Clinical Trial Protocol

	Document Number:	**c17450485-02**
EudraCT No.: **EU Trial No:**	2017-004072-59	
BI Trial No.:	1245-0167	
BI Investigational Product(s):	Empagliflozin	
Title:	A phase III randomised, double-blind trial to evaluate the effect of 12 weeks treatment of once daily EMPagliflozin 10 mg compared with placebo on ExeRcise ability and heart failure symptoms, In patients with chronic **H**eArt **F**aiLure with **p**reserved **E**jection **F**raction (**HFpEF**) (EMPERIAL – preserved)	
Lay Title:	This study tests empagliflozin in patients with chronic heart failure with preserved ejection fraction (HFpEF). The study looks at how far patients can walk in 6 minutes and at their heart failure symptoms.	
Clinical Phase:	III	
Trial Clinical Monitor:	Phone: ; Fax:	
Coordinating Investigators:	Phone: ; Fax: Phone: , Fax:	
Status:	Final Protocol (Revised protocol based on Global Amendment 1)	
Version and Date:	**Version: 2.0**	**Date: 16 May 2018**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Finished product name	Jardiance
Active ingredient name:	Empaglifozin
Protocol date	10 Nov 2017
Revision date	16 May 2018
Trial number	1245-0167
Title of trial:	A phase III randomised, double-blind trial to evaluate the effect of 12 weeks treatment of once daily EMPagliflozin 10 mg compared with placebo on ExeRcise ability and heart failure symptoms, In patients with chronic **H**eArt **F**aiLure with **p**reserved **E**jection **F**raction (**HFpEF**) (EMPERIAL – preserved)
Principal Investigator < for single-centre trial or > Coordinating Investigator< for multi-centre trial if applicable >:	Phone: ; Fax: Phone: , Fax:
Trial site(s):	Multi-centre trial
Clinical phase:	III
Objective(s):	The primary objective of the study is to evaluate the effect of empagliflozin 10 mg versus placebo on exercise ability using the 6 minute walk test (6MWT) in patients with chronic heart failure (CHF) with preserved ejection fraction (LVEF > 40%). Secondary objectives are to assess Patient-Reported Outcome (PRO).
Methodology:	Randomised, double blind, placebo controlled, parallel group trial.

Number of patients entered:	300
Number of patients on each treatment:	150 (2 treatment groups)
Diagnosis :	Heart failure with preserved ejection fraction (EF)
Main in- and exclusion criteria	Main Inclusion Criteria: • 6MWT distance ≤350 m at screening and at baseline. • Patients with CHF diagnosed for at least 3 months before Visit 1 and currently in NYHA class II-IV • CHF with preserved EF defined as left ventricular ejection fraction (LVEF) > 40 % as per echocardiography at Visit 1 per local reading and no prior measurement of LVEF ≤ 40% under stable conditions. • Elevated NT-proBNP > 300 pg/ml for patients without atrial fibrillation (AF), OR > 600 pg/ml for patients with AF, as analysed at the Central laboratory at Visit 1 • Patients must have at least one of the following evidence of HF: · Structural heart disease (left atrial enlargement and/or left ventricular hypertrophy) documented by echocardiogram at Visit 1, OR · Documented hospitalisation for HF within 12 months prior to Visit 1 • Consistent with prevailing cardiovascular (CV) guidelines, if oral diurectics are prescribed to control symptoms, patients must be on an appropriate and stable dose for at least 2 weeks prior to Visit 1. • Clinically stable at randomization with no signs of heart failure decompensation (as per investigator judgement). Main Exclusion Criteria: • 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 • Acute decompensated HF (exacerbation of CHF) requiring intravenous (i.v.) diuretics, i.v. inotropes or i.v. vasodilators, or left ventricular assist device within 4 weeks to Visit 1, and during screening period until Visit 2

	• Previous or current randomisation in another Empagliflozin Heart Failure trial (i.e. studies 1245.110, 1245.121, 1245-0168) • Type 1 Diabetes Mellitus (T1DM) • Impaired renal function, defined as eGFR < 20 mL/min/1.73 m2 (CKD-EPIcr) or requiring dialysis, as determined at Visit 1 • Symptomatic hypotension and/or a systolic blood pressure (SBP) < 100 mmHg at Visit 1 or 2 • SBP ≥ 180 mmHg at visit 1 or 2, or SBP >160mmHg at both Visit 1 and 2 • Atrial fibrillation or atrial flutter with a resting heart rate > 110 bpm documented by ECG at Visit 1 • Unstable angina pectoris in past 30 days prior to Visit 1 • Largest distance walked in 6 minutes (6MWTD) at baseline < 100m. • Any presence of condition that precludes exercise testing such as: · claudication, · uncontrolled (according to investigator judgement) bradyarrhythmia or tachyarrhythmia, · significant musculoskeletal disease, · primary pulmonary hypertension, · severe obesity (body mass index ≥ 40.0 kg/m^2), · orthopedic conditions that limit the ability to walk (such as arthritis in the leg, knee or hip injuries) · amputation with artificial limb without stable prosthesis function for the past 3 months · Any condition that in the opinion of the investigator would contraindicate the assessment of 6MWT • Patients in a structured (according to Investigator judgement) exercise training program in the 1 month prior to screening or planned to start one during the course of this trial. • ICD implantation within 1 month prior to Visit 1 or planned during the course of the trial • Implanted cardiac resynchronisation therapy (CRT) • Treatment with i.v. iron therapy or erythropoietin (EPO) within 3 months prior to screening.

Test product(s):	Empagliflozin
dose:	10 mg q.d.
mode of administration:	p.o.
Comparator products:	Placebo
dose:	Not applicable
mode of administration:	p.o.
Duration of treatment:	12 weeks
Endpoints	Primary Endpoints: • Change from baseline to week 12 in exercise capacity as measured by the distance walked in 6 minutes Key Secondary Endpoints: • Change from baseline to week 12 in Kansas City Cardiomyopathy Questionnaire (KCCQ) Total Symptom Score (TSS) • Change from baseline to week 12 in Chronic Heart Failure Questionnaire Self-Administered Standardized format (CHQ-SAS) dyspnea score Other Secondary Endpoints: • Change from baseline to week 6 in exercise capacity as measured by the distance walked in 6 minutes • Change from baseline in Clinical Congestion Score at week 12. • Change from baseline in Patient Global Impression of Severity (PGI-S) of Heart Failure Symptoms at week 12. • Change from baseline in Patient Global Impression of Dyspnea Severity at week 12. • Patient Global Impression of Change (PGI-C) in Heart Failure Symptoms at week 12. • Patient Global Impression of Change in Dyspnea at week 12. • Change from baseline in N-terminal pro-brain natriuretic peptide (NT-proBNP) at week 12
Safety criteria:	• Adverse events (AE) • Serious adverse events (SAE) • AE of special interest (AESI) (hepatic injury, decreased renal function and ketoacidosis) • 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 • Heart rate and blood pressure in conjunction with exercise

	testing • ECG findings at scheduled visits reported as AEs
Statistical methods:	The primary model will be a Wilcoxon rank test on change from baseline to week 12 in 6MWT. The primary model will be conducted on all randomized patients. Both key secondary endpoints will be tested using a Wilcoxon rank test, and both will be tested if the primary endpoint revealed a significant result in favour of empagliflozin. For adjustment of multiplicity of the two key secondary endpoints a Hochberg procedure will be followed. The other secondary endpoints will not be part of the testing hierarchy. Change from baseline to week 6 in exercise capacity as measured by the distance walked in 6 minutes will be evaluated using the same model as for the primary endpoint Change from baseline to week 12 of Clinical Congestion Score will be evaluated using a mixed model repeated measure analysis over time. The model will include the factor treatment and the linear covariate of baseline Clinical Congestion Score. Proportion of patients in every category of global impression of change at week 12 will be evaluated using Cochran-Mantel-Haenszel test. Proportions of patients categorized by the shift in scores between baseline and week 12 in patient global impression of severity score will be evaluated using Cochran-Mantel-Haenszel test. The endpoint “Change from baseline in NT-proBNP at week 12” (after log-transformation) will be evaluated using a mixed model repeated measure analysis over time with baseline log-transformed NT-proBNP as a covariate without imputation of missing values.

FLOW CHART

Trial Period	**Screening***	**Randomized Treatment Period**				**FU Period**
Visit	**1**	**2**	**3**	**4 (EOT)**	**Early Discontinuation Visit[11]**	**FU Visit**
Trial week	**-3**	**1**	**6**	**12**		**EOT/early d/c + 7 days**
Days of treatment	**-21 to -4**	**1**	**43**	**85**		
Time Window	**-**	**-**	**±7**	**±7**		**+7**
Informed consent	X					
In/exclusion criteria	X	X				
Demographics	X					
Medical history/Concomitant diagnoses	X					
Vital signs[1]	X	X	X	X	X	X
Physical examination	X	X		X	X	
Height	X					
Weight	X	X		X	X	
Urine Pregnancy test[2]	X	X	X	X	X	
HbA1c		X		X	X	
eGFR (CKD-EPIcr formula)	X*	X	X	X	X	X
Safety lab: blood tests	X*[,3]	X	X[4]	X	X	X
Safety lab: urinalysis including ketones	X*	X	X	X	X	X
ECG exam[5]	X			X	X	
Echocardiogram[6]	X					
NT-proBNP	X*	X	X	X	X	
6 min walk test[7]	X[8]	X[9]	X	X[9]	X	
Concomitant therapy	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
KCCQ[10]		X	X	X	X	
CHQ-SAS[10]		X	X	X	X	
Clinical Congestion Score		X	X	X	X	
Patient Global Impression of Severity of Heart Failure Symptoms[10]		X	X	X	X	
Patient Global Impression of Severity of Dyspnea[10]		X	X	X	X	

Trial Period	**Screening***	**Randomized Treatment Period**				**FU Period**
Visit	**1**	**2**	**3**	**4 (EOT)**	**Early Discontinuation Visit[11]**	**FU Visit**
Trial week	**-3**	**1**	**6**	**12**		**EOT/early d/c + 7 days**
Days of treatment	**-21 to -4**	**1**	**43**	**85**		
Time Window	**-**	**-**	**±7**	**±7**		**+7**
Patient Global Impression of Change in Heart Failure Symptoms[10]			X	X	X	
Patient Global Impression of Change in Dyspnea[10]			X	X	X	
Clinician Global Impression of Severity of CHF		X	X	X	X	
Clinician Global Impression of Change in CHF Severity			X	X	X	
NYHA Classification	X	X	X	X	X	
HCRU		X	X	X	X	
Randomization (IRT)		X				
Dispense trial medication		X	X			
Return medication / Medication compliance check			X	X	X	

* The screening procedures can be performed on different days within the time window. Specifically, it is recommended to have the NT-proBNP and safety lab measures (via central lab) measured as first step, especially in patients with no previous natriuretic peptide value available from clinical routine assessment in the past 6 months (refer to section 6.2.1).

1. Blood pressure and heart rate will be measured with the patient seated and rested for at least 5 minutes.
2. For female patients of child-bearing potential, local urine pregnancy test should be performed.
3. For the screening Visit 1, the safety laboratory is limited to liver transaminases, alkaline phosphatase, haemoglobin, serum creatinine, eGFR calculation. Patients do not have to be fasting.
4. For Visit 3, the safety laboratory is limited to liver transaminases, bilirubin and serum creatinine, eGFR calculation
5. A 12-lead ECG will be performed at screening and EOT visits. For this 12-lead ECG, the interpretation of the tracing must be made locally by the investigator or designee. In case of any cardiac symptom (indicating rhythm disorders or cardiac ischaemia), additional 12-lead ECG(s) should be done and any abnormal findings will be reported as AEs.
6. An echocardiogram should be performed on all patients at Visit 1 to assess left ventricular ejection fraction (LVEF) for eligibility.

7. 6MWT to be performed by qualified and experienced personnel. The assessments should be performed by the same qualified and experienced personnel at all visits, where possible. Testing of the 6MWT at each clinic visit should be preferably performed about the same time of day to minimize intraday variability. Prior to performing the 6MWT, the relative contraindications to exercise should be assessed as per appendix 10.1.3. Heart rate and blood pressure will be measured before exercise, at end-exercise, five minutes after termination of exercise and when, for clinical reasons, it is required.
8. One 6 minute walk test (6MWT) will be performed at the screening visit. The 6MWT will be performed after vital signs have been captured and prior to any other study procedures at this visit. If the distance walked is > 350m the patient will be considered a screen failure.
9. Two 6 minute walk tests will be performed at visits 2 and 4 at least 1 hour apart. The largest distance measured will be used for the analysis. If at Visit 2 the distance walked on any test is > 350m or the largest distance walked is < 100m the patient will be considered a screen failure.
10. For the order of completion of patient reported outcome measures please refer to section 6.2.2.
11. Patients who prematurely discontinue from trial medication will be required to return to the study site as soon as possible after treatment discontinuation for the early discontinuation visit and the follow up visit. In addition, the patient should return to clinic for their regularly scheduled week 12 study visit as outlined in section 3.3.4.1.

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ABBREVIATIONS

6MWT	Six Minute Walk Test
6MWTD	Distance walked in six minutes
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine-Aminotransferase
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor-Neprilysin Inhibitor
AST	Aspertate-Aminotransaminase
BI	Boehringer Ingelheim
BMI	Body Mass Index
CA	Competent Authority
CEC	Clinical Event Committee
CHF	Chronic Heart Failure
CHQ	Chronic Heart Failure Questionnaire
CHQ-SAS	Chronic Heart Failure Questionnaire – Self-Administered Standardized format
CK	Creatine Kinase
CKD-EPIcr	Chronic Kidney Disease Epidemiology Collaboration Equation
CML	Clinical Monitor Local
CPET	Cardiopulmonary Exercise Testing
CRA	Clinical Research Associate
CRF	Case Report Form, electronic
CRO	Contract Research Organization
CRT	Cardiac Resynchronization 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
DOMS	Delayed Onset Muscular Soreness
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
EMPA-REG	Empaglifozin – Reducing Excess Glucose
EOT	End of Trial
EPO	Erythropoietin
EU	European Union

EudraCT	European Clinical Trials Database
ExC	Executive Committee
FC	Flow Chart
FDA	US Food and Drug Administration
FEV1	Forced Expiratory Volume at 1 Second
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HA	Health Authority
HCRU	Health Care Resource Utilisation
HDL	High Density Lipoprotein
HF	Heart Failure
HFmrEF	Heart Failure with mid-range Ejection Fraction
HfpEF	Heart Failure with Preserved Ejection Fraction
HfrEF	Heart Failure with Reduced Ejection Fraction
HHF	Hospitalization for Heart Failure
i.v.	intravenous
IB	Investigator's Brochure
ICD	Implantable Cardioverter Defibrillator
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ITT	Intention to Treat
JVD	Jugular Venous Distension
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-CSS	Kansas City Cardiomyopathy Questionnaire - Clinical Summary Score
KCCQ-TSS	Kansas City Cardiomyopathy Questionnaire - Total Symptom Score
LA	Left Atrium
LDL	Low-Density Lipoprotein
LPDD	Last Patient Drug Discontinuation
LV	Left Ventricle
LVEF	Left Ventriclar Ejection Fraction
LVMI	Left Ventricle Mass Index
MACE	Major Adverse Cardiovascular Events
MedDRA	Medical Dictionary for Drug Regulatory Activities
MI	Myocardial infarction
MMRM	Mixed Model Repeated Measure
MOA	Mode of Action
MRA	Mineralcorticoid Receptor Antagonist
MRI	Magnetic Resonance Imaging
NT-proBNP	N-Terminal Pro-Brain Natriuretic Peptide
NYHA	New York Heart Association
OPU	Operative Unit
p.o.	per os (oral)

PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PRO	Patient Reported Outcome
PROM	Patient Reported Outcome Measures
q.d.	quaque die (once a day)
QoL	Quality of Life
RA	Regulatory Authority
RS	Randomised Set
REP	Residual Effect Period
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SC	Steering Committee
SD	Standard Deviation
SGLT-1	Sodium Glucose Co-Transporter 1
SGLT-2	Sodium Glucose Co-Transporter 2
SMQ	Standardised MedDRA Query
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reactions
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TCM	Trial Clinical Monitor
TIA	Transient Ischemic Attack
TMF	Trial Master File
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper Limit of Normal
UTI	Urinary Tract Infections
VAS	Visual Analogue Scale
VO_2	Volume of Oxygen - oxygen consumption
WHO	World Health Organization
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Chronic heart failure (CHF) 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. Heart Failure (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]. HF is the most common cause of hospitalisation among individuals above 65 years of age in the Western countries [P16-03760].

Two main types of HF have been defined mainly based on the left ventricle (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]. European Society of Cardiology in their 2016 guideline introduced a third type of heart failure with LVEF ranging between 40-49% named heart failure with mid-range ejection fraction (HFmrEF). The exact characteristics of these patients, response to therapy, or prognosis is yet to be determined. In current empagliflozin exercise capacity trials patients with HFmrEF is covered under HFpEF protocol. It should be noted that the current trial and the companion trial in HFpEF patients will allow participation of the full spectrum of HF patients with reduced, mid-range, or preserved EF. 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 readmission rate among patients with HFrEF is close to 29% within 60-90 days post discharge which is equal to HFpEF [R16-1527]. After HHF, the one year mortality rate is high and essentially not different between patients with preserved or reduced LVEF [R16-2217], underscoring a high unmet medical need in this population.

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 treatment of HFrEF still appears suboptimal as evidenced by the high mortality rate (6-7% / year) and high hospitalization and readmission for heart failure (9-10% / year) hospitalization and up to 30% readmissions within 90 days post discharge. For HFpEF, however, no specific therapy exists and therefore control of congestive symptoms during acute episodes is the mainstay of management of these patients. No class of drugs have shown to increase survival or reduce hospitalizations for HFpEF [P16-03760, P16-05920, R17-1584; R17-0953; R16-1527].

About 25 to 45% of patients with HF have concomitant type 2 diabetes mellitus (T2DM), and nearly 15-25% has borderline diabetes (pre-diabetes), indicating a potential link between

heart failure and glucometabolic disturbances [R16-2382, R16-2384].

Empagliflozin is an orally available inhibitor of the renal dependent sodium 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 cardiovascular (CV) risk factors (e.g. uric acid, visceral fat mass, albuminuria) [P15-00589, P15-09541].

In 2010 Boehringer Ingelheim (BI) initiated the EMPA-REG (Empaglifozin – Reducing Excess Glucose) OUTCOME trial to explore CV benefit of the drug as well as to establish the safety profile of empagliflozin [P15-09840].

This trial was completed in 2015 and showed that 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" by 34% and HHF by 35%.

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 reduction in CV death, HHF, and composite of "HHF or CV death" [P16-01253].

Currently, two large clinical outcome trials are ongoing in patients with HFpEF (EMPEROR-preserved) or HFrEF (EMPEROR-reduced) to evaluate the effect of empaglifozin for the reduction of cardiovascular death and heart failure hospitalization

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 urinary sodium excretion returns to normal within few days of empagliflozin administration, the effect on urinary glucose continues for as long as the medication is used.

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) [c01678844-09] and local prescribing information for empagliflozin.

1.3 RATIONALE FOR PERFORMING THE TRIAL

In addition to impacting cardiovascular outcomes (death and hospitalization), HF also leads to a substantial reduction in quality of life (QoL) and a high symptom burden on a daily basis due to limitation of physical activity [increasingly from New York Heart Association (NYHA) Class I to IV].

Therefore, improving heart failure symptoms and assessing the activity of daily living such as exercise ability continues to be an unmet medical need in HF patients [R17-1588].

Some HF medications (e.g. Digoxin, Beta blocker, Spironolactone) demonstrated discordant results in exercise ability test versus mortality and morbidity outcomes [R17-1587]. Empagliflozin, by inhibiting SGLT2 transporter in kidneys, induces glucosuria and natriuresis through the decreased reabsorption of glucose and sodium and consequent osmotic diuresis, [P13-16965]. The glucosuric effect of empagliflozin is persistent for as long as the medications is used [P16-01830]. This is important as in case of other diuretics such as thiazide or loop diuretics, natriuresis may be compensated within days of drug administration through changes in tubulo-glomerular feedback resulting in reduced efficacy. Also, no clinically significant change in serum Na^+ or K^+ was observed with empagliflozin as shown in the EMPA-REG-OUTCOME trial [P15-09840], while these changes are common with loop or thiazide diuretics (hypokalemia), with MRAs (hyperkalemia), or with vasopressin antagonists / vaptans (hypernatremia).

For empagliflozin, the mode of action (MOA) suggests a potential for improving of exercise capacity tests and patients` symptoms:

- The glucosuria mediated osmotic diuresis, is thought to result in long-lasting hemodynamic changes associated with modest osmotic diuresis, less extracellular volume, increase of hemoglobin (hemoconcentration), shift in fuel supply from glucose to fat oxidation and towards more energy-efficient ketones, possible reduction of vascular wall stress, decrease ventricular load and improving cardiac function as well as improving symptom and functional capacity [P15-00589; P15-09541]. While empagliflozin lowers blood pressure, this change is not associated with an increase in heart rate unlike what has been observed for vasodilators [P14-01668].
- The described effects start as early as with the first dose of empagliflozin taken or within the first few weeks of its administrations [P16-01830], which would be in line with the observed early effects on reduction in HHF as shown in the EMPA-REG OUTCOME trial. See figure 1.3:1.

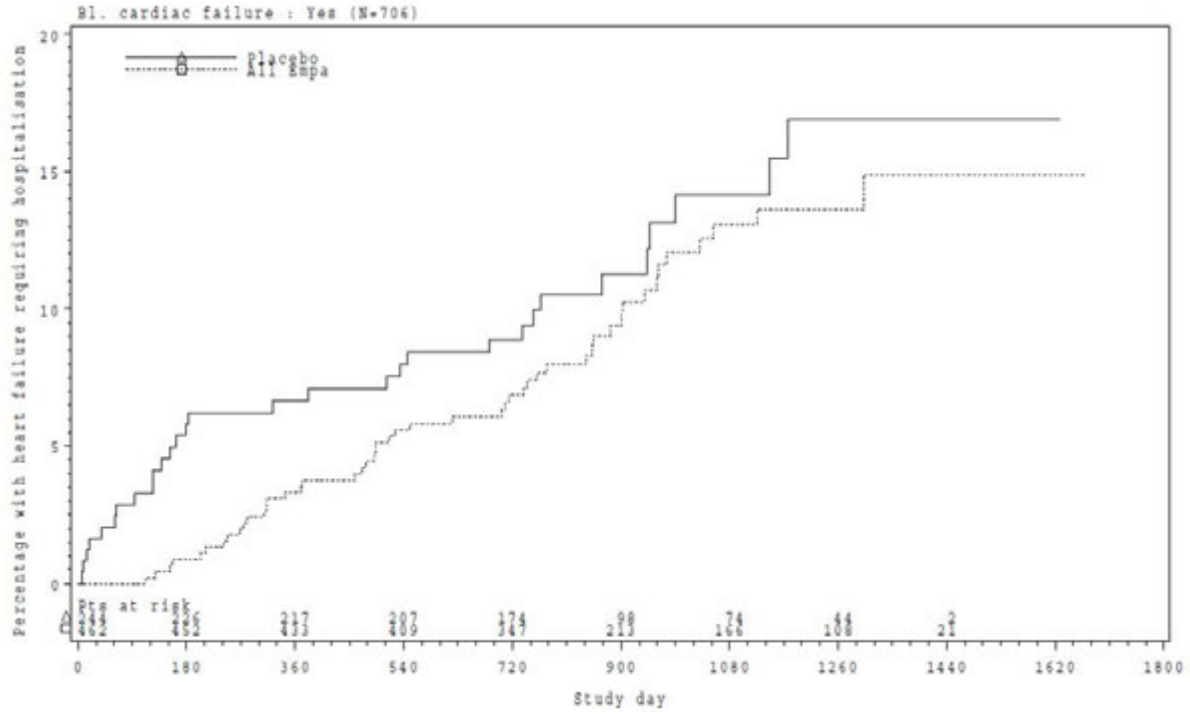

Figure 1.3:1 Kaplan-Meier estimates of time to first heart failure requiring hospitalization in patients with baseline cardiac failure [narrow standardized MedDRA query (SMQ)], pooled empagliflozin doses versus placebo-treated set. X-axis: study day [c02695839-01].

- Patients with HFpEF are thought to benefit from combined beneficial effects of empagliflozin (see above). This benefit is expected based on the increased prevalence of obesity, hypertension, and anemia in patients with HFpEF [R17-1562], as these concomitant conditions may affect heart failure (obesity: increased peripheral resistance; hypertension: increased cardiac workload and oxygen consumption; anemia: reduced cardiac oxygen supply). Due to the combination of positive effects, empagliflozin is expected to address the unmet medical need of improving exercise ability in this patient population.

- Although HFpEF and HFrEF are considered as different disease entities, patients with HFrEF are thought to profit from the same combined effects of empagliflozin, with potentially different weighing of the individual beneficial effects. In HFrEF, reducing congestion by osmodiuresis is considered as a prominent beneficial effect that may contribute to improved exercise ability.

Taken together, it is anticipated that empagliflozin will show effects on exercise ability and mortality & morbidity in both HF subpopulations and supports the scientific rationale of performing this trial to explore the effect of empagliflozin on exercise ability in patients with HFpEF.

1.4 BENEFIT - RISK ASSESSMENT

The overall benefits and safety 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.

It has been shown in healthy volunteers dosing with empagliflozin results in glycosuria summing up to about 2/3 the average glucosuria in patients with T2DM. This is similar to the amount of glucose lost in T2DM subjects with moderate renal impairment. Because in the EMPA REG Outcome study no difference in CV benefit was detected for patients with renal impairment vs. the overall population, it is hypothesized that this amount of glucosuria is not the main factor for obtaining 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 occurrence of symptomatic hypoglycaemia was detected [U12-2707-01]. It is noted that in patients with T2DM, the risk of hypoglycaemia was only increased with empagliflozin compared to the placebo group in patients who were concomitantly treated with insulin or a sulfonylurea. Further, in a mechanistic study [c11963611-01], subjects without Diabetes Mellitus (DM) were shown to increase endogenous glucose production in response to glucosuria after administration with empagliflozin. As a result, blood glucose levels remained in the normal range for these individuals [P16-01830]. Therefore it seems scientifically reasonable to hypothesize that in non-diabetic patients, with no medical indication for insulin or sulfonylurea treatment the risk of hypoglycaemia associated with empagliflozin treatment would be lower than in patients with T2DM.

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

There is also currently limited therapeutic experience with empagliflozin in patient aged 85 years and older. The prevalence of chronic heart failure increases with age and the therapeutic options in the elderly above 85 years are limited. The inclusion of this population in the clinical trial setting will help support the assessment of benefit-risk of empagliflozin for patients over 85 years. Special caution should be used in these patients, who may be at increased risk of adverse consequences attributed to empagliflozin related volume depletion.

Many patients with CHF have renal impairment, and to ensure that the trial results reflect this population, patients with estimated glomerular filtration rate (eGFR) ≥ 20 ml/min/1.73m^2 can be included. In the EMPA-REG Outcome trial, the cardiovascular benefits for empagliflozin were not driven by its pharmacological effect of lowering blood glucose and were

consistently noted in patients with different degrees of renal impairment, including patients with eGFR between > 30 and < 45 ml/min/1.73m^2. In previous trials in patients with T2DM, the safety profile in moderate and severe renal impairment was comparable to the overall trial population [P17-10453]. Renal safety will be closely monitored throughout the trial. Refer to section 5.2.4.1 and 5.2.7.1.

The overall tolerability and safety profile as outlined in section 1.2, and the current Investigator's Brochure (IB), supports chronic safe administration of empagliflozin 10 mg in human studies.

Potential benefits:

Patients with HF are thought to benefit from combined beneficial effects of empagliflozin such as persistent osmodiuresis, reduction in blood pressure, weight loss, increase in hematocrit, and changes in cardiometabolic parameters as early as the first few weeks of empagliflozin administrations. Due to the combination of positive effects, empagliflozin is expected to address the unmet medical need of improving exercise ability in this patient population. The details of the potential benfits of empagliflozin in addressing short-term symptoms and exercise ability of patients wih HFpEF was discussed in section 1.3.

Lack of correlation between blood glucose lowering effects and CV outcome improvement in EMPA-REG-OUTCOME [P15-09840] as well as a mechanistic study in non diabetic subjects [P16-01830] provide supporting evidence that the benefit of empaglifozin in treating HF patients should also be expected in patients without diabetes.

Due to the combination of several positive effects, empagliflozin is expected to address the unmet medical need of improving exercise ability in the HFpEF patient population.

Known and potential risks:
The safety profile of empagliflozin has been well established in over 15000 patients with T2DM treated in clinical studies (of which more than 10000 were treated with empagliflozin) with maximum treatment duration of 4 years. Empagliflozin was tested in over 4600 patients with T2DM and high CV risk for median treatment duration of 2.6 years. In addition, approximately 550 healthy volunteers were exposed to empagliflozin (up to 800 mg single dose and up to 50 mg multiple dosing). Based on the mode of action of empagliflozin, which is independent of insulin and potential concomitant T2DM, it is not expected that the safety profile in patients without T2DM would be different than in the patients with T2DM [P17-04479].

In clinical studies, empagliflozin was well tolerated in both healthy volunteers and patients with T2DM including patients with high CV risk. The frequency of overall adverse events (AEs), AEs leading to discontinuation and serious adverse events (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.It is not expected that patients without DM use insulin and/or sulfonylurea. 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 clinically relevant changes in electrolytes were observed with empagliflozin [c01678844-09].

Empagliflozin causes intravascular volume contraction. Patients with known cardiovascular disease, patients on antihypertensive therapy with a history of hypotension or patients aged 75 years and older are at increased risk of volume depletion.

Rare cases of Diabetic Ketoacidosis (DKA) were observed in patients with T2DM treated with empagliflozin [c01678844-09].

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, women of child bearing potential must agree to the requirements for pregnancy testing and contraceptive methods described in this protocol

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.Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors 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 5.2.6, adverse events of special interest.

Special attention will be paid to prevent metabolic acidosis, ketoacidosis and DKA. For further details refer to section 4.2.1.

To continue the assessment of the safety of empagliflozin, adjudication of 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). Further details are described in section 8.7, the adjudication charter and the DMC charter.

6MWT risks:

The 6 minute walk test (6MWT) is a standard procedure to assess the functional capacity of patients with chronic heart failure. The exercise testing and the safety measures during the test (including the conditions to stop the test) are based on the recommendations outlined by the American Thoracic Society (2002) [R03-0725]. The selection of the sites will ensure that the sites are well equiped and qualified to perform the 6MWT.

Overall the potential benefits, coupled with an acceptable safety profile and a well controlled environment during the exercise testing, support the initiation of the trial.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The primary objective of this trial is to evaluate the effect of empagliflozin 10 mg versus placebo on exercise ability using the 6 minute walk test in patients with CHF with preserved ejection fraction (LVEF > 40%).

Secondary objectives are to assess Patient-Reported Outcome.

This trial is part of an investigational clinical trial program of empagliflozin in patients with CHF. A comparable trial (study number 1245-0168) to investigate the same objectives in patients with reduced EF (LVEF≤ 40%) is ongoing in parallel.

2.1.2 Primary endpoint(s)

The primary endpoint is the change from baseline to week 12 in exercise capacity as measured by the distance walked in 6 minutes in standardised conditions as described in the 6MWT appendix (appendix 10.1).

2.1.3 Secondary endpoint(s)

Key secondary endpoints are

- Change from baseline to week 12 in Kansas City Cardiomyopathy Questionnaire (KCCQ) Total Symptom Score (TSS)
- Change from baseline to week 12 in Chronic Heart Failure Questionnaire Self-Administered Standardized format (CHQ-SAS) dyspnea score

Other secondary endpoints are:

- Change from baseline to week 6 in exercise capacity as measured by the distance walked in 6 minutes
- Change from baseline in Clinical Congestion Score at week 12.
- Change from baseline in Patient Global Impression of Severity (PGI-S) of Heart Failure Symptoms at week 12.
- Change from baseline in Patient Global Impression of Dyspnea Severity at week 12.
- Patient Global Impression of Change (PGI-C) in Heart Failure Symptoms at week 12.
- Patient Global Impression of Change in Dyspnea at week 12.
- Change from baseline in N-terminal pro-brain natriuretic peptide (NT-proBNP) at week 12

2.2 FURTHER OBJECTIVES AND FURTHER ENDPOINTS

2.2.1 Further objectives

Further objectives are to evaluate additional details of patient reported outcome (PRO), heart failure class and exercise ability.

2.2.2 Further endpoints

Further endpoints are:

- Increase in 6MWT ≥ 30 m from baseline at week 12
- Response in KCCQ domains at week 12*
- Response in CHQ domains at week 12*
- Change from baseline in Patient Global Impression of Severity of Heart Failure Symptoms at week 6.
- Change from baseline in Patient Global Impression of Dyspnea Severity at week 6.
- Patient Global Impression of Change in Heart Failure Symptoms at week 6.
- Patient Global Impression of Change in Dyspnea at week 6.
- Change from baseline in Clinician Global Impression of Severity of CHF at Week 6 and week 12
- Clinician Global Impression of Change in CHF Severity at Week 6 and week 12
- Change from baseline in KCCQ overall summary score, CSS, and individual domains at Week 6 and week 12
- Change from baseline in KCCQ TSS at Week 6
- Change from baseline in CHQ individual domains at week 6 and week 12
- Change from baseline in Clinical Congestion Score at week 6.
- Change from baseline in N-terminal pro-brain natriuretic peptide (NT-proBNP) at week 6
- Changes in NYHA class at Week 6 and week 12
- Change from baseline to week 6 and week 12 in patient-rated assessment of dyspnea and fatigue by the Borg scale as part of the 6MWT
- Occurrence of HHF and CV death
- Occurrence of all-cause mortality
- Occurrence of CV death
- Occurrence of all-cause hospitalization (first and recurrent)
- Occurrence of hospitalization for HF (first and recurrent)
- Occurrence of all-cause emergency room visits (first and recurrent)
- Emergency room visit for HF (requires use of i.v. diuretics; first and recurrent)
- Occurrence of unscheduled outpatient visit (first and recurrent)
- Intensification of diuretic therapy (adding a new diuretic, increase of dose)
- Occurrence of MI (fatal or non-fatal)
- Occurrence of Stroke (fatal or non-fatal)
- Occurrence of TIA

* Criteria for response will be explored based on anchor-based methods – further detail will be specified in the TSAP.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a randomised, double-blind, parallel-design, placebo controlled, multinational and multi center study.

A total of approximately 300 male and female patients with chronic heart failure will be randomised (1:1) in the study in about 8 countries.

The screening period will last up to 3 weeks and patients will receive the study drug for 12 weeks.

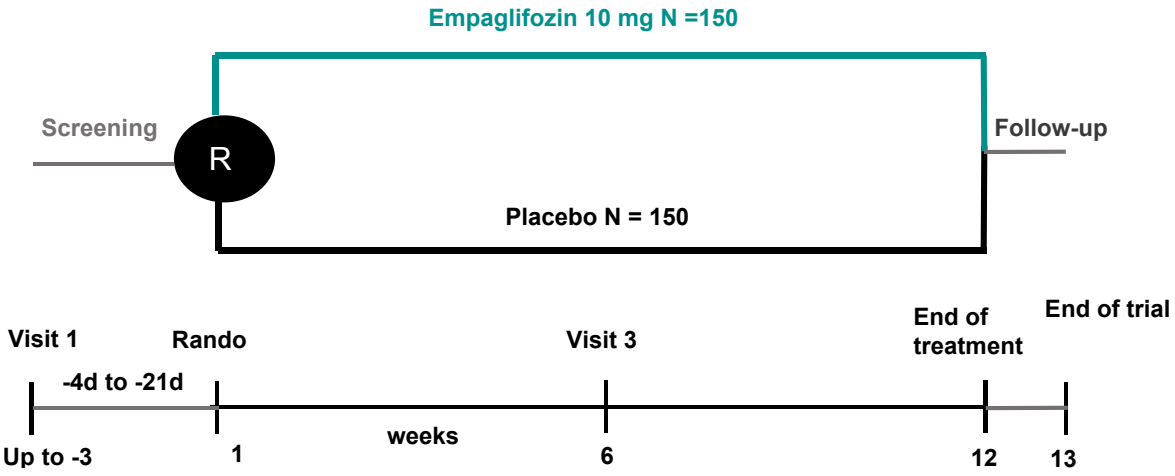

Figure 3.1:1 Overview of trial design

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 (specifically reduction of hospitalizations for heart failure) and mortality. The aim of this trial is to recruit patients with HFpEF on various background therapies for concomitant diseases to evaluate the effect of empagliflozin on exercise ability in a real life clinical setting.

Choice of endpoint:

Various tests are available to assess exercise ability, which can be grouped in two main categories: self-paced submaximal exercise capacity tests (e.g. 6MWT), and maximal

exercise capacity tests (e.g. Cardiopulmonary Exercise Testing (CPET)). For CPET, which measures peak volume O_2 (VO_2) as primary variable, patients must reach their maximal exercise ability which implies a high burden on patients with HF and requires centers with advanced exercise equipment and highly experienced staff. In addition, peak VO_2 testing is not widely available, is time consuming and costly, and is difficult to implement as an endpoint in large scale clinical trials [R17-1588]. Evaluating HF patients and their limitations in daily activities, however, does not require these patients to reach their maximal exercise ability and these limitations could be identified after mild to moderate exertion during a self-paced 6MWT [R17-1341]. The 6MWT, therefore, better reflects activities of daily living that are mostly done at submaximal levels of exertion [R17-1340; R17-1367].

In a systematic review of the literature 6MWT showed concordance (positive or neutral) in 41 out of 47 studies with patient's symptoms, indicating the relevance of this test in assessing short term symptoms improvement [P17-05077]. Pulmonary hypertension trials routinely assessed 6MWT as a primary endpoint, supported by a secondary efficacy endpoint of time to clinical worsening, which has served as the basis for approval of investigational drugs in that specific indication. Despite the outlined differences, studies have shown good correlations between peak VO_2 and 6MWT [R17-1592] with up to 80% positive or neutral concordance. The 6MWT was also found to be reliable and valid in patients with mild-to-moderate CHF and to have good correlation with the maximal exercise capacity supporting the validity of the test [R17-1367]. These findings indicate the clinical utility of the 6MWT for HF clinical trials and emphasize its reliability by being concordant to the peak VO_2 test, without burdening HF patients with maximal exercise testing. The 6MWT has limitations as it is self-paced (the patient may limit her/his performance which is not objectively assessable as a performance marker such as peak VO_2), but adhering to certain recommendations such as providing standard phrases of encouragement during the test will help reducing variability of the test and increase chance of assessing a clinical effect.

Patient Related Outcome Measures (PROM):

PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else [R12-5607].

PRO can provide information on a range of patients' health status outcome including the following: symptoms; functional limitations; impacts on daily activities; social, emotional, psychological and overall well-being [R17-1342].

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is one of the most widely used HF PRO instruments [R17-2687].

KCCQ has prognostic significance, which may aid in their clinical interpretation and decision making based on risk stratification.

The Chronic Heart Failure Questionnaire (self-administered standardized format) (CHQ-SAS) is a heart failure-specific PRO measure with 16-items, designed to assess PRO [R17-

2668], [R17-2969] in adult heart failure patients and specifically evaluates longitudinal change over time. The subscales of the CHQ-SAS are: dyspnea, fatigue and emotional function. Items are rated on a 7-point Likert scale ranging from 1 (e.g. extremely short of breath) to 7 (e.g. not at all short of breath) [R17-2969].

Control group:

Due to its mode of action empagliflozin has the potential be efficacious in treating patients with HF and could provide additional efficacy in combination with any given background therapy. However, the effect of empaglifozin in patients with heart failure has not yet been systematically assessed in a randomised clinical trial. Currently, two large clinical outcome trials are ongoing in patients with HFpEF (EMPEROR-preserved) or HFrEF (EMPEROR-reduced) to evaluate empaglifozin for the reduction of cardiovascular death and heart failure hospitalization.

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

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

Duration:

Due to the potential early effect of empagliflozin (see above for mode of action and EMPA-REG-OUTCOME results) empagliflozin is expected to exert its effect within the early weeks of administration and therefore the peak effect on improving exercise ability is expected to be seen as early as approximately 4-8 weeks from baseline. Thus, a 12 week time point is considered suitable for the assessment of the primary endpoint.

3.3 SELECTION OF TRIAL POPULATION

A sufficient number of patients will be screened to ensure that an adequate number of patients will be randomised. It is planned that approximately 300 male and female patients who meet the eligibility criteria will be randomised in the study. The planned number of patients per site is approximately 4 (at approximately 80 sites).

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

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

Re-screening and/or re-testing (of assessments) should be discussed with Clinical Monitor Local (CML). 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 blood pressure, electrocardiogram (ECG) measurements and laboratory result which is obviously received beyond stability at the central laboratory or thought to be a spurious or transient result based on previously available laboratory results or in the opinion of the investigator. The re-test should be carried out as soon as possible so the laboratory test results will be received within the next planned visit window in order to avoid protocol window violations.

Re-screening will be allowed on a case by case basis.
Patients must be clinically stable with no signs of heart failure decompensation when entering the study. If the patient is not clinically stable, rescreening is allowed:

- Re-screening of the same patient is only allowed once.
- The patient must be clinically stable for at least 4 weeks and satisfy all eligibility criteria.
- 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.

If a patient is a screen failure in one of the other Heart Failure trials with Empagliflozin they could be considered for this trial as long as they meet all eligibility criteria.

In instances where a patient is a screen failure in 1245-0168, all relevant completed screening procedures can be used for the eligibility assessment of the patient in 1245-0167 as long as they are completed during the original screening timeframe. The decision to screen the patient in the 1245-0167 trial should be based on Investigator judgement and in consultation with the Sponsor.

3.3.1 Main diagnosis for trial entry

The trial will be performed in patients with chronic heart failure with a left ventricular ejection fraction > 40 % (this includes patients with preserved and mid-range heart failure).

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

3.3.2 Inclusion criteria

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

2. Male or female patients. WOCBP[1] must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information. For sites in Portugal please refer to the contraception methods described in appendix 10.8.

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

4. 6MWT distance ≤350 m at screening and at baseline.

5. Patients with CHF diagnosed for at least 3 months before Visit 1, and currently in NYHA class II-IV

6. CHF with preserved EF defined as LVEF > 40 % as per echocardiography at Visit 1 per local reading and no prior measurement of LVEF ≤ 40% under stable conditions.

7. Elevated NT-proBNP > 300 pg/ml for patients without atrial fibrillation (AF), OR > 600 pg/ml for patients with AF, as analysed at the Central laboratory at Visit 1

8. Patients must have at least one of the following evidence of HF:
    a. Structural heart disease[2] (left atrial enlargement and/or left ventricular hypertrophy) documented by echocardiogram at Visit 1, OR
    b. Documented HHF[3] within 12 months prior to Visit 1

[1] A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Please note that tubal ligation is NOT accepted as a method of permanent sterilisation and therefore a woman who underwent tubal ligation is still considered as WOCBP. However tubal ligation is considered as a method of highly effective birth control.
[2] Structural heart disease is further defined in appendix 10.7
[3] The main reason for HHF must be HF. Documentation for HHF must be provided in the source documents

9. Consistent with prevailing CV guidelines, if oral diuretics are prescribed to control symptoms, patients must be on an appropriate and stable dose of oral diuretics for at least 2 weeks prior to Visit 1 to control symptoms.

10. Clinically stable at randomization with no signs of heart failure decompensation (as per investigator judgement).

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 transient ischemic attack in past 90 days prior to Visit 1

2. Acute decompensated HF (exacerbation of CHF) requiring intravenous (i.v.) diuretics, i.v. inotropes or i.v. vasodilators, or left ventricular assist device within 4 weeks prior to Visit 1, and/or during screening period until Visit 2

3. Previous or current randomisation in another Empagliflozin Heart Failure trial (i.e. studies 1245.110, 1245.121, 1245-0168).

4. Type 1 Diabetes Mellitus (T1DM)

5. Impaired renal function, defined as eGFR < 20 mL/min/1.73 m^2 (CKD-EPIcr) or requiring dialysis, as determined at Visit 1

6. Symptomatic hypotension or a systolic blood pressure (SBP) < 100 mmHg at Visit 1 or 2

7. SBP ≥ 180 mmHg at Visit 1 or 2, or SBP >160mmHg at both Visit 1 and 2

8. Atrial fibrillation or atrial flutter with a resting heart rate > 110 bpm documented by ECG at Visit 1 (Screening)

9. Unstable angina pectoris in past 30 days prior to Visit 1

10. Largest distance walked in 6 minutes (6MWTD) at baseline <100m.

11. Any presence of condition that precludes exercise testing such as:
    - claudication,
    - uncontrolled (according to investigator judgement) bradyarrhythmia or tachyarrhythmia,
    - significant musculoskeletal disease,
    - primary pulmonary hypertension,
    - severe obesity (body mass index ≥40.0 kg/m2),
    - orthopedic conditions that limit the ability to walk (such as arthritis in the leg, knee

or hip injuries)
- amputation with artificial limb without stable prosthesis function for the past 3 months
- Any condition that in the opinion of the investigator would contraindicate the assessment of 6MWT

12. Patients in a structured (according to Investigator judgement) exercise training program in the 1 month prior to screening or planned to start one during the course of this trial.
13. Heart transplant recipient or listed for heart transplant
14. ICD implantation within 1 month prior to Visit 1 or planned during the course of the trial
15. Implanted cardiac resynchronisation therapy (CRT)
16. 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
17. Any severe (obstructive or regurgitant) valvular heart disease that either represents a risk for the conduct of the 6MWT or is expected to lead to surgery during the trial in the Investigator's opinion
18. Chronic pulmonary disease i.e. with known FEV1 <50% requiring home oxygen, or 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
19. 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
20. Haemoglobin < 9 g/dl at Visit 1
21. History of ketoacidosis
22. 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 or knee replacement) during the course of the trial.
23. Gastrointestinal (GI) surgery or GI disorder that could interfere with trial medication absorption in the investigator's opinion
24. 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 or in situ carcinoma of uterine cervix or low risk prostate cancer (biopsy Gleason score of ≤ 6 and clinical stage T1c or T2a)

25. 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

26. 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.

27. Treatment with i.v. iron therapy or erythropoietin (EPO) within 3 months prior to screening.
28. 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

29. Known allergy or hypersensitivity to empagliflozin or other SGLT-2 inhibitors

30. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable trial patient or unlikely to complete the trial

31. Women who are pregnant, nursing, or who plan to become pregnant while in the trial

32. 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 Withdrawal of patients from therapy or assessments

Patients may potentially be withdrawn from trial treatment or from the trial as a whole ("withdrawal of consent") with very different implications, please see section 3.3.4.1 and section 3.3.4.2 below.

Every effort should be made to keep the randomised patients in the trial if possible on treatment, or at least to collect important trial data.

Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to randomization, as well as the explanation of the consequences of withdrawal.

The decision to withdraw from trial treatment or from the whole trial as well as the reason must be documented in the patient files and CRF.

An excessive withdrawal rate can have a severe negative impact on the scientific value of the trial. The "Intention To Treat (ITT)" 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.

3.3.4.1 Withdrawal from trial treatment

An individual patient is to be withdrawn from trial treatment if:

- The patient wants to withdraw from trial treatment, without the need to justify the decision.
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication (see section 4.2.2.1 for restricted medication).
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy).
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to comply with the trial requirements in the future.

Given the patient's agreement, the patient will undergo the procedures for the early discontinuation visit as soon as possible after treatment discontinuation and the follow up visit as outlined in the Flow Chart and section 6.2.3. In addition, if the patient discontinues early, the patient should return to clinic for their regularly scheduled week 12 study visit and have all study procedures performed except those pertaining to drug intake.

Every effort should be made for the patient to attend the regularly scheduled study visits, however if this is not possible, then the remaining visits should be conducted by phone.

For all patients the reason for withdrawal from trial treatment (e.g. adverse events) must be recorded in the CRF. These data will be included in the trial database and reported.

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 5.2.7.2). As pregnancy is not a contraindication for the 6MWT, the patient will be expected to attend the regularly scheduled study visits as outlined above.

3.3.4.2 Withdrawal of consent for trial participation

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

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

The Investigator must be involved in the discussions with the patient regarding a withdrawal of consent and should explain the difference between treatment withdrawal and withdrawal of consent for trial participation and explain the options for continued follow up after withdrawal from trial treatment, please see section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

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

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

The investigator / the trial site 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 Boehringer Ingelheim Pharma GmbH & Co.KG.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of test products are below:

Table 4.1.1: 1 Test products:

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

Substance:	Placebo matching empagliflozin
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim
Unit strength:	-
Posology	1 tablet once daily
Route 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 heart rate and reduction in heart rate multiplied by pressure product, an index of myocardial oxygen consumption. These modes of actions support the scientific rationale of testing 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 a glucosuria of about 50g per day.

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

For further details see current version of the IB [c01678844-09].

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 a randomization plan. The assignment will occur in a blinded fashion via IRT.

To facilitate the use of the IRT, the Investigator or delegate 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 section 4.1.5.2.

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

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 by the pharmacist or the investigator in a double-blind and single-dummy manner.

IRT will be used to allocate study medication to patients at visit 2 and 3 for a 6 week period and one week reserve (i.e. 49 tablets total) each time. Treatment starts on the day of visit 2 and ends on the day of visit 4 (or early discontinuation visit). 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. No double doses should be taken.

Patients should be instructed to take their medication on the morning of trial visits 3 and 4. 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 randomization 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 / pharmacist / investigational drug storage manager via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be

documented in the source documents and/or appropriate CRF page along with the date and the initials of the person who broke the code.

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 be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational products will be provided by BI or a designated contract research organization (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 an IRT system, which will also monitor expiry dates of supplies available at the sites.

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

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) must be contacted immediately. 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 when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the Institutional Review Board (IRB) / ethics committee,
- Availability of a signed and dated clinical trial contract between the sponsor and 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,
- Availability of Food and Drug Administration (FDA) Form 1572 (if applicable).

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. Patients should be instructed to return unused investigational drug.

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 or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor 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 Clinical Trial Protocol (CTP) and reconcile all investigational products received from the sponsor. At the time of return to the sponsor and/or appointed 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

Concerning the 6MWT, the following is required:

The test should be performed in a location where a rapid, appropriate response to an emergency is possible. Adequate safety equipment must be readily available at the test site according to local institutional requirements and emergency medications are to be administered at the discretion of the Investigator such as: oxygen, fast-acting nitrate, antiplatelet agent, sphyngomanometer and telephone.

The 6MWT should be immediately stopped in case of acute chest pain, sudden pallor, loss of coordination / staggering, mental confusion, extreme dyspnea, leg cramps, diaphoresis. The subject should be monitord in the unit until the signs / symptoms / ECG modifications have been completely cleared.

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

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 T2DM 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., 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.

In patients with heart failure who receive empagliflozin, elderly patients with heart failure and in case of conditions that may lead to fluid loss (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, laboratory tests including haematocrit), blood pressure measurement and electrolytes is recommended since empagliflozin may potentially lead to hypotension. Temporary interruption of the study drug should be considered until the fluid loss is corrected.

Temporary interruption of empagliflozin should be considered in patients with complicated urinary tract infections.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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 7 day period between the End of Trial (EOT) and the Follow Up Visit.

Consistent with prevailing CV guidelines, if oral diuretics are prescribed, patients must be on an appropriate and stable dose for 2 weeks prior to Visit 1 to control volume status and symptoms.

Concomitant diseases should be treated according to best standard of care in accordance with local guidelines and recommendations.

Patients should not receive treatment with i.v. iron therapy and EPO during the course of the trial.

If any restricted treatment is given during the conduct of the trial, the trial medication must 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.

4.2.2.2 Restrictions on diet and life style

Prior to each visit during which a 6MWT is performed, patients should be advised not to perform vigorous exercise on the day of testing. Patients should be advised to take only a light meal prior to a 6MWT.

Patients must remain in the building where the exercise testing is performed and must return to the study personnel at least 10 minutes prior to the start of the 6MWT.

For further details on restrictions on diet and life style please refer to appendix 10.1.

4.2.2.3 Restrictions regarding women of childbearing potential

Women of childbearing potential must use the contraception methods described in the patient information. For sites in Portugal please refer to the contraception methods described in appendix 10.8.

4.3 TREATMENT COMPLIANCE

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

Based on tablet counts, treatment compliance will be calculated as shown in the formula below. Compliance will be verified by the Clinical Research Associate (CRA) authorised by the sponsor.

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

Compliance should be between 80% and 120%. If the number of doses taken is not between 80-120%, site staff will explain to the patient the importance of treatment compliance. 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. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 Six Minute Walk Test

At all sites, patients will perform an exercise capacity assessment using the 6-minute walk test. One 6MWT will be performed at the screening visit, visit 3 and the early discontinuation visit (if applicable). At visits 2 and 4, two 6MWTs will be performed at least 1 hour apart for increasing reliability of the test as well as for decreasing variability. The distances from both tests will be recorded in the eCRF and the largest distance measured will used for analysis. Testing of the 6MWT at each clinic visit should be preferably performed about the same time of day to minimize intraday variability.

The 6MWTs at Visit 1 and 2 will be performed to assess patient eligibility and as well the screening test will serve as the training test to familiarize patients with the procedure. If the distance walked during any of these 6MWTs is > 350m the patient will be considered a screen failure. If the largest distance walked at Visit 2 is < 100m, the patient will be considered a screen failure. The 6MWT of largest distance performed at Visit 2, will be the baseline result.

Prior to and at the end of the 6MWT, patients will be asked to rate their breathing discomfort and overall fatigue using the Borg Scale.

The 6MWT methodology is described in detail in the ISF and appendix 10.1. Please refer to section 6.2.2 for preferred order of completion of assessments.

5.1.2 Kansas City Cardiomyopathy Questionnaire

KCCQ is a commonly used 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 (refer to appendix 10.3.1).

The questionnaire takes less than 15 minutes to complete and will be assessed according to the Flow Chart. Please refer to section 6.2.2 for order of completion of patient reported outcome measures.

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 10.2.

5.1.3 Chronic Heart Failure Questionnaire Self Administered Standardized

The CHQ-SAS is a heart failure-specific PRO measure that assesses the patients' perception of their heart failure and measures the impact of heart failure symptoms. The CHQ-SAS refers to the CHQ-self-administered format and contains 16 standardised questions pertaining to 3 domains: dyspnea, fatigue and emotional function. Items are rated on a 7-point Likert scale ranging from 1 (e.g. extremely short of breath) to 7 (e.g. not at all short of breath) [R17-2969].

Patients will complete the first administration of the questionnaire at Visit 2 and complete the follow-up administration questionnaire at Visits 3 and 4 and early discontinuation (if applicable).

Please refer to section 6.2.2 for order of completion of patient reported outcome measures.

Please refer to appendix 10.3.2 for the first administration of the questionnaire and the ISF for the follow-up administration of the questionnaire.

5.1.4 NT-proBNP

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.

5.1.5 New York Heart Association classification

The NYHA functional classification will be used to classify the severity of the patients' heart failure (appendix 10.5). 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 if needed, telephone visits until end of the trial.

5.1.6 Clinical Congestion Score

Patient's congestion will be assessed using a clinician-based outcome assessment of 6 different signs and symptoms: dyspnea, orthopnea, fatigue, jugular venous distention (JVD) (as assessed by the investigator), rales, and edema. Each category will be assessed through a four-measure questionnaire which will be further converted to a standardized 4-point scale ranging from 0 to 3 as shown in table 5.1.6:1.

Table 5.1.6:1 Clinical congestion score

Signs/Symptoms	**0**	**1**	**2**	**3**
Dyspnea	None	Seldom	Frequent	Continuous
Orthopnea	None	Seldom	Frequent	Continuous
Fatigue	None	Seldom	Frequent	Continuous
JVD (cm H2O) (jugular venous distension)	≤6	6< JVD < 10	10≤ JVD <15	≥15
Rales	None	Bases	From base to <50%	From base to >50%
Edema	Absent/ trace	Slight	Moderate	Marked

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

5.1.7 Patient Global Impression of Change in Heart Failure Symptoms

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The PGI-C asks the patient to choose one response that best describes the overall change (if any) in his/her Heart Failure Symptoms, specifically: shortness of breath, fatigue and swelling since he/she started taking the trial medication &/ 4"# 0&%%&A:#2(4#2&,8=(%#?

- Very much better (+3)
- Much better (+2)
- A little better (+1)
- No change (0)
- A little worse (-1)
- Much worse (-2)
- Very much worse (-3)

Please refer to section 6.2.2 for order of completion of patient reported outcome measures and appendix 10.3.3.

5.1.8 Patient Global Impression of Change in Dyspnea

The Patient Global Impression of Change in dyspnea is a 1-item questionnaire designed to assess the patient's impression of change in dyspnea.

The PGI-C asks the patient to choose one response that best describes the change (if any) in his/her shortness of breath when performing usual activities since he/she started taking the trial medication on the following 7-category scale:

- Very much better (+3)
- Much better (+2)
- A little better (+1)
- No change (0)
- A little worse (-1)
- Much worse (-2)
- Very much worse (-3)

Please refer to section 6.2.2 for order of completion of patient reported outcome measures and appendix 10.3.4.

5.1.9 Patient Global Impression of Severity of Heart Failure Symptoms

Patient Global Impression of Severity of Heart Failure Symptoms .- (9:.4#* ;6#-4.&//(.,# 4& (--#-- +(4.#/4<- .*+,#--.&/ &0 -8*+4&*- -#D#,.48>+#=.0.=(%%&&,4/#-- &0,#(4"> 0(4.26# (/@ -A#%%./2B

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

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

Please refer to section 6.2.2 for order of completion of patient reported outcome measure and appendix 10.3.5.

5.1.10 Patient Global Impression of Severity of Dyspnea

Patient Global Impression of Severity of Dyspnea is a 1-item questionnaire designed to assess patient's impression of symptom severity, specifically dyspnea.

The PGI-S item asks the patient to choose one response that best describes how his/her dyspnea is now on a 5-point scale:

- Not at all (1)

- Mild (2)
- Moderate (3)
- Severe (4)
- Very severe (5)

Please refer to section 6.2.2 for order of completion of patient reported outcome measures and appendix 10.3.6.

5.1.11 Clinician Global Impression of Change in CHF Severity

Clinician Global Impression of Change in CHF Severity is a 1-item questionnaire designed to assess Investigator's (physician's) overall impression of change in the patient's chronic heart failure severity related to his/her participation in the study; specifically signs and symptoms associated with chronic heart failure on a 7-point scale.

This questionnaire is assessing change from baseline. For consistency, the same Investigator should assess the patient at each visit. If this is not possible, then the response 'N/A = cannot be assessed' should be selected.

N/A = Cannot be assessed
1 = Very much improved
2 = Much improved
3 = Minimally improved
4 = No change
5 = Minimally worse
6 = Much worse
7 = Very much worse

Please refer to section 6.2.2 for preferred order of completion of assessments and appendix 10.4.1.

5.1.12 Clinician Global Impression of Severity of CHF

Clinician Global Impression of Severity of CHF is a 1-item questionnaire designed to assess Investigator's overall impression of severity of chronic heart failure, specifically signs and symptoms associated with chronic heart failure now (at the time-point of assessment) on the 5-point scale:

- Normal, not at all ill (1)
- Mildly ill (2)
- Moderately ill (3)
- Severely ill (4)
- Very severely ill (5)

Please refer to section 6.2.2 for preferred order of completion of assessments and appendix 10.4.2.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

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

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

5.2.2 Vital signs

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

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 appendix 10.6.

5.2.3 Body weight and height

Measurements of body weight and height will be performed at the time points specified in the Flow Chart.

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

Body weight should be measured as follows:

- 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.).

5.2.4 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in table 5.2.4:1. For the sampling time points please see the Flow Chart.

All analyses will be performed by a central laboratory, the respective reference ranges will be provided in the ISF.

Patients do not have to be fasted for the blood sampling for the safety laboratory. Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual in the ISF.

The central laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (please refer to section 5.2.7.1).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see section 5.2.7.1 and the DILI Checklist provided in the ISF and electronic data capture (eDC) system. The amount of blood taken from the patient concerned will be increased due to this additional sampling.

The central laboratory will transfer the results of the analysis to the sponsor.

Table 5.2.4:1 Safety laboratory tests

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 • Chloride • Creatinine • Creatine kinase (CK) • Hs Troponin I (reflex tests if CK is elevated) • Glucose • Potassium • Protein total

• Sodium • Urea (BUN) • Uric acid
Urine
• Urinalysis: standard dipstick test including ketones semi-quantitative measurement

5.2.4.1 Renal function

The estimated glomerular filtration rate (eGFR) will be derived from serum creatinine values, age sex and race based on the Chronic Kidney Disease Epidemiology creatinine (CKD-EPIcr) equation [R12-1392].

5.2.4.2 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 5.2.7.2.

5.2.4.3 Criteria for hypoglycaemic events

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.

5.2.4.4 Urinary tract infection and genital infections

Patients having a history of chronic/recurrent UTIs 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.

5.2.5 Electrocardiogram

12-lead ECGs will be performed at the screening and EOT Visits as indicated in the Flow Chart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and whether it is clinically relevant, if abnormal. ECGs may be repeated for quality reasons and the repeated recording used for analysis.

In case of any cardiac symptom (indicating rhythm disorders or cardiac ischaemia), or for safety reasons additional 12-lead ECG(s) should be done and any abnormal findings will be reported as AEs. Dated and signed printouts of ECG with findings should be documented in patient's medical record.

Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as adverse events and will be followed up and/or treated as medically appropriate.

5.2.6 Other safety parameters

There are no additional safety parameters in the trial.

5.2.7 Assessment of adverse events

5.2.7.1 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.

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

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
- requires inpatient hospitalisation or
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect,
  or
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

AEs considered "Always Serious"

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

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

Note: Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the duration between discontinuation of the drug and must be reported as described in section 5.2.7.2, subsections "AE Collection" and **AE reporting to sponsor and timelines"**

Adverse events of special interest

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

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

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

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

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

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

Causal relationship of AEs
Medical judgement 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 drug treatment continues or remains unchanged.

5.2.7.2 Adverse event collection and reporting

AE Collection

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

- From signing the informed consent onwards until the individual patient's end of trial:
  All AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of trial:
  The investigator does not need to actively monitor the patient for AEs but should only 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 in the CRF.

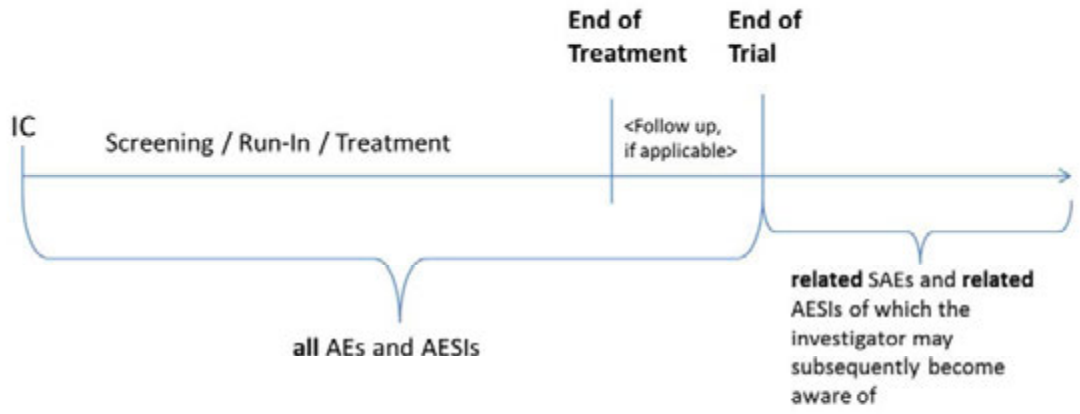

Figure 5.2.7.2: 1 Adverse Event Collection Periods

AE reporting to sponsor and timelines
The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

Information required
For each AE, the investigator should provide the information requested on the appropriate eCRF pages and the BI 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 BI SAE form (if applicable):

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

If such abnormalities already pre-exist prior to trial inclusion they will be considered as baseline conditions and should be collected in the eCRF only. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable" , or no further information can be obtained.

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

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

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

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical 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.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

This study will not analyse pharmacokinetic or pharmacodynamics parameters.

5.4 ASSESSMENT OF BIOMARKER(S)

This study will not analyse exploratory biomarkers. Please refer to section 5.1.4 for details on NT-proBNP.

5.5 OTHER ASSESSMENTS

5.5.1 Echocardiogram

An echocardiogram will be performed on all patients as part of the screening procedures. The standard methodology of the institution will be used and the following clinical information will be recorded:

- Left Ventricular Ejection Fraction
- Left ventricular end-diastolic and end-systolic diameters
- Left ventricular end-diastolic and end-systolic volumes
- Wall motion abnormalities (if any)
- Septal and posterior wall thickness
- Left Atrium (LA) diameter
- Heart valve status
- Any other abnormal findings (according to investigator judgement)

Optional measurements:

- LV mass index (LVMI)
- E/e′
- LA volume
- LA area

For details on echocardiographic parameters please refer to appendix 10.7.

5.5.2 Health Care Resource Utilisation (HCRU)

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

- All-cause hospital admissions (first and recurrent)
- Hospital admission due to worsening of chronic heart failure (first and recurrent)
- All-cause emergency room visits (first and recurrent)
- Emergency room visits due to worsening of chronic heart failure (requiring i.v. diuretic therapy) (first and recurrent)
- Any unscheduled outpatient visits (first and recurrent)
- Unscheduled outpatient visits related to heart failure (first and recurrent)

5.6 APPROPRIATENESS OF MEASUREMENTS

The primary endpoint measurement will be consistent with the recognized standard for conducting the 6MWT to assess treatment changes in heart failure patients (R03-0725).

All secondary and further endpoint measurements performed during this trial are standard measurements and will be performed in order to determine empagliflozin efficacy in an appropriate way. The scheduled measurements are appropriate to see drug induced changes in vital signs, standard laboratory values and biomarkers specific to efficacy of treatment of HF. The endpoints are widely used and accepted for evaluation of efficacy on an oral HF drug.

Patient Reported Outcome measures are an essential part for this phase III trial.

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

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

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

6.2.1 Screening and run-in period(s)

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

For patients with no BNP or NT-proBNP measurement available from clinical routine in the past 6 months indicative of the likelihood of eligibility for this study, it is recommended to split the screening visit into two steps and start with the measurement of NT-proBNP and safety lab measures (via central laboratory), wait for the results, and do the remaining screening assessments on a separate day (within the allowed visit window)

One 6MWT will be performed at the screening visit (visit 1) to assess patient eligibility and if the distance walked during the 6MWT is > 350m, the patient will be considered a screen failure. If the distance walked during the 6MWT is < 100m at screening, the patient is allowed to return to the baseline assessment to account for a learning effect that may result in some improvement of the walking distance.

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, (i.e. fail to meet one or more of the inclusion criteria, and/or meet one or more of the exclusion criteria) following Visit 1 procedures, they should be registered as a screen failure in IRT.

Re-testing for certain eligibility criteria can be performed once for abnormal laboratory, blood pressure and / or ECG results as outlined in section 3.3. Resceening will be considered on a case-by-case basis as described in section 3.3.

6.2.2 Treatment period(s)

Randomisation will occur at Visit 2 using IRT. The patients will return to the clinic for regularly scheduled visits 6 and 12 weeks after randomisation 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.

All Visit 2 assessments must be performed before the first dose is taken at the site. The assessments at Visits 3 and 4 must be performed post-dose. Patients should be instructed to take their medication on the morning of trial Visits 3 and 4. Visits should be routinely scheduled at approximately the same time of day for each visit.

At all treatment visits (Visits 2, 3 and 4/EOT) and the early discontinuation visit, patient reported outcome measures should be completed first.

Patient reported outcome measures should be completed in the following order:

- KCCQ
- PGI – Severity – Heart Failure Symptoms
- PGI – Change – Heart Failure Symptoms
- PGI - Severity - Dyspnea
- PGI - Change – Dyspnea
- CHQ-SAS

The order of the remaining assessments should be preferably completed as follows and according to the visits specified in the Flow Chart:

- Physical examination, body weight, height and vital signs
- Completion of clinician impression scales and clinical congestion score by Investigator
- ECG
- 6MWT conducted in duplicate (at visits 2 and 4 only) at least 1 hour apart. At visits 1, 3 and the early discontinuation visit, only one 6MWT will be conducted.
- Laboratory sample, urine pregnancy

Testing of the 6MWT at each clinic visit should be performed about the same time of day to minimize intraday variability. Prior to performing the 6MWT the relative contraindications to exercise should be assessed as per appendix 10.1.3.

All other medications the patient is receiving should be taken as instructed by the physician.

At any time during the treatment period the HF background therapy is allowed to be

adjusted and optimised according to local and international guidelines.

If any additional therapy is considered necessary for the patient's welfare during the treatment period it may be given at the discretion of the Investigator (see also restrictions in section 4.2.2.

Patients will be dispensed medication at visits 2 and 3 and allocation of new kit number(s) will be managed through the IRT. Visit 4 is the last day of treatment and the patient should return all remaining medication during this visit.

Permanent trial medication discontinuation is only justified when clear persistent contraindications arise, or when the patient requests to stop trial medication. See section 3.3.4.1 for details on how to handle trial medication discontinuations.

6.2.3 Follow up period and trial completion

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

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

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.

The primary endpoint is the change from baseline to week 12 in exercise capacity as measured by the distance walked in 6 minutes. The statistical model will be a Wilcoxon rank test on change from baseline to week 12 in distance walked in the 6MWT.

The primary model will be conducted on all randomized patients. Where more than one measurement is available on the same day (duplicate measurements), the highest distance walked will be used for analysis.

The two key secondary endpoints ‘Change from baseline to week 12 in KCCQ-TSS’ and ‘Change from baseline to week 12 in CHQ-SAS dyspnea score’ are part of the testing strategy.

Both key secondary endpoints will be tested using a Wilcoxon rank test, and both will be tested if the primary endpoint revealed a significant result in favour of empagliflozin. For adjustment of multiplicity of the two key secondary endpoints a Hochberg procedure will be followed.

The other secondary endpoints will not be part of the testing hierarchy.

7.2 NULL AND ALTERNATIVE HYPOTHESES

Both key secondary endpoints will be tested if the primary endpoint revealed a significant result in favour of empagliflozin. For adjustment of multiplicity of the tests of the two key secondary endpoints a Hochberg procedure will be followed. The trial is designed to achieve a power of 90% for the primary endpoint at level $\alpha = 0.05$ to detect a difference between empagliflozin and placebo.

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. Change from baseline to week 12 in exercise capacity as measured by the distance walked in 6 minutes

2. Hochberg procedure of :

    - Change from baseline to week 12 in KCCQ TSS
    - Change from baseline to week 12 in CHQ-SAS dyspnea score

If the null hypothesis for the primary analysis is rejected, and the result is more favourable for empagliflozin, superiority is concluded in the primary endpoint, and the overall type I error is preserved for the test in the next step.

In the next step a Hochberg procedure will be applied to account for multiplicity of testing of the key secondary endpoints.

If the primary hypothesis is not rejected, the tests of the key secondary endpoints are conducted in an exploratory fashion.

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

7.3 PLANNED ANALYSES

The 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.

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

Note that for the primary endpoint the higher measurement for each day is selected as the test result for that day. Therefore the last available measurement before start of trial medication will refer to the higher value on the day of the last measurement before treatment intake.

7.3.1 Primary endpoint analyses

The primary endpoint 'change from baseline to week 12 in exercise capacity' will be evaluated using a normal approximation of the Wilcoxon rank test using the randomized set. For estimation of effect the non-parametric Hodges-Lehmann estimate for the median difference will be calculated. Any confirmatory conclusion such as for hierarchical testing will be based on the result of the Wilcoxon rank test and will not consider the Hodges-Lehmann estimate or the corresponding confidence interval, which are given to support interpretation.

If repeated distance walked in 6 minutes (6MWTD) measurements on the same day are available the longest distance will be used for this day.

Change from baseline will be defined as distance walked in 6 minutes (6MWTD) at week 12 assessment minus the distance walked at baseline.

If no value for the 6MWTD is available at week 12, an imputed value as defined in table 7.5: 1 will be used.

Sensitivity analysis for the primary endpoint will include using a mixed model repeated measure analysis (MMRM) with baseline 6MWT as a covariate without imputation of missing values.

7.3.2 Secondary endpoint analyses

Key secondary endpoints

Both key secondary endpoints 'Change from baseline to week 12 in heart failure symptoms as measured by the KCCQ TSS' and 'Change from baseline to week 12 in CHQ-SAS dyspnea score' will be evaluated using a normal approximation of the Wilcoxon rank test using the randomized set. For estimation of effect the non-parametric Hodges-Lehmann estimate for the median difference will be calculated.

Change from baseline in both scores will be defined as the endpoint value at week 12 minus the last available endpoint value before start of randomised trial medication.

If no questionnaire is available at week 12, an imputed value as defined similar to the imputation for the primary endpoint will be used.

Sensitivity analysis for the key secondary endpoint will include using a mixed model repeated measure analysis with baseline of the key secondary endpoint as a covariate without imputation of missing values.

Other secondary endpoints

Change from baseline to week 6 in exercise capacity as measured by the distance walked in 6 minutes will be evaluated using the same model as for the primary endpoint.

Change from baseline of Clinical Congestion Score at week 12 will be evaluated using an mixed model repeated measure analysis (MMRM) analysis over time. The model will include the factor treatment and the linear covariate of baseline Clinical Congestion Score.

Proportion of patients in every category of global impression of change at week 12 will be evaluated using Cochran-Mantel-Haenszel test. Details on combining categories if the proportion of patients in one of the categories is small will be given in the TSAP.

Proportions of patients categorized by the shift in scores between baseline and week 12 in patient global impression of severity score will be evaluated using Cochran-Mantel-Haenszel test. Details on combining categories if the proportion of patients in one of the categories is small will be given in the TSAP.

The endpoint “Change from baseline in NT-proBNP at week 12” (after log-transformation) will be evaluated using a MMRM analysis over time with baseline log-transformed NT-proBNP as a covariate without imputation of missing values.

7.3.3 Further endpoint analyses

Endpoints describing responders such as increase in 6MWT ≥ 30 m or response in KCCQ or CHQ domains will be evaluated using a Chi-Square test.

Proportions of patients categorized by the shift in scores between baseline and week 6 in patient global impression of severity score will be evaluated using Cochran-Mantel-Haenszel test. Details on combining categories if the proportion of patients in one of the categories is small will be given in the TSAP.

Proportion of patients in every category of patient global impression of change at week 6 will be evaluated using Cochran-Mantel-Haenszel test. Details on combining categories if the proportion of patients in one of the categories is small will be given in the TSAP.

Proportion of patients in every category in clinician global impression of change at week 6 and week 12 will be evaluated using Cochran-Mantel-Haenszel test. Details on combining categories if the proportion of patients in one of the categories is small will be given in the TSAP.

Proportions of patients categorized by the shift in scores between baseline and week 6 (week 12) in clinician global impression of severity score will be evaluated using Cochran-Mantel-Haenszel test. Details on combining categories if the proportion of patients in one of the categories is small will be given in the TSAP.

Change from baseline continuous endpoints such as KCCQ domains or CHQ domains at week 6 and Week 12 will be evaluated using a MMRM analysis over time. The model will include treatment as fixed categorical effect and baseline of the respective endpoint as fixed continuous effect.

Change from baseline in Clinical Congestion Score at week 6 will be evaluated by the same MMRM used to evaluate Clinical Congestion Score at week 12 described for the secondary endpoint.

Change from baseline in NT-proBNP at week 6 will be evaluated by the same MMRM used to evaluate NT-proBNP at week 12 described for the secondary endpoint.

Proportions of patients categorized by the shift in scores between baseline and week 12 in NYHA class will be evaluated using Cochran-Mantel-Haenszel test. Details on combining categories if the proportion of patients in one of the categories is small will be given in the TSAP.

Change from baseline to week 12 in patient-rated assessment of dyspnea and fatigue by the Borg scale as part of the 6MWT will be presented descriptively.

Other further endpoints will be analysed descriptively.

7.3.4 Safety analyses

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

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

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

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

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised. Treatment

groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

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

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

The details of the analysis will be specified in the Trial Statistical Analysis Plan (TSAP).

7.3.5 Pharmacokinetic and pharmacodynamic analyses

Not applicable.

7.4 INTERIM ANALYSES

No interim analysis is planned but a DMC will be in place with tasks as described in section 8.7.

7.5 HANDLING OF MISSING DATA

Patients with an available week 12 measurement of the 6MWT, regardless of whether on or off-treatment, will be ranked based on change from baseline in 6MWT distance at week 12.

If a patient performs the visit at week 12 but is unable to walk or unable to perform the 6MWT due to safety concerns, then this will be noted accordingly in the case report form and will not be regarded as missing data. This case will be evaluated as a measured distance of 0m.

Missing data will be imputed according to the rules outlined in table 7.5: 1, and ranks will be assigned based on the imputed data. Imputed data will also be used to calculate the Hodge Lehmann estimates for the median difference. Note that no imputation will be used in the MMRM analysis that serves as sensitivity analysis in this trial.

All imputed data due to missing data will be lower than measured values. The lowest measurable value of the primary endpoint of change from baseline in 6MWT distance is a reduction by 350m, i.e. the highest possible baseline value (350 m), and at week 12 the lowest possible value of 0m. Therefore, all imputed values for change from baseline for patients with missing walking distance at week 12 are below -350 m.

Table 7.5: 1 Imputation rules for missing primary endpoint

	Category	Ranking	Case description	Imputed change from baseline in 6MWTD for described case (in m)*
1	Missing data on 6MWT at week 12 and no clinical event: Patients with missing 6MWT at week 12 and no event as in category 2 or 3	If post-baseline value is available, rank by last available value. Rank below if no post-baseline value is available	Patient has a change from baseline to last available value of x m, no clinical event	-352 +x/1000
			No information of post-baseline 6MWT distance and no clinical event	-354
2	Missing data and clinical event (except death). A clinical event is defined as ongoing SAE or AE leading to treatment discontinuation and patient is alive at week 12	Ranked above patients who died, but below patients with missing data and no clinical event.	Patient has ongoing SAE or AE leading to treatment discontinuation, no information of week 12 6MWT distance and patient alive at week 12.	-356
3	Patient died before the measurement of 6MWT at week 12 was conducted.	Ranked by time to death from randomization	Patient died y days after randomization	-358+y/1000

Similar rules following the same strategy will be defined in the TSAP to impute missing values for the key secondary endpoints.

7.6 RANDOMISATION

The trial will be performed as a double-blind design with respect to placebo and empagliflozin. Patients will be randomised to the trial treatments in a 1:1 ratio.
No stratification will be performed in this trial.

Patients will be randomised in blocks to double-blind treatment via an IRT system. Approximately equal numbers of patients will be randomised to each treatment group.

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

7.7 DETERMINATION OF SAMPLE SIZE

In clinical studies, 30-50 meters have been variably reported as a meaningful distance achieved as a result of therapy [R17-1227].

The stardard deviation (SD) of 72 m is assumed for sample size considerations of this trial [R17-1225]. The risk of observing a higher SD in this trial will be mitigated by using duplicate measurements of 6MWT at baseline, Week 6 and Week 12 [R17-2791]. For none-missing values a normal distribution for change from baseline in distance walked in 6 minutes is assumed in all below sample size estimations.

The trial is designed to achieve a power of 90% for a two sided test at level $\alpha = 0.05$ to detect a difference between empagliflozin and placebo.

Using a normal distribution to calculate the probability that an observation X in Empagliflozin group will be less than an observation Y in the control group under the alternative, the following table presents the number of required evaluable patients for different assumed means of absolute difference in distance walked within 6 minutes as obtained by using the Wilcoxon sample size estimation procedure from commercial software nQuery Advisor® 7.0 statistical package by Statistical Solutions Ltd.

Table 7.7: 1 Sample size calculation

True treatment difference in distance walked in 6 minutes	SD	P(X<Y)	Required number of patients per group
30 m	72 m	0.384	131
40 m	72 m	0.347	76
50 m	72 m	0.312	50

A true treatment difference of 30 m is used as a conservative measure for sample size calculation to ensure that the study could detect the lowest effect size reported to be meaningful.

Therefore, a total of 131 evaluable patients per group are needed in order show a significant result for a two-sided test at level $\alpha = 0.05$ with a power of 90% not considering missing data.

To assess the impact of missing data a simulation with 100000 iterations was performed. A normal distribution for 6MWT distance was assumed and a total of 5%, 8% and 10% patients imputed to worst case as outlined in section 7.5 in each treatment group were investigated. The results are summarized in table 7.7: 2.

Table 7.7: 2 Simulation of imputation rules

N per group	Simulated true treatment difference for non-missing data [mean ± SD]	Percentage of missing data imputed to worst case	Power
150	30 ± 72	5%	90%
150	30 ± 72	8%	87%
150	30 ± 72	10%	85%

Therefore, a total of 150 patients per treatment group will allow for a drop-out and imputation of about 5% of the patients in order to show a significant result for a two-sided test at level $\alpha = 0.05$ with a power of 90%. With a drop-out rate of 10%, a total of 150 patients per treatment group would still yield a power of 85%.

7.7.1 Power estimation for key secondary endpoints

KCCQ

For power estimation of the KCCQ TSS a treatment difference of 5 points is assumed. In patients with heart failure previous studies have reported a standard deviation of the KCCQ TSS between 13 in the CONFIRM-HF trial and 19-21in the FAIR-HF trial [R17-1226, R17-3097].

Using a normal distribution to calculate the probability that an observation X in Empagliflozin group will be less than an observation Y in the control group under the alternative, a sample size of 150 per treatment group will result in approximately 55% to 90% power to detect a 5 point difference between treatment groups at an alpha-level of 5% using a Wilcoxon test, if all questionnaires are available at the end of the trial (see table 7.7.1: 1).

Due to the Hochberg procedure, if CHQ dyspnea is not significant, an alpha-level of 2.5% will become applicable. Table 7.7.1:1 therefore additionally shows an alpha-level of 2.5 %.

Table 7.7.1: 1 Power Estimation for KCCQ TSS

SD	P(X<Y)	Power for α = 5%	Power for α = 2.5%
13	0.393	89%	83%
15	0.407	79%	71%
17	0.418	69%	59%
20	0.430	55%	44%

While every effort will be made to collect the questionnaire for randomized patients regardless of being on or off treatment, about 5% missing questionnaires may be assumed and are considered for power evaluation in analogy with the primary endpoint.

Results of a simulation of the power with 100000 iterations to detect a 5 point difference between treatment groups in a Wilcoxon test with imputation rules analogously to the primary endpoint, assuming 5% missing questionnaires at week 12 in each treatment arm, a normal distribution for non-missing scores, and alpha of 5% is summarized in the table 7.7.1:2 below.

Table 7.7.1: 2 Simulation of Imputation Rules for KCCQ TSS

SD	Power for α = 5%	Power for α = 2.5%
13	85%	76%
15	73%	61%
17	61%	49%
20	47%	35%

Overall power is reasonable to evaluate superiority of empagliflozin versus placebo assuming a treatment effect of 5 points and a standard deviation that does not exceed 15 points.

CHQ

For power estimation of the CHQ dyspnea a treatment difference of 0.5 points is assumed [R99-1220]. CHQ and CRQ (an instrument almost identical to CHQ used in respiratory disease) are reported as performing similarly [R99-1220]. A standard deviation of the change from baseline of the standardized CRQ dyspnea score of 1.15 has been reported [R05-1404]. Similar data were also reported for CHQ [R17-2917]. Therefore, for power estimation, a standard deviation of 1 to 1.4 is assumed.

Using a normal distribution to calculate the probability that an observation X in Empagliflozin group will be less than an observation Y in the control group under the alternative, a sample size of 150 per treatment group will result in approximately 84% to 98% power per score to detect a 0.5 point difference between treatment groups at an alpha-level of 5% using a Wilcoxon test, if all questionnaires are available at the end of the trial (see Table 7.7.1:3).

Due to the Hochberg procedure, if KCCQ-TSS is not significant, an alpha-level of 2.5% will become applicable. Table 7.7.1: 3 therefore additionally shows an alpha-level of 2.5 %.

Table 7.1.1: 3 Power Estimation for CHQ-SAS

SD	P(X<Y)	Power for α = 5%	Power for α = 2.5%
1	*0.362*	98%	97%
1.2	*0.384*	93%	89%
1.4	*0.400*	84%	77%

While every effort will be made to collect the questionnaire for randomized patients regardless of being on or off treatment, about 5% missing questionnaires may be assumed and are considered for power evaluation in analogy with the primary endpoint.

Results of a simulation of the power with 100000 iterations to detect a 0.5 point difference between treatment groups in a Wilcoxon test with above imputation rules, assuming 5% missing questionnaires at week 12 in each treatment arm, a normal distribution for non-missing scores, alpha of 5% is summarized in the table 7.7.1: 4 below.

Table 7.1.1: 4 Simulation of Imputation Rules for CHQ-SAS

SD	Power for α = 5%	Power for α = 2.5%
1	98%	95%
1.2	90%	83%
1.4	79%	69%

Overall a power of approximately 70% or higher is expected to detect a difference of 0.5 for each score given the planned sample size of 150 patients per treatment group.

Calculations were performed using nQuery Advisor® 7.0 statistical package by Statistical Solutions Ltd and simulation was performed using R version 3.3.2 by The R Foundation for Statistical Computing.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in accordance with the Medical Devices Directive (93/42/EEC) and the harmonised standards for Medical Devices (ISO 14155, current version).

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 Standard Operating Procedures (SOPs), the European Union (EU) regulation 536/2014 and other relevant regulations.

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

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim 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 finalization 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.

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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 informed consent and any additional patient-

information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative."

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 informed consent form after confirming that the patient understands the contents. The investigator (or delegate) must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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

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

8.2 DATA QUALITY ASSURANCE

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

CRFs for individual patients will be provided by the sponsor. 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 patient. 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 CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the patient 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.
During the site visit the sponsor's CRA or auditor must be granted access to the original patient file (please see section 8.3.2). 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 from any copy of the patients' source documents before sending them to the sponsor.

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 CRF, data must be derived from source documents which must be stored appropriately, for example:

- Patient identification: gender, 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 (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, images and report of echocardiogram (from Visit 1) for the assessment of LVEF, ECG tracings 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 will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of 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 allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF 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). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

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

Sponsor:
The sponsor 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 and regulatory reporting obligation in accordance with regulatory requirements.

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. 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 World Health Organization (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, by the IRB / IEC and the regulatory authorities.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed insent.

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 (HA) 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).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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

An Executive Committee (ExC) consisting of independent experts (the Coordinating Investigators of this trial and of the 1245-0168 trial) and sponsor representatives will be established to support the Sponsor in designing the trials and successful execution. The composition of the ExC will be documented in the Trial Master File (TMF). The tasks and responsibilities will be agreed in contracts between the ExC members and the sponsor.

A Steering Committee (SC) consisting of independent experts and sponsor representatives will be established to support the Coordinating Investigators who will be the chairs of the SC. The composition of the SC will be documented in the Trial Master File (TMF). The tasks and responsibilities will be agreed in contracts between the SC members and the sponsor.

A Data Monitoring Committee (DMC) will be established. Members of the DMC are independent of BI, they are physicians experienced in the treatment of the disease under investigation and a statistician. The DMC will evaluate safety data. While DMC members may be unblinded, measures are in place to ensure the blinding for everyone else involved in the trial. Regular DMC meetings will be held at specified intervals. The DMC will recommend continuation, modification or termination of the trial as detailed in the DMC charter. DMC recommendations as well as the final BI decision will be reported to the

appropriate Regulatory Authorities (RAs)/ HAs, IRBs/ECs, and to investigators as requested by local law. The tasks and responsibilities of the DMC are specified in a charter.

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

Hepatic External adjudication for hepatic events
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 for example laboratory values, histological analysis, reports from ultrasound, computed tomography (CT), magnetic resonance imaging (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).

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

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

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

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

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

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

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

A central laboratory service and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.

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U12-2707-01 SCS appendix and integrated summary of safety 08 Feb 2013

10. APPENDICES

10.1 SIX MINUTE WALK TEST

10.1.1 General considerations for exercise testing

The methodology of the six minute walk test protocol is based on recommendations outlined by the American Thoracic Society (2002) [R03-0725, R17-3628].

10.1.2 Exercise performance variability

A number of physiological and psychological factors are known to affect exercise performance. Lack of attention to controlling these extraneous factors may result in a certain degree of variability in exercise performance. As such, the following pre-defined requirements have been put in place to reduce exercise performance variability:

Physiological:

- The patient's usual medical regimen should be continued
- Pre-exercise diet: Subjects are to be encouraged to eat breakfast before coming to the clinic. However, subjects should not eat within 2 hours of exercise tests.
- Hydration state: Subjects are to be encouraged to maintain an adequate hydration state during the morning of the exercise tests.
- Environmental conditions (temperature, humidity): Temperature and humidity should be controlled within the testing environment at comfortable levels.

Previous exercise:

- Fatigue: Subjects should be encouraged to stay well-rested and to refrain from any strenuous, fatiguing or exhausting activities (e.g., walking up hills, walking up many flights of stairs, running, cycling, shovelling snow, strenuous household chores) on the morning of exercise tests.

- Delayed onset muscular soreness (DOMS): Very strenuous, heavy type of activities, especially activities to which the subject is unaccustomed, can lead to muscle soreness 24-48 hours after the activity. Subjects should be encouraged to refrain from any type of heavy lifting, exhaustive digging in the garden etc., for 2-3 days prior to each clinic visit, especially if the subject has not performed these activities recently.

Psychological:

- Verbal encouragement: During exercise testing, the wording and intensity of verbal encouragement provided to the subject will be standardized, and will preferably only be

provided by one member of the trial team. Appropriate positive words should be used to encourage the patient to continue walking.

- Familiarity with surroundings: Trial staff should allow as much time as necessary for the subject to become comfortable with the testing environment surroundings.

- Distractions: During the exercise tests, access to the testing environment should be restricted to trial staff as much as possible. The noise level in the testing environment should be kept to a minimum, except for those sounds specifically related to the conduct of the test. This will ensure that the subject is able to concentrate on the task at hand, and will also ensure that the subject is attentive to the verbal encouragement provided by the designated member of the trial team.

- Comfort during the test: Subjects should be appropriately dressed for exercise (e.g., shorts or track pants, gym shoes, T-shirt or sweat shirt), and should use their usual walking aids during the test (cane, walker, etc.). Trial staff should ensure that the subject is comfortable with the environment prior to starting the exercise.

- Familiarity with test: Before starting exercise, a member of the trial team should make sure that the subject is completely familiar with the type of exercise that is to be performed.

- Performance incentives: No external incentives for performance (i.e., rewards for performance) should be given to the subject, especially as the subject nears the point of limitation, but also prior to or at any time during the exercise.

Heart rate and safety monitoring

- Heart rate and blood pressure will be measured before exercise, at end-exercise, five minutes after termination of exercise and when, for clinical reasons, it is required.

Personnel qualifications

- Exercise challenges should be conducted by adequately trained personnel with a basic knowledge of exercise physiology.

- Technicians familiar with normal and abnormal responses during exercise and trained in cardiopulmonary resuscitation (CPR) should be present throughout the test (see Safety Issues).

- Medically qualified personnel are required to be present for the first test. However, the supervising physician must be readily available during all tests to respond as needed. The degree of subject supervision should be increased if warranted by the clinical status of the subject.

10.1.3 Safety issues

Relative Contraindications:
The following conditions that preclude exercise testing should be assessed at each site visit prior to the 6MWT and patients with any of these findings can return to the study site within the visit window to complete the 6MWT if these measurements are resolved:

- Acute decompensated heart failure,
- A resting heart rate > 120bpm, SBP > 180mmHg and diastolic blood pressure (DBP) > 100mmHg.
- Symptomatic hypotension and symptomatic bradycardia
- Any condition that, in the opinion of the investigator, would impact the ability of the patient to perform the 6MWT

Stable exertional angina is not an absolute contraindication for a 6MWT, but patients with these symptoms should perform the test after using their antiangina medication, and rescue nitrate medication should be readily available.

Stopping rules:

Cardiac (e.g. bradyarrhythmias, ventricular tachycardia, myocardial infarction, heart failure, hypotension, and shock) and non-cardiac (musculoskeletal trauma, severe fatigue, dizziness, fainting, body aches) complications of exercise challenges have been reported.

Consequently during the test, study personnel should be alert to any abnormal event.

Indications to stop the test must be clearly established and known by the personnel involved in testing. Such symptoms are listed below:

- Acute chest pain,
- Sudden pallor,
- Loss of co-ordination / staggering,
- Mental confusion,
- Extreme dyspnea,
- Leg cramps,
- Diaphoresis.

The subject will be withdrawn from performing the 6MWT should any of these symptoms occur.

Safety requirements and rescue medication:

If the exercise test has been stopped for one of these reasons, the subject should be monitored in the laboratory until signs / symptoms / ECG modifications have completely cleared. Adequate safety equipment must be available at the test site according to local institutional

requirements and emergency medications are to be administered at the discretion of the Investigator such as:

- Oxygen,
- Fast-acting nitrate
- Anitplatelet agent
- Sphygmomanometer
- Telephone
- Automated electronic defibrillator or other safety measures as per institutional requirements

10.1.4 Conduct of the 6MWT

Location of the 6MWT:

The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The walking course must be 30 m in length and therefore a 100-ft hallway is required. The length of the corridor should be marked every 1m to 3m however the recommendation is to mark the course every 1m. The turnaround points should be marked with a cone (such as an orange traffic cone) and placed 0.5m from each extremity to enable the subject to not have to turn too abruptly. A starting line, which marks the beginning and end of each 60-m lap, should be marked on the floor using brightly colored tape.

Required equipment for the 6MWT:
The following equipment is required by the staff:

- Countdown timer
- Mechanical lap counter
- Two cones to mark the turnaround points
- A chair that can be easily moved along the walking course
- Worksheet on a clipboard
- Borg CR-10 scale
- 30 meters measuring tape
- Safety requirements as outlined in Section 10.1.3

Measurements:

- Repeat testing should be performed about the same time of day to minimize intraday variability.

- A “warm-up” period before the test should not be performed.

- The patient should sit at rest in a chair, located near the starting position, for at least 5 minutes before the test starts. During this time, check for contraindications, measure heart rate and blood pressure, and make sure that clothing and shoes are appropriate.

- Set the lap counter to zero and the timer to 6 minutes. Assemble all necessary equipment (e.g. lap counter, timer, worksheet, BORG CR-10 scale) and move the patient to the starting point.

- The patient should be asked to rate their baseline breathing discomfort and overall fatigue using the Borg Scale.

- The patient should be instructed as follows:

    - "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

    - You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

    - Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

    - "Are you ready to do that? I am going to use this counter to keep track of the number of shuttles (distance between the two cones) you complete. I will click it each time you turn around at this starting line. Remember that the objective is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.

    - Do you have any questions? Are you ready to start? Start now."

- You should stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.

- Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the shuttles. Each time the patient walks one length of the corridor, click the lap counter once (and mark the shuttle on the worksheet). Let the participant see you do it.

    - After the first minute, tell the patient the following (in even tones): "You are doing well. You have 5 minutes to go."

    - When the timer shows 4 minutes remaining, tell the patient the following: "Keep up the good work. You have 4 minutes to go."

- When the timer shows 3 minutes remaining, tell the patient the following: "You are doing well. You are halfway done."

- When the timer shows 2 minutes remaining, tell the patient the following: "Keep up the good work. You have only 2 minutes left."

- When the timer shows only 1 minute remaining, tell the patient: "You are doing well. You have only 1 minute to go."

- Do not use other words of encouragement (or body language to speed up).

- If the patient stops walking during the test and needs a rest, say this: "You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer. While the patient is stopped, standardised encouragement should be provided every 30 seconds: "Please resume walking whenever you feel able." The time that the patient stopped and the time that walking is recommenced should be recorded.

- If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

- When the timer is 15 seconds from completion, say this: "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."

- When the timer rings (or buzzes), say this: "Stop!" Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

- At the end of exercise the blood pressure and heart rate should be recorded. Repeat blood pressure and heart rate measurements will be taken 5 minutes later to assess recovery rate.

- The patient should be asked to rate their end of exercise breathing discomfort and overall fatigue using the Borg Scale.

- Record the number of shuttles from the counter (or tick marks on the worksheet).

- Record the additional distance covered (the number of meters in the final partial shuttle) using the course distance markers. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.

- Congratulate the patient on good effort and ask if they have any symptoms.

10.2 INCLUSION OF ILLITERATE PATIENTS

10.2.1 Patient Reported Outcome Measures

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

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

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

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

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

10.3 PATIENT REPORTED OUTCOME

10.3.1 KCCQ (Kansas City Cardiomyopathy Questionnaire)

THE KANSAS CITY CARDIOMYOPATHY QUESTIONNAIRE:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Please place an X in one box on each line

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

10.3.2 Chronic Heart Failure Questionnaire Self Administered – Standardized (CHQ-SAS)

First Administration

CHRONIC HEART FAILURE QUESTIONNAIRE
SELF ADMINISTERED – STANDARDIZED ACTIVITIES (CHQ-SAS)
FIRST ADMINISTRATION

Date completed: ☐☐ ☐☐ ☐☐☐☐
DAY MONTH YEAR

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. In the first section, you will be asked to answer questions about activities which make some people feel short of breath. In the next section, you will answer questions about your mood and how you have been feeling.

Please read these instructions for completing this questionnaire:

- Please read each question carefully and then place an "x" in the box beside the answer that best describes you.
- If you are unsure about how to answer a question, please give the best answer you can.
- If you would like to change an answer, put a line through the box you want to change. Place an "x" in the box beside the option you would like to choose instead.
- There are no right or wrong answers.
- Your answers to this questionnaire will be kept confidential.

Please continue to the next page.

CHRONIC HEART FAILURE QUESTIONNAIRE
SELF-ADMINISTERED STANDARDIZED ACTIVITIES (CHQ-SAS)
FIRST ADMINISTRATION

Below is a list of activities that make some people with heart problems feel short of breath.

For each of the items below, place an "x" in the box that best describes how much shortness of breath you have had while doing that activity during the **LAST 2 WEEKS**.

The last column has been provided for you to indicate if you have **NOT DONE** an activity during the last two weeks.

(Place an "x" in one box on each line.)

	Extremely short of breath	Very short of breath	Quite a bit short of breath	Moderate shortness of breath	Some shortness of breath	A little shortness of breath	Not at all short of breath	Not done
1 Feeling emotional, such as angry or upset	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐
2 Taking care of your basic needs (bathing, showering, eating or dressing)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐
3 Walking	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐
4 Performing chores (such as housework, shopping, groceries)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐
5 Participating in social activities	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐

Please continue to the next page.

CHRONIC HEART FAILURE QUESTIONNAIRE
SELF ADMINISTERED – STANDARDIZED ACTIVITIES (CHQ-SAS)
FIRST ADMINISTRATION

These next questions ask you about your energy in general and how your mood has been during the **LAST 2 WEEKS**. Please put an "x" in a box, from 1 to 7, that best describes how you have felt.

6. In general, how much of the time during the **LAST 2 WEEKS** have you felt frustrated or impatient?

1	All of the time	☐	
2	Most of the time	☐	
3	A good bit of the time	☐	
4	Some of the time	☐	(Place an "x" in one box only.)
5	A little of the time	☐	
6	Hardly any of the time	☐	
7	None of the time	☐	

7. What about fatigue? How tired have you felt over the **LAST 2 WEEKS**?

1	Extremely tired	☐	
2	Very tired	☐	
3	Quite a bit of tiredness	☐	
4	Moderately tired	☐	(Place an "x" in one box only.)
5	Somewhat tired	☐	
6	A little tired	☐	
7	Not at all tired	☐	

8. How often during the **LAST 2 WEEKS** have you felt inadequate, worthless, or as if you were a burden on others?

1	All of the time	☐	
2	Most of the time	☐	
3	A good bit of the time	☐	
4	Some of the time	☐	(Place an "x" in one box only.)
5	A little of the time	☐	
6	Hardly any of the time	☐	
7	None of the time	☐	

Please continue to the next page.

CHRONIC HEART FAILURE QUESTIONNAIRE
SELF-ADMINISTERED STANDARDIZED ACTIVITIES (CHQ-SAS)
FIRST ADMINISTRATION

9. How much energy have you had in the **LAST 2 WEEKS**?

1	No energy at all	☐	
2	A little energy	☐	
3	Some energy	☐	
4	Moderately energetic	☐	(Place an "x" in one box only.)
5	Quite a bit of energy	☐	
6	Very energetic	☐	
7	Full of energy	☐	

10. In general, how much of the time did you feel upset, worried or depressed during the **LAST 2 WEEKS**?

1	All of the time	☐	
2	Most of the time	☐	
3	A good bit of the time	☐	
4	Some of the time	☐	(Place an "x" in one box only.)
5	A little of the time	☐	
6	Hardly any of the time	☐	
7	None of the time	☐	

11. How much of the time during the **LAST 2 WEEKS** did you feel relaxed and free of tension?

1	None of the time	☐	
2	A little of the time	☐	
3	Some of the time	☐	
4	A good bit of the time	☐	(Place an "x" in one box only.)
5	Most of the time	☐	
6	Almost all of the time	☐	
7	All of the time	☐	

Please continue to the next page.

CHRONIC HEART FAILURE QUESTIONNAIRE
SELF-ADMINISTERED STANDARDIZED ACTIVITIES (CHQ-SAS)
FIRST ADMINISTRATION

12. How often during the **LAST 2 WEEKS** have you felt low in energy?

1	All of the time	☐	
2	Most of the time	☐	
3	A good bit of the time	☐	
4	Some of the time	☐	(Place an "x" in one box only.)
5	A little of the time	☐	
6	Hardly any of the time	☐	
7	None of the time	☐	

13. In general, how often during the **LAST 2 WEEKS** have you felt discouraged or down in the dumps?

1	All of the time	☐	
2	Most of the time	☐	
3	A good bit of the time	☐	
4	Some of the time	☐	(Place an "x" in one box only.)
5	A little of the time	☐	
6	Hardly any of the time	☐	
7	None of the time	☐	

14. How often during the **LAST 2 WEEKS** have you felt worn out or sluggish?

1	All of the time	☐	
2	Most of the time	☐	
3	A good bit of the time	☐	
4	Some of the time	☐	(Place an "x" in one box only.)
5	A little of the time	☐	
6	Hardly any of the time	☐	
7	None of the time	☐	

Please continue to the next page.

CHRONIC HEART FAILURE QUESTIONNAIRE
SELF-ADMINISTERED STANDARDIZED ACTIVITIES (CHQ-SAS)
FIRST ADMINISTRATION

15. How happy, satisfied, or pleased have you been with your personal life during the **LAST 2 WEEKS**?

1	Very dissatisfied, unhappy most of the time	☐
2	Generally dissatisfied, unhappy	☐
3	Somewhat dissatisfied, unhappy	☐
4	Generally satisfied, pleased	☐ (Place an "x" in one box only.)
5	Happy most of the time	☐
6	Very happy most of the time	☐
7	Extremely happy, could not be more satisfied or pleased	☐

16. In general, how often during the **LAST 2 WEEKS** have you felt restless, tense or uptight?

1	All of the time	☐
2	Most of the time	☐
3	A good bit of the time	☐
4	Some of the time	☐ (Place an "x" in one box only.)
5	A little of the time	☐
6	Hardly any of the time	☐
7	None of the time	☐

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE

10.3.3 Patient Global Impression of Change in Heart Failure Symptoms: shortness of breath, fatigue and swelling

Please choose one response below that best describes the overall change in your Heart Failure Symptoms specifically shortness of breath, fatigue and swelling, since you started taking the trial medication:

- ☐ Very much better
- ☐ Much better
- ☐ A little better
- ☐ No change
- ☐ A little worse
- ☐ Much worse
- ☐ Very much worse

10.3.4 Patient Global Impression of Change in Dyspnea

Please choose one response below that best describes the overall change in your shortness of breath (dyspnea) since you started taking the trial medication:

- ☐ Very much better
- ☐ Much better
- ☐ A little better
- ☐ No change
- ☐ A little worse
- ☐ Much worse
- ☐ Very much worse

10.3.5 Patient Global Impression of Severity of Heart Failure Symptoms: shortness of breath, fatigue and swelling

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

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

10.3.6 Patient Global Impression of Severity of Dyspnea

Please choose one response below that best describes your most recent experience of shortness of breath (dyspnea) when performing your usual activities:

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

10.4 CLINICIAN GLOBAL IMPRESSION

10.4.1 Clinician Global Impression of Change in CHF Severity

Considering your total clinical experience with this particular population, compared to the patient's condition at the baseline, this patient's condition is:

- ☐ N/A = Cannot be assessed
- ☐ 1 = Very much improved
- ☐ 2 = Much improved
- ☐ 3 = Minimally improved
- ☐ 4 = No change
- ☐ 5 = Minimally worse
- ☐ 6 = Much worse
- ☐ 7 = Very much worse

If the same Investigator is not able to assess the patient at each visit then please select the response 'N/A = cannot be assessed'.

10.4.2 Clinician Global Impression of Severity of CHF

Considering your total clinical experience with this particular population, how severely ill is the patient at this time?:

- ☐ Normal, not at all ill
- ☐ Mildly ill
- ☐ Moderately ill
- ☐ Severely ill
- ☐ Very severely ill

10.5 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

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

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 eCRF entry, 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).

10.7 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

10.8 ACCEPTED FORMS OF CONTRACEPTION FOR PATIENTS IN PORTUGAL

Women of child-bearing potential* must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. Such methods should be used throughout the study and the patient must agree to periodic pregnancy testing during participation in the trial.

Highly effective birth control methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence

*Women of child-bearing potential are defined as follows: Any female who has experience menarche and is not post-menopausal (defined as at least 12 months with no menses without an alternative medical cause) or who is not permanently sterilised (e.g. hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		16 May 2018
EudraCT number **EU number**		2017-004072-59
BI Trial number		1245-0167
BI Investigational Product(s)		Empagliflozin
Title of protocol		A phase III randomised, double-blind trial to evaluate the effect of 12 weeks treatment of once daily EMPagliflozin 10 mg compared with placebo on ExeRcise ability and heart failure symptoms, In patients with chronic **H**eArt **F**aiLure with **p**reserved **E**jection **F**raction (**HFpEF**) (EMPERIAL – preserved)
To be implemented only after approval of the IRB / IEC / Competent Authorities		X
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		Clinical Trial Protocol Cover Page and Synopsis.
Description of change		Phone: , Fax: **Was changed to:** Phone: , Fax:
Rationale for change		The contact information for the Coordinating Investigator was updated.
Section to be changed		Clinical Trial Protocol Synopsis: Main Inclusion Criteria, Section 3.3.2 Inclusion Criteria 9 and Section 4.2.2.1.

Description of change		Patients must be on appropriate and stable dose of oral diuretics, consistent with prevailing cardiovascular (CV) guidelines for at least 2 weeks prior to Visit 1. **Was changed to:** **Consistent with prevailing CV guidelines, if oral diuretics are prescribed to control symptoms,** patients must be on an appropriate and stable dose of oral diuretics~~, consistent with prevailing cardiovascular (CV) guidelines~~ for at least 2 weeks prior to Visit 1 **to control symptoms**.
Rationale for change		To clarify that it is not mandatory for patients to be on diurectics to be included in the trial. If diurectics are prescribed to relieve symptoms and volume overload as per heart failure guidelines, the dose must be appropriate and stable as per the inclusion criterion.
Section to be changed		Clinical Trial Protocol Synopsis: Main Exclusion Criteria, Section 3.3 and Section 3.3.3 Exclusion Criteria 3.
Description of change		**Clinical Trial Protocol Synopsis: Main Exclusion Criteria and Section 3.3.3 Exclusion Criteria 3:** Previous or current participation in another Empaglifozin Heart Failure trial (i.e. studies 1245.110, 1245.121, 1245-0168) **Was changed to:** Previous or current ~~participation~~ **randomisation** in another Empagliflozin Heart Failure trial (i.e. studies 1245.110, 1245.121, 1245-0168). **Section 3.3 the following text was added:** If a patient is a screen failure in one of the other Heart Failure trials with Empagliflozin they could be considered for this trial as long as they meet all eligibility criteria.
Rationale for change		This was clarified as only patients randomized in another Empagliflozin HF trial are not eligible for participation and patients who screen-failed in one of these other trials may be included into this trial.
Section to be changed		Flowchart and Section 6.2.1.
Description of change		**The following footnote was added to the flowchart for eGFR, safety labs, NT-proBNP:**

		* The screening procedures can be performed on different days within the time window. Specifically, it is recommended to have the NT-proBNP and safety lab measures (via central lab) measured as first step, especially in patients with no previous natriuretic peptide value available from clinical routine assessment in the past 6 months (refer to section 6.2.1) **The following text was added to section 6.2.1:** For patients with no BNP or NT-proBNP measurement available from clinical routine in the past 6 months indicative of the likelihood of eligibility for this study, it is recommended to split the screening visit into two steps and start with the measurement of NT-proBNP and safety lab measures (via central laboratory), wait for the results, and do the remaining screening assessments on a separate day (within the allowed visit window)
Rationale for change		To allow flexibility for performing screening procedures and to reduce screening efforts: By measuring NTproBNP first, the remaining screening procedures will no longer apply, if the NTproBNP result is indicative that the patient does not qualify for the study.
Section to be changed		Section 3.2, Section 5.1.3, Appendix 10.3.2
Description of change		**Section 3.2:** The Chronic Heart Failure Questionnaire (self-administered standardized format) (CHQ-SAS) is a heart failure-specific PRO measure with 20-items, designed to assess PRO [R17-2668], [R17-2969] in adult heart failure patients and specifically evaluates longitudinal change over time. The subscales of the CHQ-SAS are: dyspnea, fatigue, emotional function, and mastery. **Was changed to:** The Chronic Heart Failure Questionnaire (self-administered standardized format) (CHQ-SAS) is a heart failure-specific PRO measure with ~~20~~ **16**-items, designed to assess PRO [R17-2668], [R17-2969] in adult heart failure patients and specifically evaluates longitudinal change over time. The subscales of the CHQ-SAS are: dyspnea, fatigue

		and emotional function~~, and mastery~~. **Section 5.1.3:** The CHQ-SAS refers to the CHQ-self-administered format and contains 20 standardised questions pertaining to 4 domains: dyspnea, fatigue, emotional function and mastery. **Was changed to:** The CHQ-SAS refers to the CHQ-self-administered format and contains ~~20~~ **16** standardised questions pertaining to **4 3** domains: dyspnea, fatigue **and** emotional function ~~and mastery.~~ **Appendix 10.3.2: The final version of the questionnaire was updated accordingly.**
Rationale for change		The questionnaire in its final version does not contain the 4 questions pertaining to the Mastery domain.
Section to be changed		Section 3.3
Description of change		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 or transient result based on previously available laboratory results or in the opinion of the investigator. The re-test should be carried out as soon as possible so the laboratory test results will be received within the next planned visit window in order to avoid protocol window violations. This is also applicable for blood pressure and electrocardiogram (ECG) measurements. **Was changed to:** Re-testing for eligibility criteria is only to be performed once for **blood pressure, electrocardiogram (ECG) measurements** and laboratory result which is obviously received beyond stability at the central laboratory or thought to be a spurious or transient result based on previously available laboratory results or in the opinion of the investigator. The re-test should be carried out as soon as possible so the laboratory test results will be received within the next planned visit window in order to avoid protocol window

		violations. ~~This is also applicable for blood pressure and electrocardiogram (ECG) measurements.~~
Rationale for change		To clarify that re-testing can only be performed once per patient regardless of the reason for the re-testing.
Section to be changed		Section 3.3
Description of change		The following text was added: In instances where a patient is a screen failure in 1245-0168, all relevant completed screening procedures can be used for the eligibility assessment of the patient in 1245-0167 as long as they are completed during the original screening timeframe. The decision to screen the patient in the 1245-0167 trial should be based on Investigator judgement and in consultation with the Sponsor.
Rationale for change		To allow patients screened failed in the HFrEF trial to be considered for the HFpEF trial without need to have all screening examinations performed again.
Section to be changed		Section 3.3.3 Exclusion Criteria 22
Description of change		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 or knee replacement) within 90 days after Visit 1 **Was changed to:** 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 or knee replacement) **during the course of the trial** ~~within 90 days after Visit 1~~.
Rationale for change		To clarify the major surgery should not be performed while the patient is participating in the trial which could be longer than 90 days after Visit 1.
Section to be changed		Section 4.2.1 and Appendix 10.1.3 Safety requirements and rescue medication
Description of change		**Section 4.2.1:** The test should be performed in a location where a

		rapid, appropriate response to an emergency is possible. Supplies that must be available are: oxygen, sublingual nitroglycerine, acetylsalicylic acid, sphyngomanometer and telephone. **Was changed to:** The test should be performed in a location where a rapid, appropriate response to an emergency is possible. ~~Supplies that~~ **Adequate safety equipment** must be **readily** available **at the test site according to local institutional requirements and emergency medications are to be administered at the discretion of the Investigator such as**: oxygen, ~~sublingual nitroglycerine,~~ **fast-acting nitrate**, ~~acetylsalicylic acid,~~ **antiplatelet agent**, sphyngomanometer and telephone. **Appendix 10.1.3: Safety requirements and rescue medication** The following safety equipment should be available in the laboratory: • Oxygen, • Sublingual nitroglycerine, • Acetylsalicylic acid • Sphygmomanometer • Telephone **Was changed to:** ~~The following~~ **Adequate** safety equipment ~~should~~ **must** be available ~~in the laboratory~~ **at the test site according to local institutional requirements and emergency medications are to be administered at the discretion of the Investigator such as**: • Oxygen, • ~~Sublingual nitroglycerine~~ **Fast-acting nitrate** • ~~Acetylsalicylic acid~~ **Anitplatelet agent** • Sphygmomanometer • Telephone • **Automated electronic defibrillator or other safety measures as per institutional requirements**

<table>
<tr><td>Rationale for change</td><td></td><td>The class of medication is included instead of the individual medication to allow flexibility in what the site uses to treat patients in case of an emergency and to ensure local institutional requirements are followed.</td></tr>
<tr><td>Section to be changed</td><td></td><td>Section 4.2.2.1</td></tr>
<tr><td>Description of change</td><td></td><td>Patients must be on appropriate and stable dose of concomitant medications, consistent with prevailing CV guidelines for 4 weeks prior to Visit 1 to control HF symptoms and concomitant diseases.

Was changed to:
<s>Patients must be on appropriate and stable dose of concomitant medications, consistent with prevailing CV guidelines for 4 weeks prior to Visit 1 to control HF symptoms and concomitant diseases.</s>
Concomitant diseases should be treated according to best standard of care in accordance with local guidelines and recommendations.</td></tr>
<tr><td>Rationale for change</td><td></td><td>In accordance with prevailing guidelines, concomitant diseases (such as hypertension and coronary artery disease) should be treated according to the best possible standard of care and according to respective guidelines for these concomitant diseases.</td></tr>
<tr><td>Section to be changed</td><td></td><td>Table 5.1.6:1</td></tr>
<tr><td>Description of change</td><td></td><td>
<table>
<tr><td>JVD (cm H2O) (jugular venous distension)</td><td><=6</td><td>6-9</td><td>10-15</td><td>>=15</td></tr>
</table>
Was changed to:
<table>
<tr><td>JVD (cm H2O) (jugular venous distension)</td><td>≤6</td><td>6 < JVD <s>9</s> < 10</td><td>10 ≤ JVD <15</td><td>≥15</td></tr>
</table>
</td></tr>
<tr><td>Rationale for change</td><td></td><td>The JVD categories were corrected to avoid any overlap across the categories.</td></tr>
<tr><td>Section to be changed</td><td></td><td>Section 5.2.1</td></tr>
<tr><td>Description of change</td><td></td><td>Complete physical examination will include general appearance as well as evaluation of organ</td></tr>
</table>

		systems according to your routine practice. **Was changed to:** Complete physical examination will include general appearance as well as evaluation of organ systems ~~according to your routine practice~~ **including an assessment of the cardiovascular system.**
Rationale for change		A few cardiovascular parameters are to be captured in the case report form which are not necessarily part of the routine practice.
Section to be changed		Section 5.5.1
Description of change		For details on echocardiographic parameters please refer to appendix 10.6 and the ISF. **Was changed to:** For details on echocardiographic parameters please refer to appendix 10.7.
Rationale for change		All details of requested parameters are provided in the protocol and appendix reference corrected.
Section to be changed		Section 6.2.2
Description of change		The following text was added: **All Visit 2 assessments must be performed before the first dose is taken at the site. The assessments at Visits 3 and 4 must be performed post-dose. Patients should be instructed to take their medication on the morning of trial Visits 3 and 4. Visits should be routinely scheduled at approximately the same time of day for each visit.**
Rationale for change		This text was added to clarify performing of the procedures in relation to dosing.
Section to be changed		Section 5.1.8 and Section 7.7
Description of change		The following links were updated: To appendix 10.3.4 Table 7.7:2 Table 7.7.1:1 Table 7.7.1:3
Rationale for change		Updated links.
Section to be changed		Appendix 10.1.2
Description of change		Physicians are required to be present for the first test and for subsequent tests the supervising physician must be readily available to respond as needed. The degree of subject supervision should be increased if warranted by the clinical status of

		the subject. **Was changed to:** **Medically qualified personnel** ~~Physicians~~ are required to be present for the first test ~~and for subsequent tests.~~ **However,** the supervising physician must be readily available **during all tests** to respond as needed. The degree of subject supervision should be increased if warranted by the clinical status of the subject.
Rationale for change		To allow for other medically qualified personnel (i.e. nurse practitioner) to supervise the first test depending on the set-up of the site and tasks delegated by the Investigator.
Section to be changed		Appendix 10.1.4
Description of change		The length of the corridor should be marked every 1m to 3m. The turnaround points should be marked with a cone (such as an orange traffic cone) and 0.5m from each extremity to enable the subject to not have to turn too abruptly. **Was changed to:** The length of the corridor should be marked every 1m to 3m **however the recommendation is to mark the course every 1m.** The turnaround points should be marked with a cone (such as an orange traffic cone) and **placed** 0.5m from each extremity to enable the subject to not have to turn too abruptly. *Required equipment for the 6MWT:* The following equipment is required by the staff: • Countdown timer (or stopwatch) • Mechanical lap counter • Two small cones to mark the turnaround points • A chair that can be easily moved along the walking course • Worksheets on a clipboard • A source of oxygen • Spygmomanometer • Telephone • Automated electronic defibrillator **Was changed to:** *Required equipment for the 6MWT:* The following equipment is required by the staff:

		• Countdown timer ~~(or stopwatch)~~ • Mechanical lap counter • Two ~~small~~ cones to mark the turnaround points • A chair that can be easily moved along the walking course • Worksheet on a clipboard • **Borg CR-10 scale** • **30 meters measuring tape** ~~• A source of oxygen~~ ~~• Spygmomanometer~~ ~~• Telephone~~ ~~• Automated electronic defibrillator~~ • **Safety requirements as outlined in Section 10.1.3** During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate. **Was changed to:** During this time, check for contraindications, measure ~~pulse~~ **heart rate** and blood pressure, and make sure that clothing and shoes are appropriate. Assemble all necessary equipment (e.g. lap counter, timer) and move the patient to the starting point. **Was changed to:** Assemble all necessary equipment (e.g. lap counter, timer, **worksheet, BORG CR-10 scale**) and move the patient to the starting point. The patient should be asked to rate their baseline shortness of breath and overall fatigue using the Borg Scale. **Was changed to:** The patient should be asked to rate their baseline ~~shortness of breath~~ **breathing discomfort** and overall fatigue using the Borg Scale. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog. **Was changed to:** Remember that the object**ive** is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog. **The following text was moved up to follow**

		actual end of test order of procedures: At the end of exercise the blood pressure and heart rate should be recorded. Repeat blood pressure and heart rate measurements will be taken 5 minutes later to assess recovery rate. The patient should be asked to rate their end of exercise shortness of breath and overall fatigue using the Borg Scale. **Was changed to:** The patient should be asked to rate their end of exercise ~~shortness of breath~~ **breathing discomfort** and overall fatigue using the Borg Scale. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. **Was changed to:** Record the additional distance covered (the number of meters in the final partial ~~lap~~ **shuttle**) using the ~~markers on the wall as distance guides~~ **course distance markers**. Congratulate the patient on good effort and offer a drink of water. **Was changed to:** Congratulate the patient on good effort and ~~offer a drink of water~~ **ask if they have any symptoms.**
Rationale for change		Editorial changes and clarifications regarding the conduct of the 6MWT.

11.2 GLOBAL AMENDMENT 2

Date of amendment		
EudraCT number **EU 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: c17450485 **Technical Version Number:2.0**

Document Name: clinical-trial-protocol-version-2

Title: A phase III randomised, double-blind trial to evaluate the effect of 12 weeks treatment of once daily EMPagliflozin 10 mg compared with placebo on ExeRcise ability and heart failure symptoms, In patients with chronic HeArt FaiLure with preserved Ejection Fraction (HFpEF) (EMPERIAL – preserved)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor		17 May 2018 14:41 CEST
Approval-Team Member Medicine		17 May 2018 14:44 CEST
Author-Trial Statistician		17 May 2018 16:33 CEST
Approval-Therapeutic Area		19 May 2018 18:20 CEST
Verification-Paper Signature Completion		23 May 2018 21:14 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed