disease affecting an estimated 26 million people worldwide. In the United States alone the prevalence is 5.7 million, and there are 670,000 new cases per year [R16-1527]. HF is associated with premature mortality and frequent hospitalisation. Approximately 50% of patients who develop HF die within 5 years after diagnosis [P16-03952]. Annually, more than 1 million patients are hospitalised with a primary diagnosis of HF. HF is the most common cause of hospitalisation among individuals above 65 years of age in the western countries [P16-03760]. Two types of HF have been defined mainly based on the LV ejection fraction (EF) and also other structural changes in heart muscle. They consist of heart failure with reduced EF (HFrEF) <40% and heart failure with preserved EF (HFpEF) ≥40%. Relative prevalence of HFpEF among HF patients is approximately 50% [R16-1528]. Amongst patients with HF who require hospitalisation, the proportion of HFpEF is rising. Analysis of a large HF registry showed that the proportion of patients hospitalised with HF (HHF) who had HFpEF increased from 33% in 2005 to 39% in 2010 [R16-1529]. The rate of rehospitalisation among patients with HFrEF is close to 29% within 60-90 days of hospitalisation discharge which is equal to HFpEF [R16-1527].

Despite advances in therapy and management, HF remains a deadly clinical syndrome. After HHF, the one year mortality rate is high and not different between patients with preserved or reduced left ventricular ejection fraction (LVEF) [R16-2217], underscoring a high unmet medical need in this population.

About 25 to 45% of patients with HF have concomitant type 2 diabetes mellitus (T2DM), and nearly 15-25% have borderline DM (pre-diabetes), indicating a potential link between the HF syndromes and glucometabolic disturbances [R16-2382, R16-2384].

Despite the current standard of care for treatment of HFrEF such as medical therapy [angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), beta blockers, mineralocorticoid receptor antagonists (MRA), ivabradine and angiotensin receptor blocker-neprilysin inhibitor (ARNI)] or device therapy, the mortality and morbidity remains high. For HFpEF, however, control of congestive symptoms during acute episodes is the mainstay of management of these patients and no class of drugs have shown to increase survival or reduce HHF [P16-03760, P16-05920].

Empagliflozin is an orally available inhibitor of the renal dependent glucose co-transporter 2 (SGLT-2) indicated for, reduction of blood glucose in patients with T2DM by promoting urinary glucose excretion. It also reduces blood pressure, arterial stiffness and measures of the myocardial workload, likely through various mechanisms, as well as improving other CV risk factors (uric acid, visceral fat mass, albuminuria) [P15-00589, P15-09541].

In 2010 Boehringer Ingelheim (BI) initiated the EMPA-REG OUTCOME trial to explore CV benefit of the drug as well as to establish the safety profile of empagliflozin [P15-09840]. This trial completed in 2015 and showed empagliflozin, when given in addition to standard care treatment in high CV risk patients with T2DM, reduces the risk of 3-point Major Adverse Cardiovascular Event (MACE) by 14% mostly driven by a 38% reduction in CV death. Furthermore this trial demonstrated reduction in the prespecified and adjudicated composite outcome of "CV death or HHF" and HHF by 34%.

Consistent with the main results of the EMPA-REG OUTCOME trial, in approximately 10% of the trial population who had investigator-reported heart failure at baseline, empagliflozin showed significant reduction in CV death, HHF, and composite of "HHF or CV death" [P16-01253].

1.2 DRUG PROFILE

Empagliflozin is an orally available, potent, and selective inhibitor of the renal SGLT-2. Its selective inhibition reduces renal reabsorption of sodium and glucose. This leads to both increased urinary sodium and glucose excretion. While the urinary sodium excretion returns to normal within few days of empagliflozin administration, the effect on urinary glucose continues.

Empagliflozin has been developed for the treatment of T2DM, and has received marketing approval in various regions including, for example, the European Union, Latin American countries, USA and Japan where it is marketed under the brand name Jardiance®.

For a more detailed description of the drug profile please refer to the current Investigator's Brochure (IB) [c01678844-06] and local prescribing information for empagliflozin.

1.2.1 Non-clinical assessment of safety

For further information regarding pre-clinical evaluation, please refer to the current version of the IB for empagliflozin.

1.2.2 Clinical pharmacokinetics

In humans, empagliflozin predominantly showed linear pharmacokinetic (PK). Empagliflozin reaches peak levels at approximately 1.5 hours and showed a biphasic decline with the terminal elimination half-life of 12.4 hours ranging from 10 to 19 hours.

Empagliflozin exposure increases with renal or hepatic impairment; however, no dose adjustment is recommended as the observed changes in exposure were not clinically meaningful. No clinically relevant PK interactions were observed with other oral antidiabetics, warfarin, verapamil, ramipril, simvastatin, digoxin, hydrochlorothiazide, torasemide, emfibrozil, rifampicin, probenecid and oral contraceptives (Microgynon®). For further details refer to the current version of the IB for empagliflozin.

1.2.3 Clinical efficacy and safety

Approximately 550 healthy volunteers were exposed to empagliflozin (up to 800 mg single dose and up to 50 mg multiple dosing). Approximately 8500 patients with T2DM have been treated with empagliflozin in research studies, of which approximately 4400 have been

treated for more than 52 weeks. Also, empagliflozin was tested in over 4600 patients with T2DM and high CV risk for median treatment duration of 2.6 years.

The EMPA-REG OUTCOME trial was a randomised, placebo-controlled trial of empagliflozin 10 and 25 mg in 7020 patients with T2DM and high CV risk. It ended in 2015 after accruing the minimum prespecified 691 major adverse CV events. Empagliflozin was associated with significant risk reduction of all-cause mortality by 32% (HR 0.68; 95% CI 0.57, 0.82 p<0.0001) and CV death by 38% (HR 0.62; 95% CI 0.49, 0.77, p value <0.0001). In addition, the EMPA-REG OUTCOME trial showed reduction in the prespecified and adjudicated composite outcome of "CV death or HHF" by 34% (HR 0.66; 95% CI 0.55, 0.79, p value <0.0001). This result was consistent across various predefined sensitivity analysis and internal consistency was confirmed by showing overall homogeneity over a wide range of subgroups, including patients with and without history of HF at baseline. There was no significant difference in improving CV outcomes between the 10 and 25 mg dose.

The Phase III studies in T2DM showed that treatment with empagliflozin 10 mg or 25 mg once daily for up to 24 weeks results in a reduction of Glycated Haemoglobin (HbA1c) up to 1%, body weight reduction between 2-3 kg, and a decrease in systolic blood pressure (SBP) between 3-5 mmHg compared with placebo. This was consistently observed with empagliflozin as monotherapy, add on to metformin, metformin and sulphonylurea, pioglitazone with or without metformin, and to basal insulin with metformin and/or sulphonylurea. Phase III studies up to 104 weeks in T2DM support the sustained effect of empagliflozin.

In clinical studies, empagliflozin was well tolerated in both healthy volunteers and patients with T2DM including patients with high CV risk up to a median duration of 2.6 years. The frequency of overall Adverse Events (AEs), AEs leading to discontinuation and Serious AE (SAEs) were comparable to placebo. There was no significant increase in frequency of hypoglycaemia with empagliflozin compared to placebo except when used in combination with a sulphonylurea or basal insulin. In general there was a small increase in frequency of urinary tract infection (UTI) compared to placebo. There was an increase in frequency of genital infections with the use of empagliflozin. There was a small increase in total cholesterol, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol and no significant changes in triglycerides. No changes in electrolytes were observed with empagliflozin.

In the EMPA-REG OUTCOME trial renal function over time, as measured by the eGFR, is shown in Figure 1.2.3:1 [P16-06807]. After the initial decrease, eGFR remained steady in the empagliflozin group and was reversed after the cessation of the trial medication (Figure 1.2.3:2). At the follow-up visit, the adjusted mean difference from placebo in the change from baseline in the eGFR with each of the two doses of empagliflozin was 4.7 ml per minute per 1.73 m2 (95% confidence interval, 4.0 to 5.5; P<0.001 for both comparisons) (Figure 1.2.3:2). The data indicated that the initial drop in eGFR after administration of empagliflozin is reversible and most likely due to hemodynamic carnages. This is very similar to what have been observed with ACEi and ARBs. The EMPA-REG OUTCOME trial also generated the hypothesis that the expected deterioration in renal function in patients with T2DM slowed

down after using empagliflozin, and this will be further tested in the HF trials using the eGFR slope analysis and composite renal endpoints (see Section 5.1.2 and 5.1.3).

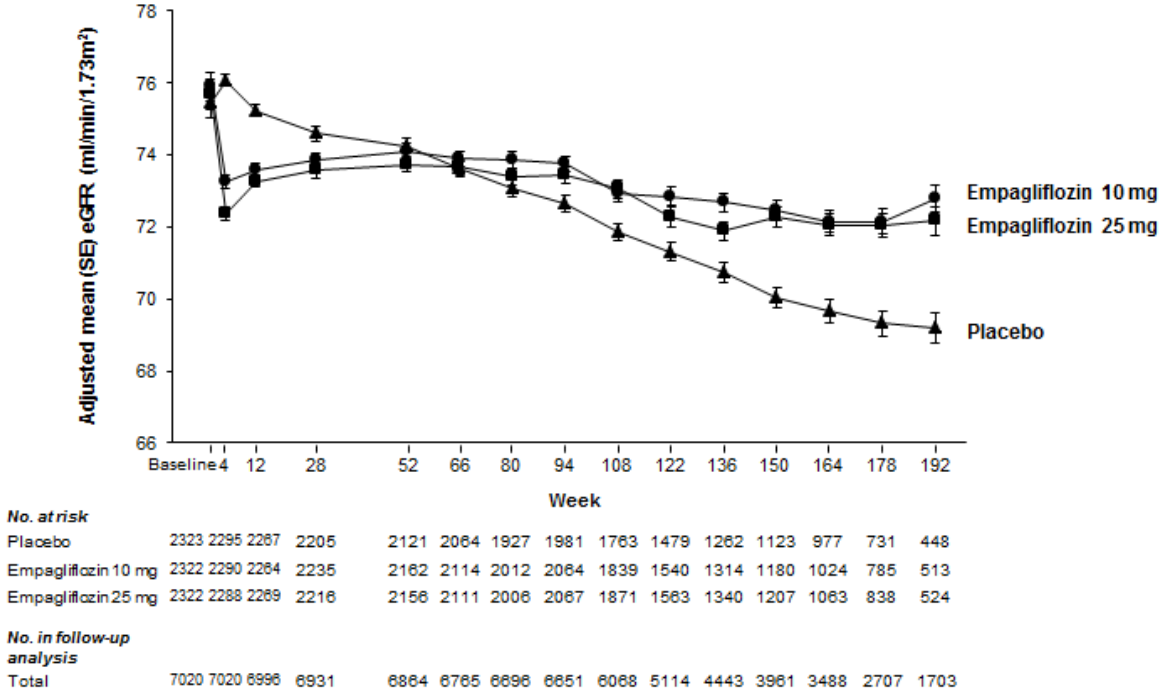

Figure 1.2.3:1 Change in eGFR over192 weeks in the EMPA-REG OUTCOME trial.

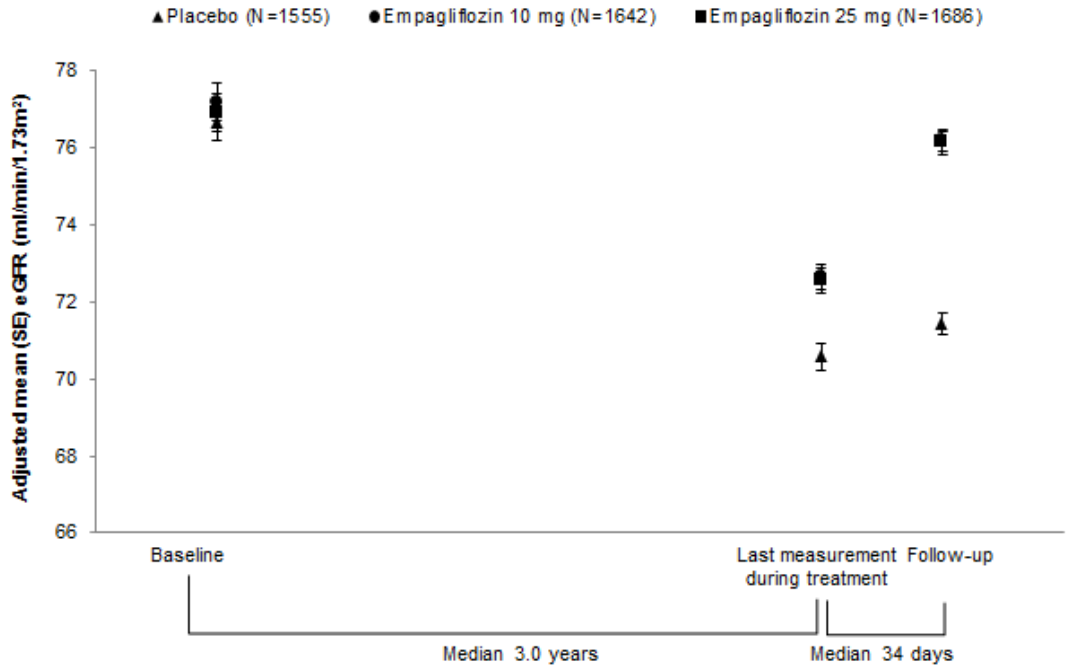

Figure 1.2.3:2 Change in eGFR from baseline to last measurement during treatment and follow-up in the EMPA-REG OUTCOME trial.

In a dedicated trial in patients with moderate and severe RI (eGFR between 15-60 mL/min/1.73 m^2 [Chronic Kidney Disease (CKD3 and CKD4)]) treatment with 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 (RI), 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 RI, 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 HFpEF. Despite advances in the management of HF, no new therapies have been found to improve outcomes by reducing mortality or morbidity (i.e. CV death or HHF) in these patients [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 m2). 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 DM [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 study, non-DM subjects showed metabolic changes such as, 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 HFpEF.

2.2 TRIAL OBJECTIVES

The objective of this event-driven trial is to demonstrate superiority of empagliflozin 10 mg versus placebo in patients with symptomatic, chronic HF and preserved ejection fraction (LVEF > 40%) under stable treatment of HF symptoms.

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 reduced 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. 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.

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 (KA) and diabetic ketoacidosis (DKA). Since an SGLT-2 inhibitor may alter the typical presentation of this condition, 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 KA 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 that 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 RI. Because in the EMPA REG Outcome study no difference in CV benefit was detected for patients with RI vs the overall population, it is 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 occurrences of symptomatic hypoglycemia were detected [U12-2707-01]. It is noted that in patients with T2DM the risk of hypoglycemia 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 of 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 hypoglycemia associated with empagliflozin treatment would be lower than in patients with T2DM.

Because the mode of action, blockade of the SGLT2 with consequent glucosuria, is the same in patients with and without diabetes, although to different degrees, it is considered likely that the tolerability of empagliflozin may be no less favourable in patients without DM compared to patients with T2DM.

There is also currently limited therapeutic experience with empagliflozin in patients aged 85 years and older. The prevalence of HF increases with age and the therapeutic options in the

elderly above 85 years are limited. The inclusion of this population in the clinical trial setting will help support the assessment of benefit-risk of empagliflozin for patients over 85. Special caution should be used in these patients, who may be at increased risk of adverse consequences attributable to empagliflozin-related volume depletion.

Many patients with chronic HF have RI, 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 RI, including patients with eGFR between > 30 and < 45 ml/min/1.37m^2. In previous trials in patients with T2DM the safety profile in moderate and severe RI were comparable to the overall trial population [P17-10453]. Renal safety will be closely monitored throughout the trial. Refer to section 5.3.4.1. and 5.3.7.1.

Investigators will be encouraged to treat participants to best standard of care in compliance with the local guidelines and recommendations for HF, and DM 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 HFpEF 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 KA 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 follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety, see also Section 5.3.6.1.

Based on the findings in the nonclinical trials conducted to date and in accordance with international regulatory guidelines, the inclusion of women of childbearing potential (WOCBP) in this trial is justified. To minimise the risk of unintentional exposure of an embryo or foetus to the investigational drug, WOCBP must agree to the requirements for pregnancy testing and contraceptive methods described in this protocol.

3 DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This randomised, double-blind, multi-national, parallel group trial compares empagliflozin 10 mg once daily to placebo as add-on to standard of care treatment in patients with HFpEF.

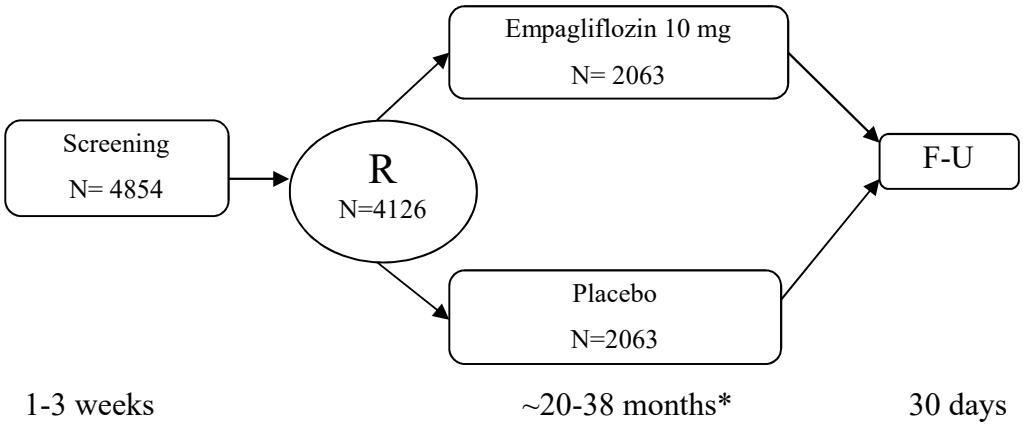

Figure 3.1: 1 Trial design

Patients are included in the trial once they have signed the informed consent form (ICF). All patients suitable after screening and who still meet the inclusion/exclusion criteria when returning for Visit 2 approximately 1-3 weeks later will be randomised into one of the treatment groups in a 1:1 manner.

Randomisation will be stratified with respect to geographical region (North America, Latin America, Europe, Asia and "Other", history of DM (DM, pre-DM, no DM), LVEF (<50%, ≥50%) and eGFR $(CKD\text{-}EPI)_{cr}$ (<60 mL/min/1.73 m², ≥60mL/min/1.73 m²) at screening.

The trial is event-driven and all randomised patients will remain in the trial until the defined number of adjudicated primary endpoint events has been reached. Estimated trial duration is 38 months with a recruitment period of approximately 18 months. The actual length of the recruitment period may be extended beyond 18 months and the follow-up period may be adjusted to achieve 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. 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 6000. 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.

The number of confirmed adjudicated primary endpoint events will be continuously monitored during the trial. As soon as the available data reliably suggests that the total 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 as 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 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 the 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 SEC-charter filed in the eTMF.

A National Coordinators Committee (NCC) will be established and will consist of leading expert(s) in each participating country. The national coordinators 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 Sponsor, ExSC, SEC, NCC, 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,
- 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, 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).

3.1.1.3 Adjudication of ketoacidosis

Events suspected to be metabolic acidosis, KA 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 HFpEF without showing benefit in morbidity and mortality. The aim of this trial is to recruit patients with HFpEF 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 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 22 countries. Approximately 560 trial centres will participate to ensure that the estimated 4126 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 centre 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 6000. 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% [R16-2382, R16-2384]. In a recent large HF outcome trial, 35% of the patients reported to have DM, another 15% found to have undiagnosed DM and around 27% had pre-DM [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 HF in real life.

Via IRT it will be ensured that approximately a minimum of 35 % of the trial population will be patients with DM, a minimum of 15 % will be patients with pre -DM 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 active treatment with antidiabetic medication (for indication of DM) or screening HbA1c $\geqslant$6.5% or history of DM. Pre-DM is defined as screening HbA1c $\geqslant$5.7% and <6.5% without the intake of antidiabetic medication (unless taken for a non-DM indication) and no history of DM, and 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].

IRT will be used to aim for a trial population consisting of approximately 35% to 50% with an LVEF $\geq$50%. To ensure adequate enrolment of patients the final decision on capping will be based on the recommendation from the ExSC during the recruitment period.

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 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 HF 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 preserved EF defined as LVEF > 40 % per local reading (obtained by echocardiography, radionuclide ventriculography, invasive angiography, MRI or CT), and no prior measurement of LVEF ≤ 40% under stable conditions[b]. A historical LVEF may be used if it was measured within 6 months prior to visit 1, and more than 90 days after any myocardial infarction (as defined in exclusion criterion No.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.

[a] Women of childbearing potential are defined as:
- having experienced menarche and
- not postmenopausal (12 months with no menses without an alternative medical cause) and
- not permanently sterilised (e.g., hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

[b] In the Investigator's opinion

5. Elevated N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) > 300 pg/ml for patients without AF, OR > 900 pg/ml for patients with AF, analysed at the Central laboratory at Visit 1
6. Patients must have at least one of the following evidence of HF:
    a. Structural heart disease[c] (left atrial enlargement and/or left ventricular hypertrophy) documented by echocardiogram at Visit 1 or within 6 months prior to Visit 1, OR
    b. Documented HHF[d] within 12 months prior to Visit 1
7. Oral diuretics, if prescribed to patient according to local guidelines and discretion of the Investigator, should be stable for at least 1 week prior to Visit 2 (Randomisation)
8. Body Mass Index (BMI) < 45 kg/m2 at Visit 1
9. Signed and dated written ICF in accordance with GCP and local legislation prior to admission to the trial

3.3.3 Exclusion criteria

1. MI (increase in cardiac enzymes in combination with symptoms of ischaemia or newly developed ischaemic ECG changes), coronary artery bypass graft surgery or other major cardiovascular surgery, stroke or transient ischaemic attack (TIA) in past 90 days prior to Visit 1
2. Heart transplant recipient or listed for heart transplant
3. Implantation of cardioverter defibrillator (ICD) within 3 months prior to Visit 1
4. Implanted cardiac resynchronisation therapy (CRT)
5. Cardiomyopathy based on infiltrative diseases (e.g. amyloidosis), accumulation diseases (e.g. haemochromatosis, Fabry disease), muscular dystrophies, cardiomyopathy with reversible causes (e.g. stress cardiomyopathy), hypertrophic obstructive cardiomyopathy or known pericardial constriction
6. Any severe (obstructive or regurgitant) valvular heart disease expected to lead to surgery during the trial in the Investigator's opinion
7. Acute decompensated HF (exacerbation of chronic HF) requiring intravenous (i.v.) diuretics, i.v. inotropes or i.v. vasodilators, or left ventricular assist device within 1 week from discharge to Visit 1, and during screening period until Visit 2 (Randomisation)
8. Atrial fibrillation (AF) or atrial flutter with a resting heart rate > 110 bpm documented by ECG at Visit 1 (screening)
9. Systolic blood pressure (SBP) ≥ 180 mmHg at Visit 2. If SBP >150 mmHg and <180 mmHg at Visit 2, the patient should be receiving at least 3 antihypertensive drugs
10. Symptomatic hypotension and/or a SBP < 100 mmHg at Visit 1 or Visit 2

[c] Structural heart disease is further defined in Appendix 10.5
[d] The main reason for HHF must be HF. Documentation for HHF must be provided in the source documents

11. Chronic pulmonary disease requiring home oxygen, oral steroid therapy or hospitalisation for exacerbation within 12 months, or significant chronic pulmonary disease in the Investigator's opinion, or primary pulmonary arterial hypertension
12. Indication of liver disease, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatase above 3 x upper limit of normal (ULN) as determined at Visit 1
13. Impaired renal function, defined as eGFR < 20 mL/min/1.73 m2 $(CKD\text{-}EPI)_{cr}$ or requiring dialysis, as determined at Visit 1
14. Haemoglobin < 9 g/dl at Visit 1
15. History of ketoacidosis
16. Major surgery (major according to the investigator's assessment) performed within 90 days prior to Visit 1, or scheduled major elective surgery (e.g. hip replacement) within 90 days after visit 1
17. Gastrointestinal (GI) surgery or GI disorder that could interfere with absorption of trial medication in the investigator's opinion
18. Any documented active or suspected malignancy or history of malignancy within 2 years prior to screening, except appropriately treated basal cell carcinoma of the skin, in situ carcinoma of uterine cervix or low risk prostate cancer (patients with pre-treatment PSA < 10 ng/mL and biopsy Gleason score of ≤ 6 and clinical stage T1c or T2a)
19. Presence of any other disease than heart failure with a life expectancy of <1 year in the investigator's opinion
20. Patients who must or wish to continue the intake of restricted medications (see Section 4.2.2) or any drug considered likely to interfere with the safe conduct of the trial
21. Current use or prior use of a SGLT-2 inhibitor or combined SGLT-1 and 2 inhibitor within 12 weeks prior to Visit 1 or during screening period until Visit 2 (Randomisation). Discontinuation of a SGLT-2 inhibitor or combined SGLT-1 and 2 inhibitor for the purposes of study enrolment is not permitted.
22. Currently enrolled in another investigational device or drug trial, or less than 30 days since ending another investigational device or drug trial(s), or receiving other investigational treatment(s). Patients participating in a purely observational trial will not be excluded
23. Known allergy or hypersensitivity to empagliflozin or other SGLT-2 inhibitors
24. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable trial subject or unlikely to complete the trial
25. Women who are pregnant, nursing, or who plan to become pregnant while in the trial
26. Any other clinical condition that would jeopardise patients safety while participating in this trial, or may prevent the subject from adhering to the trial protocol

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

This is a long-term outcome trial and every effort should be made by the site staff to encourage patients to remain in the trial and on trial medication unless medical condition substantially changes to alter the safety profile. If a patient is withdrawn from the trial the ExSC and the Sponsor should be informed immediately about each individual case.

Prematurely discontinuation of trial medication
For patients who prematurely discontinue trial medication all efforts should be made to observe these patients and ask them to continue to attend the scheduled visits until the end of trial. It is expected that all efforts are made to follow up on the collection of all adverse events, outcome events and concomitant therapy, and to have a complete dataset without missing data.

If a patient who prematurely discontinued trial medication is not willing to return to the predefined trial visits, at minimum a telephone call every 24 weeks (preferably every 12 weeks) and a telephone call at trial end will be required, to document the occurrence of 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.

The right to withdraw informed consent at any time for any reason also applies to the optional informed consent to biobanking (including deoxyribonucleic acid (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 procedures prior to enrolment as well as an explanation of the consequences of premature withdrawal.

3.3.4.2 Discontinuation of the trial by the Sponsor

BI reserves the right to discontinue the trial overall or at a particular trial centre at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial centre
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial (see also Section 3.1.1).
3. Violation of GCP, the Clinical Trial Protocol (CTP), or the contract disturbing the appropriate conduct of the trial

The Investigator / the trial centre will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4 TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The trial medication will be provided by BI.

4.1.1 Identity of the investigational Medicinal product and comparator

The characteristics of test products are below:

Substance:	empagliflozin
Pharmaceutical formulation:	film-coated tablet
Source:	Boehringer Ingelheim
Unit strength:	10 mg
Posology:	1 tablet once daily
Rout of administration:	oral

Substance:	placebo matching empagliflozin
Pharmaceutical formulation:	film-coated tablet
Source:	Boehringer Ingelheim
Unit strength:	-
Posology:	1 tablet once daily
Rout of administration:	oral

4.1.2 Selection of doses in the trial

Empagliflozin 10 mg and 25 mg are approved for the treatment of T2DM.

Empagliflozin exerts its effect by promoting glucosuria and consequent hemodynamic changes associated with diuresis, improvement in arterial stiffness, blood pressure lowering effect with no increase in HR and reduction in HR x Pressure product, an index of myocardial oxygen consumption. These modes of actions support the scientific rationale of using empagliflozin in patients with HF.

In the EMPA-REG-OUTCOME trial both doses were administered to patients with T2DM and showed to be equally effective in reducing CV death, HHF, and composite of HHF or CV death in patients with HF at baseline.

In subgroup analysis empagliflozin improved the main outcome of CV death and HHF with the similar magnitude in patients with low or high levels of HbA1c at baseline. This indicates the risk reduction for HF outcome is independent of the degree of glycaemic control at baseline, suggesting that these benefits can be achieved with the 10 mg dose similar to the 25

mg dose in the non-diabetic population as well. The mechanism of action is supported by studies in healthy volunteers where both doses were associated with about 50g glucosuria.

Given the lower exposure with 10 mg empagliflozin similar general safety, and CV effects similar for both doses, empagliflozin 10 mg once daily has been selected in this trial.

For further details see current version of the IB.

4.1.3 Method of assigning patients to treatment groups

During Visit 2 eligible patients will be randomised to receive empagliflozin 10 mg, or matching placebo, in a 1:1 ratio according to the randomisation plan. The assignment will occur in a blinded fashion via Interactive Response Technology (IRT).

To facilitate the use of the IRT, the Investigator will receive a manual including all necessary instructions for using the system. A copy of the manual will be available in the ISF.

Patient assignment to the treatment group will be determined by a computer generated random sequence. Access to the randomisation code will be controlled and documented - for further details please refer to Section 4.1.5.1. and 4.1.5.2.

Using this procedure, relevant parties will be blinded to the treatment group assignment.

For information on stratification and capping please refer to Section 3.3.

4.1.4 Drug assignment and administration of doses for each patient

Patients who qualify will be randomised to one of the dosages described in Section 4.1.1. Trial medication will be dispensed in a double-blind and single-dummy manner.

Dispensing of kits for the double-blind treatment period will begin at Visit 2 and continue at every visit until end of trial. For further details regarding packaging (e.g. number of tablets per container) please refer to Section 4.1.6.

From the start of the treatment period patients will be instructed to take the trial medication once daily with a glass of water. Empagliflozin can be taken with or without food.

To ensure a dose interval of about 24 hours, the medication should be taken in the morning at approximately the same time every day. If a dose is missed by more than 12 hours, that dose should be skipped and the next dose should be taken as scheduled. On days before the next visit, the dose should be taken 22-26 hours before the planned dose at the visit. No double doses should be taken.

Patients should be instructed not to take their medication on the morning of trial visits as they will be dosed whilst in the clinic. Visits should be routinely scheduled at approximately the same time of day for each visit. The actual date and time of administration of the trial medication at the trial visit will be recorded in the eCRF.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, Investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial, will remain blinded with regard to the randomised treatment assignments until after database lock.

The DMC will be provided with unblinded data in order to allow them to review efficacy and safety and to fulfil their tasks as outlined in the data monitoring committee charter. An independent team, not otherwise involved in the conduct of the trial, will provide the unblinded results to the DMC.

The randomisation code will be kept secret by Clinical Trial Support up to database lock.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the Investigator via the IRT. It must only be used in an emergency situation when the identity of the trial medication must be known to the Investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. Whenever possible and if time allows, the need for unblinding will be discussed with the medical representative from the Sponsor or delegate before the unblinding of trial medication takes place. The reason for unblinding must be documented in the source documents and/or appropriate eCRF page along with the date and the initials of the person who broke the code.

The patient could continue with trial medication after unblinding.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's Pharmacovigilance group to access the randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives and not to be shared further.

For Japan only: In this blinded trial, an emergency code break will be available to the Investigator / the sub-Investigators via the IRT. This code break may only be accessed in emergency situations when the identity of the trial medication must be known to the Investigator /the sub-Investigators in order to provide appropriate medical treatment or if required to assure the safety of trial participants. Each site receives a manual from the IRT provider that contains instructions on how to unblind the treatment of a patient via the IRT (via 24-hour Emergency helpline). If the code break for a patient is accessed, the Sponsor or delegate must be informed immediately. The reason for accessing the code break, together with the date, must be documented on the appropriate eCRF page. In case third party needs to break the code, however, when the Investigator cannot be reached, the code can be opened by calling emergency code manager.

4.1.6 Packaging, labelling and re-supply

The investigational products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice

(GMP). Re-supply to the sites will be managed via the IRT, which will also monitor expiry dates of supplies available at the sites.

For details of packaging and the description of the label, please refer to the ISF.

4.1.7 Storage conditions

Trial medication must be stored under the recommended storage conditions indicated on the label. A temperature log must be maintained by the investigator / pharmacist / investigational drug storage manager to make certain that the drug supplies are stored at the correct temperature. If the storage conditions are found to be outside the specified range, the process outlined in the ISF should be followed.

4.1.8 Drug accountability

The Investigator and/or Pharmacist and/or investigational drug storage manager will receive the investigational drugs delivered by the Sponsor or delegate when the following requirements are fulfilled:

- Approval of the trial protocol by the Institutional Review Board (IRB) / ethics committee
- Availability of a signed and dated clinical trial contract between the Sponsor or delegate and the head of the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority (CA),
- Availability of the curriculum vitae of the principal Investigator,
- Availability of a signed and dated clinical trial protocol
- Availability of the proof of a medical license for the principal Investigator
- For USA; Availability of Form 1572

The Investigator and/or Pharmacist and/or investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the Sponsor, CRO or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the Sponsor, CRO or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. The Investigator / Pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the Sponsor or delegate. At the time of return to the Sponsor/CRO, the Investigator / Pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the Investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

The use of medication for the treatment of HF will be at the discretion of the Investigator and should be in accordance with local/international guidelines.

All concomitant (additional) medications and other therapies should be recorded on the appropriate pages of the eCRF.

Concomitant antidiabetic medications should be adjusted individually as clinically indicated by the patient's usual diabetes care provider. Restrictions of antidiabetic background therapy are described in Section 4.2.2.

Patients without a diagnosis of DM experiencing repeated or severe symptoms such as nervousness, sweating, intense hunger, trembling, weakness and palpitations should contact the Investigator or other healthcare professional, as these symptoms might be suggestive of hypoglycaemia. In the case of hypoglycaemia, in patients with or without DM, that may put the patient at risk (e.g. repeated symptomatic hypoglycaemia or severe hypoglycaemia), appropriate care should be provided at the discretion of the Investigator.

Special attention must be paid to the prevention of KA. All patients must be made aware of this risk and need to be instructed to contact the Investigator or other healthcare professional in case of symptoms of metabolic acidosis, KA and DKA. Cases of DKA have been reported in patients treated with empagliflozin, including fatal cases. In a number of reported cases, the presentation of the condition was atypical with only moderately increased blood glucose values; below 14 mmol/l (250 mg/dl).

The risk of DKA must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness.

Patients should be assessed and treated for KA immediately according to local guidelines if these symptoms occur, regardless of blood glucose level. If KA is suspected, the trial medication should be discontinued, the patient should be evaluated, and prompt treatment should be initiated.

Patients who may be at higher risk of KA while taking empagliflozin include patients on a very low carbohydrate diet (as the combination may further increase ketone body production), patients with an acute illness, pancreatic disorders suggesting insulin deficiency (e.g. Type 1 diabetes mellitus (T1DM), history of pancreatitis or pancreatic surgery), insulin dose reduction (including insulin pump failure), alcohol abuse, severe dehydration, and patients with a history of KA. Empagliflozin should be used with caution in these patients. In patients requiring insulin, caution should be taken when the dose of insulin is reduced.

In clinical situations known to predispose to KA (e.g. prolonged fasting due to acute illness or surgery), the Investigator should consider monitoring for KA and temporarily discontinue the trial medication.

There are no trial specific emergency procedures to be followed.

4.2.2 Restrictions

The use of any SGLT-2 inhibitors or combined SGLT-1 and 2 inhibitors except the blinded trial medication is prohibited during the course of the trial. This does not include the 30 days

period between the EOT and the Follow Up Visit occurring at study close-out (see section 6.2.3) .

If any restricted treatment is given during the conduct of the trial, the trial medication can be discontinued temporarily, or if needed permanently.

If the patient is in need of any additional treatment during this period, this may be given at the discretion of the Investigator. The patient can still remain on trial medication.

WOCBP must use the contraception methods as described in the patient information.

4.3 TREATMENT COMPLIANCE

Patients are requested to bring all remaining trial medication including empty package material with them when attending visits.

The Investigator or his/her designate will count the number of the returned tablets and calculate the compliance based on the number of tablets taken, divided by the number of tablets that should have been taken since last visit, multiplied by 100. See formula below.

$$\text{Compliance (\%)} = \frac{\text{Number of tablets actually taken since last tablet count x 100}}{\text{Number of tablets which should have been taken in the same period}}$$

Compliance should be between 80% and 120%. Compliance should be emphasised with a goal of at least 80% compliance rate. However, randomised patients will not be discontinued for poor compliance without prior discussion with the monitor or designee.

Patients who are not compliant with their medication should again be carefully interviewed and again re-informed about the purpose and the conduct of the trial.

5 VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL EFFICACY ENDPOINTS

5.1.1 Primary endpoint(s)

The composite primary endpoint for this trial is the time to first event of adjudicated CV death or adjudicated HHF in patients with Heart Failure with preserved Ejection Fraction (HFpEF).

5.1.2 Secondary endpoint(s)

The key secondary endpoints which are part of the testing strategy, are the following:

1. Occurrence of adjudicated HHF (first and recurrent),
2. eGFR $(CKD\text{-}EPI)_{cr}$ slope of change from baseline

Other secondary endpoints (not part of confirmatory testing hierarchy on trial level) are the following:

- Time to first occurrence of chronic dialysis or renal transplant or sustained* reduction of ≥40% eGFR $(CKD\text{-}EPI)_{cr}$ or
    - 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
    - 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

*An eGFR $(CDK\text{-}EPI)_{cr}$ reduction is considered sustained, if it is determined by two or more consecutive post-baseline central laboratory measurements separated by at least 30 days (first to last of the consecutive eGFR values).

Chronic dialysis is defined as dialysis with a frequency of twice per week or more often for at least 90 days.

- Time to first adjudicated HHF
- Time to adjudicated CV death
- Time to all-cause mortality
- Time to onset of DM (defined as HbA1c ≥6.5% or as diagnosed by the Investigator) in patients with pre-DM defined as no history of DM and no HbA1c ≥6.5 before treatment, and a pre-treatment HbA1c value of ≥ 5.7 and <6.5
- Change from baseline in clinical summary score (HF symptoms and physical limitations domains) of the Kansas City Cardiomyopathy Questionnaire (KCCQ) at week 52
- Occurrence of all-cause hospitalisation (first and recurrent)

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 $(CKD\text{-}EPI)_{cr}$ < 30mL/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 $(CKD\text{-}EPI)_{cr}$ < 30mL/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
- Changes in NT-proBNP from baseline over time
- Change in albuminuria from baseline over time
- Change in albuminuria from baseline over time by baseline 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 the 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 KCCQ

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 will 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 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.).

5.2.5 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.

5.3 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).

Table 5.3.4: 1 Safety laboratory parameters – whole blood, serum or plasma

Haematology

- Hematocrit
- Haemoglobin
  - Reticulocyte Count (reflex test if Hb outside normal range)
- Red Blood Cells (RBC) / Erythrocytes
- White Blood Cells / Leukocytes
- Platelet Count / Thrombocytes
- Differential Automatic (relative and absolute count):
  Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes

Clinical chemistry

- Albumin
- Alkaline phosphatase
  - γ-GT (gamma-glutamyl transferase) reflex test triggered by elevated alkaline phosphatase on two sequential measures
- ALT (alanine transaminase, SGPT)
- AST (aspartate transaminase, SGOT)
- Bicarbonate
- Bilirubin total, fractionated if increased
- Calcium
- Chloride
- Creatinine
- Creatine kinase (CK)
- Hs Troponin I (reflex tests if CK is elevated)
- Glucose
- Magnesium
- Phosphate
- Potassium
- Protein total
- Sodium
- Urea (BUN)
- Uric acid

Lipids

- Cholesterol (total)
- HDL cholesterol
- Calculated LDL cholesterol
- Triglycerides (reflex test for direct measurement of LDL cholesterol triggered if triglycerides are > 400 mg/dl or 4.52 mmol/l)

5.3.4.1 Renal function

Urine albumin/creatinine ratio (UACR) in spot urine will be determined and calculated at the central laboratory.

The estimated glomerular filtration rate (eGFR) will be derived from serum creatinine values, age, sex and race based on the CKD-EPI equation [R12-1392]:

$GFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black]

where:
Scr is serum creatinine in mg/dL,
κ is 0.7 for females and 0.9 for males,
α is -0.329 for females and -0.411 for males,
min indicates the minimum of Scr /κ or 1, and
max indicates the maximum of Scr /κ or 1.

The race of the patient will be entered because of potential differences due to race. The CKD-EPI equation considers the race as an adjustment factor, therefore the race must be known for accurate estimation.

In case of an eGFR loss of ≥ 40% since baseline, or when the eGFR drops to < 15 mL/min/1.73 m^2 for patients with an eGFR ≥ 30 mL/min/1.73 m^2 at baseline (<10 mL/min/1.73 m^2 for patients with an eGFR < 30 mL/min/1.73 m^2 at baseline); an additional visit between 30 days to preferably 60 days after detection should be scheduled (unless detected at the EOT visit at trial end) to collect a blood sample for repeat central analysis of creatinine for calculation of the eGFR. If a signal of abnormal creatinine or eGFR is reported to the site by others (e.g. treating physicians from local labs), an additional sample should be sent to central lab, and if it is still abnormal, another sample should be sent to central lab between 30 days and preferably 60 days.

Kidney function will be classified as described in the table below (Table 5.3.4.1:1):

Table 5.3.4.1: 1 Classification of kidney function

CKD stage	eGFR
1	≥ 90
2	60-89
3a	45-59
3b	30-44
4	15-29
5	< 15

5.3.4.2 Pregnancy testing

Pregnancy testing (urine) will be performed in female patients of child bearing potential according to the time points indicated in the Flow Chart. Pregnancy kits will be provided by the Central Laboratory. For reporting of pregnancy event refer to Section 5.3.7.2.

5.3.4.3 Criteria for hypoglycaemic events

In DM patients, all symptomatic hypoglycaemia events, or severe hypoglycaemias (e.g. if the patient required assistance of another person), or any hypoglycaemia episode with glucose values < 54 mg/dl (< 3.0 mmol/l), or if the investigator considered the event to be an AE should be documented as an AE "hypoglycaemic event". In non-diabetic or pre-diabetic patients, the investigator should consider and rule out other alternative causes for such symptoms and can perform blood glucose levels to confirm the diagnosis of hypoglycaemia.

5.3.4.4 Urinary tract infections and genital infections

Patients having a history of chronic/recurrent urinary tract infections (UTI) or genital infections or an acute episode of UTI or genital infection at screening will be identified, and

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 be advised to measure their ketones at least one 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 KA, e.g. nausea, vomiting, and abdominal pain. Patients must be reminded about the signs and symptoms of KA, 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 KA 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 reports 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 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 adverse event (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:

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

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "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" the patient needs 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, KA 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 KA which may occur at lower plasma glucose levels in patients with DM and potentially also in non-diabetic patient population. The diagnosis of KA 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 KA are urine ketones and anion gap >10.

Investigators should note that not all criteria mentioned above need to apply for the diagnosis of KA, 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).

Each lower limb amputation, disarticulation, or auto-amputation should be reported separately. The SAE report should include the date of the procedure, the level of amputation or disarticulation, the medical condition(s) leading to the procedure and if the patient had some of the known risk factor(s) for lower limb amputation.

Intensity of AEs

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

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

Causal relationship of AEs

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

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

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).

  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial medication continues or remains unchanged.

For Japan only: The reason for the decision on causal relationship for unlisted AEs needs to be provided in the eCRF.

5.3.7.2 Adverse event collection and reporting

AE Collection

The Investigator shall maintain and keep detailed records of all AEs in their patient files. The following must be collected and documented on the appropriate eCRF(s) by the Investigator:

- From signing the ICF onwards through the Residual Effect Period (REP), until individual patient's end of trial:
  - all AEs (serious and non-serious), Outcome events and all AESIs.
- After the individual patient’s end of trial:

  The Investigator does not need to actively monitor the patient for AEs, but must report related SAEs and related AESIs of which the Investigator may become aware of by any means of communication (e.g. phone call). Those AEs should however, not be reported on the eCRF.

The rules for Adverse Event Reporting exemptions still apply.

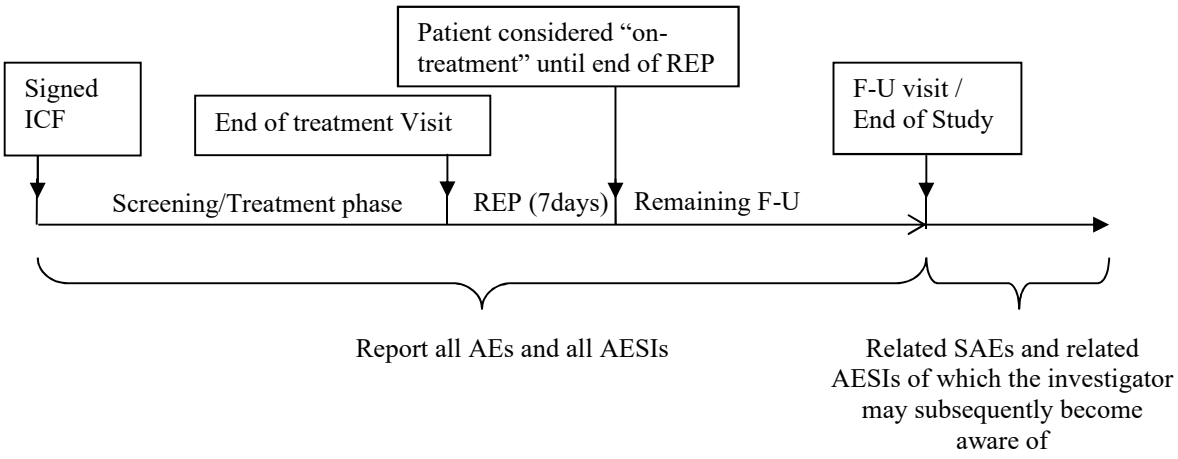

Figure 5.3.7.2: 1 Timelines for adverse event collection

The REP (timeframe after last dose of trial medication when measurable drug levels or pharmacodynamic effects are still likely to be present) is defined as 7 days after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment. Please also refer to Section 7.3.4.

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 specified 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, appropriate follow-up forms have 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 CRF 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 CRF 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 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 above) 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 TIA

CV hospitalisation events

Pneumonia (fatal and non-fatal)

New or exacerbated COPD (fatal and non-fatal)

Based on the same conclusion that it is not possible to perform a causality assessment on these events based on a single case, the trial investigators are exempted from performing a causality assessment and reporting these adverse events on the SAE form to the Sponsor, if event onset is after randomization and the event does not qualify as AESI.

All exempted events must be collected systematically on the eCRF (within 24 hours). The investigator is also required to provide all defined supporting documentation (ref to ISF).

If the events specified above occur before randomization, they are not exempted from immediate reporting on the SAE form. In addition, whenever such events meet the definition of an AESI, then no exemption applies, regardless of occurrence before or after randomization.

An independent Data Monitoring Committee (DMC) will monitor the safety data in the trial on an ongoing basis. Reported SAEs occurring after randomisation that are protocol exempted events will be collected in the eCRFs and evaluated by the DMC. These events will not be collected on SAE forms for expedited review or reporting.

Aggregate analysis of endpoint data to determine any potential benefit or risk and to ensure patient safety during the clinical trial will be performed on a regular basis by the DMC.

If any exempted event or any other adverse event (serious or non-serious) occurs, the investigator or attending physician has the responsibility and will take direction and

appropriate action to provide care for the patient and to decide whether or not the trial medication should be discontinued.

This reporting policy assumes global regulatory agency approval.

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS (SUBSTUDY)

5.4.1 Pharmacokinetic endpoints

The PK sampling will be done from a limited number of randomised patients (approximately 1650 patients) and at sites in pre-selected countries only. The pre-dose blood samples will be collected at visit 4 to determine plasma empagliflozin trough concentrations. These samples will serve to determine steady state trough concentrations of empagliflozin.

The date and exact clock time of trial medication intake the day before this visit will be recorded together with the date and exact clock time of drawing the trough PK sample.

5.4.2 Methods of sample collection

The time interval for blood sample collection relative to the most recent intake of trial medication should be between 22 and 26 h. For quantification of empagliflozin trough plasma concentrations, 3 mL of blood will be drawn from a forearm vein in an EDTA-anticoagulant blood drawing tube at each time-point. Details of sample handling and sample logistics can be found in the ISF (Central lab manual).

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 BIOMARKERS

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 informed consent 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

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 completing 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.

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 patient 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 (refer to the 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

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 the trial participation, she/he is considered to be enrolled in the trial and have started screening. The patient should be registered in the enrolment log and be registered in the IRT as a screened patient. Patients will continue to take 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.

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 (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.

Consenting patients with T1DM are to 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).

For 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.

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 (ref. 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 prematurely discontinued trial medication is not willing to return to the clinic for predefined trial visits, a telephone call at trial end will be required, to document the occurrence of outcome events and vital status. Other AEs and concomitant therapy changes since the last visit should be recorded in the eCRF. 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)

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

Patients who discontinue trial medication prematurely should thereafter continue to follow scheduled visits until trial end. For patients reluctant to attend the scheduled visits after prematurely discontinuing trial medication, some trial assessments may be negotiated with exception of collection of adverse events, outcome events and concomitant therapy.

Please refer to Section 3.3.4.1 for detailed procedures to be followed in case a patient wants to stop trial medication.

In case of early trial termination (e.g. based on recommendation by the DMC, a reasonable timeframe to stop the trial (perform last patient visits) will be defined and communicated to the Investigators.

7 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The eligible patients for this trial will be randomised to empagliflozin 10 mg and placebo in 1:1 ratio, stratified by geographical region, status of DM (DM, pre-DM, no DM) , LVEF (<50%, ≥50%) and eGFR $(CKD\text{-}EPI)_{cr}$ (<60 mL/min/1.73 m², >=60 mL/min/1.73 m²) at screening visit.

To ensure the trial population consist of a reasonable combination of non-, pre- and DM patients, and to aim for approximately 35% to 50% of the population or more with an LVEF ≥50% capping will be used on trial level (see also Section 3.3). Capping on regional level may be applied to achieve a contribution of each region to each category of diabetes status.

The composite primary endpoint is the time to first event of adjudicated CV death or adjudicated HHF. The statistical model for the primary analysis is the Cox proportional hazards model. The hazard ratio and its confidence limits will be determined for evaluating the superiority of empagliflozin to placebo for the primary endpoint.

The key secondary endpoints, which are part of the testing strategy, are

- occurrence of adjudicated HHF (first and recurrent), and
- $eGFR\ (CKD\text{-}EPI)_{cr}$ slope of change from baseline

7.2 NULL AND ALTERNATIVE HYPOTHESES

A hierarchical testing procedure will be followed for the assessment of the primary and the key secondary endpoints. For all endpoints, superiority of empagliflozin vs. placebo will be evaluated with a two-sided test in the following structure:

Null hypothesis: There is no difference between the effect of placebo and the effect of empagliflozin in terms of the endpoint in question.

Alternative hypothesis: There is a difference between the effect of placebo and the effect of empagliflozin in terms of the endpoint in question. The tests will be performed in the following hierarchical order:

1. Time to first event of adjudicated CV death or adjudicated HHF
2. Occurrence of adjudicated HHF (first and recurrent)
3. $eGFR\ (CKD\text{-}EPI)_{cr}$ slope of change from baseline

Starting from step 1, if the null hypothesis is rejected, and the result is more favourable for empagliflozin, superiority is concluded in the tested endpoint, and the overall type I error is preserved for the test in the next step. If at any step the null hypothesis is not rejected, subsequent tests are conducted in an exploratory fashion.

The overall type one error rate will be preserved at a level of 0.05 (2-sided). The type one error rate used at the final analysis will be influenced by the pre-planned interim analysis – see Section 7.4.

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.

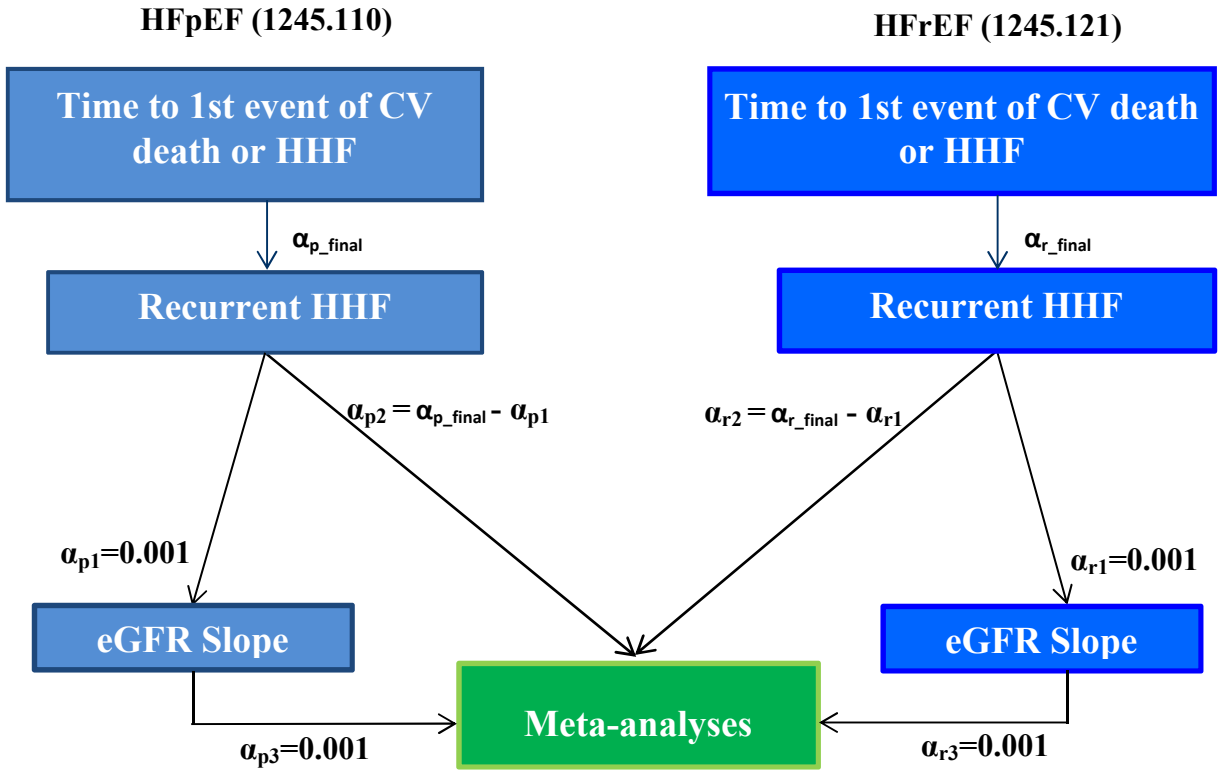

Figure 7.2: 1 Hierarchical analysis of trial in HFpEF (1245.110) and the parallel trial in HFrEF (1245.121) showing the alpha-spending at the final analysis.

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.

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 evaluated on the randomised set using a Cox proportional hazards model with treatment, age (continuous), gender, geographical region, baseline status of DM (DM, pre-DM, no DM), LVEF (continuous) and eGFR $(CKD\text{-}EPI)_{cr}$ at baseline (continuous) as covariates.

The time to the event of interest will be computed as (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 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. The time to censoring will be computed as (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 will be used for 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 the diabetic status by treatment interaction term into the Cox model.

Standard subgroup analyses of the primary endpoint include geographical region, sex, BMI, LVEF, 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 TS only including any events up to 30 days after treatment discontinuation.

7.3.2 Secondary endpoint analyses

The key secondary endpoints 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, and status of DM as fixed effects and eGFR $(CKD\text{-}EPI)_{cr}$ at baseline (continuous), LVEF (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 repeated measures (MMRM) model including LVEF (continuous), 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 and status of DM and 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 as adjudicated HHF and will be evaluated with a joint model 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 and history of DM as fixed effect and baseline eGFR $(CKD\text{-}EPI)_{cr}$ (continuous), age (continuous), LVEF (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 MMRM, including age, LVEF and eGFR $(CKD\text{-}EPI)_{cr}$ at baseline as linear covariates and visit by treatment

interaction, baseline by visit interaction, geographical region, gender 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 of 7 days will be considered 'treatment-emergent'. 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 (CTR).

7.3.6 Prespecified meta-analysis

On project level, meta-analyses are pre-specified. Data from this trial and a parallel trial in HFrEF patients, 1245.121, 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 time of interim analysis, the ExSC, the SEC, Sponsor, CRO, and all trial 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:

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

For an interim analysis at the timepoint of approximately 60% of information, the chosen alpha-spending function gives an alpha-level of 0.001 at time of interim.

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 cutoff to be evaluated from the alpha-spending function (planned at 0.001 one-sided), then 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 of data for safety data or for time-to event endpoints. For patients who discontinue the trial treatment prematurely, all efforts will be made to follow patients for survival and for any other endpoints including the primary and 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 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 $(CDK\text{-}EPI)_{cr}$ reduction is considered sustained, if it is determined by two or more consecutive post-baseline central laboratory measurements separated by at least 30 days (first to last of the consecutive eGFR values). If there is no additional measurement after the eGFR reduction is observed and the patient dies within 60 days of this measurement without second measurement >= 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:
  - no DM (HbA1c < 5.7% without the intake of antidiabetic medication, unless taken for a non-DM indication, and no history of DM), or
  - pre-DM (HbA1c >=5.7% and <6.5% without the intake of antidiabetic medication unless taken for a non-DM indication, and no history of DM), or
  - DM (HbA1c >= 6.5% or intake of antidiabetic medication for a DM indication, or a history of DM)
- $eGFR\ (CKD\text{-}EPI)_{cr}$ at screening
  - <60 mL/min/1.73 m²
  - ≥60 mL/min/1.73 m²
- LVEF
  - LVEF < 50%
  - LVEF ≥ 50%

Patients will be randomised in blocks to double-blind treatment via an IRT system. Approximately equal numbers of patients will be randomised to each treatment group. BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the CTR. Access to the codes will be controlled and documented.

7.7 DETERMINATION OF SAMPLE SIZE

For the sample size calculation, a yearly event rate in the placebo group of 10% is assumed. The assumption is based on the CHARM-Preserved study and part of the TOPCAT study from the Americas [R07-4374, R16-1458]. The annual event rates in CHARM-Preserved were 8.1% in the candesartan group and 9.1% in the placebo group. The annual rates from the Americas in the TOPCAT study were 10.4 in the spironolactone group and 12.6 in the placebo group.

The trial is designed to achieve a power of 90% for a two sided test at level $\alpha = 0.05$.

The following table presents the number of required events together with the number of to be randomised and treated patients assuming an accrual period of 18 months and a follow-up period of 20 months for different assumed true hazard ratios. However, the follow-up period is not fixed but the trial will continue until the necessary number of events has been observed, which are confirmed by the adjudication committee.

The drop-out rate from the trial is assumed to be low (< 1% per year) and is therefore not further considered for the determination of sample size.

Table 7.7: 1 Sample size calculation – not including interim analyses:

Yearly event rate for HHF+CV Death (Placebo)	**Hazard ratio**	**Number of events for 90% power for HHF+CV Death**	**Number of patients for 18 months accrual and 20 months follow up**
10%/Year	0.70	331	1710
10%/Year	0.75	509	2562
10%/Year	0.80	841	4126
10%/Year	0.85	1601	7656
10%/Year	0.90	3814	17814

A hazard ratio of 0.8 was chosen as a conservative estimate based on the results of the EMPA-REG OUTCOME trial described in Section 1.2.3

Therefore, at least 841 confirmed primary events should be observed and at least 4126 patients should be randomised and treated in order to achieve a power of 90% assuming a true hazard ratio of 0.8.

Including interim analysis with Hwang-Shih-deCani alphaspending with gamma=-8 at 60% of information will diminish the power only slightly to 89.98%.

The event rate and recruitment progress will be assessed in a blinded manner during recruitment before any interim unblinding. If the accumulated blinded data suggests a slower accrual of primary outcome events over calendar time than originally projected, then the number of randomised patients may be increased to a maximum of 6000 patients. 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 confirmed primary outcome events will not be affected by this consideration and will remain 841 events.

Calculations were performed using ADDPLAN6.1.1 by ADDPLAN Inc.

Based on the abovementioned assumptions, and considering that HHF (first and recurrent) will only be tested if the primary endpoint is successful, the chance of showing significance for HHF (first and recurrent) in a positive trial is at least 70%.

For the integration of a Japanese population in this global phase III trial, and in order to comply with the regulatory requirements for bridging the trial results to this population, the Japanese patients to be randomised will be followed and controlled if necessary. Approximately 145 patients are expected to be randomised to each treatment arm for the Japanese population.

8 INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), relevant BI SOPs and CRO SOPs, the EU regulation 536/2014, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The Investigator will inform the Sponsor or delegate immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

The BI transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the Investigator and of the Sponsor with regard to publication of the results of this trial are described in the Investigator contract. As a rule, no trial results should be published prior to finalisation of the CTR.

For Japan only: The rights of the investigator / trial site and of the Sponsor or delegate with regard to publication of the results of this trial are described in the investigator contract / trial site's contract. As a general rule, no trial results should be published prior to finalisation of the CTR.

The certificate of insurance cover is made available to the Investigator and the patients, and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB / Independent Ethics Committee (IEC) and CA according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH / GCP and to the

regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory, and the ICF and any additional patient-information form retained by the Investigator as part of the trial records. A signed copy of the ICF and any additional patient information must be given to each patient or the patient's legally accepted representative.

The Investigator must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible. The patient must be given sufficient time to consider participation in the trial. The Investigator obtains written consent of the patient's own free will with the ICF after confirming that the patient understands the contents. The Investigator must sign (or place a seal on) and date the ICF. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the ICF.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the Sponsor's or delegate's instructions.

The respective procedure for illiterate patients is described in the Appendix 10.1.

The consent and re-consenting process should be properly documented in the source documentation.

The patient must be informed that his/her personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorised monitors (CML/CL/ Clinical Research Associate (CRA)) or Clinical Quality Assurance auditors appointed by BI, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

In order to achieve a high level of standardised processes, data collection of efficacy and safety endpoints is coordinated centrally:

- central lab analysis of efficacy endpoints, biomarkers and safety lab
- central IRT for stratification, randomisation and kit allocation at each visit
- central adjudication of HHF and cardiovascular events, and hepatic adjudication.

The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan available in eTMF.

A quality assurance audit/inspection of this trial may be conducted by the Sponsor, Sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the Investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

ECRF for individual patients will be provided by the Sponsor or delegate. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements the Investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial subject. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail).

Data reported on the eCRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the subject may not be sufficient to confirm eligibility for the trial and the Investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case the Investigator must make three documented attempts to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

Before providing any copy of patients' source documents to the Sponsor or delegate the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted to ensure patient confidentiality.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For the eCRF, data must be derived from source documents, for example:

- Patient identification: gender, date or year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of Patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- SAEs (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of Patient's Participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant

meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The Sponsor or delegate will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of on-site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

The Investigator / institution will permit trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the eCRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). The CRA and auditor may review all eCRFs and ICFs. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The Sponsor or delegate will also monitor compliance with the protocol and ICH GCP.

An adaptive approach to clinical trial monitoring will be utilised. This is initiated by an assessment of the risk associated with the trial combined with an assessment of critical data and processes. A Risk Assessment Mitigation Plan and Integrated Project Management Plan collectively document the strategies involved with the implementation of onsite, remote and central monitoring activities in order to direct focus to the areas of greatest risk which have the most potential impact to safety patient and data quality. Trial oversight is achieved by regular review of a report of risk which then influences any required changes to the monitoring strategy.

The Investigator /institution will allow on-site trial-related monitoring, audits, IRB/IEC review and regulatory inspections. Direct access should be granted to all source documents (paper and e-records) including progress notes, copies of laboratory and medical test results The CRA and auditor may review all CRFs and ICFs. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1.
The Sponsor/CRO will also monitor compliance with the protocol and ICH GCP.

8.3.3 Storage period of records

Trial site(s):

The trial site(s) must retain the source documents and essential documents (including ISF) according to the national or local requirements (whatever is longer) valid at the time of the end of the trial.

Sponsor:

The Sponsor or delegate must retain the essential documents according to the Sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal regulatory reporting obligation in accordance with regulatory requirements. Exemptions from expedited reporting are described in Section 5.3.7.2.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below and in Section 5.5.1. Patient privacy will be ensured by using patient identification code numbers.

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.

The end of the trial is defined as the date of the last visit of the last patient in the whole trial "Last Patient Out").

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 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 / CA 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 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 should prepare and submit the records explaining the reasons thereof to the Sponsor or delegate, 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 APPENDICES

10.1 INCLUSION OF ILLITERATE PATIENTS

10.1.1 Patient reported outcome forms

In the event of recruiting an illiterate patient, the following process should be followed with respect to completion of the EQ-5D self-report questionnaire and the KCCQ:

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

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

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

In the same way as for all other patients, the completion of the EQ-5D questionnaire and the KCCQ should be performed in a quiet area where the patient can consider his/her responses to both the descriptive system and VAS.

10.1.2 Patient information and informed consent (including biobanking)

In the event of recruiting an illiterate patient, the following process should be followed with respect to patient information and informed consent:

- The designated site personnel performing the informed consent process will read the trial approved patient information sheet and ICFs to the patient, and explain the details of the trial, all in the presence of an impartial witness.

- This impartial witness must be literate, and can be the patient's relative or caregiver, or a member of staff employed by the clinic but not part of the immediate trial team. In addition, if there are any further local regulations with respect to the consent of illiterate patients, these should also be followed.

- The requirements of the trial will be explained thoroughly and the patient will be given ample time to ask questions and consider his/her participation. If he/she wishes, the patient can take the patient information sheet and ICFs home for further consideration.

- If patient agrees to take part in the trial, he/she would then return to the clinic for the consent process to be completed. The site designated personnel responsible for this process will confirm that the patient has no further questions in the presence of the

same impartial witness (if the patient returns on another day). If a different impartial witness is present, the entire informed consent 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 ICFs.

- 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 and ICFs 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 ICFs.

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

10.2 PATIENT REPORTED OUTCOMES

10.2.1 EQ-5D

Health Questionnaire

English version for the USA

USA (English) © 2009 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group

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 ❑

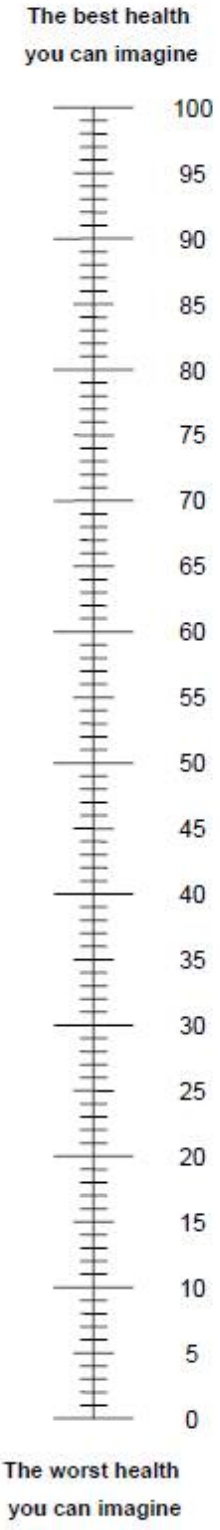
USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*
- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable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

- 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 = ☐



10.2.2 KCCQ

THE KANSAS CITY CARDIOMYOPATHY QUESTIONNAIRE:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Please place an **X** in one box on each line

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

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

10.5 STRUCTURAL HEART DISEASE

Left atrial (LA) enlargement is defined by at least one of the following measurements:

- LA width ≥ 4.0 cm, or
- LA length ≥ 5.0 cm, or
- LA area ≥ 20 cm^2, or
- LA volume ≥ 55 ml, or
- LA volume index ≥ 34 ml/m^2

Left ventricular hypertrophy is defined by at least one of the following measurements:

- Septal thickness or posterior wall thickness ≥ 1.1 cm.
- LV mass index (LVMI) ≥115 g/m2 for males and ≥95 g/m2 for females
- E/e′ (mean septal and lateral) ≥13
- e’ (mean septal and lateral) <9 cm/s

11 DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of CTP revision		23 Nov 2017
EudraCT number		2016-002278-11
BI Trial number		1245.110
BI Investigational Product(s)		Empagliflozin
Title of protocol		A phase III randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic **H**eart **F**ailure with **p**reserved **E**jection **F**raction (**HFpEF**).
		☐
		☒
Section to be changed		Clinical Trial Protocol Synopsis: Main criteria for inclusion
Description of change		Patients with chronic HF diagnosed for at least 3 months before Visit 1 and currently in HF NYHA class II-IV **Was changed to:** Patients with chronic HF diagnosed for at least 3 months before Visit 1 and currently in ~~**HF**~~ NYHA **HF** class II-IV
Rationale for change		Editorial correction
Section to be changed		Clinical Trial Protocol Synopsis: Main criteria for inclusion
Description of change		• Chronic HF with preserved EF defined as LVEF > 40 % per local reading (obtained by echocardiography, radionuclide ventriculography, invasive angiography, MRI or CT), and no prior measurement of LVEF ≤ 40% under stable conditions. The EF must have been obtained and documented at visit 1or within 6 months prior to Visit 1 and more than 90 days after any MI (as defined in exclusion criterion No. 1) Was changed to: • Chronic HF with preserved EF defined as LVEF > 40 % per local reading (obtained by echocardiography, radionuclide

		ventriculography, invasive angiography, MRI or CT), and no prior measurement of LVEF ≤ 40% under stable conditions. **A historical LVEF may be used if it was measured within 6 months prior to visit 1, and more than 90 days after any myocardial infarction (as defined in exclusion criterion No.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.** ~~The EF must have been obtained and documented at visit 1or within 6 months prior to Visit 1 and more than 90 days after any MI (as defined in exclusion criterion No. 1)~~
Rationale for change		To clarify that the LVEF must be documented in an official report prior to randomization and that a historical LVEF may be used as long as the LVEF was measured within 6 months prior to visit 1.
Section to be changed		Clinical Trial Protocol Synopsis: Duration of treatment
Description of change		• 4-21 days screening period **Was changed to:** • 4-~~21~~ **28** days screening period
Rationale for change		To provide sites with additional time to complete all screening procedures.
Section to be changed		Clinical Trial Protocol Synopsis: Duration of treatment
Description of change		Approximately 20-38 months double-blind treatment until the required number of primary events is reached with empagliflozin or placebo. **Was changed to:** ~~Approximately 20-38 months double-blind treatment until the required number of primary events is reached with empagliflozin or placebo.~~ **The study was designed based on an assumption of 18 months recruitment and an event rate of 10%. 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**.

Rationale for change		To clarify that the overall recruitment and follow-up period will vary depending on the observed event rate.
Section to be changed		Clinical Trial Protocol Synopsis: Duration of treatment
Description of change		The trial will continue until required number of adjudicated primary endpoint events have occurred to be able to comply with the objective of the trial. **Was changed to:** 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.
Rationale for change		Editorial correction
Section to be changed		Clinical Trial Protocol Synopsis: Endpoints
Description of change		Other secondary endpoints are: Time to first occurrence of sustained reduction of ≥40% eGFR $(CKD\text{-}EPI)_{cr}$ or **Was changed to:** Time to first occurrence of **chronic dialysis or renal transplant or** sustained reduction of ≥40% eGFR $(CKD\text{-}EPI)_{cr}$ or
Rationale for change		The requirement to initiate chronic dialysis or a renal transplant is considered to indicate a sustained reduction in renal function compared to baseline. Dialysis at baseline is considered exclusionary for study entry.
Section to be changed		Flow Chart
Description of change		Visit 1 window was revised from -21 to -4 days to **-28** days to -4 days
Rationale for change		To provide sites with additional time to complete all screening procedures.
Section to be changed		Flow Chart
Description of change		ECG to be collected at **visit 1** instead of at visit 2.
Rationale for change		To allow the investigator to determine if patient is in AF at time of screening.
Section to be changed		Flow Chart Footnote #6
Description of change		Informed consent may be obtained prior to visit 1 in order to give time to collect medical records. Visit 1 should be performed within 30 days of signing the informed consent form (ICF). **Was changed to:** ~~**Informed consent may be obtained prior to visit 1 in order to give time to collect medical**~~

		~~**records.**~~ **All** visit 1 **procedures** should be performed within ~~30~~ **28** days of signing the informed consent form (ICF).
Rationale for change		Footnote was revised to ensure consistency with flow chart visit window.
Section to be changed		Flow Chart Footnote #10
Description of change		Protocol specified outcome events should be collected on the appropriate eCRF page only. The outcome events which are exempted from SAE reporting are listed in Section 5.3.6. **Was changed to:** Protocol specified outcome events should be collected on the appropriate eCRF page ~~only~~. ~~The outcome events which are exempted~~ **Exemptions** from ~~SAE~~ reporting **on the SAE form** are ~~listed~~ **specified** in **Section 5.3.7.**
Rationale for change		Process clarification for reporting of outcome events. Correction to the section number referenced.
Section to be changed		Flow Chart Footnote # 12
Description of change		For the 12-lead ECG done at the baseline and EOT visit, the interpretation of the tracing must be made locally by a qualified physician and documented on the ECG section of the eCRF. **Was changed to:** For the 12-lead ECG done at ~~the baseline~~ **screening** and EOT visit, the interpretation of the tracing must be made locally by a qualified physician **or appropriately qualified designee** and documented on the ECG section of the eCRF.
Rationale for change		Footnote was updated to reflect ECG collection at visit 1 versus visit 2. ECGs can be interpreted by appropriate qualified site staff.
Section to be changed		Flow Chart Footnote #14
Description of change		For the screening Visit 1, the safety laboratory is limited to liver transaminases, alkaline phosphatase, serum creatinine and urinalysis. Patients do not have to be fasting. **Was changed to:** For the screening Visit 1, the safety laboratory is limited to liver transaminases, alkaline phosphatase, serum creatinine and ~~urinalysis~~ **haematology panel**. Patients do not have to be fasting.

Rationale for change		Routine urinalysis is not required to assess eligibility however haematology panel is required to assess exclusion criteria #14.
Section to be changed		Abbreviations
Description of change		The following abbreviations were added: AF: Atrial fibrillation or Atrial flutter HRQOL: Health-related quality of life KA: Ketoacidosis NCC: National Coordinator Committee NYHA definition was revised from New York Heart Association Classification to: New York Heart Association ~~Classification~~ The following abbreviations were removed as they are not used in the protocol. ACR: Albumin creatinine ratio BNP: B-type Natriuretic Peptide CHF: chronic heart failure EDC: electronic data capture TDMAP: trial data management and analysis plan UGE: urinary glucose excretion
Rationale for change		Administrative corrections
Section to be changed		1.1 Medical Background
Description of change		Chronic heart failure (HF) is a progressive syndrome characterised by the inability of the heart to provide adequate blood supply to meet the metabolic demand of different tissues or do it at the expense of elevated left ventricle filling pressure. **Was changed to:** Chronic heart failure (HF) is a progressive syndrome characterised by the inability of the heart to provide adequate blood supply to meet the metabolic demand of different tissues or **to be able to** do ~~it~~ **so only** at the expense of elevated left ventricle filling pressure.
Rationale for change		Editorial correction.
Section to be changed		1.2 Drug Profile
Description of change		Empagliflozin has been developed for the treatment of T2DM, and has received marketing approval in various regions including the European Union, Latin America, USA and Japan where it is marketed under the brand name Jardiance®. **Was changed to:** Empagliflozin has been developed for the treatment of T2DM, and has received marketing approval in

		various regions including, **for example**, the European Union, Latin American **countries**, USA and Japan where it is marketed under the brand name Jardiance®.
Rationale for change		Editorial correction.
Section to be changed		2.3 Benefit Risk Assessment
Description of change		**The following information was added:** 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 (KA) and diabetic ketoacidosis (DKA). Since an SGLT-2 inhibitor may alter the typical presentation of this condition, 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 KA 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 that 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 RI. Because in the EMPA REG Outcome study no difference in CV benefit was detected for patients with RI vs the overall population, it is 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 occurrences of symptomatic hypoglycemia were detected [U12-2707-01]. It is noted that in patients with T2DM the risk of hypoglycemia 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 of 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 hypoglycemia associated with empagliflozin treatment would be lower than in patients with T2DM. Because the mode of action, blockade of the SGLT2 with consequent glucosuria, is the same in patients with and without diabetes, although to different degrees, it is considered likely that the tolerability of empagliflozin may be no less favourable in patients without DM compared to patients with T2DM. There is also currently limited therapeutic experience with empagliflozin in patients aged 85 years and older. The prevalence of HF increases with age and the therapeutic options in the elderly above 85 years are limited. The inclusion of this population in the clinical trial setting will help support the assessment of benefit-risk of empagliflozin for patients over 85. Special caution should be used in these patients, who may be at increased risk of adverse consequences attributable to empagliflozin-related volume depletion.

		Many patients with chronicHF have RI, 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 RI, including patients with eGFR between > 30 and < 45 ml/min/1.37m^2. In previous trials in patients with T2DM the safety profile in moderate and severe RI were comparable to the overall trial population [P17-10453]. Renal safety will be closely monitored throughout the trial. Refer to section 5.3.4.1. and 5.3.7.1.
Rationale for change		Information was added to provide the risk benefit assessment for inclusion of patients who are elderly, have T1DM or may not have DM or with reduced renal function.
Section to be changed		2.3 Benefit Risk
Description of change		The following was deleted. ~~Special attention will be paid to prevent metabolic acidosis, KA and diabetic ketoacidosis (DKA). For further details refer to Section 4.2.1~~.
Rationale for change		Information was included in the 3rd paragraph in section 2.3.
Section to be changed		Figure 3.1:1
Description of change		An asterisk was added to: “20-38 months” in Figure 3.1:1
Rationale for change		To clarify that the overall recruitment and follow-up period will vary depending on the observed event rate.
Section to be changed		3.1 Overall trial design and plan
Description of change		The estimated length of the double-blind treatment will vary from approximately 20 to 38 months for each patient. The trial duration may be prolonged in case the number of patients and/or primary endpoint events is not reached within the planned timelines. **Was changed to:** The **actual** ~~estimated~~ length of the ~~double-blind treatment will vary from approximately 20 to 38 months for each patient~~ **recruitment period may be extended beyond 18 months and the follow-**

		up period may be adjusted to achieve 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. ~~The trial duration may be prolonged in case the number of patients and/or primary endpoint events is not reached within the planned timelines.~~
Rationale for change		To clarify that the overall recruitment and follow-up period will vary depending on the observed event rate.
Section to be changed		3.1 Overall trial design and plan
Description of change		A footnote was added for Figure 3.1:1 * based on an 18 months recruitment and event rate as outlined as Section 7.7.
Rationale for change		To clarify that the overall recruitment and follow-up period will vary depending on the observed event rate.
Section to be changed		3.1.1 Administrative structure of the trial
Description of change		**The following paragraph was added:** A National Coordinators Committee (NCC) will be established and will consist of leading expert(s) in each participating country. The national coordinators 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.
Rationale for change		A national coordinator committee was set up to advise on the trial.
Section to be changed		3.1.1 Administrative structure of the trial
Description of change		Measures are in place to ensure blinding of the Sponsor, ExSC, SEC, CRO and all other trial participants. **Was changed to:** Measures are in place to ensure blinding of the Sponsor, ExSC, SEC, **NCC,** CRO and all other trial participants.
Rationale for change		The NCC will also be blinded in a similar manner to other committees, sponsor and CRO.
Section to be changed		3.3 Selection of trial population

Description of change		Approximately 500 trial centres will participate to ensure that the estimated 4126 patients are randomised to trial medication and complete the trial. **Was changed to:** Approximately ~~500~~ **560** trial centres will participate to ensure that the estimated 4126 patients are randomised to trial medication and complete the trial.
Rationale for change		Additional sites will participate in the trial.
Section to be changed		3.3.2 Inclusion Criteria #4
Description of change		The EF must have been obtained and documented at Visit 1 or within 6 months prior to Visit 1, and more than 90 days after any myocardial infarction (as defined in exclusion criterion No. 1) **Was changed to:** **A historical LVEF may be used if it was measured within 6 months prior to visit 1, and more than 90 days after any myocardial infarction (as defined in exclusion criterion No.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.**~~The EF must have been obtained and documented at Visit 1 or within 6 months prior to Visit 1, and more than 90 days after any myocardial infarction (as defined in exclusion criterion No. 1)~~
Rationale for change		To clarify that the LVEF must be documented in an official report prior to randomization and that a historical LVEF may be used as long as the LVEF was measured within 6 months prior to visit 1.
Section to be changed		3.3.2 Inclusion Criteria footnote a
Description of change		- not permanently sterilised (e.g., tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy). **Was changed to:** - not permanently sterilised (e.g., ~~tubal occlusion~~, hysterectomy, bilateral oophorectomy or bilateral salpingectomy).
Rationale for change		Tubal occlusion is considered to be a highly effective method of contraception but is not considered to be permanent sterilisation.
Section to be changed		3.3.3 Exclusion Criteria #8

Description of change		Atrial fibrillation or atrial flutter with a resting heart rate > 110 bpm documented by ECG at Visit 2 (Randomisation) **Was changed to:** Atrial fibrillation or atrial flutter with a resting heart rate > 110 bpm documented by ECG at Visit ~~2~~ **1 (**~~Randomisation~~ **Screening)**
Rationale for change		ECG to be performed at visit 1 instead of visit 2. Therefore exclusion criterion is updated accordingly.
Section to be changed		3.3.3 Exclusion Criteria # 21
Description of change		Treatment with any SGLT-2 inhibitor or combined SGLT-1 and 2 inhibitor within 1 week prior to Visit 1 or during screening period until Visit 2 (Randomisation) **Was changed to:** **Current use or prior use of a** ~~Treatment with any~~ SGLT-2 inhibitor or combined SGLT-1 and 2 inhibitor within 1**2** week**s** prior to Visit 1 or during screening period until Visit 2 (Randomisation). **Discontinuation of a SGLT-2 inhibitor or combined SGLT-1 and 2 inhibitor for the purposes of study enrolment is not permitted.**
Rationale for change		Patients should not have standard of care therapy withheld or changed for the purposes of study enrolment.
Section to be changed		3.3.4.1 Removal of individual patients
Description of change		The following was added to option 3. **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.**
Rationale for change		To encourage complete reporting of all relevant information for patients who have discontinued study drug.
Section to be changed		5.1.2 Secondary endpoint(s)
Description of change		Time to first occurrence of sustained* reduction of ≥40% eGFR $(CKD\text{-}EPI)_{cr}$ or **Was changed to:** Time to first occurrence of **chronic dialysis or renal transplant or** sustained* reduction of ≥40% eGFR $(CKD\text{-}EPI)_{cr}$ or

Rationale for change		The requirement to initiate chronic dialysis or renal transplant is considered to indicate a sustained reduction in renal function compared to baseline. Dialysis at baseline is considered exclusionary for study entry.
Section to be changed		5.1.2 Secondary endpoint(s)
Description of change		Added to this section: **Chronic dialysis is defined as dialysis with a frequency of twice per week or more often for at least 90 days.**
Rationale for change		The requirement to initiate chronic dialysis is considered to indicate a sustained reduction in renal function compared to baseline.
Section to be changed		5.2.1 KCCQ
Description of change		Added to this section: **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.**
Rationale for change		To clarify the evaluation of the further endpoint of: Change from baseline in KCCQ based on patient-preferred outcome at week 52
Section to be changed		5.2.2 New York Heart Association classification
Description of change		The classification of patient's physical activity according to NYHA will be performed at all on-site and telephone visits until end of the trial. **Was changed to:** The classification of patient's physical activity according to NYHA will be performed at all on-site ~~and telephone~~ visits 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.**
Rationale for change		To clarify when NYHA function classification should be performed.
Section to be changed		5.2.5 Blood Pressure
Description of change		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. All

		recordings should be made using a similar type of and validated certified blood pressure recording instrument on the same arm. Further details on blood pressure measurement procedure are provided in Appendix 10.6. **Was changed to:** 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, ~~All~~ blood pressure** recordings should be ~~made~~ **measured** using a similar type of and validated certified blood pressure recording instrument on the same arm, **when possible**. ~~Further details on blood pressure measurement procedure are provided in Appendix 10.6.~~
Rationale for change		Detailed procedure for measurement of blood pressure is not required as changes in SBP and DBP will be analysed descriptively.
Section to be changed		5.3.4.5 Ketone monitoring in patients with type 1 diabetes (T1DM) only
Description of change		New section added: 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 be advised to measure their ketones at least one 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 KA, e.g. nausea, vomiting, and abdominal pain. Patients must be reminded about the signs and symptoms of KA, 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 KA 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.
Rationale for change		To include, in the protocol, the ketone monitoring strategy for patients with T1DM. Information is currently contained in the ISF.
Section to be changed		5.3.5 Electrocardiogram
Description of change		ECGs will be performed at Visit 2, and at the EOT Visit 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 and stored locally. **Was changed to:** ECGs will be performed at ~~Visit 2, and at the EOT Visit~~ **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.

Rationale for change		ECG to be measured at visit 1 instead of at visit 2. ECGs can be interpreted by appropriate qualified site staff.
Section to be changed		5.3.7.1 Definitions of AEs
Description of change		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. Any suspected transmission via a medicinal product of an infectious agent is considered a serious adverse reaction. **Was changed to:** 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. ~~Any suspected transmission via a medicinal product of an infectious agent is considered a serious adverse reaction.~~
Rationale for change		Editorial correction.
Section to be changed		5.3.7.1 Definitions of AEs
Description of change		AESIs need to be reported to the Sponsor's/CRO's Pharmacovigilance Department within the same timeframe that applies to SAE, see below **Was changed to:** AESIs need to be reported to the Sponsor's/CRO's Pharmacovigilance Department within the same timeframe that applies to SAE, see ~~below~~ **Section 5.3.7.2**
Rationale for change		Editorial clarification.
Section to be changed		5.3.7.2 Adverse event collection and reporting
Description of change		From signing the ICF onwards through the Residual Effect Period (REP), until individual patient's end of trial participation: **Was changed to:** From signing the ICF onwards through the Residual Effect Period (REP), until individual patient's end of trial ~~participation~~:
Rationale for change		Editorial clarification.
Section to be changed		5.3.7.2 Adverse event collection and reporting

Description of change		• After the individual patient's end of trial: The Investigator does not need to actively monitor the patient for AEs, but must report relevant SAEs and relevant AESIs of which the Investigator may become aware of. **Was changed to:** • After the individual patient's end of trial: The Investigator does not need to actively monitor the patient for AEs, but must report ~~relevant~~ **related** SAEs and ~~relevant~~ **related** AESIs of which the Investigator may become aware of **by any means of communication (e.g. phone call). Those AEs should however, not be reported on the eCRF.** **The rules for Adverse Event Reporting exemptions still apply.**
Rationale for change		Clarification that related SAEs and AESIs are to be reported and that exemptions to AE reporting will apply.
Section to be changed		5.3.7.2:1 Timelines for adverse event collection
Description of change		Remaining F-U (~23days) **Was changed to:** Remaining F-U ~~(~23days)~~ And: Relevant SAEs and AESIs of which the investigator may subsequently become aware of **Was changed to:** ~~Relevant~~ **Related** SAEs and **related** AESIs of which the investigator may subsequently become aware of
Rationale for change		To clarify the requirement to report related SAEs and AESIs at the end of the trial and to clarify that the follow-up period is not contained to 23 days.
Section to be changed		5.3.7.2 Adverse event collection and reporting
Description of change		The following text was moved from above Figure 5.3.7.2:1 to below. The REP (timeframe after last dose of trial medication when measurable drug levels or pharmacodynamic effects are still likely to be present) is defined as 7 days after the last trial

		medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment. Please also refer to Section 7.3.4. Events which occurred after the REP will be considered as post treatment events.
Rationale for change		Editorial correction
Section to be changed		5.3.7.2 Adverse event collection and reporting
Description of change		The Investigator must report all non-exempted SAEs, AESI and any non-serious AE relevant for the reported SAE, immediately (within 24 hours) on the BI SAE form. The same timeline applies if follow-up information becomes available. **Was changed to:** The Investigator must report all non-exempted SAEs, AESI**s** and ~~any~~ non-serious AE**s which are** relevant for the reported SAE **or AESI, on the BI SAE form** immediately (within 24 hours) ~~on the BI SAE form~~ t**o the specified 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, appropriate follow-up forms have to be provided. For follow-up information the same rules and timeline apply as for initial information.**
Rationale for change		Editorial clarifications.
Section to be changed		5.3.7.2 Adverse event collection and reporting
Description of change		The following text was removed: ~~For Japan only: All SAEs must be reported immediately to the head of the trial site.~~ ~~Any protocol exempted event that occurs prior to randomisation and fulfils the criteria of an SAE will be reported immediately (within 24 hours) by the Investigator on the BI SAE form via fax immediately (within 24 hours) to the Sponsor's/CRO's unique entry point (country specific contact details will be provided in the ISF);~~

		~~**however, if the patient has been randomised, the exempted events will not be reported as SAEs to the sponsor and no causality assessment will be performed. These events will be entered only on the AE eCRF pages (within 24 hours). The investigator is also required to provide all defined supporting documentation.**~~ ~~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.~~ ~~If any exempted event or any other adverse event (serious or non-serious) occurs, the investigator or attending physician has the responsibility and will take direct and appropriate action to provide care for the patient and to decide whether or not the trial medication should be discontinued.~~ ~~An independent Data Monitoring Committee (DMC) will monitor the safety data in the trial on an ongoing basis. Reported SAEs occurring after randomisation that are protocol exempted events will be collected in the eCRFs and evaluated by the DMC. These events will not be collected on SAE forms for expedited review or reporting.~~ ~~Aggregate analysis of endpoint data to determine any potential benefit or risk and to ensure patient safety during the clinical trial will be performed on a regular basis by the DMC.~~ ~~With receipt of any further information to these events, appropriate follow-up forms have to be provided. For follow-up information the same rules and timeline apply as for initial information.~~
Rationale for change		Editorial clarification. Information is found elsewhere in Section 5.3.7.2.
Section to be changed		5.3.7.2 Adverse event collection and reporting
Description of change		For each AE, the Investigator should provide the information requested on the appropriate eCRF pages and the paper SAE form. **Was changed to:** For each AE, the Investigator should provide the information requested on the appropriate eCRF pages and the paper SAE form, **if applicable**.
Rationale for change		To clarify that not all AEs will need to be reported on the SAE form.

Section to be changed		5.3.7.2 Adverse event collection and reporting
Description of change		Once a patient has been enrolled into this clinical trial and has taken trial medication, the Investigator must report immediately (within 24 hours) a potential drug exposure during pregnancy (DEDP) to the Sponsor's/CRO's unique entry point (country-specific contact details will be provided in the ISF). **Was changed to:** Once a patient has been enrolled into this clinical trial and has taken trial medication, the Investigator must report ~~-~~**any** drug 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).
Rationale for change		Editorial clarification.
Section to be changed		5.3.7.2 Adverse event collection and reporting
Description of change		A list of serious adverse events that commonly occur in the trial population or which are components of trial endpoints are exempted from expedited reporting. **Was changed to:** A list of ~~serious~~ adverse events that commonly occur in the trial population or which are components of trial endpoints are exempted from ~~expedited~~ reporting **on the SAE form, if the event onset is after randomization and the event does not qualify as AESI**.
Rationale for change		Clarification on handling of exempted events.
Section to be changed		5.3.7.2 Adverse event collection and reporting
Description of change		**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.** **Was changed to:** **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 above) with fulfilment of expedited regulatory safety reporting requirements.**
Rationale for change		To clarify handling of AESIs and exempted reporting.

Section to be changed		5.3.7.2 Adverse event collection and reporting
Description of change		Based on the same conclusion that it is not possible to perform a causality assessment on these events based on a single case, the trial investigators are exempted from performing a causality assessment and reporting these adverse events on the SAE form to the Sponsor. All exempted events will be collected systematically on the eCRF (within 24 hours) from the time of randomisation throughout follow up. **Was changed to:** Based on the same conclusion that it is not possible to perform a causality assessment on these events based on a single case, the trial investigators are exempted from performing a causality assessment and reporting these ~~serious~~ adverse events on the SAE form to the Sponsor**, if event onset is after randomization and the event does not qualify as AESI**. All ~~such~~ **exempted** events ~~will~~ **must** be collected systematically on the eCRF (within 24 hours) ~~from the time of randomisation throughout follow up~~. **The investigator is also required to provide all defined supporting documentation (ref to ISF).** **If the events specified above occur before randomization, they are not exempted from immediate reporting on the SAE form. In addition, whenever such events meet the definition of an AESI, then no exemption applies, regardless of occurrence before or after randomization.** **An independent Data Monitoring Committee (DMC) will monitor the safety data in the trial on an ongoing basis. Reported SAEs occurring after randomisation that are protocol exempted events will be collected in the eCRFs and evaluated by the DMC. These events will not be collected on SAE forms for expedited review or reporting.** **Aggregate analysis of endpoint data to determine any potential benefit or risk and to ensure patient safety during the clinical trial will be performed on a regular basis by the DMC.**

		If any exempted event or any other adverse event (serious or non-serious) occurs, the investigator or attending physician has the responsibility and will take direction and appropriate action to provide care for the patient and to decide whether or not the trial medication should be discontinued.
Rationale for change		Additional clarification on handling of exempted events.
Section to be changed		5.4.1 Pharmacokinetic Endpoints
Description of change		The PK sampling will be done from a limited number of randomised patients (approximately 1650 patients) and at pre-selected sites only. **Was changed to:** The PK sampling will be done from a limited number of randomised patients (approximately 1650 patients) and at sites in pre-selected ~~sites~~ **countries** only.
Rationale for change		To clarify that PK samples will be collected from all sites within a country selected for PK collection.
Section to be changed		5.5.1.1. Methods and timing of sample collection
Description of change		Approx. 8.5 mL blood will be drawn into a PAXgene Blood DNA Tube, preferably at Visit 2. **Was changed to:** 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.**
Rationale for change		In Korea a different tube type must be used due to local regulations.
Section to be changed		5.5.1.1. Methods and timing of sample collection
Description of change		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. **Was changed to:** 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**.
Rationale for change		DNA samples collected from patients in China will not be exported out of the country.

Section to be changed		6.1 Visit schedule
Description of change		If a patient mistakenly takes trial medication on the morning of Visit 4 before attending the clinic the visit should be rescheduled for another day as soon as possible, reminding the patients about expected time of dosing. **Was changed to:** 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 (refer to the Flow Chart),** the visit should be rescheduled for another day as soon as possible, reminding the patients about expected time of dosing.
Rationale for change		Editorial clarification.
Section to be changed		6.2.1 Screening
Description of change		The following paragraph was added after the first paragraph in this section. **Patients who have been diagnosed with T1DM are to be provided with the consent form that contains information relevant for patients with T1DM.**
Rationale for change		To include in the protocol, the guidance to site on the consent process for patients with T1DM. This information is currently included in the ISF.
Section to be changed		6.2.1 Screening
Description of change		The following was added to this section. **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.**
Rationale for change		To clarify that screening procedures may be performed on different days.
Section to be changed		6.2.2. Treatment period
Description of change		The following paragraph was added to this section. **Consenting patients with T1DM are to 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.
Rationale for change		To provide guidance on ketone monitoring for patients with T1DM. This information is currently provided in the ISF.
Section to be changed		6.2.3 End of Treatment, Follow Up Period and Trial Completion
Description of change		The following paragraph was added to this section. **If a patient has prematurely discontinued trial medication is not willing to return to the clinic for predefined trial visits, a telephone call at trial end will be required, to document the occurrence of outcome events and vital status. Other AEs and concomitant therapy changes since the last visit should be recorded in the eCRF. Sites should encourage the patient to return to the clinic for the final study visit (ref. Section 3.3.4.1).**
Rationale for change		To encourage complete reporting of all relevant information for patients who have discontinued study drug.
Section to be changed		8.2 Data Quality Assurance
Description of change		The following was removed from this section: ~~central ECG collection (for clinically relevant ECG changes documented as an AE or suspected clinically relevant ECG changes)~~
Rationale for change		ECGs will not be collected for and submitted for central reading. However, they will be collected as part of the source documentation submitted for adjudication of endpoints for which they are clinically relevant
Section to be changed		8.4 Expedited reporting of adverse events
Description of change		BI is responsible to fulfil their legal regulatory reporting obligation and in accordance to the regulatory requirements. As this trial is primarily

		intended to evaluate the cardiovascular impact of empagliflozin in patients with HF, the Sponsor will not report the SAEs included in the protocol exempted events list of the eCRF as described in Section 5.3.7.2. Events will be recorded and reported regularly to the DMC. The Sponsor will ensure that all appropriate regulatory agencies confirm that this approach is acceptable to them. **Was changed to:** BI is responsible to fulfil their legal regulatory reporting obligation ~~and~~ in accordance ~~to the~~**with regulatory requirements. Exemptions from expedited reporting are described in Section 5.3.7.2**. ~~As this trial is primarily intended to evaluate the cardiovascular impact of empagliflozin in patients with chronic heart failure, the Sponsor will not report the SAEs included in the protocol exempted events list of the eCRF as described in Section 5.3.7.2. Events will be recorded and reported regularly to the DMC. The Sponsor will ensure that all appropriate regulatory agencies confirm that this approach is acceptable to them.~~
Rationale for change		Aligned section 8.4 with section 5.3.7.2 and removed redundancy.
Section to be changed		9.1 Publish references
Description of change		Updated reference information was provided for the following references: P15-00589 P16-01253 P16-05920 R16-2382 The following new references were added: P17-10453 P16-01830
Rationale for change		To provide complete reference information.
Section to be changed		9.2 Unpublished references
Description of change		The following new reference was provided: c11963611-01 U12-2707-01
Rationale for change		To provide complete reference information.
Section to be changed		10.6 Blood pressure measurement procedure
Description of change		The following appendix was deleted. **10.6 BLOOD PRESSURE MEASUREMENT**

		PROCEDURE ~~The preferred method for blood pressure measurement is by a standard mercury sphygmomanometer. If a standard mercury sphygmomanometer is not available, alternative devices recommended by website www.dableducational.org may be used or devices approved for use by the appropriate national agency/ies.~~ ~~At visit 1, blood pressure should be taken 3 times in both arms. If the pressures differ by more than 10 mmHg (as in the presence of a subclavian steal syndrome), the arm with the higher pressure (systolic or diastolic) should be used for subsequent measurements.~~ ~~After the patient has rested quietly, in the seated position for five minutes, three blood pressure measurements will be taken approximately two minutes apart and all three results must be entered in the eCRF. The seated HR will be taken during one of the two-minute intervals.Blood pressure measurements should be recorded to the nearest 2 mmHg only when measured with a manual sphygmomanometer; when digital devices are used the value from the device should be rounded to the nearest 1 mmHg.~~ ~~For calculation of mean values, decimal places should be rounded to integers (e.g. a DBP of 94.5 would be rounded to 95 mmHg and a DBP of 109.4 would be rounded to 109 mmHg).~~
Rationale for change		Blood pressure procedure was simplified and included in Section 5.2.5.

11.2 GLOBAL AMENDMENT 2

Date of CTP revision		19 Jul 2018
EudraCT number		2016-002278-11
BI Trial number		1245.110
BI Investigational Product(s)		Empagliflozin

Title of protocol		A phase III randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic **H**eart **F**ailure with **p**reserved **E**jection **F**raction (**HFpEF**).
		☐
		☒
Section to be changed		Cover Page and Clinical trial protocol synopsis
Description of change		Change in address of Coordinating investigators was change from: Professor Stefan Anker, MD Universitaetsmedizin Goettingen Robert-Koch-Strasse 40 D-37075 Göttingen, Germany Phone: +49-551-39-20911, Fax: +49-551-39-20918 Professor Javed Butler, MD Cardiology Division, Health Sciences Center Stony Brook University Hospital NY 11794, USA Phone: +1 631-444-1066, Fax: +1 631-444-1054 to: Professor Stefan Anker, MD Berlin-Brandenburg Center for Regenerative Therapies (BCRT) Charité - Universitätsmedizin Berlin Division of Cardiology and Metabolism – Heart Failure, Cachexia & Sarcopenia, Augustenbuger Platz 1 13353 Berlin, Germany Phone: +49-30-450-553025 Fax: +49-30-450-553951 Professor Javed Butler, MD Prof. and Chairman of the Department of Medicine, The University of Mississippi Medical Center, 2500 North State Street Jackson, Mississippi, USA 39216 Phone: +1 601-984-5600 Fax: +1 601-984-5608
Rationale for change		Both Coordinating Investigators had moved to new institutions.

Section to be changed		Clinical trial protocol synopsis (number of patients and statistical methods) 3.1 Overall trial design and plan 3.3 Selection of the trial population 7.7 Determination of sample size
Description of change		**Clinical trial protocol synopsis: number of patients** Based on blinded assessment of the event rate of the primary endpoint, which is performed during recruitment before any interim unblinding, the number of patients randomised may be increased up to 6000. The number of primary outcome events required is not affected by this consideration. **Was changed to:** ~~Based on~~ **If the accumulated** blinded ~~assessment~~ **data suggests a slower accrual of primary outcome events over calendar time, than was originally projected, then** ~~of the event rate of the primary endpoint, which is performed during recruitment before any interim unblinding,~~ the number of patients randomised may be increased up to 6000. **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. Such a decision would be made during recruitment and before any interim unblinding.** The number of primary outcome events required is not affected by this consideration. **Clinical trial protocol synopsis: statistical methods** The number of patients randomised may be increased up to 6000 patients based on the recruitment progress and a blinded assessment of the event rate, which is performed during recruitment before any interim unblinding. The number of 841 confirmed primary outcome events is not affected by this consideration. **Was changed to:** **If the accumulated blinded data suggests a slower accrual of primary outcome events over calendar time than originally projected, then** ~~T~~the number of patients randomised may be increased up to 6000 patients. **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. Such a decision would be made ~~based on the recruitment progress and a blinded assessment of the event rate, which is performed~~ during recruitment before any interim unblinding. The number of 841 confirmed primary outcome events is not affected by this consideration. **Overall trial design and plan:** The total number of randomised patients may be adapted based on assessment of the blinded event rate. For further details refer to Section 7.7. **Was changed to:** 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 6000. 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. **Selection of the trial population** The total number of randomised patients may be adapted based on assessment of the blinded event rate. For further details refer to Section 7.7. **Was changed to:** 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 6000. 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.

		Determination of sample size: The event rate will be assessed in a blinded manner during recruitment before any interim unblinding. If the accumulated blinded data suggests a lower event rate based on an assumed hazard ratio of 0.8 between the groups, then the number of randomised patients may be increased to a maximum of 6000 patients. The number of confirmed primary outcome events will not be affected by this consideration and will remain 841 events. **Was changed to:** The event rate **and recruitment progress** will be assessed in a blinded manner during recruitment before any interim unblinding. If the accumulated blinded data suggests a **s**lower **accrual of primary outcome** event**s over calendar time than originally projected, then** ~~rate based on an assumed hazard ratio of 0.8 between the groups, then~~ the number of randomised patients may be increased to a maximum of 6000 patients. **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 confirmed primary outcome events will not be affected by this consideration and will remain 841 events.
Rationale for change		Allows an increase in the number of patients to safeguard the overall duration of the study whether a slower accrual of primary outcome events is due to initial slower recruitment or lower event rate or both, compared to that projected in planning.
Section to be changed		Clinical trial protocol synopsis (number of patients and sample size)
Description of change		Approximately 2063 (2 treatment groups). **Was changed to:** Approximately 2063 (2 treatment groups) **This may be increased up to approximately 3000 per treatment group.**
Rationale for change		To clarify that the number of patients that are randomized per treatment group may be increased.
Section to be changed		Flow Chart (footnote 11) 5.3.6.1 Outcome of non-fatal stroke
Description of change		**Flow Chart footnote 11:**

		For patients with non-fatal stroke the Modified Rankin Scale (MRS) should be scored by the investigator based on an interview 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. **Was changed to:** For patients with non-fatal stroke the Modified Rankin Scale (MRS) should be scored by the investigator based on an interview 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.** **Outcome of non-fatal stroke:** 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. Detailed information on the stroke (date and time of onset, type, symptoms, method of detection, outcome) will be collected in the eCRF. **Was changed to:** 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.

Rationale for change		To clarify that the collection of the MRS assessment for a stroke that occurs within the last 90 days before the end of the trial will be done at the final study visit for that individual patient. As severity of non-fatal stroke is not part of the primary, secondary, or other endpoints of this study the last MRS assessment in these patients will be less than 90 days after their stroke in order not to delay the end of the trial.

11.3 GLOBAL AMENDMENT 3

Date of amendment		20 Nov 2019
EudraCT number **EU number**		2016-002278-11
BI Trial number		1245.110
BI Investigational Product(s)		Empagliflozin
Title of protocol		A phase III randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic **H**eart **F**ailure with **p**reserved **E**jection **F**raction (**HFpEF**).
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		4.2.2 Restrictions
Description of change		The use of any SGLT-2 inhibitors or combined SGLT-1 and 2 inhibitors except the blinded trial medication is prohibited during the course of the trial. This also includes the 30 days period between the EOT and the Follow Up Visit. **Was changed to:** The use of any SGLT-2 inhibitors or combined SGLT-1 and 2 inhibitors except the blinded trial medication is prohibited during the course of the trial. This **does not include** the 30 day~~s~~ period between the EOT and the Follow Up Visit **occurring at study close-out (see section 6.2.3)**.
Rationale for change		The use of SGLT-2 inhibitors or combined SGLT-1 and 2 inhibitors does not need to be prohibited

		during the follow-up period as the patient is no longer taking the study medication, and because events which occur during the follow-up period at study close out are not to be included in the primary analysis. Furthermore investigators are encouraged to treat patients to the best standard of care in compliance with local guidelines and recommendations for HF and diabetes if present (see section 2.3).
Section to be changed		7.3.1 Primary endpoint analyses
Description of change		All events observed after randomisation until trial termination will be included in the analysis. Patients who do not have an event during the trial period will be censored at the individual day of trial completion or the last day that the patient was known to be free of the event, whichever is earlier. The time to censoring will be computed as (individual day of trial completion or the last day known to be free of the event – randomisation date) + 1. **Was changed to:** 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 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. The time to censoring will be computed as (individual **end of the planned treatment phase** or the last day known to be free of the event – randomisation date) + 1.
Rationale for change		The intention-to-treat analysis approach was chosen to as closely as possible reflect real-life conditions, disregarding any occurrences of treatment stop or restart of treatment, that may happen in clinical practice. The study defined treatment discontinuation in the close-out period is administrative and does not resemble clinical practice. Therefore, its inclusion does not reflect the objective of the primary analysis. Consequently, only events up to the completion of the planned treatment phase will be included in the

		primary analysis.
Section to be changed		7.3.2 Secondary endpoint analyses
Description of change		The model will include the factors treatment, gender, geographical region, and status of DM as fixed effects and eGFR $(CKD\text{-}EPI)_{cr}$ at baseline (continuous), LVEF (continuous), age (continuous), time and interaction of treatment by time as linear covariates and allow for randomly varying slope and intercept between patients. **Was changed to:** The model will include the factors treatment, gender, geographical region, and status of DM as fixed effects and eGFR $(CKD\text{-}EPI)_{cr}$ at baseline (continuous), LVEF (continuous), age (continuous), time**, ~~and~~** 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.
Rationale for change		Implemented to allow for slope varying with baseline eGFR since this is a medically more reasonable model.
Section to be changed		7.3.2 Secondary endpoint analyses 7.3.3 Further endpoint analyses
Description of change		**Secondary endpoint analyses** 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 repeated measures (MMRM) model including baseline score, LVEF (continuous), age (continuous) and eGFR (CKD-EPI)cr at baseline (continuous) as linear covariates and treatment, visit, baseline score by visit, visit by treatment, gender, geographical region and status of DM and as fixed effects. All on-treatment data up to week 52 will be included. **Was changed to:**

		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 repeated measures (MMRM) model including ~~**baseline score,**~~ LVEF (continuous), age (continuous) and eGFR (CKD-EPI)cr at baseline (continuous) as linear covariates and ~~**treatment, visit,**~~ baseline score by visit, visit by treatment, gender, geographical region and status of DM and as fixed effects. All on-treatment data up to week 52 will be included. **Further endpoint analyses** Further longitudinal continuous endpoints will be analysed in a MMRM, including baseline value, age, LVEF and eGFR (CKD-EPI)$_{cr}$ at baseline as linear covariates and treatment group, visit, visit by treatment interaction, baseline by visit interaction, geographical region, gender and baseline history of DM as fixed effects. **Was changed to:** Further longitudinal continuous endpoints will be analysed in a MMRM, including ~~**baseline value,**~~ age, LVEF and eGFR (CKD-EPI)$_{cr}$ at baseline as linear covariates and ~~**treatment group, visit,**~~ visit by treatment interaction, baseline by visit interaction, geographical region, gender and baseline history of DM as fixed effects.
Rationale for change		Individual model terms were removed from the MMRM if already included as interaction term with treatment or visit to specify MMRMs in condensed form. This simplifies the model and reduces the chance of convergence issues.
Section to be changed		7.3.3 Further endpoint analyses
Description of change		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. 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. 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 Rogers 2014 [R16-4909] and analysis of the unmatched win ratio will be conducted as described in Pocock 2012 [R16-4813]. **Was changed to:** 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**. ~~**and**~~ **The** analysis of the unmatched win ratio will be conducted as described in Pocock 2012 [R16-4813].
Rationale for change		Time to first HHF event is also considered relevant information to avoid ties in case the number of HHF events is identical.

APPROVAL / SIGNATURE PAGE

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Title: A phase III randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic Heart Failure with preserved Ejection Fraction (HFpEF).

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	21 Nov 2019 20:13 CET
Approval-Team Member Medicine		21 Nov 2019 20:19 CET
Approval-Therapeutic Area Head		21 Nov 2019 20:48 CET
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(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed

Trial Statistical Analysis Plan

c14526274-02

BI Trial No.:	1245.110
Title:	A phase III randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic Heart Failure with preserved Ejection Fraction (HFpEF). EMPEROR-Preserved
Investigational Product:	Empagliflozin, BI 10773
Responsible trial statistician:	[redacted]
Date of statistical analysis plan:	21 FEB 2017 SIGNED
Version:	Final

1. TABLE OF CONTENTS

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ACE	Angiotensin Converting Enzyme
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor blocker-Neprelysin Inhibitor
ASA	Acetylsalicylic acid
AST	Aspartate transaminase
ATC	Anatomical-Therapeutic-Chemical
BI	Boehringer Ingelheim
BicMQ	Boehringer Ingelheim customized MedDRA Query
BMI	Body mass index
BP	Blood pressure
CCB	Calcium channel blocker
CEC	Clinical Event Committee
CI	Confidence interval
CIF	Cumulative Incidence Function
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRF	Case report form
CRT	Cardiac resynchronisation therapy
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Cardiovascular
DBL	Data base lock
DBP	Diastolic Blood Pressure
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DM&SM	Data Management and Statistics Manual
ECG	Electrocardiogram
eCRF	Electronic Case Report Form

Term	Definition / description
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EoT	End-Of-Text
EOT	End of treatment
EQ5D	EuroQoL 5 dimensions
EudraCT	European Clinical Trials Database
FPG	Fasting plasma glucose
FU	Follow-up
GI	Gastrointestinal
HbA_{1c}	Glycosylated haemoglobin
HCRU	Health Care Resource Utilisation
HDL-C	High density lipoprotein cholesterol
HF	Chronic Heart Failure
HHF	Hospitalisation for heart failure
HLT	High level term
hsTnT	high-sensitivity troponin T
HR	Hazard ratio
ICD	Implantable Cardioverter Defibrillator
ICH	International Conference on Harmonisation
IPV	Important protocol violation
IRT	Interactive Response Technology
ITT	Intention-to-treat
IVRS	Interactive voice response system
JFM	Joint frailty model
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAVD	Left ventricular assist device
LDL-C	Low density lipoprotein cholesterol
LLT	Low level term
LVEF	Left ventricular ejection fraction
LVOT	Last value on treatment
LTFU	Lost to follow-up

Term	Definition / description
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
Min	Minimum
MMRM	Mixed models repeated measures
MRA	Mineralocorticoid Receptor Antagonist
Non-CV	Non-cardiovascular
NT pro-BNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association Classification
OC-AD	Observed Case including data after discontinuation
OC-OT	Observed Case on-treatment
PK	Pharmacokinetic
PAOD	Peripheral Arterial Occlusive Disease
PT	Preferred term
Q1	Lower quartile
Q3	Upper quartile
PDMAP	Project data management and analysis plan
RS	Randomized set
SAE	Serious adverse event
SAS	Statistical Analysis System
SBP	Systolic blood pressure
SCR	Screened set
SD	Standard deviation
SE	Standard error
SGLT-1	Sodium-glucose co-transporter 1
SGLT-2	SGLT-2 Sodium-glucose co-transporter 2
SI	Système international d'unités
SMQ	Standardized MedDRA query
SOC	System organ class
TBILI	Total bilirubin
TS	Treated set
TS-FU	Treated set – Follow-up

Term	Definition / description
TSAP	Trial statistical analysis plan
UACR	Urine Albumin Creatinine Ratio
ULN	Upper limit of normal
UTI	Urinary tract infection
WHO DD	World Health Organization Drug Dictionary

3. INTRODUCTION

As per the International Conference on Harmonisation (ICH) E9 guidance (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

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

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

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

N/A

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

The primary endpoint is defined in the CTP Section 5.2.1.

For further clarification: Adjudicated CV death always includes death adjudicated as death due to undetermined cause. This is applicable throughout all analyses wherever adjudicated CV death is mentioned.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

Secondary endpoints are specified in the CTP Sections 5.1.2.

5.2.2 Other Secondary endpoints

Other secondary endpoints are specified in the CTP Sections 5.1.2 and 5.2.

5.3 FURTHER ENDPOINTS

Further endpoints are listed in the CTP Section 5.1.3. The definition and assessment can be found in Section 5.2.

Further endpoints added include:

- Time to non-cardiovascular (non-CV) death
- Fasting plasma glucose (FPG) change from baseline to last value on treatment (LVOT) and follow-up (FU), overall and by status of diabetes mellitus (DM)

5.4 OTHER VARIABLES

5.4.1 Kansas City Cardiomyopathy Questionnaire (KCCQ) scores

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

1. Physical Limitation

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

- Extremely limited = 1
- Quite a bit limited = 2
- Moderately limited = 3
- Slightly limited = 4
- Not at all limited = 5

- Limited for other reasons or did not do = <missing value>

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

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

2. Symptom Stability

Code the response to Question 2 as follows:

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

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

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

3. Symptom Frequency

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

Question 3

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

Questions 5 and 7

- All of the time = 1
- Several times a day = 2
- At least once a day = 3

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

Question 9

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

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

S3 = [(Question 3) – 1]/4

S5 = [(Question 5) – 1]/6

S7 = [(Question 7) – 1]/6

S9 = [(Question 9) – 1]/4

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

4. Symptom Burden

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

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

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

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

5. Total Symptom Score

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

Symptom Frequency Score and Symptom Burden Score

6. Self-Efficacy

Code responses to Questions 10 and 11 as follows:

Question 10

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

Question 11

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

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

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

7. Quality of Life

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

Question 12

- It has extremely limited my enjoyment of life = 1

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

Question 13

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

Question 14

- I felt that way all of the time = 1
- I felt that way most of the time = 2
- I occasionally felt that way = 3
- I rarely felt that way = 4
- I never felt that way = 5

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

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

8. Social Limitation

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

- Severely limited = 1
- Limited quite a bit = 2
- Moderately limited = 3
- Slightly limited = 4
- Did not limit at all = 5

- Does not apply or did not do for other reasons = <missing value>

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

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

9. Overall Summary Score

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

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

10. Clinical Summary Score

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

Physical Limitation Score and Total Symptom Score

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

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

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

not

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

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

There will be 4 basic treatment phases in this trial: screening, study treatment phase (with either empagliflozin 10mg or matching placebo), post-treatment and post-study. However, during the study treatment phase, patients are allowed to go off-treatment and subsequently re-start treatment. This may happen not at all or repeatedly for a given patient.

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

Table 6.1: 1 Treatment regimens / study intervals

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

Details on the definition of on-treatment period for different endpoints are listed in Table 6.1:2. The efficacy analyses will follow the intention-to-treat (ITT) principle in assigning patients to treatment groups, i.e. patients will be analysed as randomised.

Safety analyses will also assign patients to the treatment group as randomized.

If a patient erroneously receives the wrong trial drug, the patient will be analysed as per the randomized treatment for all analyses, since patients are to be brought back to the site and dispensed correct drug as soon as possible. Additionally, the AEs with an onset during the time of the incorrect study treatment will be listed separately.

Table 6.1: 2 Endpoint specific follow-up period for the assignment to active treatment

Endpoint	Last day of assignment to treatment phase (days after study drug stop date)
Adverse events	7
Safety laboratory measurements	3
Heart rate	1
Glycosylated haemoglobin (HbA_{1c})	7
FPG	1
Body weight	1
Creatinine and estimated glomerular filtration rate (eGFR)	1
N-terminal pro b-type natriuretic peptide (NT pro-BNP)	1
Blood pressure	1

6.2 IMPORTANT PROTOCOL VIOLATIONS (IPVS)

A protocol violation (PV) is important, if it affects the rights or safety of the study patients or if it can potentially influence the primary outcome measures for the respective patients in a way that is neither negligible nor in accordance with the study objectives.

The IPVs will be described in the clinical trial report (CTR). A listing of patients with medication code broken will be provided.

Table 6.2: 1 Important protocol violations

Category / Code		Description	Requirements	Excluded from
A		**Entrance criteria not met**		
A1		**Target indication not met**		
	A1.06	No chronic HF NYHA class II-IV	Inclusion criterion #3 violated	None
	A1.07	Conditions on ejection fraction (EF) violated	Inclusion criterion #4 violated	None
	A1.08	Conditions on NT-proBNP violated	Inclusion criterion #5 violated	None
	A1.09	Conditions on HF violated	Inclusion criterion #6 violated	None
A2		**Inclusion criteria not met**		
	A2.02	Age out of range	Inclusion criterion #1 violated	None
	A2.08	Specific inclusion criterion for women of child-bearing potential violated	Inclusion criterion #2 violated	None
A3		**Exclusion criteria not met**		
	A3.27	Patient with unstable conditions	Exclusion criteria #1, #2, #7, #11, or #16 violated	None

Table 6.2: 1 Important protocol violations (cont.)

Category / Code		Description	Requirements	Excluded from
	A3.42	Recently implanted ICD	Exclusion criterion #3 violated	None
	A3.43	Implanted CRT	Exclusion criterion #4 violated	None
	A3.29	Cardiomyopathy infiltrative diseases (e.g. amyloidosis), accumulation diseases (e.g. hemochromatosis, Morbus Fabry), muscular dystrophies, with reversible causes (e.g. stress cardiomyopathy), hypertrophic obstructive cardiomyopathy or known pericardial constriction	Exclusion criterion #5 violated	None
	A3.30	Any severe (obstructive or regurgitant) valvular heart disease, obstructive or regurgitant, or any valvular disease expected to lead to surgery during the trial in the opinion of the investigator	Exclusion criterion #6 violated	None
	A3.31	Atrial fibrillation or atrial flutter with a resting heart rate >110bpm	Exclusion criterion #8 violated	None
	A3.32	Systolic blood pressure at visit 1 or 2 out of range	Exclusion criterion #9 or #10 violated	None
	A3.06	Indication of liver disease	Exclusion criterion #12 violated	None
	A3.09	Renal insufficiency or renal impairment (assessed by eGFR)	Exclusion criterion #13 violated	None
	A3.34	Haemoglobin at visit 1 below cut-off	Exclusion criterion #14 violated	None
	A3.35	History of Ketoacidosis	Exclusion criterion #15violated	None
	A3.36	Gastrointestinal (GI) surgery or GI disorder that could interfere with study medication absorption in the investigator's opinion	Exclusion criterion #17 violated	None
	A3.37	Documented or active malignancy	Exclusion criterion #18	None
	A3.38	Life expectancy of <1 years in the opinion of the investigator	Exclusion criterion #19 violated	None
	A3.39	Intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial	Exclusion criterion #20 violated	None
	A3.40	Treatment with any SGLT-2 inhibitor or SGLT-1 and 2 inhibitor	Exclusion criterion #21 violated	None
	A3.11	Intake of an investigational drug in another trial within 30 days prior to intake of study medication in this trial	Exclusion criterion #22 violated	None
	A3.41	Known allergy or hypersensitivity to empagliflozin	Exclusion criterion #23 violated	None
	A3.13	Relevant alcohol or drug abuse and condition affected study compliance	Exclusion criterion #24 violated	None
	A3.12	Specific exclusion criterion for premenopausal women violated	Exclusion criterion #25 violated	None
	A3.14	Any other clinical condition unsafe for participation	Exclusion criterion #26 violated	None
B		**Informed consent**		
	B1	Informed consent not available/not done	Informed consent date missing or inclusion criterion #9 violated	All
	B2	Informed consent too late	Informed consent date was after Visit 1	None

Table 6.2: 1 Important protocol violations (cont.)

Category / Code		Description	Requirements	Excluded from
C		**Trial medication and randomisation**		
	C1.02	Incorrect trial medication taken	Wrong medication taken for more than 20% of the overall treatment duration Can only be finally judged after data base lock (DBL) since unblinding information is required.	None
D		**Concomitant medication**		
	D2.02	Use of prohibited medication	Use of SGLT-2 or combined SGLT-1 and 2 – inhibitors after randomization before trial termination	None

6.3 PATIENT SETS ANALYSED

The following patient sets are defined

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

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

- *Treated set (TS)*
  This patient set includes all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.

- *Treated Set-Follow-up (TS-FU)*
  All patients in the TS, for whom a follow-up visit was performed between 23 and 45 days after last intake of study medication.

6.4 SUBGROUPS

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

If there is missing information directly from central laboratory for any of the subgroups of parameters, where data is also collected in the IRT system, then the information as transferred from IRT will be used to assign a patient to a certain category.

Table 6.4: 1 Categories of covariates for displays of baseline characteristics and subgroup analyses

Variable	Categorization	Demo-graphics*	Subgroups for Efficacy endpoints**	Safety
Age (years)	<50 50 to <65 65 to <75 75 to <85 >= 85	X		
	<50 50 to <65 65 to <75 >= 75	X	X§	X
	< 65 ≥65	X	X	
Gender	male female	X	X	X
Region	NA, LA, Europe, Asia, Other+	X	X	X
Ethnicity	Hispanic/ Latino Not Hispanic/ Latino	X	X	X
Race	White Black/ African-American Asian Other including mixed race	X	X	X
BMI (kg/m^2)	<30 ≥30	X	X	
eGFR at baseline	>=90 60 to <90 45 to <60 30 to <45 15 to <30 <15	X		
	>=90 60 to <90 45 to <60 30 to <45 <30	X	X§	X
	>=60 <60	X	X	
UACR	UACR (in mg/g): <30 >=30 to <=300 >300	X	X§	

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

Variable	Categorization	Demo-graphics*	Subgroups for Efficacy endpoints**	Safety
Diabetes at baseline	DM, no-DM	X	X	X
	DM, pre-DM, non-DM	X	X	
History of hypertension	Yes / No	X	X	
Baseline SBP	< / >= median	X	X	
Baseline BP	SBP<140 and DBP<90 vs. SBP>= 140 or DBP>=90	X	X	X (volume depletion AEs)
Atrial Fibrillation at baseline	Yes/ No	X	X	
Baseline LVEF	</>=50	X	X	
	< / >= median		X	
History of HHF	Yes / No	X	X	
Cause of HF	Ischemic / Non-ischemic	X	X	
Time since diagnosis of HF	<= 1 year, 1-5 years, > 5 years	X	X[§]	
NYHA at baseline	I/II vs. III/IV	X	X	
NT-proBNP at baseline	< / >= median	X	X	
Baseline use of ACE-inibitor, ARB or ARNi	Yes / No	X#	X	X (renal AEs and volume depletion AEs)
Baseline use of ACE-inhibitor or ARB but no ARNi	Yes / No	X#	X	
Baseline use of ARNi	Yes / No	X#	X	
Baseline use of MRA	Yes / No	X#	X	
Baseline use of diuretics	Yes / No	X#	X	X (renal AEs and volume depletion AEs)
Baseline use of loop or high-ceiling diuretics	Yes / No	X#	X	X (renal AEs and volume depletion)
Baseline use of thiazides	Yes / No	X#	X	

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

Variable	Categorization	Demo-graphics*	Subgroups for Efficacy endpoints**	Safety
Baseline use of diuretics low-ceiling excluding thiazides	Yes / No	X#	X	
Baseline use of beta-blockers	Yes / No	X#	X	
Baseline use of Ivabradine	Yes / No	X#	X	
Baseline use of CCB dihydropyridines	Yes / No	X#	X	
Baseline use of CCB non-dihydropyridines	Yes / No	X#	X	
Baseline use of digitalis	Yes / No	X#	X	
baseline hemoglobin	< / >= median		X	
hsTnT at baseline	< / >= median		X	

* The column demographics shows categories shown in the overall demographics. Demographics are not planned by subgroup.
** Subgroups planned for the primary endpoint, time to cardiovascular (CV) death, time to first HHF, HHF (first and recurrent), renal slope.
[+] Region categorization: see Table 9.1.1.
part of the presentation of baseline concomitant therapy as outlined in section Section 7.2
[§]The interaction tests for these subgroups will be trend tests taking into account ordering of the subgroups.

6.5 POOLING OF CENTRES

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

6.6 HANDLING OF MISSING DATA AND OUTLIERS

6.6.1 Imputation methods

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

There will be different methods of looking at continuous longitudinal data.

Observed case on-treatment (OC-OT):
Only the available data that were observed while patients were on study medication (defined as time from first drug intake until last permanent treatment stop date plus the endpoint specific follow-up time (as defined in Table 6.1:1)) are considered.
Measurements are assigned to planned weeks according to Table 6.7: 1

Observed case including data after discontinuation (OC-AD):
All available data are considered, including values obtained on treatment or post-treatment.
Measurements are assigned to planned weeks according to Table 6.7: 1

KCCQ imputation
For endpoints of KCCQ scores, for patients who die, a worst score (score of 0) will be imputed for the score at all subsequent scheduled visits after the date of death where the score would have been assessed.

The following is used for longitudinal and time to event-data:

Multiple imputations:
A multiple imputations approach will be considered to impute missing data. Multiple imputation approaches taken are further specified in Section 7 with the planned sensitivity analyses.

6.6.2 Missing data

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

Adverse event onset dates, including partial onset dates from clinical event committee (CEC):
In the unlikely case that only the year is documented, the day and month will be imputed as 01 Jan unless the subsequently derived date is before randomisation; in this case the date of randomisation will be used as start date.
If year and month is present the day will be imputed as first of the month unless the subsequently derived date is before randomisation; in this case the date of randomisation will be used.

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

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

Missing date of last FU for non-fatal events.

If the date of last FU for non-fatal events is missing, it will be imputed as the last of any of the following data:

- visit dates
- date if any assessment such as NYHA, blood pressure, EQ5D, KCCQ, pregnancy test, central laboratory
- adverse event/outcome event start and end dates except fatal events
- onset dates of adjudicated (confirmed and non-confirmed) events except fatal events
- drug administration dates, last drug stop date,
- date of clinical routine exam
- date of trial completion (if patient did not die)

Missing date of trial completion (=last contact or date of death)
If the date is completely missing the following rules will be applied:

- If a patient has withdrawn informed consent, this date will be imputed by the date of IC withdrawal.
- If a patient died and has not withdrawn consent, this date will be imputed by the date of death.
- If the date is incomplete with only month and year reported, the date will be imputed by the first day of the month.
- If a patient did not die, the date of trial completion will be imputed by the last date the patient was known to free of non-fatal events.

All other cases need to be assessed by the trial team on an individual basis, using the above points as guidance.

Missing information on the date of trial medication stop

- If this date is missing and the end-of treatment visit date is available, date of trial medication stop will be imputed by the date of the end-of-treatment visit.
- If the date is incomplete with only month and year and the respective visit date is missing, the date of last drug administration will be imputed by the last day of this month. If this would be later than the date of trial completion, then the date of trial completion will be used for imputation.
- If a patient is lost-to-follow up, no date of last drug administration is reported and the date of the end-of treatment visit is not available, the date of last drug administration is set as the date of last FU for non-fatal events.
- For a patient who dies in the treatment phase with no information on the date of last drug administration, the date is set as the date of death, assuming that the patient took the medication until the date of death.

If the imputed date based on the above rules is later than the longest treatment duration based on drug supply, then trial medication stop will be imputed based on the longest treatment duration based on drug supply.

If after imputation, the date of trial completion is before the date of last drug administration, the start of the post-study period is defined as the maximum of last drug administration +1 day and the date of the trial completion +1 day.

All other cases need to be assessed by the trial team on an individual basis, trying to use the points above as guidance.

Missing information on concomitant therapy dates
For incomplete date information always the midpoint of the possible interval will be used. If only the year is present the day and month will be imputed as 01 July, if year and month is present the day will be imputed as 15. If the year is missing, the date will be considered missing.
If this leads to contradictions for the start or end date of a concomitant therapy (e.g. imputed end date before documented start date) a partial end date will be imputed as the end of the interval or a partial start date will be imputed as the start of the interval in the database to resolve this contradiction.

All other cases or conflicting cases resulting from these imputation rules need to be assessed by the trial team on an individual basis.

Missing measurement to confirm “sustained” decrease
An eGFR $(CDK\text{-}EPI)_{cr}$ reduction is considered sustained, if it is determined by two or more consecutive post-baseline central laboratory measurements separated by at least 30 days (first to last of the consecutive eGFR values). If there is no additional measurement >= 30 days after the eGFR reduction is observed and the patient dies within 60 days of this measurement, then the eGFR reduction is also considered sustained.

Pharmacokinetic (PK) variables
Missing data and outliers of PK data are handled according to (3)

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

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

Since the protocol specifies, that all measurements are taken at visit 2 before any intake of trial medication, all measurements at the first day of drug intake are analysed as before any intake of randomised trial medication.

For randomised patients without any treatment intake: 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 and including the day of randomisation. For all other endpoints, baseline will be defined as the last available measurement before or on the day of randomisation.

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

Measurements taken after the end of the endpoint specific follow-up period and after the last intake of study drug will be considered post-treatment values.

On-treatment (for OC-OT analysis) or all post-randomisation (for OC-AD analysis) efficacy and safety measurements will be assigned to visits based on time windows around the planned visit dates. These time windows are defined based on the planned number of days after the date of first administration of study drug.

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

Table 6.7: 1 Time windows for post-baseline efficacy measurements scheduled for each on-treatment visit for the first 3 years

			Time window (actual days after baseline)	
Visit number	Visit label	Planned days	Start	End
Endpoints assessed at each on-site visit (e.g. creatinine / eGFR)				
2	Baseline	0	NA	1
3	Week 4	28	2	56
4	Week 12	84	57	154
6	Week 32	224	155	294
8	Week 52	364	295	448
10	Week 76	532	449	616
12	Week 100	700	617	784
14	Week 124	868	785	952
16	Week 148	1036	953	1120
18	…			
FU	FU	Trt stop + 30 days	Trt stop + 23 days	Trt stop + 45 days
KCCQ				
2	Baseline	0	NA	1
3	Week 4	28	2	126
6	Week 32	224	127	294
8	Week 52	364	295	532
FU	FU	Trt stop + 30 days	Trt stop + 23 days	Trt stop + 45 days

[A] Only values taken prior to the start of treatment with randomised study drug can be considered baseline values. Time windows will be used for assignment of measurements to scheduled visits.

For examinations that are not planned at every on-treatment visit, the time windows will be defined according to the same algorithm, based on the midpoint between the planned visit day of such an examination. Examples for eGFR and KCCQ can be found in Table 6.7: 1

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

Time windows for assignment of planned off-treatment measurement

For evaluation of the off-treatment assessment 'at 30 day follow-up' only values obtained at >= 23 days to <= 45 days after last trial drug stop will be considered.

The value that is closest to the planned day of 30 days after last trial drug stop will be used. If there are 2 values equally close, the later value will be used.

6.8 CALCULATION OF TIME TO EVENT

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

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

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

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

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

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

6.8.1 Start date

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

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

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

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

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

6.8.2 Date of event

For adjudicated events, the date determined by the adjudication committee will be used; this can be different from the investigator reported date.

For the endpoints of time to CV death, time to all-cause mortality and time to non CV death the respective death date will be used rather than time to the first onset of the fatal AE.

For composite outcomes, e.g. time to adjudicated HHF or adjudicated CV death, the earliest onset date of the corresponding components will be used. For the component of CV death or other death components, date of death will always be used rather than the onset date also for composite outcomes.

For endpoints, where myocardial infarction (MI) and stroke are included as a fatal and non-fatal component, the onset of the event is considered for the derivation of time to first occurrence, not the date of death. For time to CV death the date of death is used for a fatal MI or fatal stroke.

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

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

For analysis of recurrent events, time at risk for the next event will start at the day after the end date of an event. For HHF and all-cause hospitalization the end date will be the day of discharge. If date of discharge is missing then it will be assumed that the discharge was the day after hospitalization unless the AE is marked as fatal, in which case date of death will be used.

6.8.3 Censoring

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

Patients without occurrence of a specific endpoint (composite endpoint or individual components) will be considered censored at the last date, the patient was known to be free of the event. For non-fatal events this is the last date the patient could be followed up for all non-fatal events as documented in the eCRF or imputed in as per Section 6.6.2..

Censoring is considered independent from study drug intake.

All-cause mortality

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

- Date of study completion
- Last AE onset date or last AE end (if complete-imputed dates not used)
- Last date known alive from the vital status page

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

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

Endpoints based on laboratory data only

Patients who already fulfil the respective condition at baseline or without post-baseline laboratory measurements are not considered in the number of patients at risk for this endpoint.

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

Composite endpoints

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

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

Censoring for analyses up to trt stop + x days

For any analyses until a certain number of x days after treatment discontinuation (e.g. sensitivity analyses until 30 days after treatment discontinuation), censoring time will be the minimum of the censoring time as described above and treatment discontinuation + x days. Patients with an event after treatment discontinuation + x days will be censored at treatment discontinuation + x days.

7. PLANNED ANALYSIS

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

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

Statistical parameters will be displayed to a defined number of decimal places as specified in the BI guideline "Reporting of Clinical Trials and Project Summaries" (4)

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

Disposition of the patient population participating in the trial will be analyzed by treatment groups and presented in the clinical trial report as a frequency-distribution. The number of patients participating (screened, randomized, screened but not randomized, etc.) in the study by region, country and, for treated patients, centre, will also be analyzed by treatment group and presented as a frequency distribution.

Disposition as required for reporting for the trial in EudraCT will be provided. Enrolment will be summarized by country and by age group for reporting in EudraCT. (see (13)).

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

The frequency of patients with IPVs will be presented by treatment group for the randomized set. The frequency of patients in different analysis sets will also be analyzed for each treatment group.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be analyzed based on RS. Standard descriptive analysis and summary tables will be presented. These summary tables will include description of subgroup variables detailed in Section 6.4. Descriptive analysis of the following variables measured at baseline will be presented: Age, height, body mass index (BMI), time since diagnosis, HbA_{1c}, systolic blood pressure (SBP), diastolic blood pressure (DBP), weight, eGFR, UACR, NT-pro BNP, low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C).

A summary of the number of patients in each randomisation stratum per treatment planned vs. actual will also be shown. The planned information will be based upon the data received from

the interactive voice response system (IVRS) provider. Analyses will be based on actual information collected via the CRF / central laboratory, not via IVRS.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report using the randomised set. Concomitant medication use will be summarised by Anatomical-Therapeutic-Chemical classification level 3 (ATC3) and preferred name. Summaries will be presented for concomitant therapies taken at randomisation and separately those taken at or after randomisation. Separate summaries of use of heart failure-related drugs (e.g. ARNi, beta-blockers, ivabradine, diuretics, ACE-inhibitors, ARBs, MRAs, digitalis), anticoagulants, acetylsalicylic acid (ASA), or lipid lowering drugs at randomisation will be presented. Use of devices at randomisation will also be summarized at randomisation.

Concomitant diseases will be summarised by system organ class and preferred term. Relevant medical history by treatment group will also be presented. Both summaries will be presented using the randomised set.

7.3 TREATMENT COMPLIANCE

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

7.4 PRIMARY ENDPOINT

7.4.1 Primary analysis

As the primary endpoint, time to the first event of adjudicated HHF or adjudicated CV death will be reported in days. The primary analysis will be based on RS, using all data available until trial completion, including the data after end of treatment.

The primary endpoint will be displayed using cumulative incidence function (CIF) curves and expressed as the hazard ratio with associated two-sided 95% confidence intervals (CIs) and two-sided CIs based available alpha-level for the analysis. The alpha levels for the interim analysis and final analysis will follow the Hwang, Shih and De Cani α-spending function as specified in Section 7.4 of the CTP, which are expected to be 0.001 and 0.0248 (one-sided) when the interim analysis occurs at the time of 60% information.

Estimator and corresponding confidence intervals will not be corrected for interim analysis.

The primary endpoint will be analysed using Cox regression, with factors of treatment (empagliflozin, placebo), region (North America, Latin America, Europe, Asia and “other” including India, South Africa, Turkey and Australia), baseline status of diabetes (diabetes, prediabetes, no diabetes), age (continuous), gender, left ventricular ejection fraction (LVEF) (continuous) and eGFR $(CKD\text{-}EPI)_{cr}$ at baseline (continuous). Since the stratification factors are included in the model as covariates, no stratified Cox regression will be used.

Breslow's method will be used for dealing with ties.

The individual relevant components of the composite will be summarized descriptively. In this descriptive analysis of the relevant component for the composite, CV death after HHF will not be counted. In all other analyses of CV death alone defined in this document, all CV deaths will be counted, disregarding any earlier events.

7.4.2 Sensitivity analyses

The following sensitivity analyses will be conducted:

- A Cox model including only treatment as covariate, not adjusting for any other variables.
- The same Cox regression will be performed on the TS, including only any events up to 30 days after treatment discontinuation.
- For patients who are without primary event and lost to follow up before trial completion, the treatment specific incidence rates for empagliflozin and placebo will be used to impute the primary events in a multiple imputations framework. The primary model will be applied to the imputed datasets. It is planned to perform 100 imputations. Rubin's rules will used to summarize the log hazard ratios and the result will be back-transformed to show a hazard ratio with confidence interval.
- The endpoint will be evaluated based on investigator reported events.
- A competing risk model by Fine-Gray will be explored, including the same set of covariates as in the primary analysis, sub-distribution hazard ratios will be provided (5)

A Kaplan-Meier curve of time to censoring for primary endpoint will be presented in order to assess whether there was differential censoring. For this analysis an event will count as censoring and a censoring (including censoring due to the competing event of non-CV death) will count as event.

7.4.3 Proportional hazards assumption violated

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

In case the proportionality assumption is violated for treatment, an attempt will be undertaken to identify groups of patients for which the proportionality assumption holds and a stratified Cox regression will be performed. The HR and corresponding CIs will be obtained from the stratified Cox model.

In addition a piecewise Cox model assuming proportional hazards in a series of consecutive time intervals as proposed by Collett (6) will be investigated.

7.4.4 Subgroup analyses

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

For those subgroups marked as § in Table 6.4.1. the interaction p-values will be conducted as trend tests, taking into account that the subgroup categorizations are ordered.

If there are less than 14 patients with events in one subgroup, then this subgroup will not be included in the model. If this leaves only one subgroup, the subgroup analysis will not be conducted.

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

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

Occurrence of adjudicated HHF (first and recurrent)

Hospitalisation for heart failure will be analysed by a joint frailty model (JFM) that accounts for the dependence between recurrent HHF and CV death (7) The primary analysis will be based on all data available until trial completion, including the data after end of treatment.

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

$$r_i(t \mid \omega_i) = \omega_i \exp\{\beta_1 z_i\} r_0(t)$$
$$\lambda_i(t \mid \omega_i) = \omega_i^{\alpha} \exp\{\beta_2 z_i\} \lambda_0(t)$$

The recurrent heart failure hospitalisations hazard function for the i-th patient conditional on the patient specific random frailty, ω_i, is given by r_i and is proportional to the baseline intensity function, r_0. The conditional hazard function for time to CV death for patient i is given by, λ_i, with the baseline hazard given by λ_0, and β_1, β_2 are p x 1 vectors of regression coefficients associated with vectors of covariates z_i. The same covariates as for the analysis of the primary endpoint will be used, e.g. ß.1=treatment (empagliflozin, placebo), ß.2=region (North America, Latin America, Europe, Asia and "other" including India, South Africa, Turkey and Australia), ß.3=baseline status of diabetes (diabetes, prediabetes, no diabetes) etc.

Patient specific independent random effects are denoted by ω_i and are assumed to follow a gamma distribution with mean 1 and variance θ. The correlation of the recurrent events is quantified by θ, with higher values corresponding to greater within-patient correlation and also greater between-patient variability. The parameter α determines the relationship between the recurrent heart failure hospitalisations and time to CV death. When $\alpha < 0$, higher frailty will result in a greater risk of recurrence and lower risk of terminal event (i.e. a negative correlation between the frailties), and when $\alpha > 0$, higher frailty will result in a greater risk of recurrence and is associated with a higher risk of CV death (i.e. a positive correlation between the frailties).

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

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

Adopting piecewise constant hazards for the recurrent events and CV death allows estimation of the likelihood by Gaussian quadrature. The implementation of Gaussian quadrature techniques is incorporated into Proc NLMIXED of SAS 9.4. SAS Code as given in (9) will be used.

The joint model gives two distinct hazard ratios:

$HR_{HHF} = \exp\{\beta_{11}\}$ is the hazard ratio associated with the effect of treatment on the recurrent event rate of HHF, and $HR_{CVD} = \exp\{\beta_{21}\}$ is the CV death hazard ratio.

Estimates and 95%-CI for the hazard ratios and for α (relationship between the recurrent heart failure hospitalisations and CV death) will be given.

The following sensitivity analyses will be conducted

- Based on the TS, including only any events up to 30 days after treatment discontinuation
- Instead of CV-death, jointly model HHF with all-cause mortality as the terminal events

- The endpoint will be additionally evaluated based on investigator reported events for HHF and CV death.

- A parametric joint gamma-frailty model will model the recurrent event component using a Poisson distribution and model the CV mortality component using a log-logistic distribution, conditional on the frailty parameter. Individual frailties are again assumed to follow a Gamma distribution. Thus HHF rates follow a negative binomial distribution and times to CV death follow a Lomax distribution (see (8))

In case the semi-parametric joint modelling cannot converge numerically with the existing SAS procedures, the parametric joint gamma-frailty model as described above may be used instead for the confirmatory analysis.

The number of HHF events per patients will be summarized descriptively. Additionally a negative binomial model will be fitted to the data of recurrent HHF. This will be done once including only treatment as covariate and once including all covariates as the primary model. Rate ratio and confidence intervals of both models will be reported.

The mean cumulative incidence will be displayed for adjudicated recurrent HHF.

Subgroup analyses will be explored as outlined in Section 6.4 for adjudicated recurrent HHF. For subgroup analyses the term of subgroup (if not already part of the model) and subgroup by treatment will be added to the model of the recurrent event. If the subgroup variable is a categorization of a continuous covariate, this covariate will be dropped from the subgroup model.

eGFR (CKD-EPI)$_{cr}$ slope of change from baseline

Slope in change from baseline of eGFR (CKD-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, and status of DM as fixed effects and eGFR (CKD-EPI)$_{cr}$ at baseline (continuous), LVEF (continuous), age (continuous), time and interaction of treatment 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.

A plot of individual patient slopes and separately of individual patient intercepts will be provided per treatment.

Multiple imputation will be used to handle missing data as a sensitivity analysis. All variables included in the analysis model will be included in the imputation model. After exploring the missing data mechanism and observed measurements on the blinded data additional variables may also be included in the imputation model. If the data is monotone missing, a regression model will be used for imputation. In the case of non-monotone missing, a Markov chain Monte Carlo (MCMC) step will be used to create monotone missing data in multiple datasets. It is planned to perform 100 imputations. The regression method will then be used to

complete the imputation in each dataset. For each imputed complete dataset, the analysis model described above will be used for the analysis. The slope results will be summarized using Rubin's rules.

Subgroup analyses as outlined in Section 6.4 will be explored for eGFR slope. The subgroup model will include additionally to the model described above, the subgroup if not already part of the model, subgroup by treatment and subgroup by treatment by time. If the subgroup variable is a categorization of a continuous covariate, this covariate will be dropped from the subgroup model.

7.5.2 Other Secondary endpoints

No correction for multiple hypotheses testing will be made for other secondary endpoints.

Time to first event of sustained reduction of ≥40% eGFR (CKD-EPI)$_{cr}$ or

- *(for patients with eGFR (CKD-EPI)$_{cr}$ ≥30 mL/min/1.73 m2 at baseline): sustained eGFR <15 mL/min/1.73m2*
- *(for patients with eGFR (CKD-EPI)$_{cr}$ <30 mL/min/1.73 m2 at baseline): sustained eGFR < 10 mL/min/1.73 m2*

Time to all-cause mortality

Time to first adjudicated HHF

Time to adjudicated CV death

Time to onset of DM in patients with baseline pre-DM

All time-to-event endpoints will be reported in days.

The same model and data frame as used in the primary analysis of primary endpoint will be applied to all these time-to-event endpoints.

For time to first HHF and time to CV death, the analysis will be repeated based on investigator reported events.

Change from baseline in clinical summary score (HF symptoms and physical limitations domains) of the Kansas City cardiomyopathy Questionnaire (KCCQ) at week 52

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 baseline score, LVEF (continuous), age (continuous) and eGFR (CKD-EPI)$_{cr}$ at baseline (continuous) as linear covariates and treatment, visit, baseline score by visit, visit by treatment, gender, geographical region and status of diabetes at baseline as fixed effects. All on-treatment data up to week 52 will be included and the analysis will be conducted on the treated set.

A sensitivity analysis will be conducted including data after discontinuation (OC-AD) on the randomized set.

Occurrence of all-cause hospitalisation (first and recurrent)

A similar joint frailty model as in the HHF will be analysed for all-cause hospitalization. Instead of CV death, all-cause mortality will be jointly modelled as the terminal events.

7.6 FURTHER ENDPOINTS

Time to event endpoints

Further time to event endpoints will generally be analysed in a Cox proportional hazards model similar to the primary analysis on RS. If the endpoint does not include any cause of death, a CIF plot with all-cause mortality as competing risk will be displayed; otherwise, a CIF plot with causes of death not included in the endpoint as competing risk will be displayed.

Continuous endpoints:

The following endpoints will be evaluated by mixed models repeated measures (MMRM) as defined in the protocol.

- HbA_{1c} change from baseline over time (OC-AD on the randomised set and OC-OT on the treated set)
- SBP, DBP change from baseline over time (OC-AD on the randomised set and OC-OT on the treated set)
- Weight change from baseline over time (OC-AD on the randomised set and OC-OT on the treated set)
- NT-pro BNP relative change from baseline over time (OC-AD on the randomised set and OC-OT on the treated set) (value will be transformed to the log scale before MMRM analysis. Estimates obtained from the model will then be back-transformed and reported on the original scale.)
- KCCQ overall summary score change from baseline at week 52 (OC-AD on the randomised set and OC-OT on the treated set) (model will include all timepoints up to week 52)
- KCCQ individual domains change from baseline at week 52 (OC-AD on the randomised set and OC-OT on the treated set) (model will include all timepoints up to week 52)
- KCCQ total symptom score change from baseline at week 52 (OC-AD on the randomised set and OC-OT on the treated set) (model will include all timepoints up to week 52)

- KCCQ based on patient-relevant outcome change from baseline at week 52 (OC-AD on the randomised set and OC-OT on the treated set) (model will include all timepoints up to week 52)

- UACR relative change from baseline over time (OC-AD on the randomised set and OC-OT on the treated set) (value will be transformed to the log scale before MMRM analysis. Estimates obtained from the model will then be back-transformed and reported on the original scale.)

- eGFR $(CKD\text{-}EPI)_{cr}$ change from baseline over time (OC-AD on the randomised set and OC-OT on the treated set)

As outlined in the protocol, the above endpoints will be analysed in a mixed model with repeated measures (MMRM), including baseline value, age, LVEF and eGFR $(CKD\text{-}EPI)_{cr}$ at baseline as linear covariates and treatment group, visit, visit by treatment interaction, baseline by visit interaction, geographical region, gender and baseline history of DM as fixed effects. An additional factor of "week reachable" for the parameter in question, which for each patient is the theoretically reachable planned measurement based on the time of randomisation will adjust for the different planned study times.

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

Descriptive statistics will be calculated for the value at visit and change from baseline based on OC-AD on the randomised set and OC-OT on the treated set.

Additionally subgroup analyses will be performed as follows:

HbA_{1c} change from baseline will be evaluated by status of diabetes (non-DM, pre-DM, DM).

UACR will be evaluated by UACR at baseline (<30 mg/g, ≥30mg/g to ≤300mg/g, >300 mg/g).

In order to evaluate the mean effect on eGFR after approximately 3 years, the above described MMRM models will be used in the following way: a mean effect of the timepoints week 124, 148 and 172 will be calculated. This will be done for the imputations of OC and OC-AD.

For MMRM subgroup analyses, the model will additionally include the term for subgroup and the interaction terms for subgroup by visit, subgroup by treatment and subgroup by treatment by visit in addition.

To support analysis of renal function, eGFR throughout the trial will be categorized according to the following CKD staging: All calculations for the staging of renal function will be based on the originally measured laboratory values and the upper limit of normals (ULNs) given by the laboratory, not on normalised values with BI standard reference ranges.

Table 7.6: 1 CKD staging

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

A shift table from baseline to last value on treatment for eGFR $(CKD\text{-}EPI)_{cr}$ will be provided.

A summary will also be created representing the number of patients per treatment group who experienced a doubling in creatinine on treatment compared to baseline that was out of the normal range.

In cases where urine albumin values are reported to be below the quantification limits (e.g. <3 mg/L) the albumin / creatinine ratio is determined as missing and will not be replaced by estimated values.

Transitions from baseline to last value on-treatment based on the following UACR categories: normal (<30mg/g), microalbuminuria (30-<=300 mg/g and macroalbuminuria (>300 mg/g) will be presented.

For an evaluation of follow-up after discontinuation of trial medication an additional summary of the NT-proBNP, FPG, eGFR, UACR, creatinine and the KCCQ endpoints as above will be produced. This summary will include descriptive statistics for baseline, actual values and change from baseline to last on-treatment value and follow-up, and change from last on-treatment assessment to follow-up. The TS-FU patient set will the basis for this summary, but only those patients with a valid baseline, last value on treatment and follow-up value will be included in all displays. Analyses will be repeated for patients with at least 52 weeks of cumulative exposure. FPG analysis will also be conducted by DM status at baseline.

Analyses of change from baseline to LVOT and FU as outlined above will be additionally modelled, separately for LVOT and FU. An analysis of covariance (ANCOVA) model including treatment group, gender, geographical region and history of DM as fixed effect and baseline eGFR $(CKD\text{-}EPI)_{cr}$ (continuous), age (continuous), LVEF (continuous) and baseline of the endpoint (if not already included) as linear covariates will be used.

Descriptive statistics will be presented also for creatinine for the value at visit and change from baseline based on OC-AD on the randomised set and OC-OT on the treated set.

Win ratio:

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 due to CV causes while the patient on empagliflozin was still alive, or if both patients did not die due to CV causes, then if the other patient had more occurrences of HHF. 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 due to a CV cause while the patient on placebo was still alive, or if both patients did not die due to a CV cause, then if the patient on empagliflozin had more occurrences of HHF. 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 Rogers 2014 (8) and analysis of the unmatched win ratio will be conducted as described in Pocock 2012 (10) .

Other types of further endpoints

For other types of endpoints e.g. change in NYHA class at week 52, HCRU and EQ5D, descriptive statistics will be provided.

For NYHA class a shift table will also be provided for changes from baseline over time and for change from baseline to EOT and FU.

Pharmacokinetic analysis

Descriptive statistics of trough concentrations of empagliflozin will be presented.

7.7 EXTENT OF EXPOSURE

There will be three methods of calculating exposure:

a. First intake to last intake of study drug, including off-treatment periods
b. First intake to last intake of study drug, excluding off-treatment periods
c. Overall observational period (randomisation until end of follow-up for vital status, see censoring for all-cause mortality in Section 6.8.3)

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

Frequency tables of number and percentage of patients belonging to categorical ranges of exposure weeks will be provided as well. Following are the categories of exposure-ranges (in weeks): 0 to 12 weeks, >12 to 26 weeks, >26 to 52 weeks, >52 to 78 weeks, >78 to 104

weeks, >104 to 156 weeks, >156 weeks. Categorical ranges may be adapted based on the actual duration of the study.

7.8 SAFETY ANALYSIS

The safety analysis will be based on the treated set (TS), treatment will be evaluated as randomised.

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

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

7.8.1 Adverse events

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

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

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

For analysis multiple AE occurrence data on the CRF will be collapsed into an AE provided that all of the following applies:

- All AE attributes are identical (including LLT, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest and also additional information of specific AEs or AESIs such as source of sepsis (urinary tract or not) or type of genital infection (fungal balanitis or vulvovaginitis versus other than fungal balinitis or vulvovaginitis)).
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence).

For further details on summarization of AE data, please refer to (2), (11).

7.8.1.1 Assignment of AEs to treatment

The analysis of adverse events will be based on the concept of treatment emergent adverse events. That means that all adverse events occurring between first drug intake till 7 days after last drug intake will be assigned to the randomised treatment. All adverse events occurring before first drug intake will be assigned to ‘pre-treatment’ and all adverse events occurring after last drug intake + 7 days with be assigned to ‘post-treatment’.

In Section 15.3 general AE analyses tables will present only on-treatment AEs (applying the rule of 7 days for assignment as on-treatment) for the treatments groups (exceptions for cancer events, hepatic events, lower limb amputations and bone fractures as well as

adjudicated events see below). When looking at BIcMQs or standardized MedDRA queries (SMQs) and including all AEs up to termination of the trial, the time at risk will match the time at risk of non-fatal CV events (see section 6.8).

Appendix 16.1.9.2 will include an analysis (overall summary table, frequency of AEs by system organ class (SOC) / preferred term (PT), frequency of serious adverse events (SAEs) by SOC/PT) where AEs and SAEs are assigned to the following phases: Screening, each treatment group, post-treatment for each treatment group.
The tables presenting frequency of AEs by SOC/PT and frequency of SAEs by SOC/PT will be repeated in Section 16.1.9.2 with treatment-specific post-treatment phase included, hereby also incidence rates for the post-treatment phase will be presented.

For listings, AEs will be assigned to one of the treatment phases of Screening, Placebo, Empa 10, Placebo post-treat, Empa 10 post-treat, post-study.

7.8.1.2 Analysis of other significant AEs

Other significant AEs will be reported and summarised according to ICH E3 (12) criterion. Thus, AEs classified as 'other significant' will include those non-serious adverse events with 'action taken = study drug permanently / temporarily discontinued'.

7.8.1.3 AE summaries

An overall summary of adverse events will be presented.

The frequency of patients with adverse events will be summarised by treatment, primary system organ class and preferred term. Incidence rates as defined in Section 7.8.1.8 will generally be included. AEs will also be reported by intensity (without incidence rates). Separate tables will be provided for patients with other significant adverse events, for patients with adverse events of special interest (AESIs), for patients with serious adverse events, for patients with AEs leading to discontinuation, and for patients with drug-related AEs.

Overall AE summaries, AEs by SOC and PT, SAEs and AEs leading to discontinuation will additionally be investigated by subgroups as outlined inTable 6.4: 1.

AEs leading to death will be summarized up to end of the trial, also separately for those adjudicated as CV and those adjudicated non-CV cause.

The system organ classes will be sorted according to the standard sort order specified by the European Medicines Agency (EMA), preferred terms will be sorted by frequency (within system organ class).

Additionally, the following analyses will be reported in Appendix 16.1.9.2 for disclosure on EudraCT and clinicaltrials.gov:

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

- Serious Adverse Events for disclosure on EudraCT by treatment

For further details, see also (13).

7.8.1.4 Adverse events of special interest (AESIs)

Hepatic injury

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

Additionally Hepatic AEs will be summarized based on an SMQ based definition. From SMQ Drug related hepatic disorders (20000006) the following narrow sub-SMQs will be used:

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

A table with frequencies of patients with these AEs by treatment, primary SOC and preferred term will be provided. This presentation will be repeated by DM status at baseline (DM vs no DM). Hepatic SAEs and hepatic AEs leading to disc based on the above SMQ definition will be presented.

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

Patients with hepatic injury will be listed.

For presentations on adjudicated hepatic events, refer to Section 7.8.1.6.

Decreased renal function

Adverse events reported as AEs of special interest relating to decreased renal function as specified in the protocol will be summarised.

A frequency tables of patients with AEs related to decreased renal function by treatment, primary SOC and preferred term will additionally be provided based on the narrow standardized MedDRA query (SMQ) Acute renal failure (20000003).

This presentation will be repeated by the subgroups as outlined in Table 6.4: 1. SAEs and AEs leading to disc based on the SMQ Acute renal failure (20000003) will be presented.

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

Patients with decreased renal function will be listed.

Ketoacidosis

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

For the narrow BIcMQ diabetic ketoacidosis (DKA), SAEs and AEs leading to discontinuation will be presented.

For presentations on adjudicated events, refer to Section 7.8.1.6

Patients with DKA based on the narrow and broad BIcMQ or investigator reported ketoacidosis will be listed.

Events leading to lower limb amputation

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

A separate tables for AEs leading to lower limb amputation which are leading to discontinuation will be presented.

For events leading to lower limb amputations in addition to the '7-day-on-treatment approach' all adverse events that occurred between first study drug intake up to study end will be presented (following censoring rules like non-fatal outcome events). For both approaches, SAEs will be presented.

Lower limb amputations (up to study end) will additionally be summarised by level of amputation, reason for amputation, history of PAOD, previous amputation and status of DM at baseline (DM / no-DM).

Patients with lower limb amputation will be listed.

7.8.1.5 Specific AEs

Hypoglycaemic events

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

- asymptomatic hypoglycaemia: event not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration ≤ 3.9 mmol/L (≤ 70 mg/dL)
- documented symptomatic hypoglycaemia with a measured plasma glucose concentration ≥ 3.0 mmol/L and ≤ 3.9 mmol/L (≥ 54 mg/dL and ≤ 70 mg/dL): event accompanied by typical symptoms of hypoglycaemia
- documented symptomatic hypoglycaemia with a measured plasma glucose concentration < 3.0 mmol/L (< 54 mg/dL): event accompanied by typical symptoms of hypoglycaemia but no need for external assistance

- severe hypoglycaemic episode: event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions
- symptomatic hypoglycaemia and plasma glucose concentration > 3.9 mmol/L (70 mg/dL)
- symptomatic hypoglycaemia and plasma glucose concentration not measured

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

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

Subgroup analyses on confirmed events with respect to age category, renal function and diabetes background (no DM, patients with pre DM, patients with DM) will be performed.

Time to the onset of the first confirmed hypoglycaemia will be displayed using a cumulative incidence function.

In addition the number of patients with hypoglycaemia according to BIcMQ will be presented.

Patients with hypoglycaemic events will be listed.

UTI and genital infections

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

- Genital infections (narrow BIcMQ list and investigator assessment)
- UTI (narrow BIcMQ and investigator assessment)

Genital infections based on investigator assessment will additionally be summarised by type (fungal balanitis or fungal vulvovaginitis, genital infection other than fungal balanitis or fungal vulvovaginits), intensity (mild, moderate or severe), time to onset of first episode (within the first 3 months of treatment or after), how the event was treated (no treatment, therapy assigned, hospitalisation), whether leading to discontinuation of treatment, and the number of episodes per patient.

UTIs based on investigator assessment will additionally be summarised by intensity (mild, moderate or severe), time to onset of first episode (within the first 3 months of treatment or after), anatomical location (upper UTI, lower UTI), how the event was treated (no treatment, therapy assigned, hospitalisation), whether leading to discontinuation of treatment, and the number of episodes per patient.

In the number of episodes analysis of UTI and genital infection AEs will be collapsed within each SSC regardless of preferred term with the collapsing following the description at the start of Section 7.8.1.

For UTIs based on the narrow BIcMQ the subgroups as outlined in Table 6.4: 1 will be presented. The same will be done for genital infections based on the narrow BIcMQ.

Complicated urinary tract infections defined as serious adverse events of narrow BIcMQ UTI, all events of sub-BIcMQ Pyelonephritis, all events of PT Urosepsis will be presented.

Complicated genital infection: defined as all serious events using the narrow BIcMQ Genital infection will also be presented.

UTIs leading to discontinuation based on the narrow BIcMQs will be presented, the same will be repeated for genital infections leading to discontinuation based on the narrow BIcMQ.

Cumulative incidence functions will also be created for time to onset of the first UTI and for time to onset of the first genital infections, both based on the respective narrow BIcMQ.

Patients will UTIs or genital infections will be listed.

Pyelonephritis and sepsis

The following specific adverse event will also be tabulated by treatment group:

- Acute Pyelonephritis (based on investigator assessment): patient incidence overall and by gender
- Pyelonephritis (based on the narrow sub-SMQ): patient incidence overall and by gender
- Sepsis (based on investigator assessment): patient incidence overall and by source of infection (UTI or not UTI)

Patients with pyelonephritis or sepsis will be listed.

Bone fracture events:

Frequency tables of patients with bone fracture by treatment, primary system organ class (SOC) and preferred term will be provided (based on BIcMQ and investigator reporting). Investigator reported fractures will be reported by type of fracture (traumatic vs. non-traumatic).

For bone fractures based on the BIcMQ the subgroups as outlined in Table 6.4: 1 will be presented. Separate tables for bone fractures based on the BIcMQ, which are serious and those which are leading to discontinuation will be presented.

For overall bone fracture based on the BIcMQ in addition to the '7-day-on-treatment approach' all adverse events that occurred between first study drug intake up to study end will be presented (following censoring rules like non-fatal outcome events).

Patients with bone fractures will be listed.

Cancer events:

Cancer will be based on the following Sub-SMQs of SMQ Malignancies (20000090):

- Sub-SMQ Malignant or unspecified tumors (20000091)
- Sub-SMQ Malignancy related conditions (20000092), excluding the PT "Acanthosis nigricans".

Presentation will be done ordered by HLT.

Frequency tables of patients with cancer by treatment, high level term and preferred term will be provided.

For cancer in addition to the '7-day-on-treatment approach' all adverse events that occurred between first study drug intake up to study end will be presented (following censoring rules like non-fatal outcome events).
There will be an additional analysis including all patients who had a minimum cumulative study drug exposure of 6 months (excluding treatment gaps). All AEs starting from date when 6 months cumulative exposure was reached up to individual day of trial completion will be shown (following censoring rules like non-fatal outcome events).

Patients with cancer will be listed.

Volume depletion

Volume depletion will be based on the BIcMQ.

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

For volume depletion events the subgroups as outlined in Table 6.4: 1 will be presented. Separate tables for volume depletion events, which are serious and those which are leading to discontinuation will be presented.

Patients with volume depletion will be listed.

A cumulative incidence function will be used to display the time to first volume depletion event.

For the analysis of laboratory data, refer to Section 7.8.2.

Venous embolic and thrombotic adverse events:

Venous embolic and thrombotic adverse events will be evaluated on the narrow SMQ.

A frequency table of patients with venous embolic and thrombotic adverse events by treatment, primary SOC and preferred term will be provided.

The subgroups as outlined in Table 6.4: 1 will be presented. Separate tables for venous embolic and thrombotic adverse events, which are serious and those which are leading to discontinuation will be presented.

Patients with venous embolic and thrombotic adverse events will be listed.

Increased urination

Frequency of increased urination will be summarised by primary SOC and preferred term based on the project-defined PT list.

7.8.1.6 Events qualifying for external adjudication by the CEC and Hepatic External Adjudication and Adjudication of ketoacidosis

An independent external CEC regularly reviews events and evaluates whether pre-specified criteria for these adjudication endpoints are met. Details on composition of the CEC, responsibilities and clinical event definitions are provided in the separate CEC Charter.

Adjudication assessments will be incorporated into the database.

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

Cardiological/neurological adverse events:
Frequency tables will be provided based on SOC and preferred for events qualifying for adjudication.

The number of patients with confirmed events per event type and breakdown of event subtype will be presented. This will be done for all CEC confirmed events.

A frequency table contrasting local vs. central (adjudicated) assessments will also be generated.

A listing will be provided, that shows the trigger events and result of adjudication.

Hepatic adverse events:
Frequency tables summarizing the relatedness and severity will be provided, including a listing showing the trigger events and adjudication results. This will include all adjudicated events up to the end of the study.

Ketoacidosis:
Frequency tables summarizing the adjudication results will be provided, including a listing showing the trigger events and adjudication results. This will include all adjudicated events up to the end of the study.

7.8.1.7 AEs while patients taking wrong medication

A listing will be provided for AEs that occurred while a patient was taking the wrong medication. Off-drug is not viewed as wrong medication.

7.8.1.8 Adverse event incidence rates

In addition to the frequency tabulations, time-adjusted adverse event analyses will be performed for all AEs, investigator defined drug-related AEs, AEs leading to discontinuation, other significant AEs, serious AEs, and adverse events of special interest by SOC, respectively HLT, and PT.

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

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

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

The standard approach will be x=7 days, but for certain AESIs in addition other approaches will be used.

Total AE-specific time at risk per treatment group is then derived as:
Time at risk (AE) [years] = Sum of time at risk [days] over all patients in a treatment group/ 365.25

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

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

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

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

7.8.2 Laboratory data

For continuous safety laboratory parameters standardized and normalized values will be derived as well as the differences to baseline. The process of standardization and normalization as well as standard analyses for safety laboratory data are described in the BI guidance for the Display and Analysis of Laboratory Data (14). All analyses considering multiple of times upper limit of normal (ULN) will be based on original and not normalized data.

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

The analyses of laboratory data will be descriptive in nature and will be based on BI standards [see Data Management and Statistics Manual (DM&SM): Display and Analysis of Laboratory Data (14)].

Baseline for safety laboratory parameters will be the last available measurement before the start of randomised trial medication. Laboratory measurements taken up to 3 days after the last administration of randomised study drug will be considered as on-treatment.
Default settings will be used for repeated values (using worst value).

Laboratory values will be compared to their reference ranges and frequency tables will be provided for the number of patients within and outside the reference range at baseline and the last measurement on treatment. Descriptive statistics will be provided by treatment group for baseline, last value on-treatment and for changes from baseline to last value on treatment. Frequency tables will summarise the number of patients with potentially clinically significant abnormalities as defined for the current XLAB macro.

Only patients with at least one available on-treatment value will be included in the analysis of an individual laboratory parameter. All individual data will be presented in listings.

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

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

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

Frequency tables of patients with elevated liver enzymes defined by ALT and/or AST, total bilirubin and AP combinations will be provided. A scatter plot of peak ALT against peak total bilirubin will be presented with reference lines for 3 x ULN ALT and 2 x ULN total bilirubin, including an indicator for treatment received. Details on patients with elevated liver enzymes will be listed.

For the following parameters: total cholesterol, HDL-C, LDL-C, trigylcerides, haemoglobin and haematocrit the time course of changes will be assessed. The analysis will be performed by applying MMRM models to OC-AD data (on the randomised set) and respectively OC-OT data (on the treated set). The MMRM models, that will be used, are specified in Section 7.6. These analyses will be conducted on data before any normalization.

The parameters LDL-C/HDL-C ratio and non-HDL cholesterol will be evaluated descriptively over time based on OC-AD data (on the randomised set) and OC-OT data (on the treated set). These analyses will be conducted on data before any normalization.

For an evaluation of follow-up after discontinuation of trial medication an additional summary of haemoglobin, haematocrit, uric acid and lipid parameters will be produced. This summary will include descriptive statistics for baseline, actual values and change from baseline from last on-treatment value and follow-up, and change from last on-treatment assessment to follow-up. The TS-FU patient set will the basis for this summary, but only those patients with a valid baseline, last value on treatment and follow-up value will be included in all displays. Analyses will be repeated for patients with at least 52 weeks of cumulative exposure.

Analyses of change from baseline to LVOT and FU as outlined above will be additionally modelled, separately for LVOT and FU. An ANCOVA model including treatment group, gender, geographical region and history of DM as fixed effect and baseline eGFR $(CKD\text{-}EPI)_{cr}$ (continuous), age (continuous), LVEF (continuous) and baseline of the endpoint as linear covariates will be used.

7.8.3 Vital signs

An MMRM analysis for heart rate over time will be provided based on OC-AD on the randomised set and OC-OT on the treated set imputations. The model will follow the MMRM analysis described in Section 7.6.

7.8.4 Electrocardiogram (ECG)

Clinically relevant abnormalities found at physical examination or ECG at Visit 2 will be considered to have already existed prior to signing of informed consent and therefore should be considered baseline conditions instead of adverse events, unless there is good reason to assume that they first appeared after signing of consent.

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

7.8.5 Others

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

Results of the Modified Rankin Scale will be summarized descriptively.

8. REFERENCES

1	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version
2	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
3	*001-MCS 36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
4	*001-MCG-159*: "Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.
5	R16-3839 Beyersmann J, Allignol A, Schumacher M Competing risks and multistate models with R. New York: Springer (2012)
6	R07-4680 Collett D Modelling survival data in medical research Chapman and Hall/CRC (2003)
7	R16-2229 Rogers JK, Yaroshinsky A, Pocock SJ, Stokar D, Pogoda J Analysis of recurrent events with an associated informative dropout time: application of the joint frailty model. Stat Med 35 (13), 2195 - 2205 (2016)
8	R16-4909 Rogers JK, Pocock SJ, McMurray JJV, Granger CB, Michaelson EL, Ostergren J, et al Analysing recurrent hospitalizations in heart failure: a review of statistical methodology, with application to CHARM-Preserved. Eur J Heart Fail 16, 33 - 40 (2014)
9	Li Lu, Chenwei Liu, Analysis of Correlated Recurrent and Terminal Events Data in SAS®, NESUG 2008
10	R16-4813 Pocock SJ, Ariti CA, Collier TJ, Wang D The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J 33, 176 - 182 (2012)
11	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
12	*CPMP/ICH/137/95*: “Structure and Content of Clinical Study Reports”, ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version
13	*001-MCG-159_RD-09*: “Additional Analysis Requirements for Disclosing Data from Clinical Trials - Display Templates", current version; IDEA for CON.
14	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.
15	*001-MCG-741*: "Clinical subgroup analyses for local and regional Populations in Asia - Clinical Bridging Study Waiver (BSW) and Descriptive Subgroup Analysis (SGA) Reports” , current version; IDEA for CON.

9. ADDITIONAL SECTIONS

9.1 REGIONS AND COUNTRIES

Countries will be assigned to regions following the assignment of the IRT system, which is outlined in Table 9.1:1. Listed countries include currently planned backup countries.

Table 9.1: 1 Regions and countries

Region	Country
Asia	China Japan Korea Singapore
Europe	Belgium Bulgaria Czech Republic Denmark Germany Hungary Italy Netherlands Poland Spain Romania Sweden UK
Latin America	Argentina Brazil Colombia Mexico
North America	Canada US
Other	India Australia South Africa Turkey

9.2 CONCOMITANT MEDICATION

Definitions of medication groups (such as ARBs, diuretics) will be based on World Health Organization Drug Dictionary (WHO DD) and will be stored in the PDMAP.

9.3 ADDITIONAL SUB-GROUP ANALYSIS FOR REGIONAL SUBMISSIONS

Disposition and demographics of the subpopulation for patients from USA and subgroup analyses for patient from the USA vs non-USA will be included in the appendix of the CTR. Efficacy endpoints evaluated will be primary endpoint, time to cardiovascular (CV) death, time to first HHF, HHF (first and recurrent) and renal slope. Safety will be summarized for patients from the USA.
Additional country or region-specific analyses will be conducted for patients from Mexico, East-Asia (China, Japan and Korea), China, Japan, Korea and India to be included into the country-specific submission documents as also outlined in (15). Primary endpoint, time to cardiovascular (CV) death, time to first HHF, HHF (first and recurrent) and renal slope will be presented. Main adverse event overviews, disposition, demographics will be presented.

9.4 INTERIM ANALYSES

An interim analysis will be conducted by the DMC as outlined in the CTP. If based on the interim analysis it is decided to stop the trial for overwhelming efficacy, all analyses belonging to the confirmatory testing strategy as described in this TSAP will be conducted on the snapshot as used for the interim analysis done by the DMC. All other analyses will be conducted on the final database lock.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**21-FEB-2017**	[redacted]	None	This is the final TSAP without any modification

Trial Statistical Analysis Plan

c14526274-04

BI Trial No.:	1245.110
Title:	A phase III randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic Heart Failure with preserved Ejection Fraction (HFpEF). Including Revised protocol # 03 [c03946327-04]
Investigational Product:	Empagliflozin, BI 10773
Responsible trial statistician:	[redacted]
Date of statistical analysis plan:	12 FEB 2021 REVISED
Version:	Revised

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ACE	Angiotensin Converting Enzyme
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor blocker-Neprilysin Inhibitor
ASA	Acetylsalicylic acid
AST	Aspartate transaminase
ATC	Anatomical-Therapeutic-Chemical
BI	Boehringer Ingelheim
BicMQ	Boehringer Ingelheim customized MedDRA Query
BMI	Body mass index
BP	Blood pressure
CCB	Calcium channel blocker
CEC	Clinical Event Committee
CI	Confidence interval
CIF	Cumulative Incidence Function
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRF	Case report form
CRT	Cardiac resynchronisation therapy
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Cardiovascular
DBL	Data base lock
DBP	Diastolic Blood Pressure
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DM&SM	Data Management and Statistics Manual
ECG	Electrocardiogram
eCRF	Electronic Case Report Form

Term	Definition / description
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EoT	End-Of-Text
EOT	End of treatment
EQ-5D	EuroQoL 5 dimensions
EudraCT	European Clinical Trials Database
FG	Fasting glucose
FU	Follow-up
GI	Gastrointestinal
HbA_{1c}	Glycosylated haemoglobin
HCRU	Health Care Resource Utilisation
HDL-C	High density lipoprotein cholesterol
HF	Chronic Heart Failure
HHF	Hospitalisation for heart failure
HLT	High level term
hsTnT	high-sensitivity troponin T
HR	Hazard ratio
ICD	Implantable Cardioverter Defibrillator
ICH	International Conference on Harmonisation
IPD	Important protocol deviation
IRT	Interactive Response Technology
ITT	Intention-to-treat
IVRS	Interactive voice response system
JFM	Joint frailty model
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVAD	Left ventricular assist device
LDL-C	Low density lipoprotein cholesterol
LLT	Low level term
LVEF	Left ventricular ejection fraction
LVOT	Last value on treatment
LTFU	Lost to follow-up
Max	Maximum

Term	Definition / description
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
Min	Minimum
MMRM	Mixed models repeated measures
MRA	Mineralocorticoid Receptor Antagonist
Non-CV	Non-cardiovascular
NT pro-BNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association Classification
OC-AD	Observed Case including data after discontinuation
OC-OT	Observed Case on-treatment
PK	Pharmacokinetic
PAOD	Peripheral Arterial Occlusive Disease
PT	Preferred term
Q1	Lower quartile
Q3	Upper quartile
PDMAP	Project data management and analysis plan
RS	Randomized set
SAE	Serious adverse event
SAS	Statistical Analysis System
SBP	Systolic blood pressure
SCR	Screened set
SD	Standard deviation
SE	Standard error
SGLT-1	Sodium-glucose co-transporter 1
SGLT-2	Sodium-glucose co-transporter 2
SI	Système international d'unités
SMQ	Standardized MedDRA query
SOC	System organ class
TBILI	Total bilirubin
TS	Treated set
TS-FU	Treated set – Follow-up
TSAP	Trial statistical analysis plan

Term	Definition / description
UACR	Urine Albumin Creatinine Ratio
ULN	Upper limit of normal
UTI	Urinary tract infection
WHO DD	World Health Organization Drug Dictionary

3. INTRODUCTION

As per the International Conference on Harmonisation (ICH) E9 guidance (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

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

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

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

1. In the random coefficient model used to estimate slope in change from baseline of eGFR $(CKD\text{-}EPI)_{cr}$, an additional fixed effect term of interaction of eGFR $(CKD\text{-}EPI)_{cr}$ at baseline (continuous) by time is included.

2. As per protocol the objective of the trial is "to demonstrate superiority of empagliflozin 10 mg versus placebo".
   The ITT analysis approach was chosen to as closely as possible reflect real-life conditions, disregarding any occurrences of treatment stop or restart of treatment, that may happen in clinical practice as well.
   However, it is also recognized and recommended by the Executive Steering Committee that the study-specific treatment discontinuation in the close-out period does not resemble clinical practice.
   Therefore for patients that complete the treatment period according to protocol after close-out announcement the time at risk for efficacy endpoints ends at the discontinuation of treatment and events occurring thereafter are not considered in the efficacy analyses.
   The primary estimand is now specified in Section 7.4.
   An analysis including all events after randomization will be conducted as sensitivity analysis for the primary endpoint and the key secondary endpoint of recurrent HHF. A corresponding approach will be used for continuous endpoints.

3. Mixed model for repeated measures (MMRM) for KCCQ at week 52 as well as other MMRMs were specified in condensed form to be in line with BI internal standards. Therefore, individual model terms were removed from the MMRM if already included as interaction term with treatment or visit. Additionally, the terms included in MMRMs were aligned throughout the TSAP

4. The rules defining 'win' and 'lose' for the win ratio calculation were clarified and adapted to also consider the time to first HHF event in case of a tie in the number of HHF events. The adaption was made since time to first HHF event is also considered relevant information to avoid ties in case the number of HHF events is identical. This approach is a modification of the rules applied by Rogers 2014 (8).

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

The primary endpoint is the composite of time to first event of adjudicated CV death or adjudicated HHF.

For further clarification: Adjudicated CV death always includes death adjudicated as death due to undetermined cause. This is applicable throughout all analyses wherever adjudicated CV death is mentioned.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

Key secondary endpoints are:

- Occurrence of adjudicated HHF (first and recurrent)
- eGFR $(CKD\text{-}EPI)_{cr}$ slope of change from baseline

5.2.2 Other secondary endpoints

Other secondary endpoints are specified in the CTP Sections 5.1.2 and 5.2, and in TSAP Section 7.5.2.

5.3 FURTHER ENDPOINTS

Further endpoints are listed in the CTP Section 5.1.3, and in TSAP Section 7.6. The definition and assessment can be found in Section 5.2.

Further endpoints added include:

- Time to non-cardiovascular (non-CV) death (i.e. death cases not included in the definition of adjudicated CV death)
- Fasting glucose (FG) change from baseline to last value on treatment (LVOT) and follow-up (FU), overall and by status of diabetes mellitus (DM)
- Time to first investigator-defined CV hospitalization. Investigator-defined CV hospitalization includes AEs ticked by the investigator as “CV hospitalization (due to reasons other than heart failure, MI or stroke)” and AEs ticked as “Hospitalization for Heart failure” as well as events ticked as “Cardiovascular (CV) Death other than CV death attributed to myocardial infarction or stroke”, MI, stroke, non-fatal TIA that are reported as requiring hospitalization.
- Time to atrial fibrillation (defined as time to first reported ECG indicating atrial fibrillation or to first AE with PT atrial fibrillation).

5.4 OTHER VARIABLES

5.4.1 Kansas City Cardiomyopathy Questionnaire (KCCQ) scores

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

1. Physical Limitation

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

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

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

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

2. Symptom Stability

Code the response to Question 2 as follows:

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

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

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

3. Symptom Frequency

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

Question 3

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

Questions 5 and 7

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

Question 9

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

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

S3 = [(Question 3) – 1]/4

S5 = [(Question 5) – 1]/6

S7 = [(Question 7) – 1]/6

S9 = [(Question 9) – 1]/4

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

4. Symptom Burden

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

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

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

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

5. Total Symptom Score

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

Symptom Frequency Score and Symptom Burden Score

6. Self-Efficacy

Code responses to Questions 10 and 11 as follows:

Question 10

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

Question 11

- Do not understand at all = 1
- Do not understand very well = 2

- Somewhat understand = 3
- Mostly understand = 4
- Completely understand = 5

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

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

7. Quality of Life

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

Question 12

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

Question 13

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

Question 14

- I felt that way all of the time = 1
- I felt that way most of the time = 2
- I occasionally felt that way = 3
- I rarely felt that way = 4
- I never felt that way = 5

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

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

8. Social Limitation

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

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

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

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

9. Overall Summary Score

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

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

10. Clinical Summary Score

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

Physical Limitation Score and Total Symptom Score

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

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

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

not

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

Patient-preferred outcome is derived from response to the question about which domain is the most difficult for the patient to cope with at baseline:

- Loss of functional abilities: Physical Limitation Score
- Symptoms due to your heart failure: Total Symptom Score
- Your concern about how to manage your heart failure: Self-Efficacy Score
- Suffering from depression, anxiety, emotional liability because you have heart failure: Quality of Life Score
- Adapting your life to heart failure: Social Limitation Score

5.4.2 LVEF

Values of LVEF will be considered valid, when appropriate methodology was used. When methodology is missing, LVEF will be disregarded.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

There will be 4 basic treatment phases in this trial: screening, study treatment phase (with either empagliflozin 10mg or matching placebo), post-treatment and post-study. However, during the study treatment phase, patients are allowed to go off-treatment and subsequently re-start treatment. This may happen not at all or repeatedly for a given patient.

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

Table 6.1: 1 Treatment regimens / study intervals

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

Details on the definition of on-treatment period for different endpoints are listed in Table 6.1:2. The efficacy analyses will follow the intention-to-treat (ITT) principle in assigning patients to treatment groups, i.e. patients will be analysed as randomised.

Safety analyses will also assign patients to the treatment group as randomized.

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

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

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

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

6.2 IMPORTANT PROTOCOL DEVIATIONS (IPDS)

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

The IPDs will be described in the clinical trial report (CTR). A listing of patients with medication code broken will be provided.

Table 6.2: 1 Important protocol deviations

Category / Code		Description	Requirements	Excluded from
A		**Entrance criteria not met**		
A1		**Target indication not met**		
	A1.06	No chronic HF or no NYHA class II-IV	Inclusion criterion #3 not met	None
	A1.07	Conditions on ejection fraction (EF) not met	Inclusion criterion #4 not met	None
	A1.08	Conditions on NT-proBNP not met	Inclusion criterion #5 not met	None
	A1.09	Conditions on HF not met	Inclusion criterion #6 not met	None
A2		**Inclusion criteria not met**		
	A2.02	Age out of range	Inclusion criterion #1 not met	None

Table 6.2: 1 Important protocol deviations (cont.)

Category / Code		Description	Requirements	Excluded from
	A2.08	Specific inclusion criterion for women of child-bearing potential not met	Inclusion criterion #2 not met	None
A3		**Exclusion criteria met**		
	A3.44	Patient with unstable conditions	Exclusion criteria #1, #2, #7, #11 or #16 met	None
	A3.42	Recently implanted ICD	Exclusion criterion #3 met	None
	A3.43	Implanted CRT	Exclusion criterion #4 met	None
	A3.29	Patients with cardiomyopathies as defined in the protocol	Exclusion criterion #5 met	None
	A3.30	Any severe (obstructive or regurgitant) valvular heart disease, obstructive or regurgitant, or any valvular disease expected to lead to surgery during the trial in the opinion of the investigator	Exclusion criterion #6 met	None
	A3.31	Atrial fibrillation or atrial flutter with a resting heart rate >110bpm	Exclusion criterion #8 met	None
	A3.33	Systolic blood pressure at visit 1 or 2 out of range	Exclusion criterion #9. #10 met	None
	A3.06	Indication of liver disease	Exclusion criterion #12 met	None
	A3.09	Renal insufficiency or renal impairment (assessed by eGFR)	Exclusion criterion #13 met	None
	A3.34	Haemoglobin at visit 1 below cut-off	Exclusion criterion #14 met	None
	A3.35	History of Ketoacidosis	Exclusion criterion #15 met	None
	A3.36	Gastrointestinal (GI) surgery or GI disorder that could interfere with study medication absorption in the investigator's opinion	Exclusion criterion #17 met	None
	A3.37	Documented or active malignancy	Exclusion criterion #18 met	None
	A3.38	Life expectancy of <1 years in the opinion of the investigator	Exclusion criterion #19 met	None
	A3.39	Intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial	Exclusion criterion #20 met	None
	A3.40	Treatment with any SGLT-2 inhibitor or SGLT-1 and 2 inhibitor	Exclusion criterion #21 met	None
	A3.11	Intake of an investigational drug in another trial within 30 days prior to intake of study medication in this trial	Exclusion criterion #22 met	None
	A3.41	Known allergy or hypersensitivity to empagliflozin	Exclusion criterion #23 met	None
	A3.13	Relevant alcohol or drug abuse and condition affected study compliance	Exclusion criterion #24 met	None
	A3.12	Specific exclusion criterion for premenopausal women not met	Exclusion criterion #25 met	None
	A3.14	Any other clinical condition unsafe for participation	Exclusion criterion #26 met	None
B		**Informed consent**		
	B1	Informed consent not available/not done	Informed consent date missing or inclusion criterion #9 not met	All
	B2	Informed consent too late	Informed consent date was after Visit 1	None

Table 6.2: 1 Important protocol deviations (cont.)

Category / Code		Description	Requirements	Excluded from
C		**Trial medication and randomisation**		
	C1.02	Incorrect trial medication taken	Wrong medication taken for more than 20% of the overall treatment duration Can only be finally judged after data base lock (DBL) since unblinding information is required.	None
D		**Concomitant medication**		
	D2.02	Use of prohibited medication	Use of SGLT-2 or combined SGLT-1 and 2 inhibitors after randomization but before EOT visit occurring at study close out.	None

6.3 SUBJECT SETS ANALYSED

The following patient sets are defined

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

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

- *Treated set (TS)*
  This patient set includes all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.

- *Treated Set-Follow-up (TS-FU)*
  All patients in the TS, for whom a follow-up visit was performed (i.e. values of planned assessments- KCCQ, EQ-5D, vital signs or lab data reported) between 23 and 45 days after last intake of study medication.

The TS-FU does not include patients, where no planned measurements were taken, which may happen in case of telephone FU visits. Patients with intake of open label SGLT-2 inhibitor between their EOT and FU visit are also excluded from the TS-FU set.

- *Pharmacokinetic Set (PKS)*
  This patient set includes all evaluable patients of the treated set who provide at least one observation for at least one further PK endpoint of Cpre,ss,N for empagliflozin.

6.4 SUBGROUPS

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

If there is missing information for any of the subgroups, where data is also collected in the IRT system, then the information as transferred from IRT will be used to assign a patient to a certain category.

Although several subgroup analyses are prespecified in Table 6.4: 1, the subgroup analysis by Diabetes at baseline (diabetic, non-diabetic) is the medically and academically most important subgroup analysis.

Table 6.4: 1 Categories of covariates for displays of baseline characteristics and subgroup analyses

Variable	Categorization	Demo-graphics[1]	Subgroups for Efficacy endpoints[2]	Safety[3]
Diabetes at baseline	diabetic, non-diabetic	X	X	X (except ketoacidosis and hypoglycaemia)
	non-diabetic (Pre-diabetes, normal (no pre-diabetes)), diabetic (type 2 diabetes, type 1 diabetes)	X		X (Ketoacidosis and hypoglycaemia)
Age (years)	<50 50 to <65 65 to <75 75 to <85 >= 85	X		X
	< 70 ≥70	X	X	
Sex	male female	X	X	X
Region	NA, LA, Europe, Asia, Other[+]	X		*X (overall[4] only)*
Ethnicity	Hispanic/ Latino Not Hispanic/ Latino	X		*X (overall[4] only)*
Race[$]	White Black/ African-American Asian Other including mixed race	X	X	*X*
BMI (kg/m^2)	<30 ≥30	X	X	
eGFR at baseline	>=90 60 to <90 45 to <60 30 to <45 20 to <30 <20	X		
	>=90 60 to <90 45 to <60 30 to <45 <30	X		X
	>=60 <60	X	X	

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

Variable	Categorization	Demo-graphics[1]	Subgroups for Efficacy endpoints[2]	Safety[3]
UACR	UACR (in mg/g): <30 >=30 to <=300 >300	X		
Baseline SBP	< / >= median		X	
Baseline BP	SBP<140 and DBP<90 vs. SBP>= 140 or DBP>=90	X		X (volume depletion AEs and hypotension AEs)
History of Atrial Fibrillation or Atrial Flutter[$$]	Yes/ No	X	X	
Baseline LVEF	</>=50	X		
	<50, 50 to <60, >=60	X	X	
History of HHF (in the last 12 months)	Yes / No	X	X	
Time since diagnosis of HF	<= 1 year, 1-5 years, > 5 - 10 years, >10 years	X		
NYHA at baseline	I/II/III/IV	X		
	II vs. III/IV		X	
NT-proBNP	< / >= median (calculated separately for patients with/without history of atrial fibrillation or atrial flutter[$$])		X	
Baseline uric acid	Tertiles (calculated separately for males and females)	X	X	
Baseline use of ACE-inhibitor, ARB or ARNi	Yes / No	X#	X	X (renal AEs, volume depletion AEs and hypotension AEs)
Baseline use of MRA	Yes / No	X#	X	

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

Variable	Categorization	Demo-graphics[1]	Subgroups for Efficacy endpoints[2]	Safety[3]
Baseline use of diuretics	Yes / No	X#		X (renal AEs, volume depletion AEs and hypotension AEs)
Baseline use of loop or high-ceiling diuretics	Yes / No	X#		X (renal AEs, volume depletion AEs and hypotension AEs)

[1] The column demographics shows categories shown in the overall demographics. Demographics are not planned by subgroup.
[2] Subgroups planned for the primary endpoint, time to cardiovascular (CV) death, time to first HHF, HHF (first and recurrent), renal slope.
[3] X means subgroups planned for overall AE summaries, AEs by SOC and PT, SAEs, AEs leading to discontinuation, decreased renal function, UTI, genital infection, volume depletion, hypotension and bone fracture.
[4] Overall means overall AE summaries, AEs by SOC and PT, SAEs and AEs leading to discontinuation
[5] Median calculated separately for baseline atrial fibrillation or atrial flutter (determined by ECG) / no baseline atrial fibrillation and atrial flutter (determined by ECG)
[+] Region categorization: see Table 9.1.1.
[#] part of the presentation of baseline concomitant therapy as outlined in Section 7.2
[$] Due to low number of patients in certain race categories, estimates for race subgroups may be unstable.
[$$] history of atrial fibrillation or atrial flutter means atrial fibrillation or atrial flutter reported in any ECG before treatment intake or history of atrial fibrillation or atrial flutter reported as medical history.

Additional subgroup analyses for specific further endpoints are defined in Section 7.6

6.5 POOLING OF CENTRES

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

6.6 HANDLING OF MISSING DATA AND OUTLIERS

6.6.1 Imputation methods

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

There will be different methods of looking at continuous longitudinal data.

Observed case on-treatment (OC-OT):
Only the available data that were observed while patients were on study medication (defined as time from first drug intake until last permanent treatment stop date plus the endpoint specific follow-up time (as defined in Table 6.1:2) are considered.
Measurements are assigned to planned weeks according to Table 6.7: 1

Observed case including data after treatment discontinuation (OC-AD):
All available data are considered, including values obtained on treatment or post-treatment.
Measurements are assigned to planned weeks according to Table 6.7: 1.

As described in Section 4, for patients that completed the treatment phase as planned (primary reason for end of treatment being completion of treatment period according to protocol), measurements after last study drug intake should not be considered. Therefore for those patients, any data after the endpoint specific follow-up time (as defined in Table 6.1:2) will not be included in the OC-AD analysis.

KCCQ imputation
If not otherwise noted, for endpoints of KCCQ scores, for patients who die, a worst score (score of 0) will be imputed for the score at all subsequent scheduled visits after the date of death where the score would have been assessed.

Multiple imputations:
A multiple imputations approach will be considered to impute missing data. Multiple imputation approaches taken are further specified in Section 7 with the planned sensitivity analyses.

Imputation of missing covariates in multivariate Cox regression models and for recurrent event analyses
To avoid excluding patients from Cox regression analyses due to missing covariates, the overall population median of the corresponding variable will be imputed for continuous covariates and the most frequent category will be imputed for categorical covariates.
No imputation will be done for covariates included in treatment by subgroup interaction terms.

6.6.2 Missing data

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

Partial onset dates from clinical event committee (CEC):
In the unlikely case that only the year is documented, the day and month will be imputed as 01 Jan unless the subsequently derived date is before randomisation; in this case the date of randomisation will be used as start date.
If year and month is present the day will be imputed as first of the month unless the subsequently derived date is before randomisation; in this case the date of randomisation will be used.

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

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

Missing date of trial completion (=last contact or date of death)
If the date is completely missing the following rules will be applied:

- If a patient has withdrawn informed consent, this date will be imputed by the date of IC withdrawal.
- If a patient died and has not withdrawn consent and is not lost to follow-up, this date will be imputed by the date of death.
- If a patient did not die, the date of trial completion will be imputed by the last date the patient was known to free of non-fatal events. This is defined as the maximum of
    - the last date the patient could be followed up for all non-fatal events as documented in the eCRF
    - last onset or end date of an AE
    - Onset of an adjudicated event
    - End of treatment
    - last visit date (NYHA class, EQ-5D, KCCQ, pregnancy test, vital signs, ECG, or central laboratory reported)

In case of a partially missing date, if the imputed date is before the first day (after the last day) of the month/year given as partial date, the first day (last day) of the month/year will be used.

All other cases need to be assessed by the trial team on an individual patient basis, using the above points as guidance.

Missing information on the date of trial medication stop

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

- End of treatment visit date if available
- Date of death
- Trial completion (last contact date)
- Longest extrapolated treatment duration (assuming 1 tablet/day)
- (in case for partially missing date) Last day of the year/month given as partial date

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

Missing information on concomitant therapy dates
For incomplete date information generally the midpoint of the possible interval will be used. If only the year is present the day and month will be imputed as 01 July, if year and month is present the day will be imputed as 15. If the year is missing, the date will be considered missing.
If this leads to contradictions for the start or end date of a concomitant therapy (e.g. imputed end date before documented start date) a partial end date will be imputed as the end of the interval or a partial start date will be imputed as the start of the interval in the database to resolve this contradiction.
If the medication is reported as being taken at visit 2 (baseline) and the imputed start/end date contradicts this then the start/end date is imputed to the earliest/latest date respectively if this can resolve the contradiction.
Similarly if the medication is reported as not taken at visit 2 (baseline) and the imputed start/end date contradicts this then the start/end date is imputed to the baseline date/ 1 day prior to baseline respectively if this can resolve the contradiction.

All other cases or conflicting cases resulting from these imputation rules need to be assessed by the trial team on an individual patient basis.

Missing measurement to confirm “sustained” decrease
An eGFR $(CDK\text{-}EPI)_{cr}$ reduction is considered sustained, if it is determined by two or more consecutive post-baseline central laboratory measurements separated by at least 30 days (first to last of the consecutive eGFR values). If there is no additional measurement >= 30 days after the eGFR reduction is observed and the patient dies within 60 days of this measurement, then the eGFR reduction is also considered sustained.

Pharmacokinetic (PK) variables
Missing data and outliers of PK data are handled according to (3)

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

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

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

For randomised patients without any treatment intake: 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 and including the day of randomisation. For all other endpoints, baseline will be defined as the last available measurement before or on the day of randomisation.

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

Measurements taken after the end of the endpoint specific follow-up period after the last intake of study drug will be considered post-treatment values.

On-treatment (for OC-OT analysis) or all post-randomisation (for OC-AD analysis) efficacy and safety measurements will be assigned to visits based on time windows around the planned visit dates. These time windows are defined based on the planned number of days after the date of first administration of study drug.

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

Table 6.7: 1 Time windows for post-baseline efficacy measurements scheduled for each on-treatment visit for the first 3 years

			Time window (actual days after baseline)	
Visit number	Visit label	Planned days	Start	End
Endpoints assessed at each on-site visit (e.g. creatinine / eGFR)				
2	Baseline[A]	1	NA	1
3	Week 4	29	2	57
4	Week 12	85	58	155
6	Week 32	225	156	295
8	Week 52	365	296	449
10	Week 76	533	450	617
12	Week 100	701	618	785
14	Week 124	869	786	953
16	Week 148	1037	954	1121
18	…			
FU	FU	Trt stop + 30 days	Trt stop + 23 days	Trt stop + 45 days
KCCQ				
2	Baseline[A]	1	NA	1
4	Week 12	85	2	154
6	Week 32	225	155	295
8	Week 52	365	296	435
EOT	EOT / Post week 52	NA	436	Trt stop
FU	FU	Trt stop + 30 days	Trt stop + 23 days	Trt stop + 45 days

[A] Only values taken prior to the start of treatment with randomised study drug can be considered baseline values. Time windows will be used for assignment of measurements to scheduled visits.

For examinations that are not planned at every on-treatment visit, the time windows will be defined according to the same algorithm, based on the midpoint between the planned visit day of such an examination. Examples for eGFR and KCCQ can be found in Table 6.7: 1

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

Baseline definition for concomitant therapies

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

Time windows for assignment of planned off-treatment measurement

For evaluation of the off-treatment assessment 'at 30 day follow-up' only values obtained at >= 23 days to <= 45 days after last trial drug stop will be considered.

The value that is closest to the planned day of 30 days after last trial drug stop will be used. If there are 2 values equally close, the later value will be used.

6.8 CALCULATION OF TIME TO EVENT

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

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

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

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

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

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

6.8.1 Start date

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

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

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

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

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

6.8.2 Date of event

For adjudicated events, the date determined by the adjudication committee will be used; this can be different from the investigator reported date.

For the endpoints of time to CV death, time to all-cause mortality and time to non CV death the respective death date will be used rather than time to the first onset of the fatal AE.

For composite outcomes, e.g. time to adjudicated HHF or adjudicated CV death, the earliest onset date of the corresponding components will be used. For the component of CV death or other death components, date of death will always be used rather than the onset date also for composite outcomes.

For endpoints, where myocardial infarction (MI) and stroke are included as a fatal and non-fatal component, the onset of the event is considered for the derivation of time to first occurrence, not the date of death. For time to CV death the date of death is used for a fatal MI or fatal stroke.

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

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

For efficacy endpoint analyses (endpoints described in sections 7.4-7.6):

As described in Section 4, the follow-up period will not be included in the time at risk for efficacy endpoints. Therefore events later than the date of treatment discontinuation (if reason for discontinuation was completion) will not be counted.

For the primary endpoint and the key secondary endpoint of recurrent HHF, additionally there will be sensitivity analysis including all events up to individual trial completion including the FU period.

6.8.3 Censoring

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

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

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

- the last date the patient could be followed up for all non-fatal events as documented in the eCRF
- last onset of an AE or date of death
- onset dates of adjudicated events
- end of treatment
- last visit date (NYHA class, EQ-5D, KCCQ, pregnancy test, vital signs, ECG, or central laboratory- reported)

Censoring is considered independent from study drug intake.

All-cause mortality

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

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

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

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

Endpoints based on laboratory data only

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

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

Composite endpoints

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

Of those, a patient with at least one event in any of the components of the composite will be considered to have an event and the date of the first event will be used for the composite

endpoint. A patient without an event will be considered censored at the earliest of all censoring dates of the component endpoints.

For efficacy endpoint analyses (endpoints described in Section 7.4-7.6):

As described in Section 4, for patients that completed the treatment phase as planned (primary reason for end of treatment being completion of treatment period according to protocol) the follow-up period will not be included in the time at risk for efficacy endpoints. Therefore for those patients, the minimum of the treatment discontinuation date and the above described dates will be used for censoring, except if specifically noted otherwise (for the sensitivity analysis). For patients that did not complete the treatment phase, the dates defined above will be used.

For the primary endpoint and the key secondary endpoint of recurrent HHF, additionally there will be a sensitivity analysis considering all events up to individual trial completion including the FU period.

Censoring for analyses up to trt stop + x days

For any analyses until a certain number of x days after treatment discontinuation (e.g. sensitivity analyses until 30 days after treatment discontinuation), censoring time will be the minimum of the censoring time as described above and treatment discontinuation + x days. Patients with an event after treatment discontinuation + x days will be censored at treatment discontinuation + x days.

7. PLANNED ANALYSIS

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

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

Statistical parameters will be displayed to a defined number of decimal places as specified in the BI guideline "Reporting of Clinical Trials and Project Summaries" (4)

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

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

Disposition as required for reporting for the trial in EudraCT will be provided. Enrolment will be summarised by country and by age group for reporting in EudraCT. (see (13)).

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

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

The frequency of patients with IPDs will be presented by treatment group for the randomised set. The frequency of patients in different analysis sets will also be analyzed for each treatment group.

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

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be analyzed based on RS. Demographics will be repeated on the TS if the analysis sets differ by more than 1%. Standard descriptive analysis and summary tables will be presented. These summary tables will include description of subgroup variables detailed in Section 6.4. Descriptive analysis of the following variables measured at baseline will be presented: Age, body mass index (BMI), time since diagnosis, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, weight, eGFR, UACR, NT-pro BNP, LVEF, hemoglobin and troponin T. HbA_{1c} will be presented for patients with diabetes at baseline. NTproBNP will be shown for patients with or without atrial fibrillation/ atrial flutter at baseline.

A summary of the number of patients in each randomisation stratum per treatment will also be shown. The information will be based upon the data received from the interactive voice response system (IVRS) provider. Analyses will be based on actual information collected via the CRF / central laboratory, not via IVRS.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant diseases will be summarised by system organ class and preferred term. Relevant medical history by treatment group will also be presented. Both summaries will be presented using the randomised set.

7.3 TREATMENT COMPLIANCE

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

7.4 PRIMARY ENDPOINT

The primary estimand of this trial is the hazard ratio of the time to first event of adjudicated HHF or adjudicated CV death between empagliflozin 10 mg and placebo in the population of patients with heart failure with preserved ejection fraction. The primary comparison will be made regardless of changes of treatment (including discontinuation of trial medication) until completion of the planned treatment phase. For clarification, this excludes events and time at risk after the protocol-specified treatment discontinuation for patients that complete the treatment period according to protocol.

7.4.1 Primary analysis of the primary endpoint(s)

As the primary endpoint, time to the first event of adjudicated HHF or adjudicated CV death will be reported in days. The primary analysis will be based on RS, using all data available until completion of the planned treatment phase, including the data after end of treatment for patients not completing the treatment phase as planned.

The primary endpoint will be displayed using cumulative incidence function (CIF) curves and expressed as the hazard ratio with associated two-sided 95% confidence intervals (CIs) and two-sided CIs based available alpha-level for the analysis.

For the interim analysis and final analysis, the following Hwang, Shih and De Cani α-spending function at information fraction t_k with parameter $\gamma = -8$ will be used:

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

The alpha levels are expected to be 0.001 and 0.0248 (one-sided) for the interim and final tests respectively, when the interim analysis occurs at the time of 60% information.

Estimator and corresponding confidence intervals will not be corrected for interim analysis.

The primary endpoint will be analysed using Cox regression, with factors of treatment (empagliflozin, placebo), region (North America, Latin America, Europe, Asia and "other" including India, South Africa and Australia), baseline status of diabetes (diabetes, prediabetes, no diabetes), age (continuous), sex, left ventricular ejection fraction (LVEF) (continuous) and eGFR $(CKD\text{-}EPI)_{cr}$ at baseline (continuous). Since the stratification factors are included in the model as covariates, no stratified Cox regression will be used.

Breslow's method will be used for dealing with ties.

The individual relevant components of the composite will be summarized descriptively. In this descriptive analysis of the relevant component for the composite, CV death after HHF will not be counted. In all other analyses of CV death alone defined in this document, all CV deaths will be counted, disregarding any earlier events.

A hierarchical testing procedure will be followed for the assessment of the primary and key secondary endpoints. For all endpoints, superiority of empagliflozin vs. placebo will be evaluated using a two-sided test.

The tests will be performed in the following hierarchical order:

1. Time to first event of adjudicated CV death or adjudicated HHF
2. Occurrence of adjudicated HHF (first and recurrent)
3. eGFR $(CKD\text{-}EPI)_{cr}$ slope of change from baseline

Starting from step 1, if the null hypothesis of no difference is rejected, and the result is more favourable for empagliflozin, superiority is concluded in the tested endpoint, and the overall type I error is preserved for the test in the next step. If at any step the null hypothesis of no difference is not rejected, subsequent tests are conducted in an exploratory manner.

The overall type I error rate will be preserved at a level of 0.05 (2-sided). The type I error rate used at the final analysis will be influenced by the pre-planned interim analysis.

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 above, the following α-split will be used for the eGFR slope analysis and the meta-analysis:

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 summarized in Figure 7.4.1: 1.

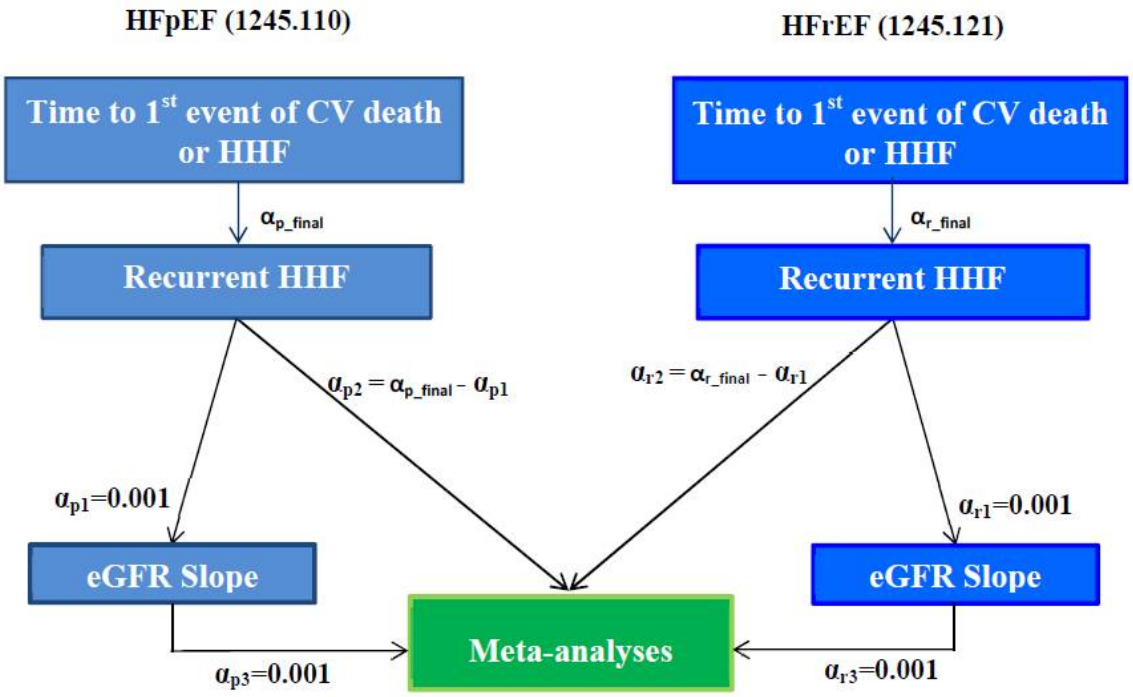

Figure 7.4.1: 1 Hierarchical analysis of trial in HFpEF (1245.110) and the parallel trial in HFrEF (1245.121) showing the alpha-spending at the final analysis

7.4.2 Sensitivity analyses

The following sensitivity analyses will be conducted:

- A Cox model including only treatment as covariate, not adjusting for any other variables.

- The same Cox regression as the primary analysis will be performed on the TS, with observation period up to 30 days after treatment discontinuation. Total number of patients with primary events occurring during the 30 days after treatment discontinuation will also be tabulated.

- For patients who are without primary event and lost to follow up before trial completion, the treatment specific incidence rates for empagliflozin and placebo for retrieved drop-outs will be used to impute the primary events in a multiple imputations framework. The primary model will be applied to the imputed datasets. It is planned to perform 100 imputations. Rubin's rules will be used to summarize the log hazard ratios and the result will be back-transformed to show a hazard ratio with confidence interval.

- The endpoint will be evaluated based on investigator defined events (same model as the primary primary analysis). Investigator defined HHF includes AEs ticked by the investigator as "Hospitalisation due to heart failure". Investigator defined CV death includes AEs ticked by the investigator as "CV death other than CV death attributed to myocardial infarction or stroke", "Undetermined cause of death" as well as HHF, CV hospitalization, MI or stroke if the event was fatal.

- A competing risk model by Fine-Gray will be explored, including the same set of covariates as in the primary analysis, sub-distribution hazard ratios will be provided (5).

- The primary analysis will be repeated to include all events up to individual trial completion including the follow-up period.

- The primary analysis will be repeated to include only confirmed primary events which meet the CDISC guidance criteria for hospitalization for heart failure (i.e., confirmed by adjudication committee, but excluding those missing a physical sign or laboratory test, or both)

- A Cox model including additional prognostic covariates, Log(NTProBNP), baseline atrial fibrillation/atrial flutter, and HHF in last 12 months, in addition to the covariates in the primary model.

- COVID-19 sensitivity analyses will be conducted:

    - The primary analysis will be repeated to include all events up to cutoff dates prior to COVID-19 outbreak – cutoff (censoring) dates are 30Nov2019 for China and 31Dec2019 for all other countries.

    - The same Cox regression model as for the primary endpoint will be fitted, however, adding an additional time dependent covariate for COVID-19 outbreak (time dependent covariate being 0 before outbreak date defined above and 1 thereafter)

- The same Cox regression model as for the primary endpoint will be fitted, however, adding an additional time dependent covariate for COVID-19 outbreak as well as a treatment by COVID-19 outbreak interaction term

- The primary analysis will be repeated to include all events up to 7 days prior a reported SARS-CoV-2 infection (based on broad scope SARS-CoV-2 infections)

A Kaplan-Meier curve of time to censoring for primary endpoint will be presented in order to assess whether there was differential censoring. For this analysis, a primary endpoint event will be counted as censoring and a censoring (including censoring due to the competing event of non-CV death) will be counted as an event.

7.4.3 Proportional hazards assumption violated

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

In case the proportionality assumption is violated for treatment, an attempt will be undertaken to identify groups of patients for which the proportionality assumption holds and a stratified Cox regression will be performed. The HR and corresponding CIs will be obtained from the stratified Cox model.

In addition a piecewise Cox model assuming proportional hazards in a series of consecutive time intervals as proposed by Collett (6) will be investigated.

7.4.4 Subgroup analyses

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

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

If there are less than 14 patients with events in one subgroup, then this subgroup will not be included in the model. If this leaves only one subgroup, the subgroup analysis will not be conducted.

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

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

Occurrence of adjudicated HHF (first and recurrent)

Hospitalisation for heart failure will be analysed by a joint frailty model (JFM) that accounts for the dependence between recurrent HHF and CV death (7). The primary analysis will be based on all data available until completion of the planned treatment phase, including the data after end of treatment for patients not completing the treatment phase as planned.

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

$$r_i(t \mid \omega_i) = \omega_i \exp\{\beta_1 z_i\} r_0(t)$$
$$\lambda_i(t \mid \omega_i) = \omega_i^{\alpha} \exp\{\beta_2 z_i\} \lambda_0(t)$$

The recurrent heart failure hospitalisations intensity function for the i-th patient conditional on the patient specific random frailty, ω_i, is given by r_i and is proportional to the baseline intensity function, r_0. The conditional hazard function for time to CV death for patient i is given by λ_i, with the baseline hazard given by λ_0, and β_1, β_2 are p x 1 vectors of regression coefficients associated with vectors of covariates z_i. The same covariates as for the analysis of the primary endpoint will be used, e.g. $ß_{.1}$=treatment (empagliflozin, placebo), $ß_{.2}$=region (North America, Latin America, Europe, Asia and "other" including India, South Africa, and Australia), $ß_{.3}$=baseline status of diabetes (diabetes, prediabetes, no diabetes) etc.

Patient specific independent random effects are denoted by ω_i and are assumed to follow a gamma distribution with mean 1 and variance θ. The correlation of the recurrent events is quantified by θ, with higher values corresponding to greater within-patient correlation and also greater between-patient variability. The parameter α determines the relationship between the recurrent heart failure hospitalisations and time to CV death. When $\alpha < 0$, higher frailty will result in a greater risk of recurrence and lower risk of terminal event (i.e. a negative

correlation between the frailties), and when $\alpha > 0$, higher frailty will result in a greater risk of recurrence and is associated with a higher risk of CV death (i.e. a positive correlation between the frailties).

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

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

Adopting piecewise constant hazards for the recurrent events and CV death allows estimation of the likelihood by Gaussian quadrature. The implementation of the used adaptive Gaussian quadrature techniques is incorporated into Proc NLMIXED of SAS 9.4. SAS Code following the strategy outlined in (9) will be used.

The size of the pieces for the piecewise constant hazards can be different and are determined separately for the terminal as well as recurrent event process with 10 pieces each. The nodes are defined by the empirical deciles of the recurrent or terminal events, respectively.
The joint frailty model using the multiplicative parametrization with non-normal random effects will be fitted using a likelihood-reformulation method (10).

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

1) An exponential model will be fitted for the terminal event and a poisson regression model for the recurrent event process including the same covariates that are included in the final joint frailty model to get initial starting values for all parameters.
2) A simplified model without random effect ω which is otherwise equal (regarding covariates, baseline hazards) to the joint frailty model is fitted using the values from step (1) as starting values for the parameters. The estimated coefficients from the simplified model will then be used as starting values for the parameters of the piecewise-constant joint frailty model.

The joint model gives two distinct hazard ratios:

$HR_{HHF} = \exp\{\beta_{11}\}$ is the hazard ratio associated with the effect of treatment on the recurrent event rate of HHF, and $HR_{CVD} = \exp\{\beta_{21}\}$ is the CV death hazard ratio.

Estimates and 95% CI for the hazard ratios and for α (relationship between the recurrent heart failure hospitalisations and CV death) will be given.

The following sensitivity analyses will be conducted

- Based on the TS, including only any events up to 30 days after treatment discontinuation
- Instead of CV-death, jointly model HHF with all-cause mortality as the terminal events (otherwise same model as initially described)

- The endpoint will be additionally evaluated based on investigator defined events for HHF and CV death (otherwise same as initially described model).

- A parametric joint gamma-frailty model will model the recurrent event component using a Poisson distribution and model the CV mortality component using a exponential distribution, conditional on the frailty parameter. Individual frailties are again assumed to follow a Gamma distribution. Thus HHF rates follow a negative binomial distribution and times to CV death follow a Lomax distribution (see (8)) (otherwise – e.g. covariates - same as initially described model).

- The analysis will be repeated to include all events up to individual trial completion including the follow-up period (otherwise same as initially described model).

- The analysis will be repeated to include only confirmed HHF which meet the CDISC guidance criteria for hospitalization for heart failure (i.e., confirmed by adjudication committee, but excluding those missing a physical sign or laboratory test, or both).

- The analysis will be repeated to include all events up to cutoff dates prior to COVID-19 outbreak – cutoff (censoring) dates are 30Nov2019 for China and 31Dec2019 for all other countries.

- The analysis will be repeated to include all events up to 7 days prior a reported SARS-CoV-2 infection (based on broad scope SARS-CoV-2 infections)

In case the semi-parametric joint modelling cannot converge numerically with the existing SAS procedures, the parametric joint gamma-frailty model as described above may be used instead for the confirmatory analysis.

The number of HHF events per patients will be summarized descriptively. Additionally a negative binomial model will be fitted to the data of recurrent HHF. This will be done once including only treatment as covariate and once including all covariates as the primary model. Rate ratio and confidence intervals of both models will be reported.

The mean cumulative incidence will be displayed for adjudicated recurrent HHF.

Subgroup analyses will be explored as outlined in Section 6.4 for adjudicated recurrent HHF. For subgroup analyses the term of subgroup (if not already part of the model) and subgroup by treatment will be added to the model of the recurrent event. If the subgroup variable is a categorization of a continuous covariate, this covariate will be dropped from the subgroup model.

eGFR (CKD-EPI)$_{cr}$ slope of change from baseline

Slope in change from baseline of eGFR (CKD-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, sex, geographical region, and status of DM as fixed effects and eGFR (CKD-EPI)$_{cr}$ at baseline (continuous), LVEF (continuous), age (continuous), time and interaction of treatment by time and interaction of eGFR (CKD-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.

A plot of individual patient slopes and separately of individual patient intercepts will be provided per treatment and by eGFR at baseline.

Subgroup analyses as outlined in Section 6.4 will be explored for eGFR slope. The subgroup model will include additionally to the model described above, the subgroup if not already part of the model, subgroup by treatment and subgroup by treatment by time. If the subgroup variable is a categorization of a continuous covariate, this covariate will be dropped from the subgroup model.

7.5.2 Other Secondary endpoints

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

- *Composite renal endpoint: Time to first event of chronic dialysis or renal transplant or sustained* reduction of ≥40% eGFR (CKD-EPI)$_{cr}$ or*
  - *(for patients with eGFR (CKD-EPI)$_{cr}$ ≥30 mL/min/1.73 m^2 at baseline): sustained eGFR <15 mL/min/1.73m^2*
  - *(for patients with eGFR (CKD-EPI)$_{cr}$ <30 mL/min/1.73 m^2 at baseline): sustained eGFR < 10 mL/min/1.73 m^2*

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

Chronic dialysis is regarded as chronic if the frequency of dialysis is twice or more per week for at least 90 days.

- *Time to first adjudicated HHF*
- *Time to adjudicated CV death*
- *Time to all-cause mortality*
- *Time to onset of DM in patients with baseline pre-DM*

All time-to-event endpoints will be reported in days.

The same model and data frame as used in the primary analysis of primary endpoint will be applied to all these time-to-event endpoints. If the endpoint does not include any cause of death, a CIF plot with all-cause mortality as competing risk will be displayed; otherwise, a CIF plot with causes of death not included in the endpoint as competing risk will be displayed. For all-cause mortality a Kaplan-Meier plot will be displayed.

For time to first HHF and time to CV death, the analysis will be repeated based on investigator defined events. In addition, the analysis of time to CV death will be repeated to include all events up to 7 days prior a reported SARS-CoV-2 infection (based on broad scope SARS-CoV-2 infections)

- *Change from baseline in clinical summary score (HF symptoms and physical limitations domains) of the Kansas City cardiomyopathy Questionnaire (KCCQ) at week 52*

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 (MMRM) including LVEF (continuous), age (continuous) and eGFR $(CKD\text{-}EPI)_{cr}$ at baseline (continuous) as linear covariates and, baseline score by visit, visit by treatment, sex, geographical region and status of diabetes at baseline as fixed effects. An additional factor of "week reachable" for the parameter in question, which for each patient is the theoretically reachable planned measurement based on the time of randomisation will adjust for the different planned study times.

All on-treatment data up to week 52 will be included and the analysis will be conducted on the treated set.

A sensitivity analysis will be conducted including data after discontinuation (OC-AD) on the randomized set.

An additional analysis will be performed for the Clinical Summary Score on OC-AD without imputing a worst score for patients who die.

- *Occurrence of all-cause hospitalisation (first and recurrent)*

A similar joint frailty model as well as negative binomial regression model as in the HHF will be analysed for all-cause hospitalization. Instead of CV death, all-cause mortality will be jointly modelled as the terminal events in the joint frailty model.

7.6 FURTHER ENDPOINTS

Time to event endpoints

Further time to event endpoints will generally be analysed in a Cox proportional hazards model similar to the primary analysis on RS. If the endpoint does not include any cause of death, a CIF plot with all-cause mortality as competing risk will be displayed; otherwise, a CIF plot with causes of death not included in the endpoint as competing risk will be displayed.

If there are less than 14 patients with events, then only descriptive statistics will be presented.

Further time to event endpoints are the following:

- Time from first to second adjudicated HHF
- Time to first all-cause hospitalisation
- Time to new onset of atrial fibrillation
- Time to adjudicated MI (fatal or non-fatal)
- Time to adjudicated stroke (fatal or non-fatal)
- Time to adjudicated TIA
- Time to first event of all-cause mortality or all cause hospitalisation
- Time to first event of adjudicated CV death or adjudicated non-fatal MI
- Time to first event of adjudicated CV death or adjudicated non-fatal stroke
- Time to first event of adjudicated CV death, adjudicated non-fatal MI or adjudicated non-fatal stroke (3-point MACE)
- Time to 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
- Time to first event of composite renal endpoint[1] or adjudicated CV death
- Time to first event of composite renal endpoint[1], adjudicated CV death or adjudicated HHF
- Time to first event of composite renal endpoint[1] or all-cause mortality

- Time to first acute kidney injury (based on the preferred term)
- Time to non-cardiovascular (non-CV) death (death cases not included in the definition of adjudicated CV death)
- Time to first investigator defined CV hospitalization

[1]Composite renal endpoint defined as: *chronic dialysis or renal transplant or sustained* reduction of ≥40% eGFR (CKD-EPI)$_{cr}$ or*

- *(for patients with eGFR (CKD-EPI)$_{cr}$ ≥30 mL/min/1.73 m^2 at baseline): sustained eGFR <15 mL/min/1.73m^2*
- *(for patients with eGFR (CKD-EPI)$_{cr}$ <30 mL/min/1.73 m^2 at baseline): sustained eGFR <10 mL/min/1.73 m^2*

Chronic dialysis is regarded as chronic if the frequency of dialysis is twice or more per week for at least 90 days.

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

<u>Continuous endpoints:</u>

The following endpoints will be evaluated by mixed models repeated measures (MMRM) as defined in the protocol.

- HbA_{1c} change from baseline over time (OC-AD on the randomised set and OC-OT on the treated set)
- SBP, DBP change from baseline over time (OC-AD on the randomised set and OC-OT on the treated set)
- Weight change from baseline over time (OC-AD on the randomised set and OC-OT on the treated set)
- NT-pro BNP relative change from baseline over time (OC-AD on the randomised set and OC-OT on the treated set) (value will be transformed to the log scale before MMRM analysis. Estimates obtained from the model will then be back-transformed and reported on the original scale.)
- KCCQ overall summary score change from baseline at week 52 (OC-AD on the randomised set and OC-OT on the treated set) (model will include all timepoints up to week 52)
- KCCQ individual domains change from baseline at week 52 (OC-AD on the randomised set and OC-OT on the treated set) (model will include all timepoints up to week 52)

- KCCQ total symptom score change from baseline at week 52 (OC-AD on the randomised set and OC-OT on the treated set) (model will include all timepoints up to week 52)

- KCCQ based on patient-preferred outcome change from baseline at week 52 (OC-AD on the randomised set and OC-OT on the treated set) (model will include all timepoints up to week 52)

- UACR relative change from baseline over time (OC-AD on the randomised set and OC-OT on the treated set) (value will be transformed to the log scale before MMRM analysis. Estimates obtained from the model will then be back-transformed and reported on the original scale.)

- eGFR $(CKD\text{-}EPI)_{cr}$ change from baseline over time (OC-AD on the randomised set and OC-OT on the treated set)

As outlined in the protocol, the above endpoints will be analysed in a mixed model with repeated measures (MMRM), including age, LVEF and eGFR $(CKD\text{-}EPI)_{cr}$ at baseline as linear covariates and visit by treatment interaction, baseline by visit interaction, geographical region, sex and status of diabetes at baseline as fixed effects. An additional factor of "week reachable" for the parameter in question, which for each patient is the theoretically reachable planned measurement based on the time of randomisation will adjust for the different planned study times.

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

Descriptive statistics will be calculated for the value at visit and change from baseline based on OC-AD on the randomised set and OC-OT on the treated set.

Additionally subgroup analyses will be performed as follows:

HbA_{1c} change from baseline will be evaluated by status of diabetes (non-DM, pre-DM, DM).

NTproBNP change from baseline will be evaluated by baseline atrial fibrillation/atrial flutter (as determined by baseline ECG).

UACR will be evaluated by UACR at baseline (<30 mg/g, ≥30mg/g to ≤300mg/g, >300 mg/g).

In order to evaluate the mean effect on eGFR after approximately 3 years, the above described MMRM models will be used in the following way: a mean effect of the timepoints week 124, 148 and 172 will be calculated. Of the three timepoints, only those with at least 5 patients with a measurement at that timepoint will be included in the average calculation. This will be done for the imputations of OC-OT and OC-AD.

For MMRM subgroup analyses, the interaction term treatment-by-visit will be replaced by a treatment-by-subgroup-by-visit interaction term.

To support analysis of renal function, eGFR throughout the trial will be categorized according to the following CKD staging: All calculations for the staging of renal function will be based

on the originally measured laboratory values, not on normalised values with BI standard reference ranges.

Table 7.6: 1 CKD staging

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

A shift table from baseline to last value on treatment for eGFR $(CKD\text{-}EPI)_{cr}$ will be provided.

In cases where urine albumin values are reported to be below the quantification limits (e.g. <3 mg/L) the albumin / creatinine ratio is determined as missing and will not be replaced by estimated values.

Transitions from baseline to last value on-treatment based on the following UACR categories: normal (<30mg/g), microalbuminuria (30-<=300 mg/g and macroalbuminuria (>300 mg/g) will be presented.

For an evaluation of follow-up after discontinuation of trial medication an additional summary of the NT-proBNP, FG, eGFR, UACR, creatinine and the KCCQ endpoints as above will be produced. This summary will include descriptive statistics for baseline, actual values and change from baseline to last on-treatment value and follow-up, and change from last on-treatment assessment to follow-up. The TS-FU patient set will the basis for this summary, but only those patients with a valid baseline, last value on treatment and follow-up value will be included in all displays. Analyses will be repeated for patients with at least 52 weeks of cumulative exposure (excluding treatment gaps). FG analysis will also be conducted by DM status at baseline (3 categories).

Analyses of change from baseline to LVOT and FU on the TS-FU outlined above will be additionally modelled, separately for LVOT and FU. An analysis of covariance (ANCOVA) model including treatment group, sex, geographical region and status of diabetes at baseline

as fixed effects and baseline eGFR (CKD-EPI)cr (continuous), age (continuous), LVEF (continuous) and baseline of the endpoint (if not already included) as linear covariates will be used.

In addition to the ANCOVA models described above, descriptive statistics will be presented also for creatinine for the value at visit and change from baseline based on OC-AD on the randomised set and OC-OT on the treated set.

In addition to the analyses defined above, KCCQ clinical summary score, clinical symptoms and physical limitations domain will be analysed in two responder analyses (1) defining an increase of 5 points or more from baseline as improvement and (2) defining a reduction of 5 points or more as deterioration.

The frequency and percentage (relative to RS) of patients with improvement as well as the frequency and percentage of patients with deterioration at week 52 will be described. Patients lost to follow-up or who withdrew consent prior week 52 as well as patients who died prior week 52 will be considered as having a deterioration (no improvement) in KCCQ.

Improvement and deterioration will be analysed in separate logistic regression models including treatment, age (continuous), eGFR (CKD-EPI)cr at baseline (continuous), region, sex, baseline LVEF (continuous), status of diabetes at baseline, and baseline value of the KCCQ domain analyzed.

Win ratio:

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 due to CV causes while the patient on empagliflozin was still alive, or if both patients did not die due to CV causes, 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 due to a CV cause while the patient on placebo was still alive, or if both patients did not die due to a CV cause, then if the patient on empagliflozin had more occurrences of HHF, or if the number of occurrences is the same but the time to the first occurrence of HHF is shorter for the empagliflozin patient. 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 (8) 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 (11) .

Other types of further endpoints

For other types of endpoints e.g. occurrence of adjudicated HHF within 30 days after first adjudicated HHF, change in NYHA class at week 52, HCRU and EQ-5D, descriptive statistics will be provided.

For NYHA class a shift table will also be provided for changes from baseline over time and for change from baseline to last value on treatment and last value in study and worst value in study.

The number of patients shifting from normal (no pre-diabetes) to pre-diabetes or diabetes as well as shifts from pre-diabetes to diabetes will be summarized.

Pharmacokinetic analysis

Descriptive statistics of trough concentrations of empagliflozin will be presented for patients, where PK data is available.

7.7 EXTENT OF EXPOSURE

There will be three methods of calculating exposure:

a. First intake to last intake of study drug, including off-treatment periods
b. First intake to last intake of study drug, excluding off-treatment periods
c. Overall observational period (randomisation until end of follow-up for vital status, see censoring for all-cause mortality in Section 6.8.3)

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

Frequency tables of number and percentage of patients belonging to categorical ranges of exposure weeks will be provided as well. Following are the categories of exposure-ranges (in weeks): 0 to <12 weeks, ≥12 to <26 weeks, ≥26 to <52 weeks, ≥52 to <78 weeks, ≥78 to <104 weeks, ≥104 to <156 weeks, ≥156 weeks. Categorical ranges may be adapted based on the actual duration of the study.

7.8 SAFETY ANALYSIS

The safety analysis will be based on the treated set (TS), treatment will be evaluated as randomised.

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

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

7.8.1 Adverse events

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

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

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

For analysis multiple AE occurrence data on the CRF will be collapsed into an AE provided that all of the following applies:

- All AE attributes are identical (including LLT, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest and also additional information of specific AEs or AESIs such as source of sepsis (urinary tract or not) or type of genital infection (fungal balanitis or vulvovaginitis versus other than fungal balinitis or vulvovaginitis)).
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence).

For further details on summarization of AE data, please refer to (2), (12).

7.8.1.1 Assignment of AEs to treatment

The analysis of adverse events will be based on the concept of treatment emergent adverse events. That means that all adverse events occurring between first drug intake till 7 days after last drug intake will be assigned to the randomised treatment. All adverse events occurring before first drug intake will be assigned to ‘pre-treatment’ and all adverse events occurring after last drug intake + 7 days with be assigned to ‘follow-up’.

In Section 15.3 general AE analyses tables will present only on-treatment AEs (applying the rule of 7 days for assignment as on-treatment) for the treatments groups (exceptions for urinary tract malignancies, hepatic events, lower limb amputations and bone fractures as well as adjudicated events see below). When looking at BIcMQs or standardized MedDRA queries (SMQs) and including all AEs up to completion of the trial, the time at risk for each patient will be calculated up to the individual day of trial completion (see Section 6.8).

Appendix 16.1.13.1 will include an analysis (overall summary table, frequency of AEs by system organ class (SOC) / preferred term (PT), frequency of serious adverse events (SAEs) by SOC/PT) where AEs and SAEs are assigned to the following phases: Screening, each treatment group, post-treatment for each treatment group.
The tables presenting frequency of AEs by SOC/PT and frequency of SAEs by SOC/PT will be repeated in Section 16.1.13.1 with treatment-specific post-treatment phase included, hereby also incidence rates for the post-treatment phase will be presented.

For listings, AEs will be assigned to one of the treatment phases of Screening, Placebo, Empa 10, Placebo post-treat, Empa 10 post-treat, post-study.

7.8.1.2 AE summaries

An overall summary of adverse events will be presented.

The frequency of patients with adverse events will be summarised by treatment, primary system organ class and preferred term. Incidence rates as defined in Section 7.8.1.7 will generally be included. AEs will also be reported by intensity (without incidence rates). Separate tables will be provided for patients with adverse events of special interest (AESIs), for patients with serious adverse events, for patients with drug related serious AEs, for patients with fatal events, for patients with AEs leading to discontinuation, and for patients with drug-related AEs.

The frequency of patients with adverse events occurring with incidence in preferred term greater than 2% by treatment will also be presented.

Overall AE summaries, AEs by SOC and PT, SAEs and AEs leading to discontinuation will additionally be investigated by subgroups as outlined in Table 6.4: 1.

Fatal AEs will be summarized up to end of the trial, also separately for those adjudicated as CV and those adjudicated non-CV cause.

The system organ classes will be sorted according to the standard sort order specified by the European Medicines Agency (EMA), preferred terms will be sorted by frequency (within system organ class).

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

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

For further details, see also (13).

7.8.1.3 Adverse events of special interest (AESIs)

Hepatic injury

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

Additionally Hepatic injury AEs will be summarized based on an SMQ based definition. From SMQ Drug related hepatic disorders (20000006) the following narrow sub-SMQs will be used:

- Narrow sub-SMQ Liver related investigations, signs and symptoms (20000008)

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

A table with frequencies of patients with these AEs by treatment, primary SOC and preferred term will be provided. This presentation will be repeated by DM status at baseline (DM vs no DM). Hepatic injury SAEs and hepatic injury AEs leading to disc based on the above SMQ definition will be presented.

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

Patients with hepatic injury will be listed.

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

Decreased renal function

Adverse events reported as AEs of special interest relating to decreased renal function as specified in the protocol will be summarised.

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

This presentation will be repeated by the subgroups as outlined in Table 6.4: 1. SAEs and AEs leading to disc based on the SMQ Acute renal failure (20000003) will be presented.

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

Patients with decreased renal function will be listed.

Ketoacidosis

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

For the narrow BIcMQ diabetic ketoacidosis (DKA), AEs leading to discontinuation and an analysis by sex and diabetes status (type 1 diabetes, type 2 diabetes, pre-diabetes and normal (no pre-diabetes)) will be presented.

For the broad BIcMQ diabetic ketoacidosis (DKA), SAEs will be presented.

For presentations on adjudicated events, refer to Section 7.8.1.5.

Patients with DKA based on the narrow and broad BIcMQ or investigator defined ketoacidosis will be listed.

Events leading to lower limb amputation

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

A separate table for AEs leading to lower limb amputation which are leading to discontinuation will be presented.

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

Lower limb amputations (up to trial completion) will additionally be summarised by renal function, level of first amputation, reason for first amputation, history of PAOD, previous amputation and status of DM at baseline (DM / no-DM).

Patients with lower limb amputation will be listed.

7.8.1.4 Specific AEs

Hypoglycaemic events

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

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

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

Different tables will be shown for (i) patients with investigator defined asymptomatic or symptomatic hypoglycaemia, and (ii) patients with confirmed hypoglycaemic adverse events,

i.e. hypoglycaemic adverse events that had a glucose concentration ≤ 70 mg/dL or required assistance.

Subgroup analyses on confirmed events with respect to age category, sex, race, renal function and diabetes background (type 1 diabetes, type 2 diabetes, pre-diabetes and normal (no pre-diabetes)) will be performed.

Time to the onset of the first confirmed hypoglycaemia will be displayed using a cumulative incidence function.

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

Patients with hypoglycaemic events will be listed.

UTI and genital infections

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

- Genital infections (BIcMQ 'Infections" narrow subsearch "Genital tract infections predisposed to by glucosuria" and investigator assessment)
- UTI (BIcMQ "Infections" narrow subsearch "UTI predisposed by glucosuria" and investigator assessment)

Genital infections episodes based on investigator assessment will additionally be summarised by type (fungal balanitis or fungal vulvovaginitis, genital infection other than fungal balanitis or fungal vulvovaginitis), intensity (mild, moderate or severe), how the event was treated (no treatment, therapy assigned and number of antimicrobials needed to treat) and whether leading to discontinuation of treatment. The number of episodes per patient will also be presented.

UTIs episodes based on investigator assessment will additionally be summarised by intensity (mild, moderate or severe), anatomical location (upper UTI, lower UTI, asymptomatic bacteriuria), occurrence of pyelonephritis or urosepsis, how the event was treated (no treatment, therapy assigned and number of antimicrobials needed to treat) and whether leading to discontinuation of treatment. The number of episodes per patient will also be presented.

For UTIs based on the BIcMQ narrow subsearch the subgroups as outlined in Table 6.4: 1 will be presented. The same will be done for genital infections based on the BIcMQ narrow subsearch. Additionally they will be analysed by presence/absence of history of chronic or recurrent UTI or genital infection respectively.

Complicated urinary tract infections defined as serious adverse events of BIcMQ narrow subsearch 'UTI predisposed by glucosuria', all events of sub-BIcMQ 'Renal infections predisposed by glucosuria', all events of PT Urosepsis will be presented.

Complicated genital infection: defined as all serious events using the BIcMQ narrow subsearch 'Genital tract infections predisposed to by glucosuria' and all event of the narrow

subsearch 'Complicated genital tract infections predisposed to by glucosuria' will also be presented.

UTIs leading to discontinuation based on the BIcMQ narrow subsearch will be presented, the same will be repeated for genital infections leading to discontinuation based on the BIcMQ narrow subsearch .

Cumulative incidence functions will also be created for time to onset of the first UTI and for time to onset of the first genital infections, both based on the respective BIcMQ narrow subsearch .
Patients will UTIs or genital infections will be listed.

Pyelonephritis and sepsis
The following specific adverse event will also be tabulated by treatment group:

- Acute Pyelonephritis (based on investigator assessment): patient incidence overall and by sex
- Pyelonephritis or urosepsis (based on the sub-BIcMQ 'Renal infections predisposed by glucosuria' and the PT 'Urosepsis'): patient incidence overall, by sex and by status of DM at baseline (DM / no-DM)
- Sepsis (based on investigator assessment): patient incidence overall, by source of infection (UTI, not UTI or missing) and by sex and source of infection

Patients with pyelonephritis or sepsis will be listed.

Bone fracture events:

Frequency tables of patients with bone fracture by treatment, primary system organ class (SOC) and preferred term will be provided (based on the narrow BIcMQ 'Bone fractures' and investigator definition). Investigator defined fractures will be reported separately for traumatic and non-traumatic bone fractures.

For bone fractures based on the BIcMQ the subgroups as outlined in Table 6.4: 1 will be presented. Separate tables for bone fractures based on the BIcMQ, which are serious and those which are leading to discontinuation will be presented.

For overall bone fracture based on the BIcMQ in addition to the '7-day-on-treatment approach' all adverse events that occurred between first study drug intake up to trial completion will be presented (following censoring rules like non-fatal outcome events).

Patients with bone fractures will be listed.

Urinary tract malignancies:

Urinary tract cancerogenicity will be shown based on the BIcMQ 'Malignancies' – broad sub-search 14.1 'Urinary bladder and tract malignancies' and broad sub-search 14.2 'Renal malignancies' :

Presentation will be done ordered by HLT.

Frequency tables of patients with urinary tract malignancies by treatment, high level term and preferred term will be provided.

For urinary tract malignancies in addition to the '7-day-on-treatment approach' all adverse events that occurred between first study drug intake up to study end will be presented (following censoring rules like non-fatal outcome events).
There will be an additional analysis including all patients who had a minimum cumulative study drug exposure of 6 months (excluding treatment gaps). All AEs starting from date when 6 months cumulative exposure was reached up to individual day of trial completion will be shown (following censoring rules like non-fatal outcome events).

Patients with urinary tract malignancies will be listed.

Volume depletion

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

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

For volume depletion events the subgroups as outlined in Table 6.4: 1 will be presented. Separate tables for volume depletion events, which are serious and those which are leading to discontinuation will be presented.

Patients with volume depletion will be listed.

A cumulative incidence function will be used to display the time to first volume depletion event.

For the analysis of laboratory data, refer to Section 7.8.2.

Hypotension:

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

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

Additionally hypotension will be presented by treatment, primary system organ class and preferred term. Hypotension is defined as preferred terms of the BIcMQ 'Volume depletion of non-haemorrhagic cause and subsequent hypotension' – narrow sub-search 2 'Volume

depletion and hypotension due to dehydration' (30000090) but excluding terms of the narrow subsearch 1 'Volume depletion due to dehydration'(30000089).

For hypotension events based on the project-defined subsearch the subgroups as outlined in Table 6.4: 1 will be presented.

The presentation of hypotension events based on investigator defined symptomatic hypotension will be repeated to show only events happening in the first 30 days after treatment start.

Separate tables for hypotension (BIcMQ) events, which are serious and those which are leading to discontinuation will be presented.

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

Patients with symptomatic hypotension events will be listed.

Additional subgroup analyses for selected adverse events of special interest or specific adverse events and other safety topics of interest are described in Section 9.7.

7.8.1.5 Events qualifying for external adjudication by the CEC and Hepatic External Adjudication and Adjudication of ketoacidosis

An independent external CEC regularly reviews events and evaluates whether pre-specified criteria for these adjudication endpoints are met. Details on composition of the CEC, responsibilities and clinical event definitions are provided in the separate CEC Charter.

Adjudication assessments will be incorporated into the database.

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

Cardiological/neurological adverse events:
Frequency tables will be provided based on SOC and preferred term for events qualifying for adjudication. This will include all trigger events up to the end of the study.

The number of patients with confirmed events per event type and breakdown of event subtype will be presented. This will be done for all CEC confirmed events up to the end of the study as well as up until completion of the planned treatment phase. Information will be provided for all patients as well as for patients with SARS-CoV-2 infection defined by broad scope SARS-CoV-2 infections. For the analysis in patients with SARS-CoV-2 infection, only events with adjudicated onset date between 7 days prior infection and completion of the planned treatment phase will be shown.

A listing will be provided, that shows the trigger events and result of adjudication.

Hepatic adverse events:
Frequency tables summarizing the relatedness and severity will be provided including all

adjudicated events up to 30 days after treatment stop. A listing will show all trigger events and adjudication results.

Ketoacidosis:
Frequency tables summarizing the adjudication results will be provided including all adjudicated events up to 7 days after treatment stop. A listing will show all trigger events and adjudication results.

7.8.1.6 AEs while patients taking wrong medication

A listing will be provided for AEs that occurred while a patient was taking the wrong medication. Off-drug is not viewed as wrong medication for the listing.

An additional adverse event table that assigns the adverse events to the actual treatment taken will be presented. A patient who took both the assigned treatment and also at least one tablet of the wrong treatment will be counted as at risk in both treatment groups for the relevant time. Off-treatment periods will be counted towards the treatment taken before the off-treatment period for the table. The table will include all adverse events by SOC and PT.

7.8.1.7 Adverse event incidence rates

In addition to the frequency tabulations, time-adjusted adverse event analyses will be performed for all AEs, investigator defined drug-related AEs, AEs leading to discontinuation, serious AEs, and adverse events of special interest by SOC, respectively HLT, and PT.

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

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

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

The standard approach will be x=7 days, but for certain AESIs in addition other approaches will be used.

Total AE-specific time at risk per treatment group is then derived as:
Time at risk (AE) [years] = Sum of time at risk [days] over all patients in a treatment group/ 365.25

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

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

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

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

7.8.1.8 COVID-19 related analyses

The subgroup of patients with SARS-CoV-2 infection will be analysed. SARS-CoV-2 infections will be defined as narrow scope by the BIcMQ SARS-CoV-2 infections. All analyses will be repeated using a broad scope defined as BIcMQ SARS-CoV-2 infections including the preferred term “Suspected Covid-19”.

An overview of adverse events will be presented for this subgroup of patients. Additionally the number of patients with adverse events, the number of serious AEs and AEs leading to discontinuation of study treatment will be presented by treatment, primary system organ class and preferred term. Only adverse events with onset date 7 days prior SARS-CoV-2 infection until the end of the on-treatment period will be included.

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

To assess the reporting of adverse events before and after the start of the COVID-19 outbreak, the number of patients with AEs including incidence rates will be presented for both time periods. The same cutoff dates as defined in Section 7.5.1 will be used.

7.8.2 Laboratory data

Standard safety tables will not include eGFR or creatinine, as those are shown separately as described in Section 7.6.

For continuous safety laboratory parameters standardized and normalized values will be derived as well as the differences to baseline. The process of standardization and normalization as well as standard analyses for safety laboratory data are described in the BI guidance for the Display and Analysis of Laboratory Data (14). All analyses considering multiple of times upper limit of normal (ULN) will be based on original and not normalized data.

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

The analyses of laboratory data will be descriptive in nature and will be based on BI standards [see Data Management and Statistics Manual (DM&SM): Display and Analysis of Laboratory Data (14)].

Baseline for safety laboratory parameters will be the last available measurement before the start of randomised trial medication. Laboratory measurements taken up to 3 days after the last administration of randomised study drug will be considered as on-treatment.
Default settings will be used for repeated values (using worst value).

Laboratory values will be compared to their reference ranges and frequency tables will be provided for the number of patients within and outside the reference range at baseline and the last measurement on treatment. Descriptive statistics will be provided by treatment group for baseline, last value on-treatment and for changes from baseline to last value on treatment. Frequency tables will summarise the number of patients with potentially clinically significant abnormalities as defined for the current XLAB macro.

Only patients with at least one available on-treatment value will be included in the analysis of an individual laboratory parameter. All individual data will be presented in listings.

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

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

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

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

Frequency tables of patients with elevated liver enzymes defined by ALT and/or AST, total bilirubin and AP combinations will be provided. A scatter plot of peak ALT against peak total bilirubin will be presented with reference lines for 3 x ULN ALT and 2 x ULN total bilirubin, including an indicator for treatment received. Details on patients with elevated liver enzymes will be listed.

For the following parameters: uric acid, total cholesterol, HDL-C, LDL-C, triglycerides, haemoglobin and haematocrit the time course of changes will be assessed. The analysis will be performed by applying MMRM models to OC-AD data (on the randomised set) and respectively OC-OT data (on the treated set). The MMRM models, that will be used, are specified in Section 7.6. These analyses will be conducted on data before any normalization.

The parameters LDL-C/HDL-C ratio and non-HDL cholesterol will be evaluated descriptively over time based on OC-AD data (on the randomised set) and OC-OT data (on the treated set). These analyses will be conducted on data before any normalization.

For an evaluation of follow-up after discontinuation of trial medication an additional summary of haemoglobin, haematocrit, uric acid and lipid parameters will be produced. This summary will include descriptive statistics for baseline, actual values and change from

baseline to last on-treatment value and follow-up, and change from last on-treatment assessment to follow-up. The TS-FU patient set will the basis for this summary, but only those patients with a valid baseline, last value on treatment and follow-up value will be included in all displays. Analyses will be repeated for patients with at least 52 weeks of cumulative exposure (exluding treatment gaps).

Analyses of change from baseline to LVOT and FU on the TS-FU outlined above will be additionally modelled, separately for LVOT and FU. An ANCOVA model including treatment group, sex, geographical region and status of diabetes at baseline as fixed effect and baseline eGFR $(CKD\text{-}EPI)_{cr}$ (continuous), age (continuous), LVEF (continuous) and baseline of the endpoint as linear covariates will be used.

7.8.3 Vital signs

An MMRM analysis for heart rate over time will be provided based on OC-AD on the randomised set and OC-OT on the treated set imputations. The model will follow the MMRM analysis described in Section 7.6.

Note that heart rate refers to the eCRF question on pulse rate.

7.8.4 ECG

Clinically relevant abnormalities found at physical examination or ECG at Visit 2 will be considered to have already existed prior to signing of informed consent and therefore should be considered baseline conditions instead of adverse events, unless there is good reason to assume that they first appeared after signing of consent.

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

7.8.5 Others

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

Results of the Modified Rankin Scale will be summarized descriptively.

8. REFERENCES

1	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version
2	*BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED.
3	*001-MCS 36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
4	*BI-KMED-BDS-HTG-0045*: "Reporting of Clinical Trials and Project Summaries", current version; KMED.
5	Beyersmann J, Allignol A, Schumacher M. Competing risks and multistate models with R. New York: Springer 2012 [R16-3839]
6	Collett D. Modelling survival data in medical research. Chapman and Hall/CRC 2003 [R07-4680]
7	Rogers JK, Yaroshinsky A, Pocock SJ, Stokar D, Pogoda J. Analysis of recurrent events with an associated informative dropout time: application of the joint frailty model. Stat Med 2016; 35 (13): 2195 - 2205 [R16-2229]
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9	Li Lu, Chenwei Liu, Analysis of Correlated Recurrent and Terminal Events Data in SAS®. NESUG 2008 [R20-1940]
10	Liu L, Yu Z A likelihood reformulation method in non-normal random effects models. Stat Med 2008; 27 (16): 3105–3124 [R19-4129]
11	Pocock SJ, Ariti CA, Collier TJ, Wang D The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J 2012; 33: 176 - 182 [R16-4813]
12	*BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED.
13	*BI-KMED-BDS-QRG-0010*: “Reference Guide for the preparation of AE, SAE outputs for results disclosure on clinicaltrials.gov and EudraCT (EU-CTR)", current version; KMED.
14	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; KMED.
15	*001-MCS-40-113:* "Clinical Trial Report (CTR) Phase I - IV, Interim Reports and Other Associated Regulatory Documents” , current version; IDEA for CON.

9. ADDITIONAL SECTIONS

9.1 REGIONS AND COUNTRIES

Countries will be assigned to regions following the assignment of the IRT system, which is outlined in Table 9.1:1. Listed countries include currently planned backup countries.

Table 9.1: 1 Regions and countries

Region	Country
Asia	China Japan Korea Singapore
Europe	Belgium Czech Republic Germany Hungary Italy Netherlands Poland Romania Spain UK
Latin America	Argentina Brazil Colombia Mexico
North America	Canada US
Other	Australia India South Africa

9.2 CONCOMITANT MEDICATION

Definitions of medication groups (such as ARBs, diuretics) will be based on World Health Organization Drug Dictionary (WHO DD) and will be stored in the PDMAP.

9.3 DEFINITION OF DM AT BASELINE

Table 9.3: 1 DM at baseline

Diabetes status at baseline	Definition
T1DM	Patients who fulfil one of the following: - investigator-reported medical history of diabetes on the medical history page AND - type of diabetes is T1DM
T2DM	Patients who do not have T1DM but fulfil one of the following: - investigator-reported medical history of diabetes on the medical history page OR - any pre-treatment HbA1c value >= 6.5 OR - stratification via IRT in group of diabetes with either missing assessment of history of diabetes on the medical history page, or no pre-treatment measurement of HbA1c available and investigator reported ‘no’ for the medical history of diabetes

Table 9.3: 1 DM at baseline (cont.)

Diabetes status at baseline	Definition
Pre-DM	Patient who fulfil one of the following: - investigator reported 'no' for the medical history of diabetes on the medical history page AND no pre-treatment HbA1c >=6.5 and a pre-treatment HbA1c value of >=5.7 and <6.5 OR - stratification via IRT in group of pre-diabetes with either o missing assessment of history of diabetes on the medical history page and no pre-treatment HbA1c >=6.5 or o no pre-treatment measurement of HbA1c and investigator reported 'no' for the medical history of diabetes OR - missing assessment of history of diabetes on the medical history page AND all pre-treatment HbA1c <6.5 and a pre-treatment HbA1c value of >=5.7 and <6.5 and stratification via IRT in group of no diabetes
Normal (excluding pre-DM)	Patients not meeting the criteria of DM or pre-DM

9.4 ADDITIONAL SUB-GROUP ANALYSIS FOR REGIONAL SUBMISSIONS

Disposition and demographics of the subpopulation for patients from USA and subgroup analyses for patient from the USA vs non-USA will be included in the appendix of the CTR. Efficacy endpoints evaluated will be primary endpoint, time to cardiovascular (CV) death, time to first HHF, HHF (first and recurrent) and renal slope. Safety will be summarized for patients from the USA.
Additional subgroup analyses will be conducted by region, baseline eGFR (>=90, 60 to <90, 45 to <60, 30 to <45, and <30), and by ethnicity for the same endpoints (primary endpoint, time to cardiovascular (CV) death, time to first HHF, HHF (first and recurrent) and renal slope). For baseline eGFR (5 category) subgroup analysis, the interaction p-value will be calculated using a trend test.

Additional country or region-specific analyses will be conducted for patients from East-Asia (China, Japan and Korea), China, and Japan and included into the country-specific submission documents as also outlined in (15). Primary endpoint, time to cardiovascular (CV) death, time to first HHF, HHF (first and recurrent) and renal slope will be presented. Main adverse event overviews, disposition, demographics will be presented.

9.5 INTERIM ANALYSES

An interim analysis will be conducted by the DMC as outlined in the CTP. If based on the interim analysis it is decided to stop the trial for overwhelming efficacy, this analysis used by the DMC will be considered the primary analysis for the primary endpoint. This analysis will be repeated using the data of the final database lock. All other analyses including analyses of the key secondary endpoints will be conducted on the final database lock to provide most complete available data.

Only events that occurred up to one day prior the predefined interim analysis cut-off date will be considered for the analysis of the primary endpoint as well as CV death at interim. Patients without events up to this time will be censored at the predefined interim analysis cut-off date.

9.6 DETERMINATION OF SAMPLE SIZE

The trial is designed to achieve a power of 90% for a two-sided test with α=0.05 and hazard ratio 0.80. To achieve this at least 841 patients with a primary event are required.

Including the interim analysis with Hwang, Shih and De Cani α-spending function at 60% information with parameter γ = -8 will diminish the power only slightly to 89.98%.

The drop-out rate from the trial is assumed to be very low (<1% per year) and is not considered for determination of sample size.

A 10% yearly event rate in the placebo group is assumed. Assuming an accrual period of 18 months and a follow-up period of 20 months, it was planned to randomise 4126 patients to accrue 841 events.

The event rate and recruitment progress is assessed in a blinded manner during recruitment before any interim unblinding. If the accumulated blinded data suggests a slower accrual of

primary outcome events over calendar time than originally projected, then the number of randomised patients may be increased to a maximum of 6000 patients. 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 confirmed primary outcome events will not be affected by this consideration and will remain 841 events.

While monitoring the event rate in the above described manner, it was planned to include approximately 5750 patients in the trial.

9.7 FURTHER SAFETY ANALYSES

The following analyses will be provided:

PT Fall

Number of patients with fall (PT only) will be presented by baseline LVEF (<50, 50 to <60, >=60).

A cumulative incidence function will be used to display the time to first fall.

The number of patients with fall and concomitant (+/- 7 days) occurrence of volume depletion (narrow BIcMQ), hypotension (narrow BIcMQ), ventricular tachyarrthymia (SMQ) or hypoglycaemia (inv-def. or narrow SMQ) will be presented.

Acute renal failure (defined by narrow SMQ)

In addition to the analyses described in section 7.8.1.3 number of patients with acute renal failure will presented who have concomitant (defined as onset within +/- 7 days respectively +/- 30 days) of onset of volume depletion (narrow BIcMQ), PTs Dehydration or Volume depletion, or symptomatic hypotension (investigator-defined).

In addition to the subgroups as outlined in Table 6.4: 1 the number of patients with acute renal failure will be presented by baseline use of NSAIDs.

The number of patients with acute renal failure within 30 days after on-treatment start of selected medication among those who were not treated with the medication at baseline will be presented for any diuretics, loop or high-ceiling diuretics, ACE-inhibitor, ARB or ARNi, and for NSAIDs.

Ventricular Tachyarrhythmia

The number of patients with ventricular tachyarrhythmia (VT, defined by narrow SMQ Ventricular Tachyarrhythmia) will be presented. VT will also be reported by intensity (without incidence rates). Separate tables will be provided for patients for patients with serious VTs, for patients with drug related VTs, for patients with fatal VTs, for patients with VTs leading to discontinuation and by prevalence of ICD/CRT-D at baseline.

In addition the number of VT episodes per patient based on the SMQ definition and considering only the PT VT only will be presented.

Sepsis

In addition to the analyses described in section 7.8.1.4 investigator defined sepsis with source of infection Non-UTI and separately with missing source of infection will be presented by age (5 cat.), eGFR (5 cat.) and DM Status (2 cat.).

The number of patients with sepsis defined by narrow SMQ "Sepsis" excluding the PT Urosepsis will be presented overall and by age (5 cat.), sex, eGFR (5 cat.) and DM status (2 cat.).

Volume Depletion/Hypotension

Volume depletion and hypotension (both based on BIcMQ) as defined in section 7.8.1.4 will be presented additionally by baseline SBP (<110, 110 – 120, > 120).

Other topics:

For the following safety topics a frequency table by treatment, primary system organ class and preferred term and a subgroup analysis by diabetes status at baseline (2 cat.) will be

presented:

- Allergic skin reactions (defined by BIcMQ 'Skin eruptions', subsearch 1.2 'Allergic skin reactions excl. angioedema and application site reactions'(30000132))
- Increased urination (PT-based defined, stored in PDMAP)
- Thirst (PT-based defined, stored in PDMAP)
- Serum lipids increased (defined by BIcMQ 'Lipid metabolism disorders', subsearch 3 'Hyperlipidaemia' (30000131))
- Angioedema (defined by narrow BIcMQ Angioedema excl. Urticaria (30000130), overall and separately for terms including and excluding the term "urticaria")
- Hypersensitivity reactions (defined by narrow SMQ 'Hypersensitivity' (20000214))

Genital infection

Genital infection as defined in section 7.8.1.4 (narrow BIcMQ) will be presented additionally by sex and DM status (2 cat.).

Hypoglycaemia

Investigator reported confirmed hypoglycaemia (see section section 7.8.1.4 for definition) will be presented by baseline use of sulfonylureas, by baseline use of insulin, by baseline use of sulfonylureas or insulin.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**21-FEB-2017**	[redacted]	None	This is the final TSAP without any modification
Revised	**23-JAN-2020**		4, 6.6.1, 6.8.2, 6.8.3, 7.4.1, 7.4.2, 7.5.1	Exclude FU period from ITT efficacy analyses and add sensitivity analysis including all events for primary endpoint and key secondary endpoint of recurrent HHF.
			4, 7.5.1	Include baseline by time interaction in the slope model
			5.3	Add time to investigator reported CV hospitalization. Definition of CV hospitalisation clarified Fasting plasma glucose was changed to fasting glucose because it was measured in serum and not plasma
			5.4, 6.3, 6.4, 7.6 and where applicable	Clarification of follow-up set, clarification of win ratio to take into account CV death, clarification of definition of atrial fibrillation at baseline vs history of atrial fibrillation, clarification of patient-preferred KCCQ score, other minor clarifications
			6.1, 7.8.1.6	Add analysis of AEs accounting for treatment switchers
			6.2 and where applicable	change important protocol “violations” to “deviations” and other minor wording changes.
			6.2	Clarifications in iPD table
			6.2, 6.3	Changes to IPD D2.02 and TS-FU set to reflect change in CTP with regards to open label SGLT-2 inhibitor use after EOT visit
			6.3, 7.6	Add PK set
			6.4	Adjustment of some subgroup analyses both for safety and for efficacy. Some subgroups added/replaced. Based on recommendation from the Executive Steering Committee, the subgroup analyses specified in the TSAP was reduced to the clinically most meaningful ones.
			6.4, 7.8.1	Update of planned subgroup analyses for safety.
			6.6, 7.5.2	KCCQ-CSS add sensitivity without imputation
			6.6.1	Imputation of missing covariates added.

Table 10: 1 History table (cont.)

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
			6.6.2 and 6.8.2	Clarification of time at risk and missing data imputations
			6.7	Add definition of baseline medication
			6.8.2	Since recurrent event analyses are based on adjudicated event dates and duration of hospital stays is not adjudicated, only the onset dates of the events are considered for the analysis.
			7.1	Modified focussed baseline presentations (e.g. show HbA1c only for patients with DM, show atrial fibrillation also by AF at baseline, include LVEF , do not include height, LDL, HDL)
			7.2	Modified presentation of medication and non-medication therapy as baseline and separately newly introduced after baseline
			7.4	Clarified the primary estimand of the trial
			7.4.2	Additional sensitivity analyses added
			7.4.2	Clarified definition of investigator reported endpoints.
			7.4.4	Section on trend test removed since not applicable due to update on subgroups
			7.5.1	Joint frailty clarification on analysis details
			7.5.1	Clarify that other secondary endpoints are exploratory
			7.5.1	Add individual patient slope and intercept plots by eGFR at baseline.
			7.5.1	Multiple imputation for eGFR slope analysis was removed. Under missing at random assumption, the specified multiple imputation approach is asymptotically equivalent to the maximum likelihood estimate and therefore not required in addition.
			7.5.2	Negative binomial regression model for occurrence of all-cause hospitalisation (first and recurrent) added.
			7.5.2	Modify renal endpoint as per protocol amendment

Table 10: 1 History table (cont.)

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
			7.5.2, 7.6	Specify MMRM in condensed form (do not include individual terms in case already included as interaction terms with visit or treatment) to be in line with BI internal standards on MMRMs. Align wording for MMRM term status of diabetes at baseline as well as factors to be included in MMRMs for the other secondary as well as further endpoints.
			7.6	Responder analyses (improvement and deterioration of 5 points or more from baseline) for KCCQ clinical summary score, clinical symptoms and physical limitations domain was added.
			7.6	Add NTproBNP change from baseline by atrial fibrillation or flutter at baseline
			7.6	Rules defining 'win' and 'lose' for the win ratio calculation were modified.
			7.6	Add analysis to mean change from baseline after approximately 3 years
			7.8.1	Changes in the safety analysis strategy in line with empagliflozin strategy (e.g. look specifically into urinary tract malignancy instead of overall malignancy, delete VTE, deleted other significant AEs, update of BIcMQ definitions, add hypotension)
			9.3	Clarification of diabetes definition
			9.5	Handling of cut-off date for interim analysis clarified.
			9.5	Clarification of primary analysis in case of interim stopping
			9.6	Region and ethnicity subgroup analyses added to regional analyses for US
			Throughout and section 9.6	Include wording from the protocol to the TSAP and clarify sample size
Revised	**12-FEB-2021**	[redacted]	6.2	Clarification on iPD
			6.4, 7.4.4,	Addition of baseline uric acid to subgroups and define trend test for baseline uric acid and baseline LVEF subgroup analyses
			6.8.3, 7.8.1.1	Clarifications with regard to censoring rules
			7, 7.4.2, 7.5.1 7.5.2 7.8.1.5	Addition of sensitivity analyses for COVID-19
			7.8.1.4	Insert word "narrow" for clarification

Table 10: 1 History table (cont.)

			7.8.1.8	Addition of safety analyses for patients with SARS-CoV-2 infection
			9.4	Addition of baseline eGFR (5 categories) subgroup for regional submission
			9.7	Addition of safety analyses to support labelling and special topics of interest