CLINICAL TRIAL PROTOCOL

	Document Number:	c14878151-05
EudraCT No.: **EU Trial No:**	2017-000376-28	
BI Trial No.:	1245.148	
BI Investigational Product:	Empagliflozin	
Title:	EMPA-VISION: A randomised, double-blind, placebo-controlled, mechanistic cardiac magnetic resonance study to investigate the effects of empagliflozin treatment on cardiac physiology and metabolism in patients with heart failure	
Lay Title:	A study that looks at the function of the heart in patients with heart failure who take empagliflozin	
Clinical Phase:	III	
Trial Clinical Monitor:	[redacted] Tel: [redacted]	
Investigators:	**Chief Investigator** [redacted] Tel: [redacted] Fax:	**Principal Investigator** [redacted] Tel: [redacted] Fax:
Status:	Final Protocol (Revised Protocol (based on Global Amendment 2))	
Version and Date:	**Version:** 3	**Date:** 14 Aug 2018

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Finished product name	Jardiance
Active ingredient name:	Empagliflozin
Protocol date	29 March 2017
Revision date	14 Aug 2018
Trial number	1245.148
Title of trial:	EMPA-VISION: A randomised, double-blind, placebo-controlled, mechanistic cardiac magnetic resonance study to investigate the effects of empagliflozin treatment on cardiac physiology and metabolism in patients with heart failure
Investigators:	**Chief Investigator** [redacted] Tel: [redacted] Fax [redacted] **Principal Investigator** [redacted] Tel: [redacted] Fax: [redacted]
Trial site:	[redacted]
Clinical phase:	III
Objective:	The objective of this trial is to assess the effect of empagliflozin on cardiac physiology and metabolism aiming to provide a scientific explanation of the underlying mechanism by which empagliflozin improves Heart Failure (HF) related outcomes in patients with chronic heart failure.
Methodology:	Randomised, double-blind, placebo-controlled trial
Number of patients entered:	Approximately 86 randomised, to achieve 60 evaluable patients (30 in each cohort)
Number of patients on each treatment:	Approximately 43 in each cohort, randomised 1:1 to treatment groups
Diagnosis :	Cohort A: Heart Failure (HF) with reduced ejection fraction

	(HFrEF) Cohort B: Heart Failure (HF) with preserved ejection fraction (HFpEF)
Main inclusion criteria	• Chronic heart failure diagnosed at least 3 months before informed consent • NYHA class II-IV at screening **Cohort A (HFrEF)** • LVEF ≤ 40% as measured by echocardiogram (ECHO) at screening • The following signs of heart failure; o Elevated NT-proBNP (>125 pg/mL) at screening in patient without atrial fibrillation (AF) o Elevated NT-proBNP (>600 pg/mL) at screening in patient with AF **Cohort B (HFpEF)** • LVEF ≥ 50% as measured by ECHO at screening and no previous measurement of LVEF ≤ 40%. • The following combined signs of heart failure; o Structural heart disease (Left Atrial (LA) enlargement [Left Atrial Volume Index (LAVI) >34 mL/m^2] and/or Left Ventricular Hypertrophy (LVH) [Left Ventricular Mass Index (LVMI) ≥ 115 g/m^2 for males and ≥ 95 g/m^2 for females]) by ECHO at screening or within 3 months prior to informed consent AND o NT-proBNP > 125pg/mL at screening in patient without AF or NT-proBNP > 600 pg/mL in patient with AF
Test product:	Empagliflozin
dose:	10 mg once daily
mode of administration:	Oral
Comparator products:	Placebo matching Empagliflozin
dose:	Not applicable
mode of administration:	Oral

Duration of treatment:	12 weeks
Endpoints	• Primary endpoint: Change from baseline to week 12 in Phosphocreatine/Adenosine Triphosphate (PCr/ATP) ratio in resting state measured by ^{31}P Magnetic Resonance Spectroscopy (MRS) • There are no secondary endpoints defined for this trial • All other endpoints are exploratory
Safety criteria:	• Adverse events (AE) • AE of special interest (AESI) • Incidence and intensity of AE including serious AE (SAE) • Withdrawal from trial medication due to AE • Clinically relevant new finding or worsening of existing condition on physical examination • Clinically relevant changes in laboratory measurements from baseline
Statistical methods:	The analysis will be performed on the per protocol set (PPS) of patients having a valid PCr/ATP ratio measurements available at baseline and at week 12, and not having an important protocol violation relevant to the primary endpoint. Change from baseline of cardiac energetics (PCr/ATP ratio) at rest after 12 weeks of treatment will therefore be analysed by an analysis of variance (ANOVA) model. The model will include treatment, presence of atrial fibrillation at baseline (Yes/No) and history of diabetes (Yes/No) as fixed effects. All planned analyses will be conducted separately on the two cohorts.

FLOWCHART

Trial Period	**Screening**	**Treatment**			**Follow-up***
Visit	**1**	**2****	**3**	**4****	**5**
Timing	**1-21 days prior to randomisation**	**Day 1**	**Day 15** ±1 day	**Day 84/ EOT** ±4 days	**7-14 days after last dose**
Informed consent	X				
Demographics, alcohol and smoking history	X				
NYHA classification	X			X	
Cardiac computed tomography (CT) scan	X[1]				
Echocardiogram (ECHO)	X[1]	X[2]	X	X	
Safety laboratory tests (blood)	X	X[2]		X	
Safety laboratory tests (urine)			X[3]		
Blood sampling for NT-proBNP asessment	X				
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
12 lead-electrocardiogram (ECG)	X[1]	X[2]		X	
Vital signs	X	X[2]	X	X	
Height	X				
Weight	X	X[2]	X	X	
Pregnancy test[4]	X	X	X	X	
Review of in-/exclusion criteria	X	X			
Medical history	X				
Physical examination	X			X	
Randomisation		X			
Dispense trial medication		X			
Administer trial medication		Continuous daily dosing[5]			
Medication compliance check			X	X	
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
Cardiac Magnetic Resonance (CMR)		X		X	
[redacted]		[redacted]		[redacted]	
Adverse events	X	X	X	X	X
Concomitant therapy	X	X	X	X	X
Telephone call to patient					X
Completion of patient participation					X

* The follow-up visit must be completed for all randomised patients, including those who withdraw prematurely (see Section 3.3.4.1), unless the patient has withdrawn consent to follow-up. The follow-up visit is expected to be performed via a telephone call, but a clinic visit may be performed at the discretion of the investigator.

** Patients must be fasting at Visits 2 and 4. See Section 6 for restrictions on the order of assessments during Visit 2 and Visit 4.

1 If ischaemic clinical testing has been performed within 6 months and written results are available and adequate to assess eligibility, a cardiac CT is not required at screening. If echocardiogram and/or electrocardiogram is/are performed as part of standard care within 3 months prior to informed consent, and written results are available, the assessment does not need to be repeated during the screening visit and the existing scan(s) can be used to assess eligibility.

2 The following assessments do not need to be repeated at visit 2 if performed within the previous 7 days; Safety laboratory tests (blood), Electrocardiogram, Vital signs, Weight. The echocardiogram does not need to be repeated at visit 2 if performed within the previous 21 days.

3 At Visit 3 only a urine test for ketone bodies is required.

4 For women of childbearing potential either a urine or serum pregnancy test is required.

5 Daily dosing should continue until the last dose is taken on the day of Visit 4.

[redacted]

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ABBREVIATIONS

[redacted]	[redacted]
ACE	Angiotensin-converting enzyme
ACR	Albumin Creatinine Ratio
AE	Adverse Event
AESI	Adverse Event of Special Interest
AF	Atrial Fibrillation
ALT	Alanine-Aminotransferase
AMP	Auxiliary Medicinal Product
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor blocker-Neprilysin Inhibitor
ARO	Academic Research Organisation
AST	Aspertate-Aminotransaminase
ATP	Adenosine Triphosphate
BI	Boehringer Ingelheim
BMI	Body Mass Index
[redacted]	[redacted]
BP	Blood Pressure
BRPM	Blinded Report Planning Meeting
CA	Competent Authority
CAD	Coronary Artery Disease
CCTA	Coronary Computer Tomographic Angiography
CEC	Clinical Event Committee
CI	Confidence Interval
CK	Creatine Kinase
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Equation
CMR	Cardiac Magnetic Resonance
CPET	Cardiopulmonary Exercise Test
CRA	Clinical Research Associate
CRO	Clinical Research Organisation
CRT	Cardiac Resynchronisation Therapy
CT	Computed Tomography
CTP	Clinical Trial Protocol
CV	Cardiovascular
DILI	Drug Induced Liver Injury
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
eC_{CR}	Estimated creatinine clearance
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
[redacted]	[redacted]
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
EOT	End of treatment
[redacted]	[redacted]
EudraCT	European Clinical Trials Database

[redacted]	[redacted]
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
[redacted]	[redacted]
HDL	High Density Lipoprotein
HF	Chronic Heart Failure
HHF	Hospitalisation for Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HR	Hazard Ratio
[redacted]	[redacted]
IB	Investigator's Brochure
ICD	Implantable Cardioverter Defibrillator
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IPV	Important Protocol Violation
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ITT	Intent to Treat
i.v.	Intravenous
[redacted]	[redacted]
LA	Left Atrial
[redacted]	[redacted]
LAVI	Left Atrial Volume Index
LDL	Low Density Lipoprotein
LGE	Late Gadolinium Enhancement
LPDD	Last Patient Drug Discontinuation
LV	Left Ventricular
LVAD	Left Ventricular Assist Device
LVEF	Left Ventricular Ejection Fraction
LVH	Left Ventricular Hypertrophy
LVMI	Left Ventricular Mass Index
MACE	Major Adverse Cardiovascular Event
MedDRA	Medical Dictionary for Drug Regulatory Activities
MI	Myocardial Infarction
MRA	Mineralocorticoid Receptor Antagonist
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NT-proBNP	N-terminal of the prohormone brain natriuretic peptide
NYHA	New York Heart Association Classification
PCr	Phosphocreatine
PK	Pharmacokinetics
PPS	Per Protocol Set
PSA	Prostate-Specific Antigen
[redacted]	[redacted]
RBC	Red Blood Cells
REP	Residual Effect Period, after the last dose of medication with measureable

	drug levels or pharmacodynamic effects still likely to be present
RER	Respiratory Exchange Ratio
RPE	Rating of Perceived Exertion
RS	Randomised Set
SAE	Serious Adverse Event
SBP	Systolic blood Pressure
SGLT-1	Sodium-glucose co-transporter 1
SGLT-2	Sodium-glucose co-transporter 2
SMQ	Standardised MedDRA Query
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TIA	Transient Ischaemic Attack
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of normal
UTI	Urinary Tract Infection
[redacted]	[redacted]
WBC	White Blood Cells
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Chronic heart failure (HF) is a progressive syndrome characterised by the inability of the heart to provide adequate blood supply to meet the metabolic demand of different tissues or do it at the expense of elevated left ventricle filling pressure. HF is a prevalent disease affecting an estimated 26 million people worldwide. In the United States alone the prevalence is 5.7 million, and there are 670,000 new cases per year [R16-1527]. In the UK, management of heart failure accounts for 1-2% of healthcare spending [P02-06417]. HF is associated with premature mortality and frequent hospitalisation. Approximately 50% of patients who develop HF die within 5 years after diagnosis [P16-03952]. Annually, more than 1 million patients are hospitalised with a primary diagnosis of HF. HF is the most common cause of hospitalisation among individuals above 65 years of age in the western countries [P16-03760]. Two types of HF have been defined mainly based on the LV ejection fraction (EF) and also other structural changes in heart muscle. They consist of heart failure with reduced EF (HFrEF) ≤40% and heart failure with preserved EF (HFpEF) ≥40%. Relative prevalence of HFpEF among HF patients is approximately 50% [R16-1528]. Amongst patients with HF who require hospitalisation, the proportion of HFpEF is rising. Analysis of a large HF registry showed that the proportion of patients hospitalised with HF (HHF) who had HFpEF increased from 33% in 2005 to 39% in 2010 [R16-1529]. The rate of rehospitalisation among patients with HFrEF is close to 29% within 60-90 days of hospitalisation discharge which is equal to HFpEF [R16-1527].

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

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

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

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

In 2010 Boehringer Ingelheim (BI) initiated the EMPA-REG OUTCOME trial to explore CV benefit of the drug as well as to establish the safety profile of empagliflozin [P15-09840]. This trial completed in 2015 and showed empagliflozin, when given in addition to standard care treatment in high CV risk patients with T2DM, reduced 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 a reduction of 35% in HHF and a reduction of 34% in the prespecified and adjudicated composite outcome of "HHF or CV death".

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

1.2 DRUG PROFILE

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

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

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

1.2.1 Non-clinical assessment of safety

For further information regarding pre-clinical evaluation, please refer to the current version of the Investigator Brochure (IB) for empagliflozin [c01678844].

1.2.2 Clinical pharmacokinetics

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

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

1.2.3 Clinical efficacy and safety

Approximately 550 healthy volunteers were exposed to empagliflozin (up to 800 mg single dose and up to 50 mg multiple dosing). Approximately 10,000 patients with T2DM have been

treated with empagliflozin in research studies. Empagliflozin was tested in over 4600 patients with T2DM and high CV risk for median treatment duration of 2.6 years in the EMPA-REG OUTCOME trial.

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

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

In clinical studies, empagliflozin was well tolerated in both healthy volunteers and patients with T2DM including patients with high CV risk up to a median duration of 2.6 years. The frequency of overall AEs, AEs leading to discontinuation and SAEs were comparable to placebo. There was no significant increase in frequency of hypoglycaemia with empagliflozin compared to placebo except when used in combination with a sulphonylurea or basal insulin. In general there was a small increase in frequency of urinary tract infections (UTIs) compared with 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 statistically or clinically significant changes in triglycerides. No clinically significant changes in electrolytes were observed with empagliflozin.

Diabetic ketoacidosis was reported infrequently and at similar rates in the empagliflozin and placebo treatment groups in the T2DM clinical program. 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).

1.3 RATIONALE FOR PERFORMING THE TRIAL

Heart failure is an important public health problem, and one of the leading causes of hospitalisation in the Western countries. With the increasingly ageing population and increasing incidence of obesity, the scope and cost to society associated with this condition will progressively rise. There is an unmet medical need in treatment of patients with HF.

Despite advances in the management of HF, no new therapies have been found to improve outcomes by reducing mortality or morbidity (i.e. CV death or HHF) in HFpEF patients [P16-03760]. HF also significantly decreases health-related quality of life (HRQOL) and pharmacological therapies have not shown consistent improvement in HRQOL.

In the EMPA REG OUTCOME® trial, empagliflozin showed clinically significant reductions of HHF events which was a prespecified exploratory endpoint (HR=0.65) in patients with T2DM and established CV disease. This led to the hypothesis that empagliflozin may provide significant benefits in HF outcome in patients with chronic heart failure. Thus two clinical trials have been designed to further investigate the efficacy and safety of empagliflozin in heart failure patients (c03946327 and c09098452). Whilst these trials will provide more information on efficacy and safety, they are not designed to provide detailed information on the mechanism of action of empagliflozin on cardiac function.

Chronic heart failure is multifactorial. There are many reasons why a human heart can fail, but the available evidence suggests that altered energetics play an important role in the mechanisms of heart failure. In cardiomyocytes, ATP is synthesised and converted to PCr by Creatine Kinase (CK). The PCr/ATP ratio reflects the energetic state of the heart and can be assessed by ^{31}P-MRS. When ATP demand outweighs synthesis (e.g. in ischemia or during exercise), PCr levels fall, resulting in a low PCr/ATP ratio. The current study will test the hypothesis that empagliflozin treatment leads to an increase in PCr and hence an increase in PCr/ATP ratio. This in turn leads to improved cardiac energetics (both resting and stress) and cardiac function, including exercise capability.

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

Investigators will be encouraged to treat participants to best standard of care in compliance with the local guidelines and recommendations for HF, and Diabetes Mellitus (DM) if present. Based on the putative mechanism of actions (reviewed in Section 1.3) and the result of the EMPA-REG OUTCOME trial, it is assumed that patients with HF should benefit from empagliflozin treatment on top of guideline-directed therapies. The safety profile of empagliflozin in these patients is expected to be comparable to that previously observed in over 10,000 patients with T2DM treated with empagliflozin, including patients with high CV risk. Safety will be ensured by close monitoring of the subjects for AEs both clinically and by laboratory testing. Special attention will be paid to prevent metabolic acidosis, ketoacidosis and diabetic ketoacidosis (DKA). For further details refer to Section 4.2.1.

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.

Some of the assessment techniques used in this trial are not standard in heart failure patients. Patients will be provided with full information about the anticipated risks of these procedures to enable them to make an informed decision about participation.

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

Although rare, a potential for drug induced liver injury (DILI) is under constant surveillance by the Sponsor and regulators. Therefore this trial requires timely detection, evaluation and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety, see also Section 5.3.5.1.

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

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The objective of this trial is to assess the effect of empagliflozin on cardiac physiology and metabolism aiming to provide a scientific explanation of the underlying mechanism by which empagliflozin improves HF related outcomes in patients with chronic heart failure.

2.1.2 Primary endpoint

The primary endpoint is the change from baseline to week 12 in PCr/ATP ratio in the resting state measured by ^{31}P MRS.

2.1.3 Secondary endpoints

There are no secondary endpoints defined for this trial.

[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This randomised, double-blind, placebo-controlled trial investigates the effects of empagliflozin on cardiac metabolism and function in heart failure patients. Empaglifozin will be compared to placebo as add-on to standard of care treatment in heart failure patients. The effects of empagliflozin will be assessed independently in two separate cohorts of patients; those with reduced ejection fraction (rEF) and those with preserved ejection fraction (pEF), but the randomised treatment and trial assessments for both cohorts are identical.

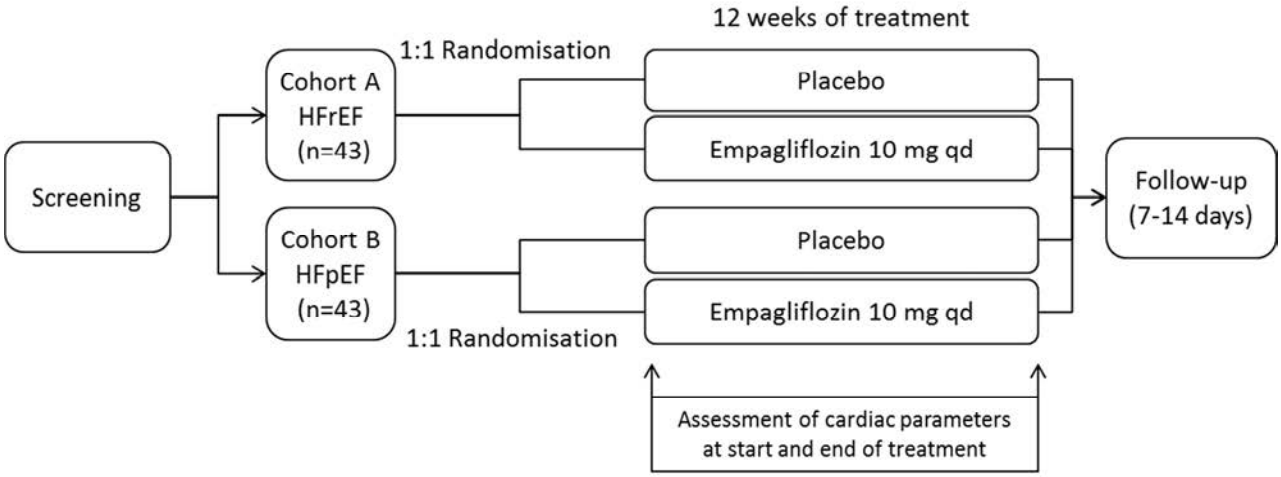


Figure 3.1: 1 Trial design

3.1.1 Administrative structure of the trial

3.1.1.1 Clinical Event Committee for Diabetic ketoacidosis (DKA)

An independent external committee (CEC) will be established to adjudicate centrally and in a blinded fashion events suspected of DKA (for further details see Section 5.3.5.1).

For any events that qualify for adjudication, study sites will be asked to provide clinical documentation such as laboratory values, discharge summaries etc. to support the external event adjudication.

The tasks and responsibilities of the CEC will be specified in a charter. The CEC will maintain the adjudication results in writing. The assessments will be analysed and reported based on empagliflozin data combined from multiple trials (i.e. on project level).

3.1.1.2 Hepatic external adjudication

Certain hepatic events will be adjudicated by external independent experts for severity and causal relationship with the trial medication in a blinded fashion. The events which will be reviewed are defined in a charter for hepatic events. Events may either be defined by abnormal laboratory values and/or relevant adverse events or both. For example, assessments will be made for hepatic injury events, including liver enzyme elevations.

For qualifying events, relevant source documents generated from any medical evaluations of these events will be requested including laboratory values, histological analysis, results of ultrasound, CT, MRI, scintigraphy, hospital discharge letters, and medical reports from other physicians. All evaluations will be performed in a blinded fashion. The assessments will be analysed based on empagliflozin data combined from multiple trials (i.e. on project level).

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

The trial follows a standard randomised double-blind design so that the effects of empagliflozin in heart failure patients can be assessed without bias. The chosen comparator is placebo so that any differences observed between the groups can be attributed to empagliflozin. The two cohorts are independent and therefore unblinding may be performed at different timepoints if required. Unblinding of a cohort will only be performed following the completion of that cohort.

The duration of treatment is 12 weeks and this has been chosen because the expected effects of empagliflozin on cardiac energetics and function are expected to be observed at this timepoint based on observations from other similar compounds [R17-1107] and from the EMPA-REG trial [P15-09840].

3.3 SELECTION OF TRIAL POPULATION

The trial will be conducted in a single centre specialising in cardiac imaging. Approximately 180 patients will be screened in total in order to identify 43 eligible patients for each cohort. Screening will continue until 43 eligible patients have been randomised into each cohort. Once one cohort is full, recruitment into that cohort will be closed and patients will only be screened for the cohort which remains open. Any patients already in screening at the time a cohort is closed will be allowed to continue to randomisation if eligible.

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 of patients who do not meet the inclusion/exclusion criteria will not be permitted, however assessments may be repeated within the screening period and the latest assessment prior to randomisation must always be used to assess eligibility.

Cohort A will contain 43 patients with heart failure with reduced ejection fraction (HFrEF) and Cohort B will contain 43 patients with heart failure with preserved ejection fraction (HFpEF). Within each cohort patients will be randomised 1:1 to receive either empagliflozin or matching placebo. A drop-out rate of 30% is expected and the total sample size for a cohort may be increased if the drop-out rate is higher than expected (Section 7.7).

Patients with T2DM will be eligible to enter the trial and are expected to account for 30-40% of randomised patients. There are no targets or restrictions on the recruitment of patients with T2DM but randomisation will be stratified according to history of diabetes (Yes/No) to ensure a balance between the arms (see also Section 7.1).

3.3.1 Main diagnosis for trial entry

The trial will be performed in patients with chronic heart failure. Patients with reduced ejection fraction (≤40%) or preserved ejection fraction (≥50%) will be included.

Patients who do not meet all of the inclusion criteria or who meet any of the exclusion criteria are not eligible for study participation and are not eligible to receive study medication. 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. Chronic heart failure diagnosed at least 3 months before informed consent
2. NYHA class II-IV at screening
3. Inclusion criterion no longer applicable
4. Age ≥ 18 years at screening
5. Male or female patients. Women of childbearing potential (WOCBP)[1] must be ready and able to use highly effective methods of birth control per ICH M3 (R2) [R09-1400] that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in Section 4.2.2 and also in the patient information.
6. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial

Cohort A (HFrEF)

7. Left ventricular ejection fraction (LVEF) ≤ 40% as measured by ECHO at screening
8. The following signs of heart failure;
    - Elevated NT-proBNP (>125 pg/mL) at screening in patient without atrial fibrillation (AF)
    - Elevated NT-proBNP (>600 pg/mL) at screening in patient with AF
9. Appropriate dose of medical therapy for HF (such as ACEi, ARB, β-blocker, oral diuretics, MRA, ARNI, ivabradine) consistent with prevailing local and international HF guidelines, stable for at least one week prior to Visit 1 and during screening period until Visit 2 (Randomisation) with the exception of diuretics which must be stable for at least one week prior to Visit 2 to control symptoms. If required, the investigator must document in the source documents the reason why the patient is not on the target dose per local guidelines.

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Tubal ligation is not a method of permanent sterilisation. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Cohort B (HFpEF)

10. Left ventricular ejection fraction (LVEF) ≥ 50% as measured by ECHO at screening and no previous measurement of LVEF ≤ 40%.
11. The following combined signs of heart failure;
    - Structural heart disease (LA enlargement [LAVI >34 mL/m^2] and/or LVH [LVMI ≥ 115 g/m^2 for males and ≥ 95 g/m^2 for females]) by ECHO at screening or within 3 months prior to informed consent

      AND

    - NT-proBNP > 125pg/mL at screening in patient without AF or NT-pro-BNP > 600 pg/mL in patient with AF
12. Oral diuretics, if prescribed, should be stable for at least one week prior to Visit 1 and during screening period until Visit 2 (Randomisation).

3.3.3 Exclusion criteria

1. Stroke or transient ischaemic attack (TIA) within 6 months prior to informed consent.
2. Any patients with myocardial scars and/or non-viable myocardium in the interventricular septum, unstable angina due to significant coronary artery disease (CAD), or major (in the opinion of the investigator) cardiovascular surgery.
3. Any contraindication for MRI, CPET and/or dobutamine stress test in accordance with the institution guidance, including implanted left ventricular assist device (LVAD), implantable cardioverter defibrillator (ICD), cardiac resynchronisation therapy (CRT) or any cardiac device.
4. Heart transplant recipient or listed for heart transplant
5. Cardiomyopathy based on infiltrative diseases (e.g. amyloidosis), accumulation diseases (e.g. haemochromatosis, Fabry disease), muscular dystrophies, cardiomyopathy with reversible causes (e.g. stress cardiomyopathy), hypertrophic obstructive cardiomyopathy or known pericardial constriction
6. Moderate to severe uncorrected valvular heart disease, obstructive or regurgitant, or any valvular heart disease expected to lead to surgery in the Investigator's opinion
7. Acute decompensated HF (exacerbation of chronic HF) requiring intravenous (i.v.) diuretics, i.v. inotropes or i.v. vasodilators, or LVAD or hospitalisation within 1 week prior to Visit 1 (Screening), or during screening period until Visit 2 (Randomisation)
8. Systolic blood pressure (SBP) ≥ 180 mmHg at screening. If SBP >150 mmHg and <180mmHg at screening, the patient is ineligible if receiving 3 or more antihypertensive drugs
9. Symptomatic hypotension and/or a SBP < 100 mmHg at Screening
10. Atrial fibrillation which is uncontrolled in the opinion of the investigator
11. Untreated ventricular arrhythmia with syncope documented within the 3 months prior to informed consent in patients without ICD
12. Diagnosis of cardiomyopathy induced by chemotherapy or peripartum within the 12 months prior to informed consent

13. Symptomatic bradycardia or second or third degree heart block in need of a pacemaker after adjusting beta-blocker therapy or any other negative inotropic agents, if appropriate
14. Chronic pulmonary disease requiring home oxygen, oral steroid therapy or hospitalisation for exacerbation within 12 months prior to informed consent, or significant chronic pulmonary disease in the Investigator's opinion, or primary pulmonary arterial hypertension
15. 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 screening
16. Impaired renal function, defined as estimated Creatinine Clearance < 30 mL/min (using Cockcroft-Gault formula) or requiring dialysis, as determined at screening
17. Haemoglobin < 10 g/dL at screening
18. Type 1 Diabetes Mellitus (T1DM)
19. History of ketoacidosis
20. Major surgery (major according to the investigator's assessment) performed within 3 months prior to informed consent, or scheduled major elective surgery (e.g. hip replacement) within 3 months after Visit 1
21. Gastrointestinal (GI) surgery or GI disorder that could interfere with absorption of trial medication in the investigator's opinion
22. Any documented active or suspected malignancy or history of malignancy within 6 months prior to informed consent, except appropriately treated basal cell carcinoma of the skin, in situ carcinoma of uterine cervix or low risk prostate cancer (patients with pretreatment PSA <10 ng/mL, and biopsy Gleason score of ≤ 6 and clinical stage T1c or T2a)
23. Presence of any other disease than heart failure with a life expectancy of <1 year in the investigator's opinion
24. 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
25. Patients with requirement for treatment with empaglifozin according to local standard of care
26. Treatment with any SGLT-2 inhibitor or combined SGLT-1 and 2 inhibitor within 1 week prior to informed consent or during screening period until Visit 2 (Randomisation)
27. Currently enrolled in another investigational device or drug study, or less than 30 days between randomisation and ending another investigational device or drug study, or receiving other investigational treatment(s). Patients participating in a purely observational trial will not be excluded.
28. Known allergy or hypersensitivity to empagliflozin or other SGLT-2 inhibitors
29. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable trial subject or unlikely to complete the trial
30. Women who are pregnant, breastfeeding, or who plan to become pregnant while in the trial

31. Any 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

Every effort should be made to keep randomised patients in the trial until the completion of visit 4. Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to randomisation, as well as an explanation of the consequences of withdrawal.

Patients may potentially be withdrawn from trial treatment or from the trial as a whole ("withdrawal of consent") as described in Sections 3.3.4.1 and 3.3.4.2 below.

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

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 does not want to undergo the trial assessments at visit 4 required to assess the primary endpoint.
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication (see Section 4.2.2).
- The patient becomes pregnant. Note that the patient must be followed until the end of the pregnancy (see Section 5.3.5.2).
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, AEs or other diseases).
- The patient has repeatedly shown to be non-compliant with important trial procedures and/or, in the opinion of both the investigator and sponsor representative, is not willing or able to stick to the trial requirements in the future.

In the event that a patient is withdrawn from trial treatment prior to Visit 4, the patient should be asked to return all remaining trial medication. If the patient's agrees, the following EOT safety assessments will be conducted;

- Pregnancy test
- Safety laboratory tests
- Vital signs

In addition, if the patient agrees, the patient will have a follow-up visit 7-14 days after the last dose of trial medication.

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

3.3.4.2 Withdrawal of consent for trial participation

If a patient wants to withdraw consent to trial participation, the investigator should explain the difference between treatment withdrawal and withdrawal of consent for trial participation and explain the safety follow up after withdrawal from trial treatment as described in Section 3.3.4.1 above.

Patients may withdraw their consent for trial participation at any time without the need to justify the decision. If this occurs, no further information may be collected for the purpose of the trial and patient follow up for safety cannot occur.

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 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

Eligible patients will receive treatment with empagliflozin or matching placebo for 12 weeks.

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Empagliflozin

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

Table 4.1.1: 2 Placebo matching Empagliflozin

Substance:	Placebo matching Empagliflozin
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim
Unit strength:	Not applicable
Posology	1 tablet, once daily
Route of administration:	Oral

4.1.2 Selection of doses in the trial

Empagliflozin 10 mg and 25 mg tablets 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 x Pressure product, an index of myocardial oxygen consumption. These modes of actions support the scientific rationale of using empagliflozin in patients with HF.

In the EMPA-REG-OUTCOME trial (P16-06807) both approved doses were administered to patients with T2DM and were found to be equally effective in reducing CV death, HHF, and composite of HHF or CV death in patients with a history of cardiac failure (MedDRA narrow SMQ 20000004) at baseline.

In subgroup analysis, empagliflozin improved the main outcome of CV death and HHF with a 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 similar benefits to those seen with the 25mg dose may also be achieved with the 10 mg dose in the non-diabetic population. The mechanism of action is supported by studies in healthy volunteers where both doses were associated with about 50g/day excretion of glucose in the urine.

Given the lower exposure attained with 10 mg empagliflozin dosing and the similar general safety profile and CV efficacy observed with both empagliflozin doses, empagliflozin 10 mg once daily has been selected for this trial.

For further details see current version of the IB (c01678844).

4.1.3 Method of assigning patients to treatment groups

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

For information on stratification, please refer to Sections 3.3 and 7.1.

4.1.4 Drug assignment and administration of doses for each patient

Trial medication will be assigned via IRT at randomisation and dispensed in a double-blind manner. At Visit 2 the patient will be dispensed sufficient medication for the whole treatment period. Further dispensing will only occur in the event that the patient requires replacement medication. For further details regarding packaging 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 at approximately the same time every day, preferably in the morning. 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. On the day of Visit 4 the dose should be taken at the usual scheduled time, regardless of the timing of assessments.

For logistical reasons, Visit 4 can be scheduled on Day 84 ± 4 days. Daily dosing should continue until the day of Visit 4, when the last dose is taken. Sufficient extra medication is provided in case Visit 4 takes place later than Day 84.

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 within a cohort until after all patients in the cohort have completed the study and database lock has taken place. Database lock and subsequent unblinding may be performed independently for each cohort if required (e.g. if one cohort completes substantially earlier than the other).

The randomisation code of a cohort will be kept secret by Clinical Trial Support up to database lock for the cohort.

There are several examples of medications showing effects for patients with HFrEF but not for patients with HFpEF. The populations of the two cohorts are therefore considered to be independent: results in one cohort do not inform about possible results in the other cohort. Therefore independent unblinding is not expected to introduce bias on the ongoing cohort.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator 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. Whenever possible and if time allows, the need for unblinding will be discussed with the medical representative of the sponsor before the unblinding of trial medication takes place. The reason for unblinding must be documented in the source documents and/or on the appropriate eCRF page along with the date and the initials of the person who broke the code.

If unblinded, the patient may continue in the trial as planned, unless in the opinion of the investigator there is a reason why the patient must discontinue (see Section 3.3.4).

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 will not be shared further.

4.1.6 Packaging, labelling, and re-supply

The empagliflozin and matching placebo tablets will be packaged into wallets, each containing 91 tablets blister packaging. This is sufficient for 12 weeks of treatment (84 tablets) and one week of reserve (7 tablets). For further details of packaging and the description of the label, refer to the ISF.

The investigational products will be provided by BI or a designated Clinical Research Organisation (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.

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 process outlined in the ISF should be followed.

4.1.8 Drug accountability

The investigator and/or pharmacist and/or investigational drug storage manager will receive the investigational drugs delivered by the sponsor or delegate when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the 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

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 returning investigational product to the sponsor/CRO at the end of the trial, the investigator / pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patients and that no supplies will remain in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

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

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

The dobutamine administered during the MRS will be commercial stock supplied by the investigator's institution. It will be considered an auxiliary medicinal product (AMP) and administered as described in Section 5.2.4. AEs/SAEs related to dobutamine will be documented as described in Section 5.3.5.

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

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

Special attention must be paid to the prevention of ketoacidosis. All patients must be made aware of this risk and need to be instructed to contact the Investigator or other healthcare professional in case of symptoms of metabolic acidosis, ketoacidosis and DKA.

Cases of DKA have been reported in patients treated with empagliflozin, including fatal cases [c01678844]. 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 in this trial include patients on a very low carbohydrate diet (as the combination may further increase ketone body production), patients with an acute illness, patients with a history of pancreatitis or pancreatic surgery, patients with a history of alcohol abuse and patients with severe dehydration. Empagliflozin should be used with caution in these patients. In patients requiring insulin, caution should be taken when the dose of insulin is reduced.

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

There are no trial specific emergency procedures to be followed.

4.2.2 Restrictions

The use of any SGLT-2 inhibitors or combined SGLT-1 and 2 inhibitors except the blinded trial medication is prohibited during the course of the trial. This also includes the 7 day period between the EOT and the Follow Up Visit.

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

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.

Women of childbearing potential must use two medically approved methods of birth control throughout the study, and for a period of at least 7 days after last study drug intake. They must use one barrier method, i.e. condom or occlusive cap with spermicide, or vasectomised partner, and one highly effective non-barrier method including oral, injected or implanted hormonal contraceptives, intrauterine device or system.

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.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of tablets actually taken} \times 100}{\text{Number of tablets which should have been taken}}$$

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.

If the assessment of compliance at Visit 4 indicates a compliance of less than 80%, the investigator may decide to perform limited Visit 4 assessments (as defined in Section 3.3.4.1) as the patient will not be used for the primary analysis.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 New York Heart Association (NYHA) classification

The NYHA functional classification will be used to classify the severity of symptoms in the patients with heart failure (Appendix 10.1). The investigator should place the patients in one of the four categories based on how limited their physical activities are.

Candidates for screening are required to have a NYHA functional class II, III or IV.

5.1.2 Body weight and height

Measurement of height and body weight will be performed at the time points specified in the Flowchart.

Body Mass Index (BMI) (kg/m2) will be calculated at Visit 1 to determine eligibility.

5.2 ASSESSMENT OF CARDIAC EFFECTS OF EMPAGLIFLOZIN

An assessment of the effect of empagliflozin on cardiac metabolism function will be performed using the techniques described in the following section.

5.2.1 Echocardiogram (ECHO)

Transthoracic echocardiography will be used to evaluate cardiac structure and function according to British Society of Echocardiography [R17-0836]. The standard methodology of the institution will be used and the following clinical information will be recorded;

- Left Ventricular Ejection Fraction (LVEF), LV end-diastolic and end-systolic volumes, LV mass index
- Diastolic function (eg E/A, e', LA index)
- Chamber size including thickness and wall motion
- Haemodynamic status (cardiac output)
- Valves status

Further exploratory parameters may be recorded if required.

[redacted]

5.2.4 Cardiac Magnetic Resonance (CMR)

CMR will be performed on a 3.0 Tesla MR scanner. The same scanner will be used for the Visit 2 and Visit 4 scan for each patient. Prior to undergoing CMR scanning, the patient will be cannulated to allow the administration of contrast agent and dobutamine while in the scanner. The cannula will also be used to collect venous blood samples. All imaging will be done under fasting conditions for all participants. All participants will undergo a CMR and MRS protocol which is standard within the institution.

Cardiac MRI
Patients will lie in a supine position and a dedicated cardiac coil will be placed around their chest. Images will be obtained using breath hold and ECG gating. Cine images will be acquired for cardiac volumes, mass and function using steady state free precession cine imaging as recommended [R17-0837]. Tagged MR images will be acquired for measurement of LV strain using an ECG-triggered segmented k-space fast gradient echo sequence with spatial modulation of magnetization in orthogonal planes creating a square grid of parallel tag lines [R17-0838]. Late gadolinium enhancement (LGE) will be performed with an inversion-recovery-prepared, segmented gradient echo sequence after a 8-10 minute time delay

following administration of a gadolinium-based contrast agent for resting perfusion [R17-0695].

T1 mapping and extracellular volume quantification (ECV) will be performed using a shortened modified look-locker inversion recovery sequence [R17-0839]

Cardiac MR spectroscopy (^{31}P MRS and proton MRS)
^{31}P MRS (rest and dobutamine stress)
Rest^{31}P MRS will be performed to obtain the PCr/ATP ratio from a voxel placed in the midventricular septum, with the subjects lying prone with their heart over the centre of the phosphorus coil in the iso-centre of the magnet as previously described [R17-0693]. After resting spectroscopy, dobutamine will be infused intravenously at incremental rates between 5 and 40 mcg/kg with a target of 65% of age maximal heart rate. During this time, blood pressure will be measured every minute. Heart rate, pulse oximetry, and ECG will also be monitored continuously during both dobutamine infusion. Heart rate will be maintained at target for the duration of the scans (8-10 minutes for 31P-MRS) [R17-0697]. Where possible, additional cine imaging will be acquired at rest and during dobutamine stress for assessment of cardiac function.

1H MRS
Myocardial ^{1}H-MR spectra will be obtained from the mid-interventricular septum. Spectroscopic acquisitions will be performed using ECG trigger at end-expiration to minimize motion artefacts. Since water is the most abundant molecule in the human body water signal will be suppressed to amplify weaker lipid signal. Both spectra with and without water suppression (used as an internal standard) will be acquired [R17-0694].

Figure 5.2.4:1 gives an overview of the scanning process; all times are approximate and may be adjusted if required.

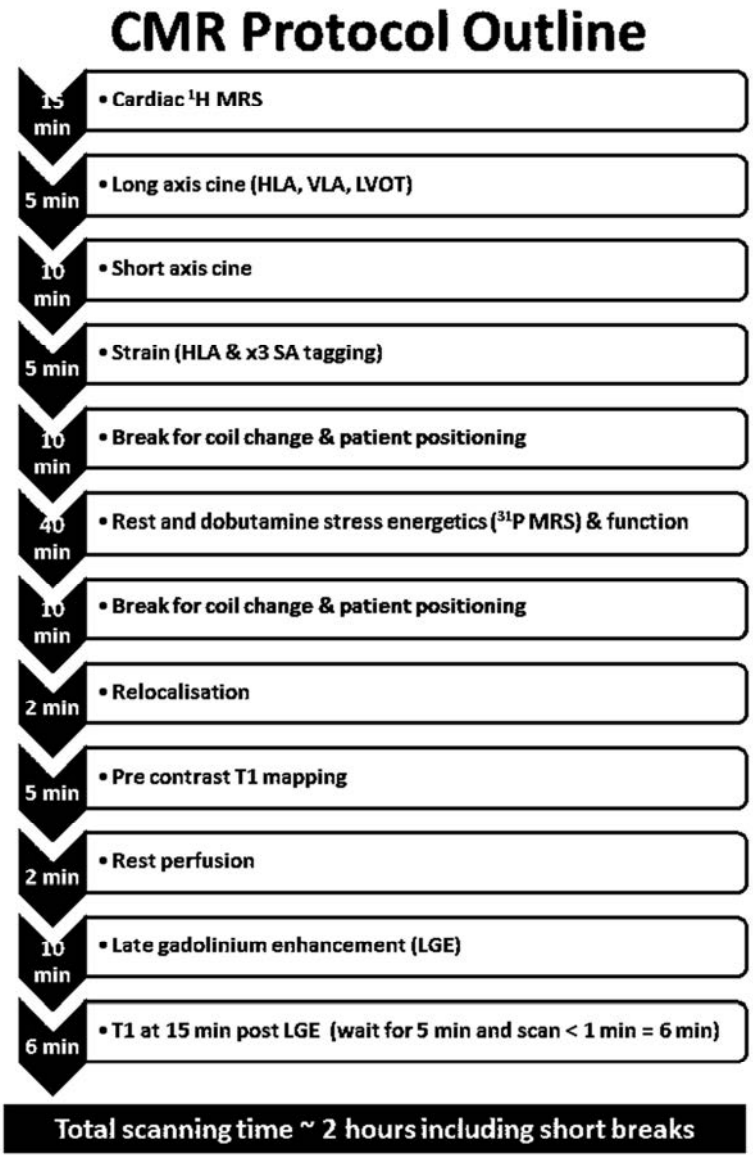


Figure 5.2.4: 1 CMR protocol summary

The following parameters are collected during the CMR assessment;

- Cardiac energetics (rest and dobutamine stress PCr/ATP ratio, ^{31}P MR Spectroscopy)
- [redacted]
- Strain (circumferential, longitudinal, radial, torsion, diastolic parameters)
- LV volumes, mass and function
- [redacted]
- Myocardial fibrosis, infarction (Late gadolinium enhancement)

[redacted]

Images obtained during CMR will be stored by the institution for at least 25 years.

5.2.5 Cardiac Computerised Tomography (CT) Scan

If ischaemic clinical testing has been performed within 6 months and written results are available and adequate (in the opinion of the investigator) to assess eligibility, a cardiac CT is not required at screening. Otherwise, a cardiac CT will be performed at screening to document the extent of any coronary artery disease. This may be performed at the investigator's institution or at an accredited facility chosen by the investigator.

Coronary computed tomographic angiography (CCTA) will be performed to assess eligibility and for quantification of epicardial fat volumes according to a standard methodology [R17-0690]. CCTA scans will be performed on 320-slice computed tomography scanner in accordance with performance guidelines from the Society of Cardiovascular Computed Tomography [R17-0840]. Participants will receive beta-blockade (intravenous metoprolol) and sublingual glyceryl trinitrate prior to the scan to achieve a heart rate of <60 beats/min. During the CCTA acquisition, intravenous iodinated contrast will be injected through a peripheral vein, followed by a saline flush. The scan will cover a region from 1 to 2 cm above the left main coronary artery to 1 to 2 cm below the myocardial apex in a single breath hold. CT images will also be reconstructed for epicardial fat volume quantification.

5.3 ASSESSMENT OF SAFETY

This trial does not have any safety endpoints. The examinations detailed in this section will be performed to monitor the safety of the patients whilst participating in the trial.

5.3.1 Physical examination

A complete physical examination will be performed at the time points specified in the Flowchart. Documentation of, and findings from the physical examination, must be part of the source documents available at the site.

5.3.2 Vital signs

Vital signs will be evaluated at the time points specified in the Flowchart, prior to blood sampling. Systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) will be measured in a supine position after 5 minutes of rest. Three measurements taken over approximately 10 minutes will be recorded. All recordings should be made using a similar type of and validated certified blood pressure recording instrument on the same arm.

5.3.3 Safety laboratory parameters

Safety laboratory samples will be collected at the timepoints indicated in the Flowchart. Safety laboratory parameters to be assessed are listed in Table 5.3.3:1. All analyses will be performed by a central laboratory. The respective reference ranges and details about sample handling and shipment will be provided in the ISF.

Table 5.3.3:1 Safety laboratory parameters – whole blood, serum or plasma tests

Haematology • Hematocrit • Haemoglobin • Reticulocyte Count • Red Blood Cells (RBC) / Erythrocytes • White Blood Cells (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) • ALT (alanine transaminase, SGPT) • AST (aspartate transaminase, SGOT) • Bicarbonate • Bilirubin total, fractionated if increased • Calcium • Chloride • Creatinine • Creatine kinase (CK) • Hs Troponin I (reflex tests if CK is elevated) • Glucose • Magnesium • Phosphate • Potassium • Protein total • Sodium • Urea (BUN) • Uric acid
Lipids • Cholesterol (total) • HDL cholesterol • Calculated LDL cholesterol • Triglycerides (reflex test for direct measurement of LDL cholesterol triggered if triglycerides are > 400 mg/dL or 4.52 mmol/L)

5.3.3.1 Creatinine

In addition to the central safety laboratory analyses above, at Visit 1, Visit 2 and Visit 4 there will be an additional creatinine test using one drop of blood from the collected blood samples. The purpose is to check patient safety and this will be analysed locally.

5.3.3.2 Renal function

Eligibility for the trial will be assessed using estimated Creatinine Clearance (eC_{CR}), calculated using the Cockcroft-Gault formula [R96-0690] (Appendix 10.3).

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

GFR = 141 × min (Scr /κ, 1)α × max(Scr /κ, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black]
where:
Scr is serum creatinine in mg/dL,
κ is 0.7 for females and 0.9 for males,
α is -0.329 for females and -0.411 for males,
min indicates the minimum of Scr /κ or 1, and
max indicates the maximum of Scr /κ or 1

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

Kidney function will be classified as described in the table below (Table 5.3.3.2:1).

Table 5.3.3.2: 1 Classification of kidney function

CKD stage	**eGFR (mL/min/1.73m²)**
1	≥ 90
2	60-89
3a 3b	45-59 30-44
4	15-29
5	< 15

5.3.3.3 Pregnancy testing

Pregnancy testing (in urine or serum) will be performed in female patients of child bearing potential according to the time points indicated in the Flowchart. Urine pregnancy test kits will be provided by the investigator site. For reporting of a pregnancy event refer to Section 5.3.5.2.

5.3.3.4 Urine test for ketone

At visit 3 (day 15) a urine sample will be taken and analysed locally for ketone.

5.3.3.5 Criteria for hypoglycaemic events

In Diabetes Mellitus (DM) patients, all symptomatic hypoglycaemia events, or severe hypoglycaemias (e.g. if the patient required assistance of another person), or any hypoglycaemia episode with glucose values < 54 mg/dL (< 3.0 mmol/L), or if the investigator considered the event to be an AE should be documented as an AE "hypoglycaemic event".

In non-diabetic or pre-diabetic patients, the investigator should consider and rule out other alternative causes for such symptoms and may measure blood glucose levels to confirm the diagnosis of hypoglycaemia.

5.3.3.6 Urinary tract infections and genital infections

Patients having a history of chronic/recurrent urinary tract infections (UTI) or genital infections, or an acute episode of UTI or genital infection at screening will be identified and the condition documented as medical history or baseline condition, as appropriate, in the eCRF.

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

5.3.4 Electrocardiogram (ECG)

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

In the event of any cardiac symptoms (i.e. suspicion of heart rhythm disorders or cardiac ischaemia) during the course of the trial, if an additional ECG is recorded at time of event, or later at the next regular visit, they will be evaluated, signed, dated and commented upon by the treating physician/Investigator and stored locally. Any clinically relevant new changes in the ECG (regardless of patients' symptoms) should be reported as AEs and followed up and/or treated locally until normal or stable condition.

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

5.3.5 Assessment of adverse events

5.3.5.1 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.

A copy of the latest list of "Always Serious AEs" will be provided in the ISF. These events should always be reported as SAEs as described above.

Note: Cancers of new histology and exacerbations of existing cancer must be classified as a serious adverse event regardless of the duration between discontinuation of the drug and the occurrence of the cancer and must be reported as described in Section 5.3.5.2.

Adverse events of special interest (AESIs)
The term 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, when observed at any timepoint after randomisation:
- an elevation of AST and/or ALT $\geq$3 fold ULN combined with an elevation of total bilirubin $\geq$2 fold ULN measured in the same blood draw sample, and/or
- aminotransferase (ALT, and/or AST) elevations $\geq$ 5 fold ULN

These laboratory 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 laboratory results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Decreased renal function

Decreased renal function is defined by a creatinine value showing a ≥ 2 fold increase from baseline and is above the ULN.

For the AESI "decreased renal function" the patient needs to be followed-up appropriately based on local clinical guidance.

Ketoacidosis

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

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

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

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.

5.3.5.2 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 eCRF(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 eCRF.

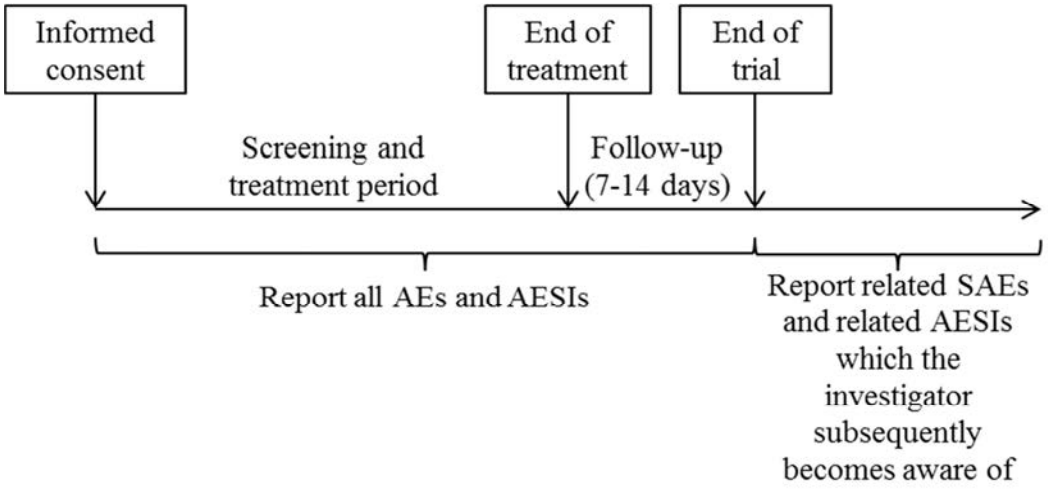


Figure 5.3.5.2: 1 Requirements for Adverse Event collection

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. The investigator should determine the causal relationship to the IMP and any possible involvement of the AMP.

The following should also be recorded as an (S)AE in the eCRF 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 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 and are captured and reported in the standard way for AEs and SAEs:

- Hypoglycaemic event

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

This list may be changed by the sponsor during the trial in response to new knowledge about the safety profile of empagliflozin.

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.

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

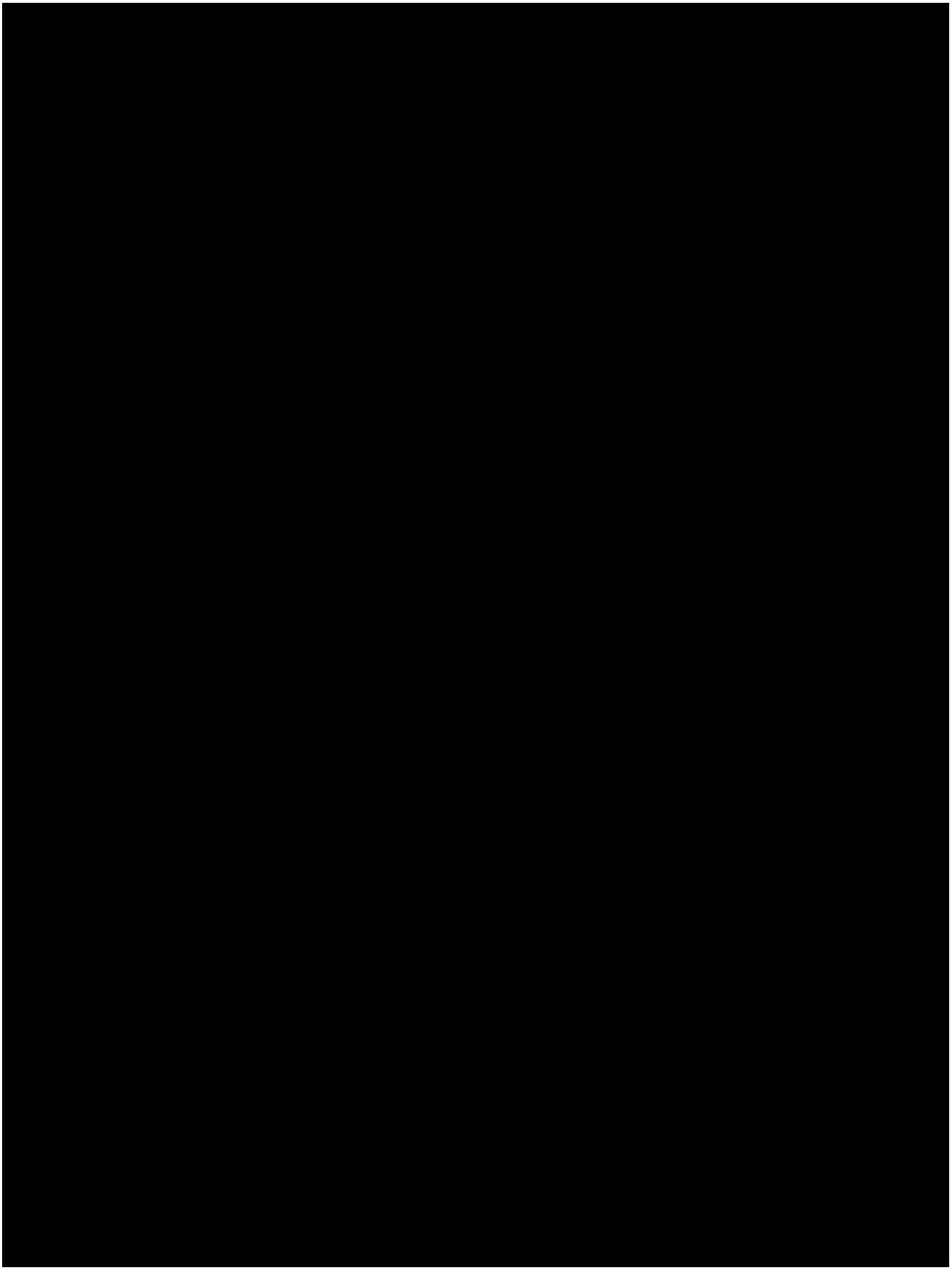
Not applicable.

5.5 ASSESSMENT OF BIOMARKERS

5.5.1 Biomarkers at screening

N-terminal-pro Brain Natriuretic Peptide (NT-proBNP) will be measured at Visit 1 (screening) by the central laboratory and used to assess patient eligibility.

[redacted]



5.7 APPROPRIATENESS OF MEASUREMENTS

The majority of methods used in this trial, including ECHO, CPET and CMR, are considered standard in heart failure patients.

The following methods are not standard in heart failure patients:

Cardiac CT
CT is the standard non-invasive procedure for the diagnosis of coronary artery disease. It is required in this trial in order to document any coronary artery disease.

Cardiac ^{31}P Magnetic Resonance Spectroscopy (MRS)
Myocardial phosphocreatine to adenosine triphosphate concentration ratio (PCr/ATP) is a sensitive indicator of the myocardial energy status, and phosphorus magnetic resonance spectroscopy (31P-MRS) allows noninvasive assessment of the PCr/ATP [R17-0687, R17-0691, R17-0693, R17-0695, R17-0696, R17-0697].

Cardiac ^{1}H MRS
Proton (1H) magnetic resonance spectroscopy (MRS) allows non-invasive measurement of myocardial lipid (triglyceride) content, and by using this technique, elevated myocardial lipid (steatosis) has been shown in aortic stenosis, metabolic syndrome, obesity and type 2 diabetes mellitus, R17-0688, R17-0689, R17-0690, R17-0692, R17-0694.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

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

6.2.1 Screening period

Following informed consent, the patient will undergo visit 1/screening assessments as indicated in the Flowchart.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.

There is no mandatory order of assessments but it is recommended that ECHO is performed prior to cardiac CT so that patients who are ineligible based on the ECHO are not required to undergo further assessment.

If the patient does not meet the eligibility criteria, the patient should be registered as a screen failure in IRT.

Re-screening is not allowed in this trial. Screening assessments may be repeated as long as they fall within the screening visit window. If more than one screening assessment is available, the latest assessment prior to randomisation must be used to assess eligibility.

If the patient meets the eligibility criteria during screening (Visit 1), Visit 2 should be scheduled. Any baseline conditions which are present at Visit 1 should be reported in the eCRF.

6.2.2 Treatment period

Visit 2 (Randomisation)

The investigator must perform a final assessment of eligibility when the results of all screening assessments are available. If the patient does not meet the eligibility criteria, the patient should be registered as a screen failure in IRT. Re-screening is not allowed in this trial.

If the patient is eligible for trial participation, the patient is randomised using IRT and treatment is allocated. The visit 2 assessments as listed in the Flowchart are then performed. Some assessments do not need to be repeated if performed during the last 7 days as part of the screening visit; see Flowchart for details.

The patient should be fasting in preparation for the blood sampling at this visit (no food or liquid except water for at least 6 hours prior to sampling). The following rules apply for the order of assessments at this visit;

- [redacted]
- Blood tests and iv cannulation must be performed before the CMR scan.
- Echo must be performed before Dobutamine stress
- CPET must be performed before Dobutamine stress
- All Visit 2 assessments must be performed before the first dose is taken

Visit 3 (Day 15)

The patient will return to the clinic for visit 3 on day 15 ± 1 day of treatment. The purpose of this visit is to check patient safety, to check medication compliance and to perform limited assessments. Assessments to be performed are indicated in the Flowchart. [redacted]

Visit 4 (Day 84)

Visit 4 will take place on Day 84 of treatment, which is also the last day of treatment. If the visit cannot be scheduled for Day 84, it should be scheduled as close as possible, but within 4 days and the patient should continue to take the medication daily until the day of the visit. All Visit 4 assessments must be performed within 48 hours of the last dose, regardless of which day this is. The patient should be asked to return all remaining medication during this visit.

The assessments to be performed at Visit 4 are indicated in the Flowchart. The patient should be fasting in preparation for the blood sampling at this visit (no food or liquid except water for at least 6 hours prior to sampling). The following rules apply for the order of assessments at this visit;

- [redacted].
- Blood tests and iv cannulation must be performed before the CMR scan.
- Echo must be performed before Dobutamine stress
- CPET must be performed before Dobutamine stress

6.2.3 Follow up period and trial completion

A follow up visit (Visit 5) will be performed 7-14 days after the last dose of trial medication. The expectation is that this visit will be performed via a telephone call, but where appropriate, a clinic visit may be scheduled. The assessments to be performed at Visit 5 are indicated in the Flowchart.

Visit 5 marks the completion of the study for the individual patient. After the completion of the study the patient will receive standard medical care.

6.2.4 Early discontinuation of trial medication

See Section 3.3.4.1 for procedures to be followed in case a randomised patient does not reach Visit 4 for any reason.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN MODEL

This is a randomised, double-blind, single-centre placebo-controlled trial. The eligible patients for this trial will be randomised to empagliflozin 10 mg or placebo in a 1:1 ratio. Randomisation will be stratified by cohort (HFpEF / HFrEF) and history of diabetes (Yes / No).

The primary endpoint of change from baseline in cardiac energetics (PCr/ATP ratio) at rest is regarded as normally distributed based on literature data.

Change from baseline of cardiac energetics (PCr/ATP ratio) at rest after 12 weeks of treatment will therefore be analyzed by an analysis of variance (ANOVA) model. The model will include treatment, presence of atrial fibrillation at baseline (Yes / No) and history of diabetes (Yes / No) as fixed effects.

The analysis will be performed on the per protocol set (PPS) of patients having a valid PCr/ATP ratio measurements available at baseline and at week 12, and not having an important protocol violation relevant to the primary endpoint.

All planned analyses will be conducted separately on the two cohorts.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The null hypothesis is that for patients in HFrEF and HFpEF cohorts, the change from baseline to week 12 in the resting state PCr/ATP ratio measured by ^{31}P MRS is not different from placebo. The alternative hypothesis is that the change is different.

If the null hypothesis is rejected, and the result is more favourable for empagliflozin, superiority is concluded in the tested cohort.

The primary objective will be addressed by a two-sided test at level alpha=0.05 conducted separately for each cohort.

7.3 PLANNED ANALYSES

Adherence to the protocol (such as inclusion/exclusion criteria, times of measurement, compliance with intake of trial medication, treatment dispensing errors, prohibited concomitant medication, completeness and consistency of data) will be checked. Important protocol violations (IPVs) will be identified no later than in the Blinded Report Planning Meeting and provided in the TSAP.

The following analysis sets will be defined for this trial:

- Randomised set (RS):
  This subject set includes all randomised patients, whether treated or not.
- Treated set (TS):

This patient set includes all subjects from the RS who were documented to have received one dose of study drug. This is the Intent to treat (ITT) population.

- Per-protocol set (PPS):
  This patient set includes all patients from the TS who provide evaluable data at baseline and on-treatment for the primary endpoint and are not affected by protocol violations relevant to the statistical evaluation of the primary endpoint.

Whether a primary endpoint data is evaluable or a protocol violation is relevant will be decided no later than at the final Blinded Report Planning Meeting (BRPM).

Relevant protocol violations may include:

- Use of prohibited medication
- Patient was non-compliant to study drug intake (e.g.: study drug compliance <80%)

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

Baseline will be defined as the last available measurement before start of randomised trial medication.

7.3.1 Primary endpoint analyses

The patient set for the evaluation of cardiac energetics endpoints will be the PPS.

Change from baseline of cardiac energetics (PCr/ATP ratio) at rest after 12 weeks of treatment will be analyzed by an analysis of variance (ANOVA) model. The model will include treatment, history of atrial fibrillation and history of diabetes as fixed effects.

A sensitivity analysis will be conducted on the randomized set (ITT population). Subgroup analyses will be performed for the primary endpoint including subgroup analyses by history of diabetes and by eGFR $(CKD\text{-}EPI)_{Cr}$ at baseline (<60 vs ≥60 mL/min/1.73m²).

For the subgroup analysis an ANOVA model as the primary will be conducted, additionally including the terms of the subgroup and subgroup by treatment interaction.

7.3.2 Secondary endpoint analyses

There are no secondary endpoints.

[redacted]

[redacted]

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard ARO 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.

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

7.4 INTERIM ANALYSES

If recruitment is different between the cohorts such that one cohort's last patient out visit is considerably earlier than the last patient out of the other cohort, an interim analysis may be planned in order to report the data the completed cohort. For this interim analysis only the completed cohort will be unblinded.
Blinded sample size re-calculations may be performed according to Section 7.7 based on the observed drop-out rate.

7.5 HANDLING OF MISSING DATA

No missing data are expected for the primary analysis since it is defined on a set of patients with available values. Therefore no imputation of missing values is planned.

Futher details on handling of other missing data will be specified in the TSAP.

7.6 RANDOMISATION

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

- Cohort (HFpEF/ HFrEF)
- History of diabetes (Yes/ No)

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

Based upon literature [R17-0695] and advice from experts the study is designed to detect a treatment effect of the primary endpoint of 0.3 with an SD of 0.28 with a power of 80%.

The significance level for the sample size calculation is 0.05 two-sided for each cohort.
In order to have an power of at least 80% in each cohort, there should be at least 30 evaluable patients for the primary analysis for each cohort.

Expecting a drop-out rate of about 30%, it is planned to randomise 43 patients to each cohort.

The drop-out rate will be monitored during the trial. If the drop-out rate in a cohort is higher or lower than expected, the sample size in this cohort may be increased or decreased accordingly but not above a maximum of 60 patients in order to achieve 30 evaluable patients for the primary analysis.

Calculations were performed using nQuery Advisor® 7.0 statistical package by Statistical Solutions Ltd.

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

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 Harmonised Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the 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.

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective 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 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 or sponsor's delegate. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial 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 eCRF 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.

The investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, NHS number, hospital number) have properly been removed or redacted from any copy of the patients' source documents before sending them to the sponsor or sponsor's delegate.

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

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

- Patient identification: gender, 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 and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The sponsor or sponsor's delegate 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 eCRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all eCRFs 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 or sponsor's delegate will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial site:
The trial site 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).

Academic Research Organisation (ARO):
During the conduct of the trial the ARO must retain the essential documents according to the ARO SOPs. At the conclusion of the trial these documents will be transferred to the sponsor.

Sponsor:
After the conclusion of the trial 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. The reporting may be delegated to an ARO where appropriate and this delegation will be documented.

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 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 consent.

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

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

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

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

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

A final report of the clinical trial data will be written only after all patients have completed the trial to incorporate and consider all data in the report. An interim report for one cohort may be produced if one cohort ends significantly earlier than the other.

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). The majority of the organisation of the trial will be delegated to an Academic Research Organisation (ARO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial. The SOPs to be followed will be documented.

Statistical Evaluation of the primary endpoint and Data Management will be done by the ARO according to ARO SOPs.

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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9.2 UNPUBLISHED REFERENCES

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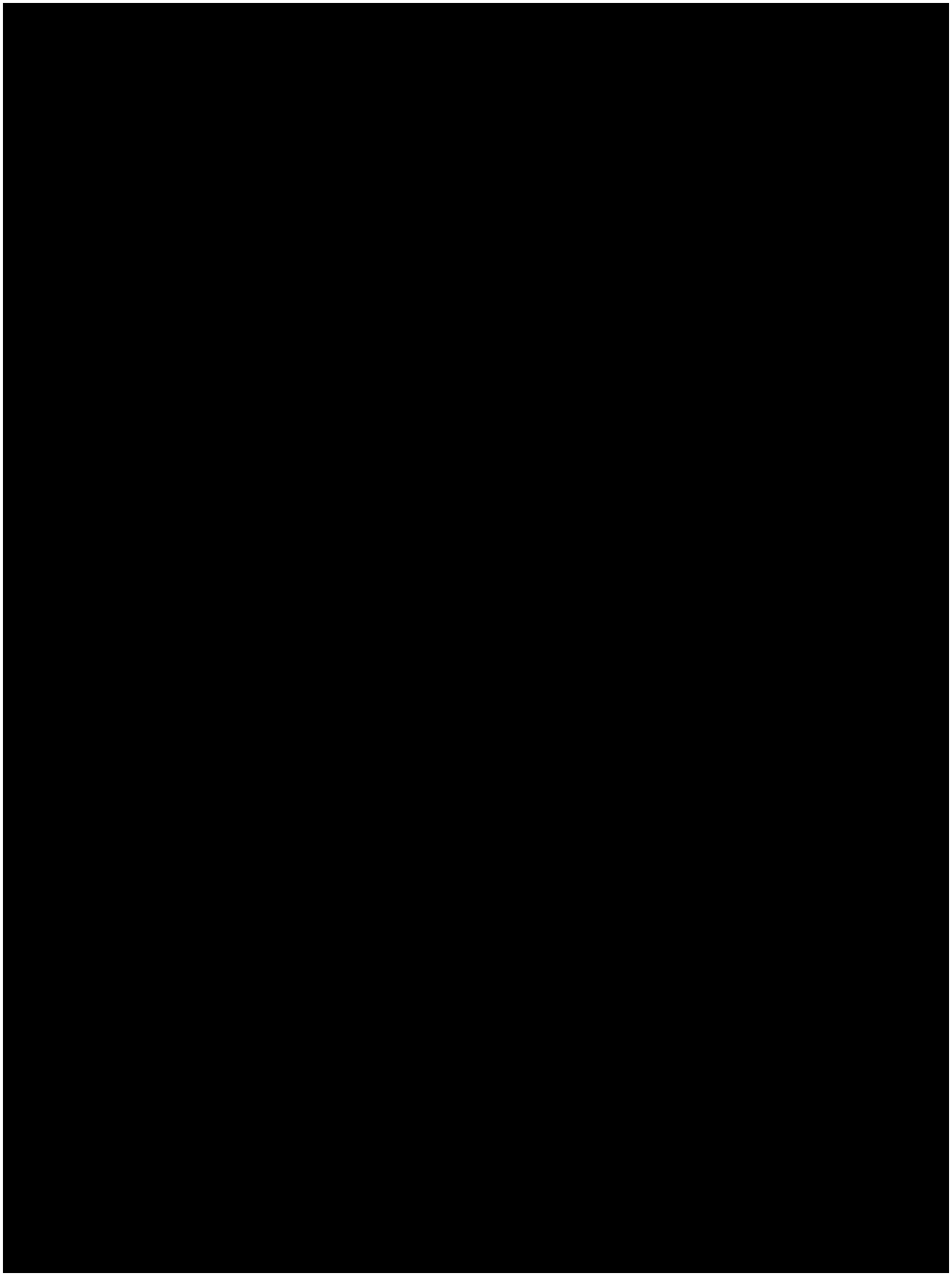
c03946327 A phase III randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic **H**eart **F**ailure with **p**reserved **E**jection **F**raction (**HFpEF**).

c09098452 A phase III randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic **H**eart **F**ailure with **r**educed **E**jection **F**raction (**HFrEF**)

10. APPENDICES

10.1 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



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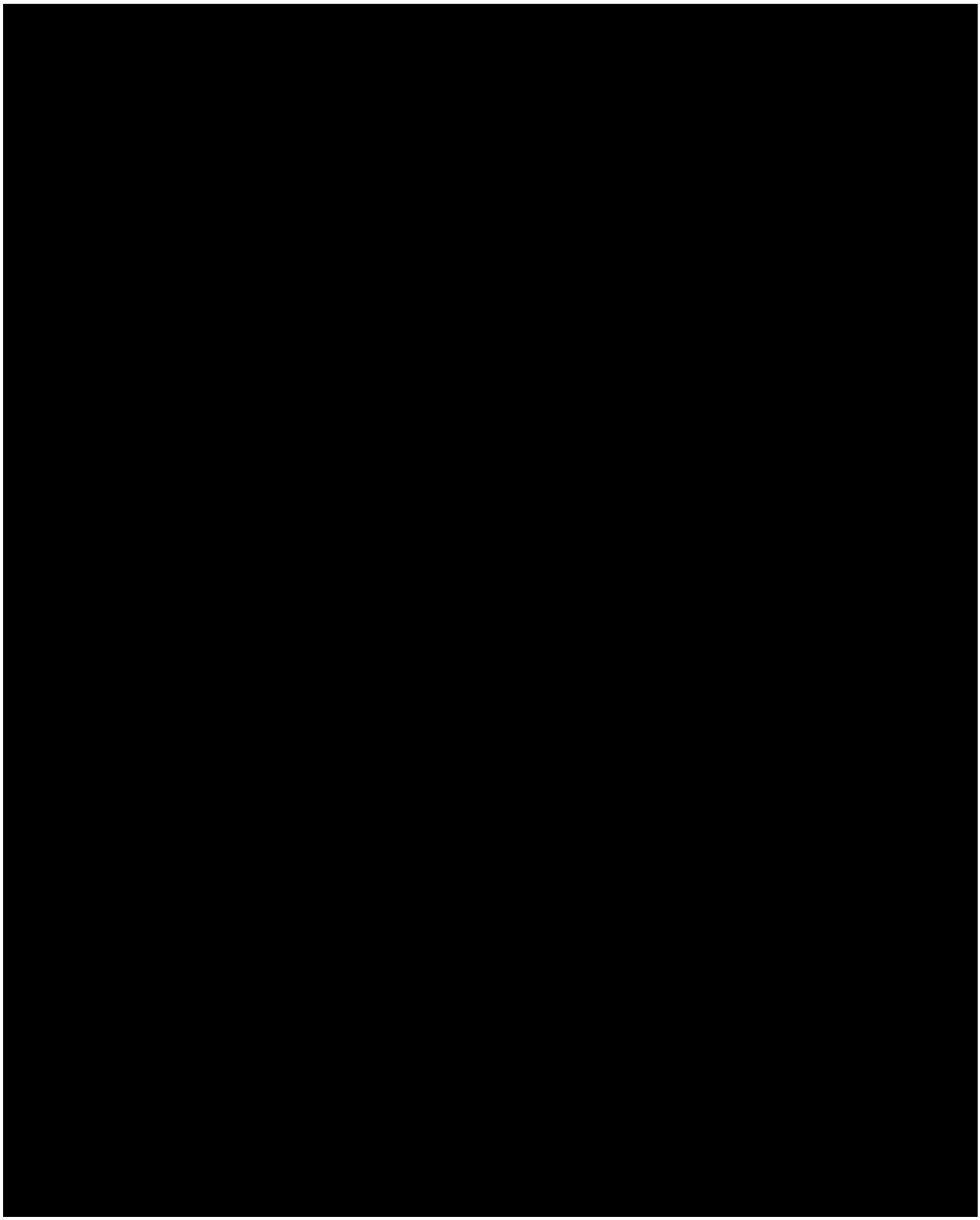

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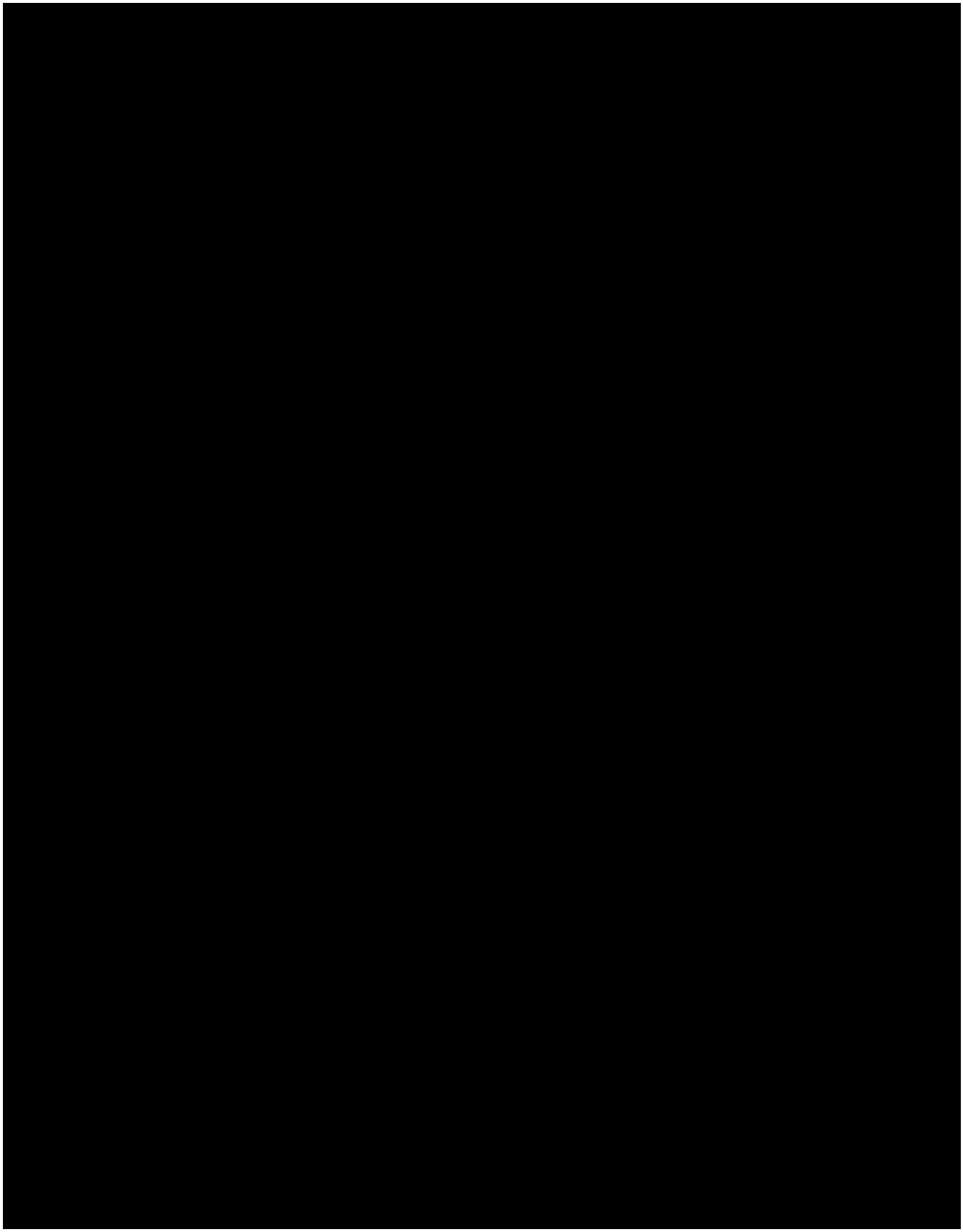

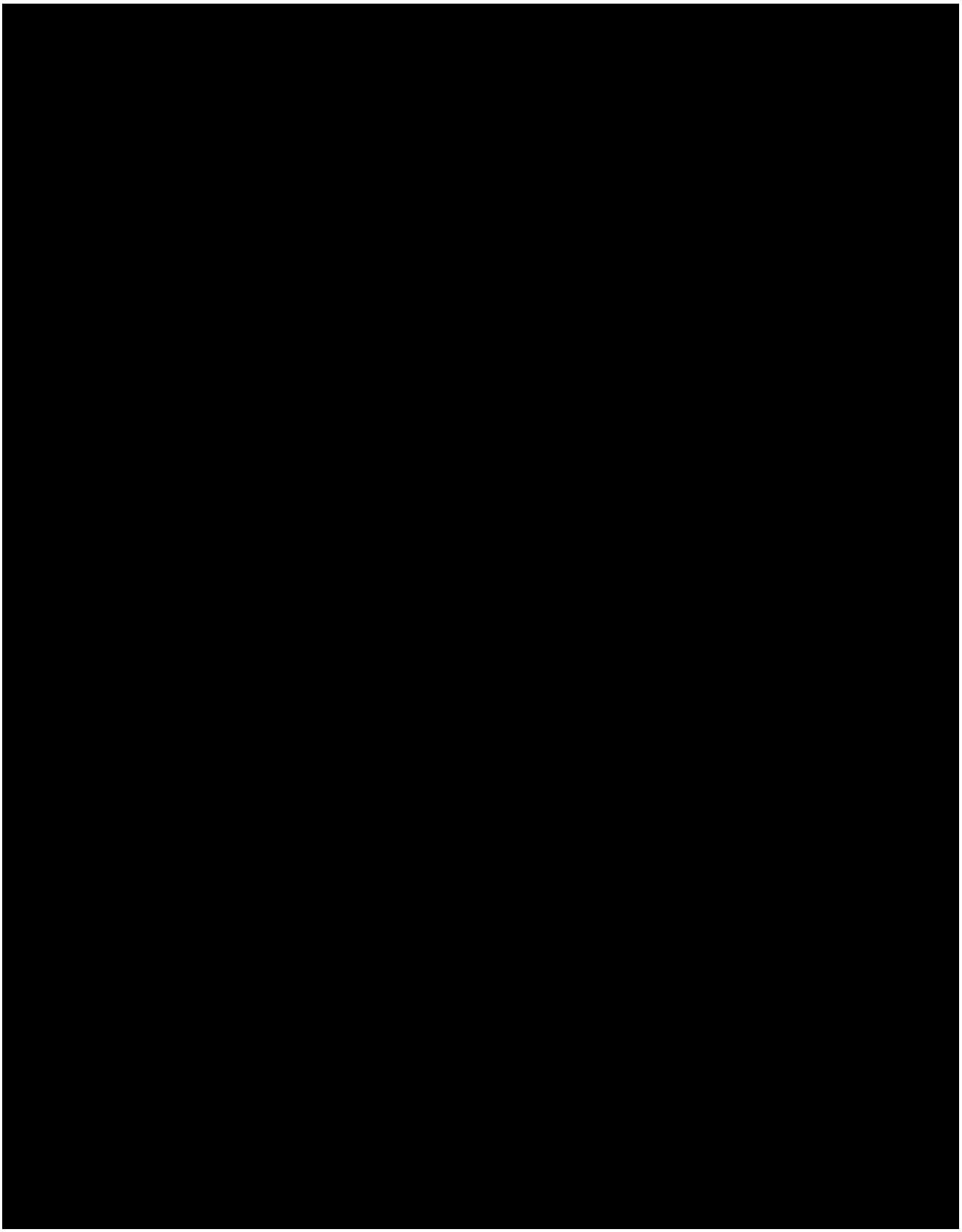

10.3 COCKCROFT-GAULT FORMULA

The following formula may be used for estimated creatinine clearance rate (eC_{CR}) using Cockcroft-Gault formula. The use of on-line calculators or formulas which are institution standards for eC_{CR} and differ slightly may also be used. The calculations and results must be filed in the patient's chart.

When serum creatinine is measured in mg/dL;

$$eC_{CR} = \frac{(140 - \text{Age}) \cdot \text{Mass}(\text{in kilograms}) \cdot [0.85 \; if \; Female]}{72 \cdot \text{Serum Creatinine}(\text{in mg/dL})}$$

When serum creatinine is measured in µmol/L;

$$eC_{CR} = \frac{(140 - \text{Age}) \cdot \text{Mass}(\text{in kilograms}) \cdot \text{Constant}}{\text{Serum Creatinine}(\text{in µmol/L})}$$

Where *Constant* is *1.23* for men and *1.04* for women.

11. DESCRIPTION OF GLOBAL AMENDMENTS

Number of global amendment		1
Date of CTP revision		26 Mar 2018
EudraCT number		2017-000376-28
BI Trial number		1245.148
BI Investigational Product(s)		Empagliflozin
Title of protocol		EMPA-VISION: A randomised, double-blind, placebo-controlled, mechanistic cardiac magnetic resonance study to investigate the effects of empagliflozin treatment on cardiac physiology and metabolism in patients with heart failure
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		Title Page and Synopsis
Description of change		Addition of EMPA-VISION to trial title
Rationale for change		Administrative
Section to be changed		Synopsis, abbreviations and section 1.3
Description of change		Correction of spelling errors in Phosphocreatine /Adenosine Triphosphate and Creatine Kinase
Rationale for change		Correction
Section to be changed		Flowchart
Description of change		Safety laboratory tests (urine and blood) split into two rows
Rationale for change		Clarification of requirements
Section to be changed		Flowchart

Description of change		Addition of blood sample for metabolomic analysis
Rationale for change		Scientific interest in performing metabolomic analysis
Section to be changed		Abbreviations
Description of change		Addition of Coronary Artery Disease (CAD)
Rationale for change		Administrative change
Section to be changed		3.1.1.1 Clinical Event Committee for Diabetic ketoacidosis (DKA)
Description of change		Removal of reference to adjudication endpoints and addition of explanation that analysis will be performed on project level.
Rationale for change		Clarification. There are no adjudication endpoints for this trial.
Section to be changed		3.3.3 Exclusion criteria
Description of change		Exclusion criteria 2 changed from Previous myocardial infarction (increase in cardiac enzymes in combination with symptoms of ischaemia or newly developed ischaemic ECG changes), unstable angina pectoris, percutaneous coronary intervention (PCI), coronary artery bypass graft surgery or other major cardiovascular surgery to Any significant coronary artery disease (CAD) with >50% luminal obstruction, unstable angina due to significant CAD, percutaneous coronary intervention (PCI), coronary artery bypass graft surgery or other major (in the opinion of the investigator) cardiovascular surgery.
Rationale for change		Patients who had previous NSTEMI or less extensive MI will still have viable myocardium to produce ATP so those patients are technically eligible for MRS and there is no reason to exclude them.
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		Requirement to take the medication in the morning changed to a recommendation. Requirement to take

		the dose at the usual scheduled time on the day of visit 2 removed.
Rationale for change		The dose at visit 2 is the first one and therefore the 'usual scheduled time' does not apply. Due to scheduling of assessments it may not be possible to take the medication in the morning at visit 2 so more flexibility has been introduced.
Section to be changed		[redacted]
Description of change		
Rationale for change		Administrative change
Section to be changed		5.2.4 Cardiac Magnetic Resonance (CMR)
Description of change		Dobutamine dose changed from g/kg to mcg/kg
Rationale for change		Correction
Section to be changed		5.2.5 Cardiac Computerised Tomography (CT) Scan
Description of change		CT scanner changed from 64-slice to 320-slice and heart rate changed from <65 beats/min to <60 beats/min.
Rationale for change		Correction
Section to be changed		5.3.3.1 Creatinine
Description of change		Addition of local creatinine test at Visit 1
Rationale for change		Required to check patient safety before administration of contrast agent
Section to be changed		Table 5.3.3:1 Safety laboratory parameters
Description of change		Reticulocyte count and γ-GT will be measured as standard rather than as reflex tests
Rationale for change		Reflex testing of these parameters is not feasible due to limited sample stability
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		[redacted]
Description of change		
Rationale for change		Clarification

Section to be changed		[redacted]
Description of change		
Rationale for change		Administrative
Section to be changed		[redacted]
Description of change		
Rationale for change		Administrative change
Section to be changed		[redacted]
Description of change		
Rationale for change		

Number of global amendment		2
Date of CTP revision		14 Aug 2018
EudraCT number		2017-000376-28
BI Trial number		1245.148
BI Investigational Product(s)		Empagliflozin
Title of protocol		EMPA-VISION: A randomised, double-blind, placebo-controlled, mechanistic cardiac magnetic resonance study to investigate the effects of empagliflozin treatment on cardiac physiology and metabolism in patients with heart failure
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		Flowchart
Description of change		Modification of requirements so that the echocardiogram does not need to be repeated at visit 2 if performed within the previous 21 days.
Rationale for change		The time window has been modified to avoid unnecessary assessments. The echocardioagram data is not expected to change significantly within 21 days so one assessment within 21 days of start of treatment is sufficient.
Section to be changed		Flowchart and section 5.2.5
Description of change		Modification of requirements so that a CT scan is not required at screening if ischaemic clinical testing has been performed within 6 months and written results are available and adequate (in the opinion of the investigator) to assess eligibility
Rationale for change		There is no medical reason to repeat the CT scan if results from within the previous 6 months are available.
Section to be changed		3.3.2 Inclusion criteria
Description of change		Inclusion criterion number 3 ‘Body mass index (BMI) <40 kg/m^2 at screening’ deleted
Rationale for change		There is no medical reason to exclude patients with a high BMI who are otherwise eligible and able to undergo MRI scanning. Patients with a high BMI who are unable to undergo MRI scanning will be excluded from the study by exclusion criterion number 3 which covers contraindications for MRI scanning.
Section to be changed		3.3.3 Exclusion criteria
Description of change		Exclusion criteria 22 changed from ‘Any documented active or suspected malignancy or history of malignancy within 2 years prior to

		informed consent……' To 'Any documented active or suspected malignancy or history of malignancy within 6 months prior to informed consent…….'
Rationale for change		Patients who received chemotherapy or radiotherapy should be considered individually by investigators as the status of malignancy after treatment varies according to individual, type of malignancy, and the effect of treatment. Taking these into account it is considered acceptable to include patients in the trial as soon as 6 months if the investigator believes it is appropriate to do so.
Section to be changed		3.3.3 Exclusion criteria
Description of change		Exclusion criterion 2 changed from; 'Any significant coronary artery disease (CAD) with >50% luminal obstruction, unstable angina due to significant CAD, percutaneous coronary intervention (PCI), coronary artery bypass graft surgery or other major (in the opinion of the investigator) cardiovascular surgery.' to 'Any patients with myocardial scars and/or non-viable myocardium in the interventricular septum, unstable angina due to significant coronary artery disease (CAD), or major (in the opinion of the investigator) cardiovascular surgery.'
Rationale for change		The measurement of PCr/ATP is performed in the interventricular septum and therefore patients with non-viable septal tissue (myocardial scars and/or non-viable myocardium in the interventricular septum) will be excluded. The current exclusion criterion also excludes patients with flow limitation of the non-septal region. Coronary flow limitation resulting in scars or non-viable myocardium elsewhere (non-septal regions) will not affect measurement of PCr/ATP so the exclusion criteria has been modified to allow inclusion of these patients.

APPROVAL / SIGNATURE PAGE

Document Number: c14878151 **Technical Version Number:5.0**

Document Name: clinical-trial-protocol-version-03

Title: EMPA-VISION: A randomised, double-blind, placebo-controlled, mechanistic cardiac magnetic resonance study to investigate the effects of empagliflozin treatment on cardiac physiology and metabolism in patients with heart failure

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Team Member Medicine	[redacted]	15 Aug 2018 14:48 CEST
Author-Trial Statistician		15 Aug 2018 14:59 CEST
Approval-Therapeutic Area [redacted]		15 Aug 2018 16:54 CEST
Author-Trial Clinical Monitor		21 Aug 2018 15:37 CEST
Verification-Paper Signature Completion		23 Aug 2018 22:27 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed