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).

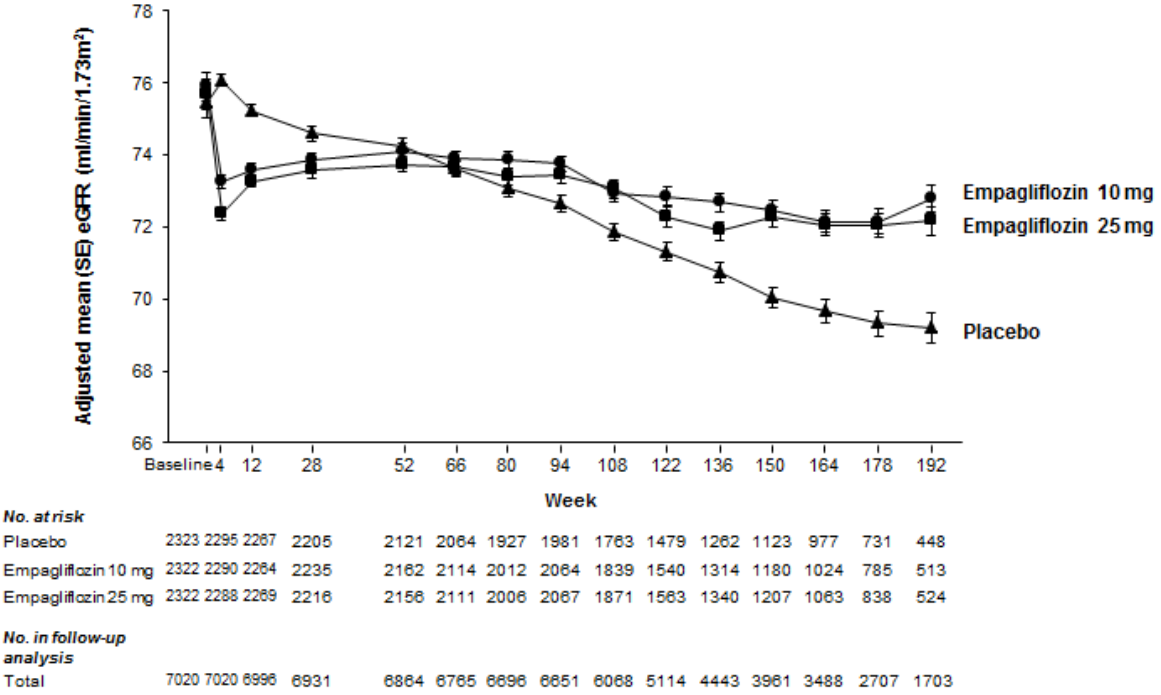

Figure 1.2.3:1 Change in eGFR over192 weeks in the EMPA-REG OUTCOME trial.

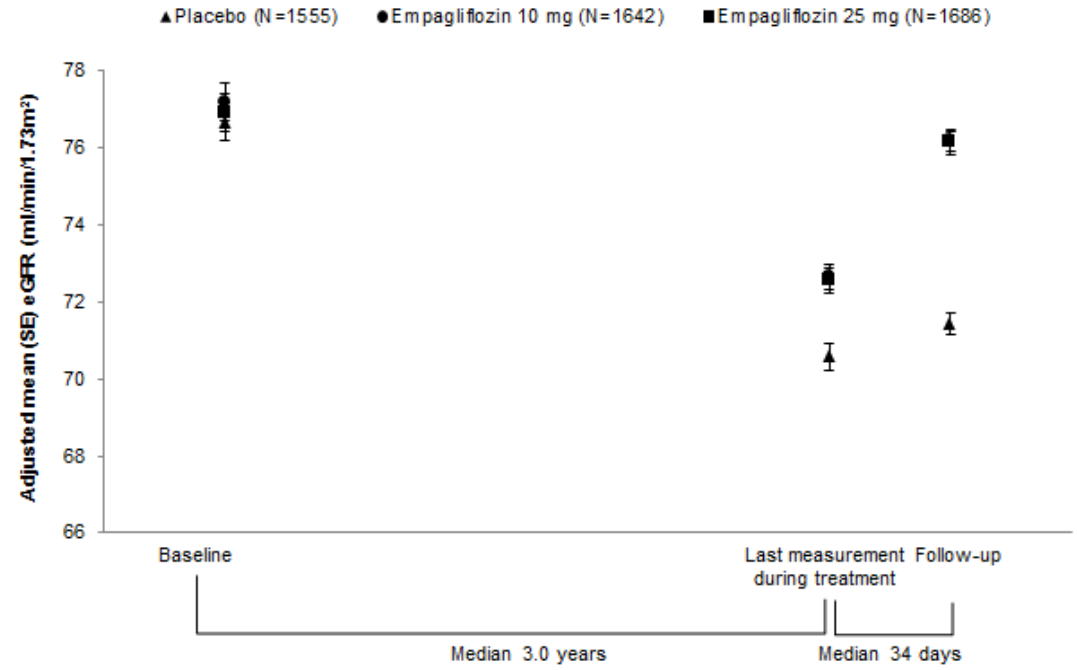

Figure 1.2.3:2 Change in eGFR from baseline to last measurement during treatment and follow-up in the EMPA-REG OUTCOME trial.

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.

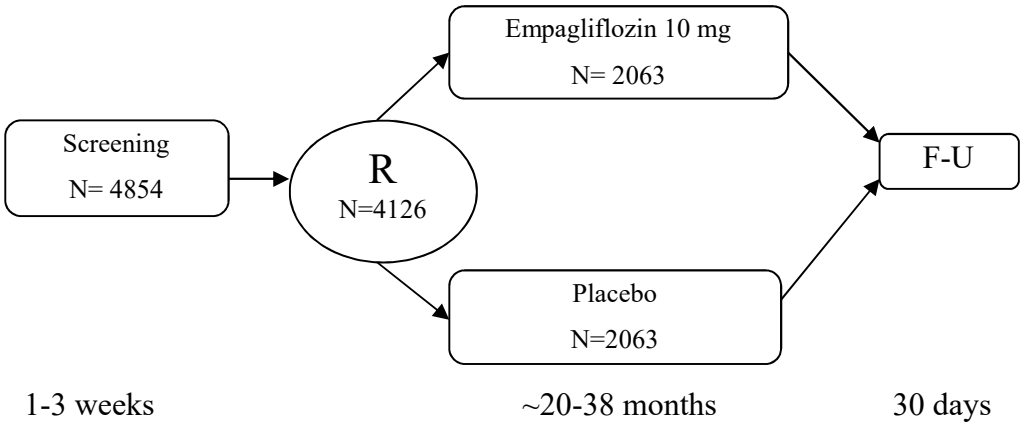

Figure 3.1: 1 Trial design

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.

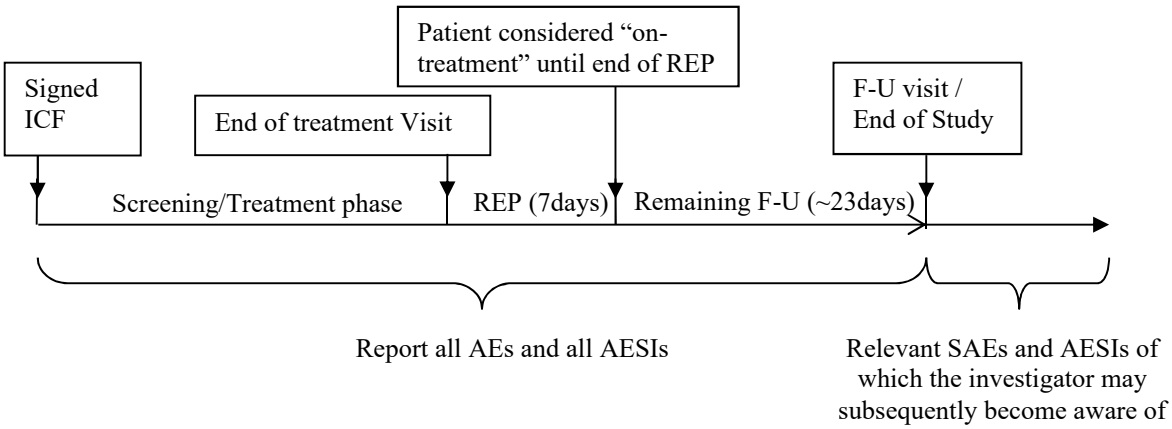

Figure 5.3.7.2: 1 Timelines for adverse event collection

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.

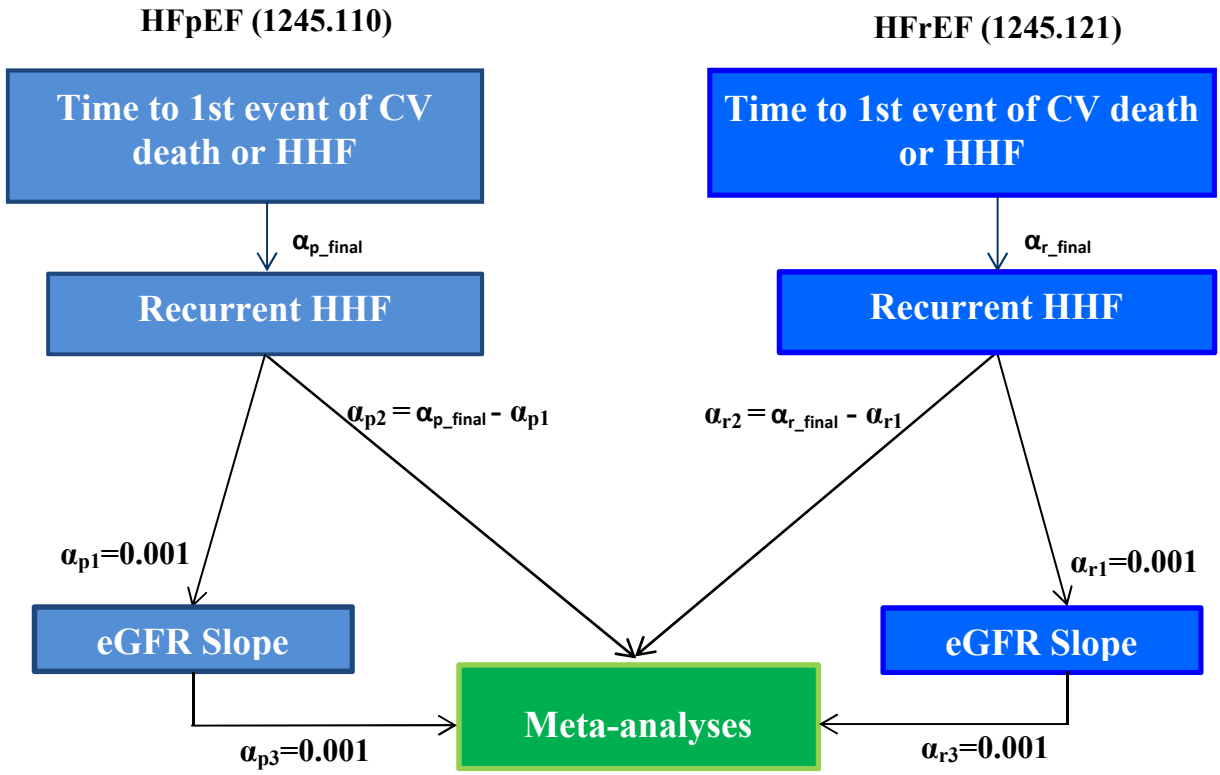

Figure 7.2: 1 Hierarchical analysis of trial in HFpEF (1245.110) and the parallel trial in HFrEF (1245.121) showing the alpha-spending at the final analysis.

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

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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

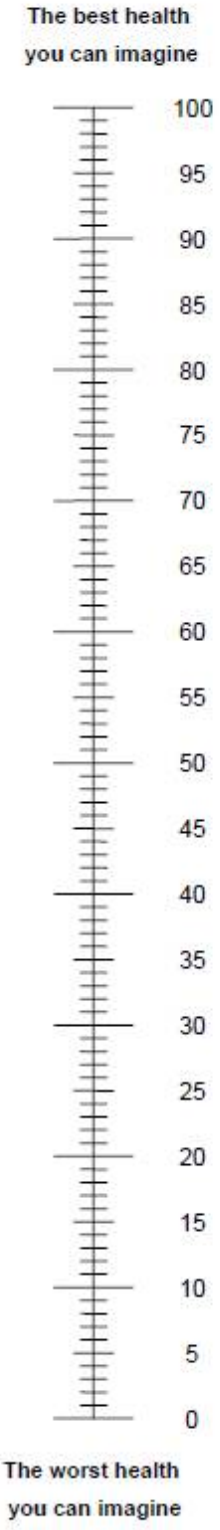
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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

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**

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

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

	· 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.

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**
	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).

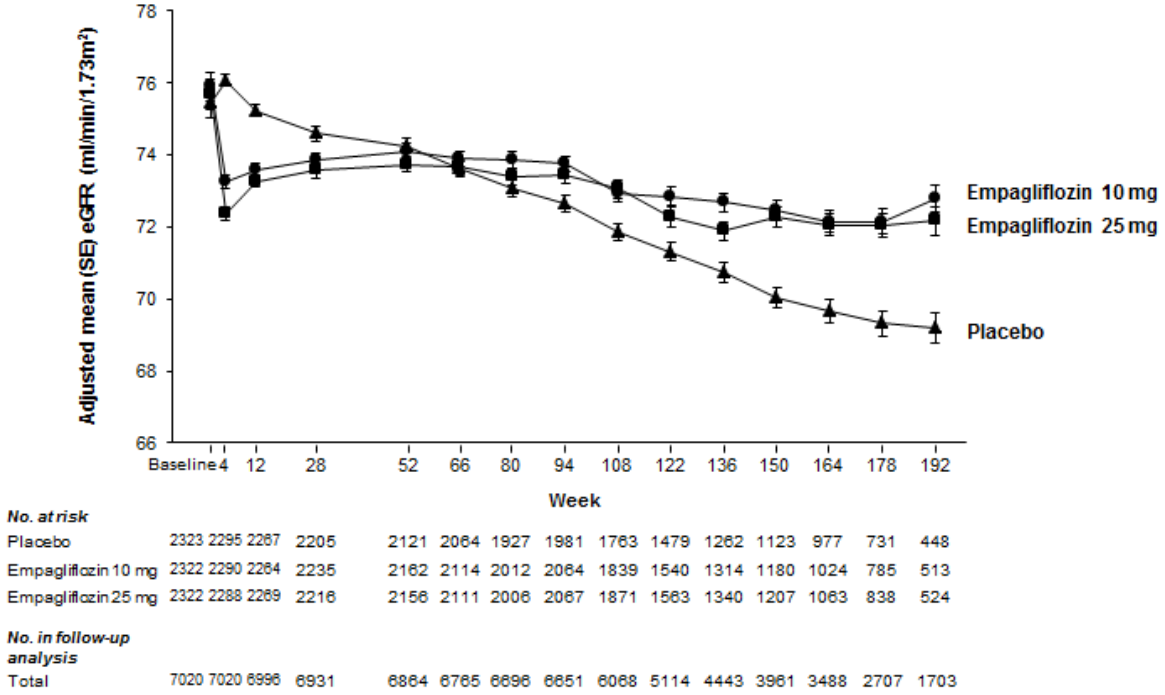

Figure 1.2.3:1 Change in eGFR over192 weeks in the EMPA-REG OUTCOME trial.

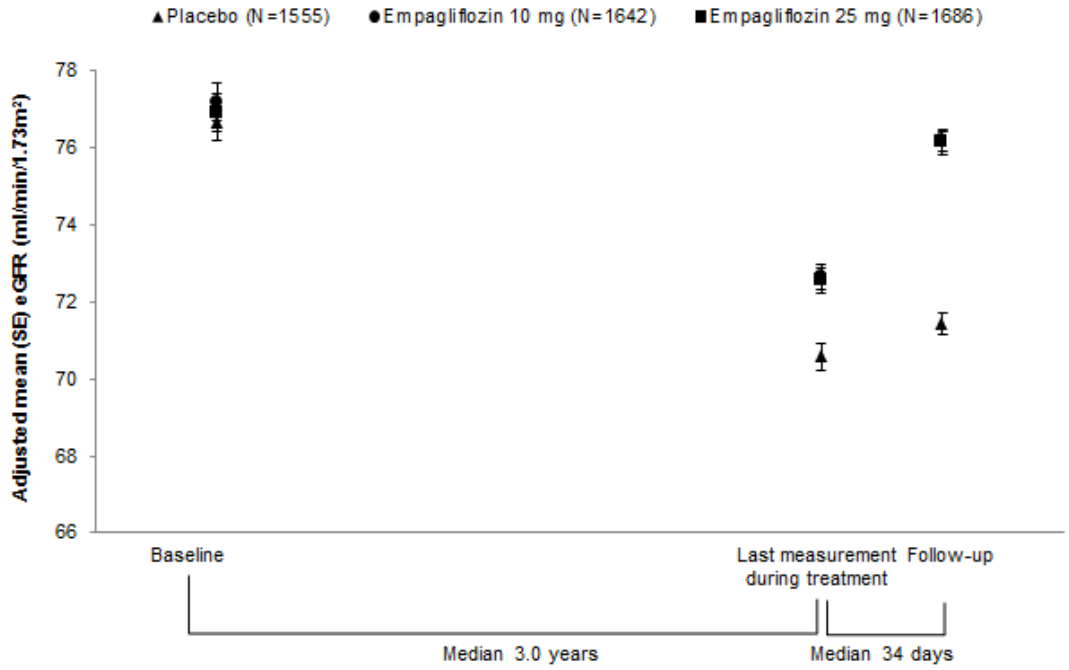

Figure 1.2.3:2 Change in eGFR from baseline to last measurement during treatment and follow-up in the EMPA-REG OUTCOME trial.

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.

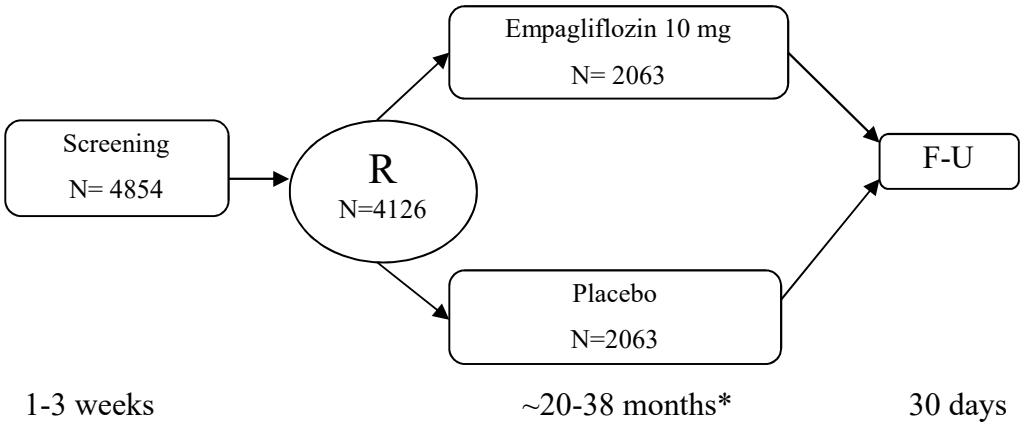

Figure 3.1: 1 Trial design

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.

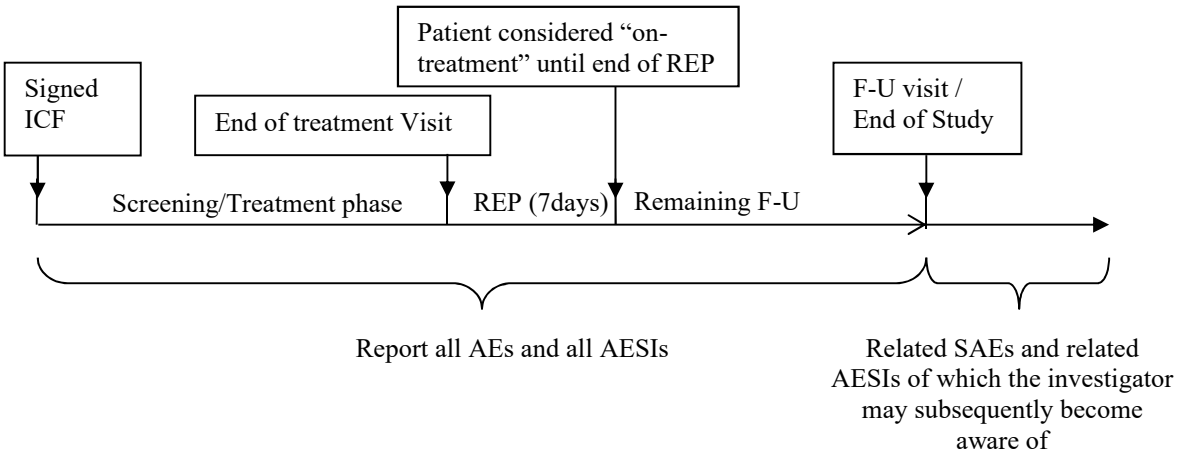

Figure 5.3.7.2: 1 Timelines for adverse event collection

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.

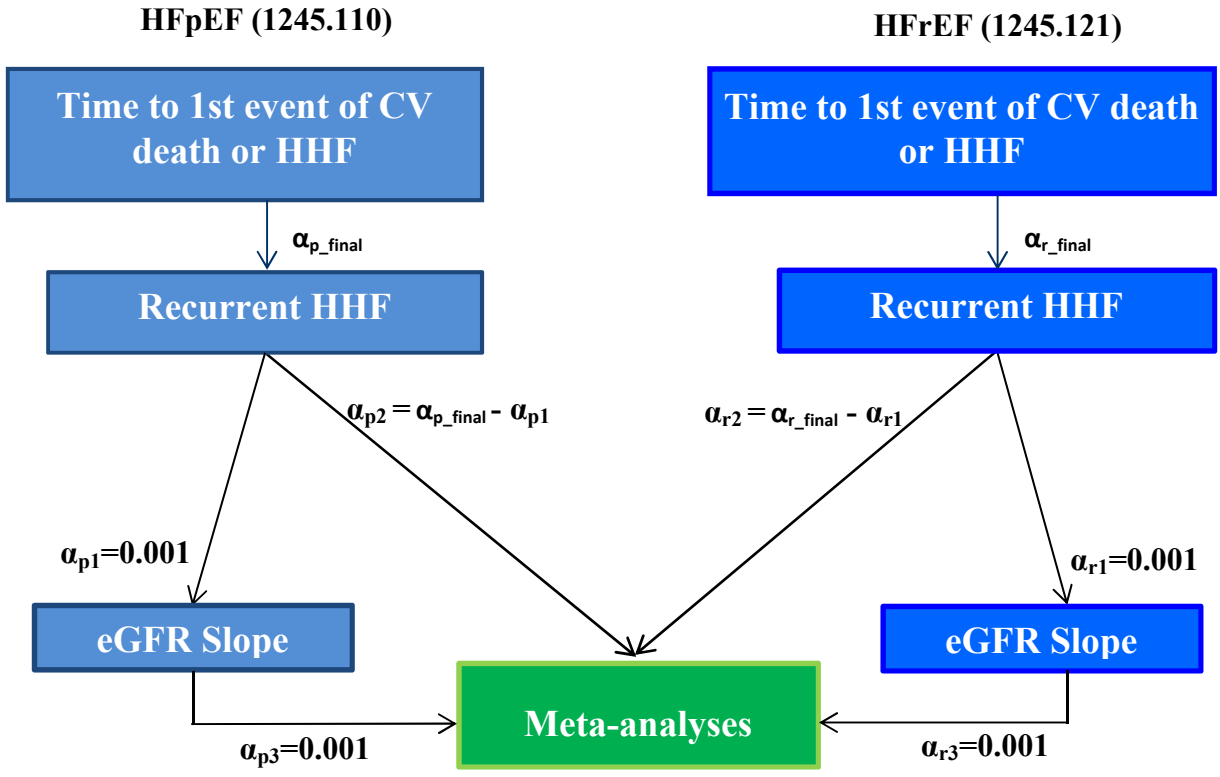

Figure 7.2: 1 Hierarchical analysis of trial in HFpEF (1245.110) and the parallel trial in HFrEF (1245.121) showing the alpha-spending at the final analysis.

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 ❑

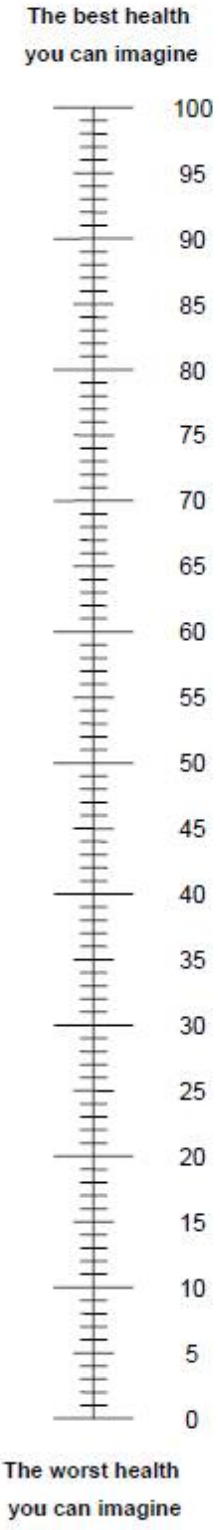
USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*
- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable 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: [redacted]
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
Author-Trial Clinical Pharmacokineticist		21 Nov 2019 20:58 CET
Author-Trial Statistician		22 Nov 2019 09:01 CET
Verification-Paper Signature Completion		25 Nov 2019 22:21 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed