Boehringer Ingelheim

Clinical Trial Protocol

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EudraCT No. **EU Trial No.**	2019-001037-13	
BI Trial No.	1245-0202	
BI Investigational Medicinal Product(s)	Jardiance®, empagliflozin	
Title	EMPACT-MI: A streamlined, multicentre, randomised, parallel group, double-blind placebo-controlled superiority trial to evaluate the effect of EMPAgliflozin on hospitalisation for heart failure and mortality in patients with aCuTe Myocardial Infarction	
Lay Title	EMPACT-MI: A study to test whether empagliflozin can lower the risk of heart failure and death in people who had a heart attack (myocardial infarction)	
Clinical Phase	III	
Clinical Trial Leader	[redacted] Phone: +[redacted], Fax: +[redacted]	
Coordinating Investigator	[redacted] Phone: +[redacted], Fax: +[redacted]	
Chair and co-chair Executive Committee	[redacted]	
Version and Date	**Version:** 2.0	**Date:** 20 Apr 2022

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	03 Jul 2020
Revision date	20 Apr 2022
BI trial number	1245-0202
Title of trial	EMPACT-MI: A streamlined, multicentre, randomised, parallel group, double-blind placebo-controlled superiority trial to evaluate the effect of EMPAgliflozin on hospitalisation for heart failure and mortality in patients with aCuTe Myocardial Infarction
Coordinating Investigator	[redacted] Phone: +[redacted], Fax: +[redacted]
Chair and co-chair Executive Committee	[redacted] [redacted]
Trial site(s)	Multi-centre trial
Clinical phase	III
Trial rationale	Acute myocardial infarction (MI) affects approximately 7 million individuals every year. Despite advancements in its treatment, a significant unmet need persists with more than one third of all MI patients having either died or developed heart failure (HF) after five years. The observed benefits of empagliflozin on mortality and hospitalisation for HF (HHF) in patients with T2D and established atherosclerotic CV disease in the EMPA-REG OUTCOME trial appeared independent of glucose control and provided a strong rationale to explore the effects of empagliflozin in populations with established HF. However, as these benefits were consistent in both patients with and without HF, a similarly strong rationale exists for exploring efficacy and safety of empagfliflozin in patients without established but at high risk of developing HF, frequently represented by patients with an acute MI. Further data with empagliflozin from animal studies have given additional support by showing benefits on cardiac remodelling and contractility in the post-acute MI setting. This trial plans to evaluate efficacy and safety of empagliflozin in

	patients with an acute MI, specifically related to effects on the risk of HHF and mortality. The main hypothesis is that early intervention with empagliflozin vs placebo on top of standard of care in this patient population reduces the subsequent risk of HHF and mortality.
Trial objective(s)	The main objective of this event-driven trial is to demonstrate the superiority of empagliflozin 10 mg once daily versus placebo, in addition to standard of care, for the reduction of the composite endpoint of time to first heart failure hospitalisation or all-cause mortality in high-risk patients hospitalised for acute MI.
Trial endpoints	Primary endpoint: • Composite of time to first HHF or all-cause mortality Key secondary endpoints which are part of the testing strategy: • Total number of HHF or all-cause mortality • Total number of non-elective CV hospitalization or all-cause mortality • Total number of non-elective all-cause hospitalisation or all-cause mortality • Total number of hospitalisation for MI or all-cause mortality Other secondary endpoints: • Time to CV mortality
Trial design	A streamlined, randomised, double-blind, parallel group, placebo controlled, multi-national and multicentre trial
Total number of patients randomised	Approximately 5000 randomised. If the accumulated blinded data suggests a slower accrual of primary outcome events over calendar time than originally projected, then the number of patients randomised may be increased up to 6500. Such a decision would be made during recruitment and before any unblinding. The number of primary outcome events required is not affected by this consideration.
Number of patients on each treatment	Approximately 2500, but can be increased based on event accrual over time to approximately 3250
Diagnosis	Patients hospitalised for acute myocardial infarction with elevated risk of heart failure hospitalisation and mortality
Main inclusion and exclusion criteria	Main Inclusion Criteria: • Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial • Diagnosis of spontaneous acute myocardial infarction (AMI): STEMI or NSTEMI with randomisation to occur no later than 14 calendar days after hospital admission. For patients with an in-hospital MI as qualifying event, randomisation must still occur within 14 days of hospital admission. Spontaneous AMI is defined as MI with a primary etiology of an acute coronary artery disease pathology (e.g., plaque rupture/erosion, in-stent restenosis, stent thrombosis) rather than MI caused by supply-

	demand mismatch (e.g., sepsis, arrhythmia, anemia, or other condition). Spontaneous AMI is established when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia due to primary coronary event. Under these conditions, the following criteria have to be met for the diagnosis of spontaneous AMI: Detection of rise and/or fall of cardiac enzymes (cardiac troponin, cTn or the MB fraction of creatinine kinase, CKMB) with at least one value above the 99th percentile of the upper reference limit (URL) or the local laboratory MI diagnosis cut-off value, together with evidence of myocardial ischemia with <u>at least one of the following:</u> • Ischemic discomfort or other ischemia symptom(s) • Electrocardiogram (ECG) characteristics of STEMI or NSTEMI including new or presumably new significant ST-segment-T wave (ST-T) changes • Newly developed pathological Q waves or left bundle branch block (LBBB) in the ECG • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology • Identification of a coronary thrombus by angiography • High risk of HF, defined as **<u>EITHER</u>** a) <u>Symptoms</u> (e.g. dyspnea; decreased exercise tolerance; fatigue), <u>or signs of congestion</u> (e.g. pulmonary rales, crackles or crepitations; elevated jugular venous pressure; congestion on chest X-ray), <u>that require treatment</u> (e.g. augmentation or initiation of oral diuretic therapy; i.v. diuretic therapy; i.v. vasoactive agent; mechanical intervention etc.) at any time during the hospitalisation. **<u>OR</u>** b) Newly developed LVEF < 45% as measured by echocardiography, ventriculography, cardiac CT, MRI or radionuclide imaging during index hospitalisation. • In addition at least one of the following risk factors: - Age ≥ 65 years - Newly developed LVEF < 35% - Prior MI (before index MI) documented in medical records - eGFR < 60 ml/min/1.73m^2 (according to creatinine from most recent local lab during the index hospitalisation and calculated with the CKD-EPI formula) - Atrial fibrillation (persistent or permanent ; if paroxysmal, only valid if associated with index MI)

	- Type 2 diabetes mellitus (prior or new diagnosis) - NTproBNP ≥1,400 pg/mL for patients in sinus rhythm, ≥2,800 pg/mL if atrial fibrillation; BNP ≥350 pg/mL for patients in sinus rhythm, ≥700 pg/mL if atrial fibrillation, measured at any time during hospitalisation - Uric acid ≥7.5 mg/dL (≥446 µmol/L), measured at any time during hospitalisation - Pulmonary Artery Systolic Pressure [or right ventricular systolic pressure] ≥40 mmHg (non-invasive [usually obtained from clinically indicated post-MI echocardiography] or invasive, at any time during hospitalisation) - Patient not revascularized (and no planned revascularization) for the index MI (Includes e.g. patients where no angiography is performed, unsuccessful revascularization attempts, diffuse atherosclerosis not amenable for intervention; but does NOT include if revascularization was not performed due to nonobstructive coronary arteries) - 3-vessel coronary artery disease at time of index MI - Diagnosis of peripheral artery disease (extracoronary vascular disease, e.g. lower extremity artery disease or carotid artery disease) Main Exclusion Criteria: • Diagnosis of chronic HF prior to index MI • Systolic blood pressure ≤ 90 mmHg at randomisation • Cardiogenic shock or use of i.v. inotropes in last 24 hours before randomisation • Coronary Artery Bypass Grafting planned at time of randomisation • Current diagnosis of Takotsubo cardiomyopathy • Any current severe (stenotic or regurgitant) valvular heart disease • eGFR < 20 ml/min/1.73m^2 (using CKD-EPI formula based on most recent creatinine from local lab during hospitalisation) or on dialysis • Type I diabetes mellitus • History of ketoacidosis
Test product(s)	Empagliflozin
dose	10 mg q.d.
mode of administration	Oral (p.o.)
Comparator product(s)	Placebo
dose	Not applicable
mode of administration	Oral (p.o.)
Duration of treatment	The trial is event-driven and all randomised patients will remain in

	the trial until the total number of patients with investigator reported primary endpoint events is projected to reach a target of 532. Estimated trial duration is depending on event accrual and is projected to be approximately 26 months with a recruitment period of approximately 21 months. Therefore, individual treatment may range between approximately 5 and 26 months. The actual length of the recruitment may be extended beyond 21 months and the follow up may be adjusted to achieve the 532 primary endpoint events. The estimated total trial duration and length of the double-blind treatment period for each patient will vary accordingly.
Statistical methods	A hierarchical testing procedure will be applied from the primary endpoint to the set of key secondary endpoints 1 and 2. If the primary endpoint is significant at α=5% (two-sided), then a Hochberg step-up procedure will be applied to test the family of two key secondary endpoints of • Total number of HHF or all-cause mortality • Total number of non-elective CV hospitalisations or all-cause mortality at α=5%. If the null hypotheses for both of these two key secondary endpoints can be rejected, only then the third key secondary endpoint of: • Total number of non-elective all-cause hospitalisations or all-cause mortality will be tested at α=5%. The fourth key secondary endpoint • Total number of hospitalisations for MIs or all-cause mortality will only be tested if all the hypotheses for key secondary endpoints 1, 2 and 3 have been rejected. The primary endpoint will be analysed using a Cox proportional hazards model with treatment, T2D at baseline (yes vs no), geographical region (North America, Latin America, Europe, Asia), age at baseline (continuous), eGFR (CKD-EPI) at baseline (<45 vs 45-<60 vs 60-<90 vs >=90 ml/min/1.73m^2), LVEF at baseline (<35% vs ≥35%), persistent or permanent atrial fibrillation at baseline (yes vs no), prior MI at baseline (yes vs no), PAD at baseline (yes vs no) and smoking at baseline (current vs non-current) as covariates. The primary analysis will be performed on the randomised (intention to treat) set. It is planned that approximately 5000 patients will be randomised to accumulate a target of 532 primary outcome events within 21 months of recruitment and approximately additional 5 months of follow-up. If the accumulated blinded data suggests a slower accrual of primary outcome events over calendar time than originally projected, then the number of patients randomised may be increased up to 6500.

FLOW CHART

Study periods	Screening	Randomised Treatment Period					EoS[10]	F-up[7]
Visit	**1**	**2a[2]**	**2b[3]**	**3**	**4**	**5-8**	**EoS**	**F-up**
Time from Randomisation	Day -14 to 1	Day 1	-	2 weeks	6 months	Every 6 months	-	
Time window for visits		None		±4 days	±21 days	±21 days	-	EoS +7 days
F2F or remote (R) visit	F2F	F2F	F2F	R	F2F	R	Telephone	Telephone
Informed consent	X							
Patients' preference for remote follow-up visits (mobile /web-based app vs telephone)[1]	X							
Demographics	X							
Medical history/ Concomitant diagnosis	X							
Physical examination		X						
Vital signs		X						
Local laboratory tests and clinical routine examinations	(X[4])	X[4]						
Urine pregnancy test[5]	X						X	
Review of in-/exclusion criteria	X	X						
Screening (register in IRT)	X							
Randomisation (via IRT)		X						
Dispense trial medication		X			X	(X)		
All SAEs, AESIs, and AEs leading to discontinuation[6]			X	X	X	X	X	X
Assessment of Endpoints			X	X	X	X	X	X
Use of / adherence to trial medication				X	X[8]	X	X[8]	
Concomitant therapy[9]		X	X		X			
Additional collection of selected concomitant medication[11]				X		X	X	

F2F = face-to-face; R = remote (phone and/or app); End of Study (EoS), synonym for End of Trial

(1) The site personnel will discuss the different remote follow-up options with the patient during the screening to ensure the patients' preferences are met. Patients are allowed to switch between the different remote contact options.
(2) Day of randomisation / Day of first intake of trial medication.The trial medication should be taken after all trial related procedures are completed.
(3) Day of discharge from hospital. Visit 2b will only be performed if the day of discharge is after day of randomisation.
(4) Most recent local laboratory test, and the last results from clinical routine examinations e.g. echocardiography prior to randomisation to be used.
(5) Women of childbearing potential only.
(6) All Endpoints and SAEs/AESIs with start after randomisation must be reported immediately (within 24 hours) in the relevant eCRF pages.

(7) For patients completing the treatment period according to the protocol, the investigators must report Endpoints and SAEs/AESIs reported by patient occurring the following 7 days after the patient's individual EoS (within 24 hours). Thereafter the investigator should report only any cancers of new histology and exacerbations of existing cancer, trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of, please see Section.5.2.1.2.1.

(8) Include return of trial medication, if applicable.

(9) If an SAE or AESI is reported, all relevant concomitant therapy that the patient received in the past and at the onset of an SAE or AESI should be reported, with the exception of the exempted events listed in Section 5.2.1.2.3.

(10) The sponsor/CRO will notify the investigator when the required number of events is expected to be reached. All patients are expected to perform their last visit (EoS) within the proposed time schedule, named "Close-out period", communicated via an investigator letter. For patients who discontinued trial treatment prematurely the information about Endpoints, SAEs, AESIs and their vital status continues to be collected until EoS, as close as possible to the time schedule defined in the protocol and in line with the follow-up method preferred by the patient. For the patients who withdraw consent for the trial, vital status should be collected during the Close-out period if allowed by local regulation, please see Sections 3.3.4.1 and 5.2.1.2.1.

(11) Use of SGLT-2 inhibitor (or combined SGLT-1 and SGLT-2 inhibitor) other than the trial treatment.

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ABBREVIATIONS

ACM	All cause mortality
AE	Adverse event
AESI	Adverse event of special interest
AKI	Acute Kidney Injury
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
AMI	Acute Myocardial Infarction
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
BI	Boehringer Ingelheim
BNP	Brain Natriuretic Peptide
CABG	Coronar Artery Bypass Grafting
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Equation
COVID-19	Coronavirus Disease 2019
CRA	Clinical Reasearch Associate
CRO	Clinical Research Organisation
CT	Computer Tomography
CTP	Clinical Trial Protocol
CV	Cardiovascular
CVD	Cardiovascular disease
DBL	Database Lock
DILI	Drug induced liver injury
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
DMC	Data Monitoring Committee
EC	Executive Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate

EoS	End of study, synonym for End of Trial
EoT	End of Treatment
F2F	Face-to-Face
FDA	Food and Drug Administration
F-up	Follow-up
GCP	Good clinical practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHD	Ischemic Heart Disease
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator site file
ITT	Intention To Treat
GMP	Good Manufacturing Practice
HbA1c	Glycosylated haemoglobin
HF	Heart Failure
HFrEF	Heart Failure with Reduced Ejection Fraction
HHF	Hospitalisation for heart failure
HR	Hazard Ratio
KA	Ketoacidosis
LBBB	Left Bundle Branch Block
LDL	Low-Density Lipoprotein
LLA	Lower Limb Amputation
LPLT	Last Patient Last Treatment
LVEF	Left Ventricular Ejection Fraction
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
NCC	National Coordinator Committee
NSTEMI	Non-ST Elevation Myocardial Infarction
NT-proBNP	N-Terminal Pro-Brain Natriuretic Peptide

PAD	Peripheral Artery Disease
PT	Preferred Term
RAAS	Renin-Angiotensin-Aldosterone-System
REP	Residual Effect Period
RS	Randomised Set
SAE	Serious adverse event
SGLT-1	Sodium Glucose Co-Transporter 1
SGLT-2	Sodium Glucose Co-Transporter 2
SOC	System Organ Class
SOP	Standard Operating Procedure
STEMI	ST-Elevation Myocardial Infarction
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes mellitus
TMF	Trial Master File
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
URL	Upper Reference Limit
UTI	Urinary Tract Infection
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Acute myocardial infarction (MI) is the most severe manifestation of ischemic heart disease, affecting approximately 7 million individuals every year. It ranks among the most significant causes of death and poor health across the globe and results in more than 1 million hospitalizations per year in the United States alone, with associated costs exceeding 450 billion USD [P20-04407, R20-1515]. Heart Failure (HF) is the most common and severe complication of MI with over one third of all MI patients being either hospitalised for HF or dead after five years [R20-0201]. Moreover, MI constitutes the most important risk factor for HF with the risk of HF development at its highest immediately after and in the early (months) post-MI phase. The management of acute MI has improved in recent decades with the widespread implementation of early revascularization, dual antiplatelet treatment and intensification of secondary preventive measures, including cholesterol lowering therapies. The resulting reduced mortality has left a larger population at risk of HF development [R20-0393]. Given the central etiological role of MI in HF development overall, all patients with an MI can be perceived to be at elevated risk of HF, although the risk magnitude will depend on various background factors. One of the most important determinants of poor outcome and progression to HF are factors associated with extensive myocardial injury, in turn reflected as impaired systolic function and early signs and/or symptoms of HF. Other more general characteristics and comorbidities, such as age, poor renal function and type 2 diabetes, are also of significant prognostic value with respect to both subsequent mortality and HF. As established chronic HF portends a particularly poor prognosis with high morbidity and mortality, early intervention in high-risk populations, including those with MI, to prevent progression to chronic HF would therefore be highly beneficial from the viewpoint of both patients and society.

1.2 DRUG PROFILE

Empagliflozin is an orally available, potent, and selective inhibitor of the renal Sodium Glucose Co-Transporter 2 (SGLT-2) receptor. Its selective inhibition reduces renal reabsorption of sodium and glucose. This leads to both increased urinary sodium and glucose excretion. While urinary sodium excretion returns to near normal within a few days of empagliflozin administration, the effect on urinary glucose continues for as long as the medication is used.
Empagliflozin has been developed for the treatment of type 2 diabetes mellitus (T2D), and has received marketing approval in various regions including for example the European Union, Latin American countries, USA and Japan where it is marketed under the brand name Jardiance®.
For a more detailed description of the drug profile please refer to the current Investigator's Brochure (IB) [c01678844] and local prescribing information for empagliflozin.

The Residual Effect Period (REP) of empagliflozin is 7 days. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects are still likely to be present.

1.3 RATIONALE FOR PERFORMING THE TRIAL

In the EMPA-REG OUTCOME trial, among patients with established cardiovascular disease (CVD) and type 2 diabetes mellitus (T2D), a significant reduction in the primary endpoint (CV death, MI, or stroke) was seen, driven by a 38% relative risk reduction in CV death [P15-09840]. In addition, there was a marked reduction of all-cause mortality (32%) and heart failure hospitalisation (HHF) (35%). The observed benefits on CV death and HHF were independent of levels of glycosylated haemoglobin (HbA1c), suggesting that the cardiovascular benefits were largely independent of its glucose-lowering mechanisms. The findings from the EMPA-REG OUTCOME trial provided a strong rationale to explore the effects of empagliflozin in populations with established HF, as currently investigated in the EMPEROR trials (BI trials 1245.110 and 1245.121). Recently, a reduced risk of HF and CV mortality was also observed for the SGLT2-inhibitor dapagliflozin in the DAPA-HF trial, extending previously observed benefits to patients with established HF with reduced ejection fraction (HFrEF) and without T2D [R19-3125]. Importantly, in the EMPA-REG OUTCOME trial there was no interaction between patients' HF status at baseline and the observed benefits on HF and mortality, indicating potential not only for the treatment of HF but also for the prevention of HF in patients at risk but without a prior HF diagnosis. The risk reduction for HHF associated with empagliflozin treatment was 0.75 (95% CI 0.48-1.19) in patients with investigator-reported HF at baseline and 0.59 (95% CI 0.43-0.82) in patients without investigator-reported HF at baseline, and for all-cause mortality 0.79 (95% CI 0.52-1.20) in patients with HF and 0.66 (0.51-0.81) in patients without HF at baseline. Moreover, in the overall trial population there was also a significant risk reduction with empagliflozin treatment for all-cause hospitalisation (HR 0.89 (95% CI 0.82-0.96)) [P17-11284]. There is currently equipoise with respect to efficacy and safety of empagfliflozin in the general acute MI population (including a majority of non-diabetic patients) as in the EMPA-REG OUTCOME trial, only patients with T2D were included, and in order to be eligible for inclusion, a recent MI (< 2 months) was not allowed. Finally, among the included T2D patients in the study, only a small proportion had an MI < 1 year of inclusion.

This trial plans to address a significant unmet need in the large acute MI population, specifically related to the risk of HHF and mortality: The trial is a randomised, double-blind, placebo-controlled trial among patients, irrespective of the presence or absence of T2D, hospitalised with a Type I acute MI [R20-0005] and at high risk for subsequent HHF and mortality. The main hypothesis is that early intervention with empagliflozin on top of standard of care in this patient population reduces the subsequent risk of HHF and mortality, compared to placebo.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

In the EMPA-REG OUTCOME trial, empagliflozin provided a robust benefit on mortality and HHF in T2D patients with established CVD. Despite only enrolling T2D patients, the observed benefits appeared to be independent of the glucose-lowering effects, thus providing a rationale to study empagliflozin as treatment in HF patients with and without T2D [P16-01253][P17-13145].

Recently, in the DAPA-HF trial, benefits of the SGLT2-inhibitor dapagliflozin in established HF were confirmed in patients with established HFrEF with and without T2D [R19-3125]. The EMPEROR-Reduced trial, which studies the effects of empagliflozin in established HFrEF, is expected to complete in 2020. The benefits on HHF and mortality in the EMPA-REG OUTCOME trial were similar in patients both with and without HF at baseline, indicating a potential for both treatment and prevention of HF. As patients with a high-risk MI (defined as signs or symptoms of HF or evidence of myocardial dysfunction resulting from the MI) are common and at high-risk of both HF and mortality, there is a strong reason to believe they could benefit from empagliflozin treatment. As patients with an acute or a recent MI were not included in the EMPA-REG OUTCOME trial, there is equipoise for further trials in this important patient population.

In addition, several acute MI animal studies in rats and pigs (both with and without T2D) showed multiple benefits from empagliflozin treatment in conjunction with and after the induced MI. Benefits included improved survival, less adverse remodelling, preserved cardiac contractility and less neurohormonal activation in animals treated with empagliflozin, compared to placebo [c01678844, P18-12030, P19-03216, P19-03653]. Further, in the EMPA-HEART trial, patients with established T2D and established ischemic heart disease (IHD) experienced a reduction in left ventricular mass over time with treatment of empagliflozin, indicating that reverse remodelling as a result of empagliflozin treatment could be a likely mediator of the overall benefits [P19-08100].

In addition to potential risk reductions for HF and mortality, empagfliflozin may provide other benefits in a high-risk post-MI population, especially related to prevalent CV and renal comorbidities. In patients with T2D, empagliflozin is known to improve glucose control over time and also have a positive influence on other CV risk factors, including reductions in blood pressure and body mass index. Importantly, marked benefits on hard renal outcomes as well as a stabilization of the eGFR slope (after an initial modest decrease) were observed for empagliflozin in the EMPA-REG OUTCOME trial [P16-06807].

1.4.2 Risks

Known and potential risks for empagiflozin that are clinically relevant in an acute and post-MI setting are outlined in the below Table 1.4.2: 1.

Table 1.4.2: 1 Overview over trial related risks

Known or potential risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: Empagliflozin		
Hypoglycaemia	The risk of hypoglycaemia was increased only when empagliflozin was used concomitantly with insulin and/or sulfonylurea. The risk of hypoglycaemia in patients without diabetes mellitus (DM) is considered very low. In a mechanistic study [c11963611-01], patients without DM had an increase of endogenous glucose production in response to glycosuria due to empagliflozin.	Patients with type 1 diabetes mellitus (T1D) are excluded from the study. Investigators will advise patients on insulin or sulfonylureas to exercise additional caution in monitoring for hypoglycaemia when initiating trial medication. Guidance for the investigator is provided in the IB.
Volume depletion	Empagliflozin may selectively reduce interstitial volume with minimal change in intravascular volume. Polyuria and consequent dehydration and hypotension were identified as risks in patients treated with empagliflozin, especially patients with known CV disease, history of hypotension, taking diuretics or other antihypertensive drugs, or elderly patients aged 75 years and older [P19-02151]. In the EMPA-RESPONSE-AHF trial, empagliflozin was safe and well-tolerated in patients with acute heart failure. [P20-00338]	Congested patients with ongoing diuretic therapy can be randomized but haemodynamically unstable or hypotensive patients are excluded. Guidance for the investigator is provided in the IB. Information and recommendations to patients are provided in the Informed Consent Form (ICF).
Diabetic ketoacidosis (DKA) /Ketoacidosis (KA)	Cases of DKA, including fatal cases, were reported in patients treated with SGLT2-inhibitors. In patients treated with SGLT2-inhibitors DKA may occur with lower than usual glucose values. The risk of DKA is increased in patients with lower than needed insulin intake, T1D, low carbohydrate intake, acute illness, major trauma, major surgery, severe dehydration or alcohol use. In the recently published DAPA-HF trial that enrolled both diabetic and non-diabetic HF patients, the incidence of DKA in the DAPA arm was 0.1%. Among non-diabetics, no ketoacidosis events were reported [R19-3125].	Patients with T1D and prior KA are excluded from the trial. Guidance for the investigator is provided in the IB. Training will be provided. Information and recommendations to patients are provided in the ICF. KA is an adverse event of special interest (AESI) and requires detailed reporting by investigator in the electronic case report form (eCRF).
Complicated urinary tract infections (UTI)	Cases of complicated UTI, including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin.	Guidance for the investigator provided in the IB. Information and recommendations to patients are provided in the ICF.
Necrotizing fasciitis of perineum (Fournier's gangrene)	Rare cases of Fournier's gangrene, including fatal cases, have been reported in patients treated with SGLT2-inhibitors.	Guidance for the investigator is provided in the IB. Information and recommendations to patients

Known or potential risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: Empagliflozin		
		are provided in the ICF.
Hypersensitivity	The risks of allergic skin reactions (e.g. rash, urticaria) and angioedema were identified for empagliflozin based on post-marketing experience. As with all drugs, the risk of severe and unexpected allergic reactions cannot be excluded.	Patients with hypersensitivity to empagliflozin or other SGLT2-inhibitors are excluded from trial participation.
Drug-induced liver injury (DILI)	No risk of DILI was identified for empagliflozin during the clinical development program. However, DILI can be severe and even lead to fatal outcome or need of liver transplant. Therefore, careful monitoring and assessment of patients for potential DILI is needed.	Hepatic injury is an AESI and requires detailed reporting by investigator in the eCRF. If DILI is suspected additional information will be collected according to the DILI checklist. Unblinded review of potential DILI cases will be performed by Data Monitoring Committee (DMC).
Lower limb amputation (LLA)	An increase of amputations in CANVAS (a clinical trial on canagliflozin) was observed. In a post-hoc analysis of all completed Phase II and III clinical trials of empagliflozin and its fixed dose combinations, including the ones with a duration less than 3 months, the incidence of LLA in patients treated with empagliflozin was not higher compared to patients treated with placebo or other comparators. No increase in the risk of LLA or potentially related AEs was observed in patients treated with empagliflozin compared with placebo in a meta-analysis of 3 large CV outcome trials (EMPA-REG OUTCOME, EMPEROR-Reduced, and EMPEROR-Preserved) [c32096554-01].	Risk of LLA has been described in the IB [c01678844]. Like for all diabetic patients it is important to counsel patients on routine preventative foot-care.LLA is an AESI and requires detailed reporting by investigator in the eCRF.
Renal safety	In clinical trials with patients with T2D, the incidence of renal impairment was similar to placebo. An initial decrease of estimated glomerular filtration rate (eGFR) was seen in patients treated with empagliflozin, which improved and stabilized during continuous treatment or discontinuation of empagliflozin. Cases of renal impairment, including those requiring dialysis, have been reported in	Decreased renal function fulfilling the definition of a SAE or an AE leading to discontinuation must be reported. Unblinded review of cases of acute kidney injury will be performed by DMC.

Known or potential risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: Empagliflozin		
	patients using SGLT2-inhibitors. In the EMPA-RESPONSE trial, empagliflozin was safe and well-tolerated in patients with acute HF, without evidence of empagliflozin being associated with renal impaiment [P20-00338].	
Women of childbearing potential (WOCBP)	The safety of empagliflozin in pregnant women was not established.	In accordance with international regulatory guidelines, WOCBP are excluded from trial participation unless they agree to use a highly effective contraceptive method. All WOCBP will undergo pregnancy testing before randomisation.

Known or potential risks in patients without T2D:
In the empagliflozin HF program, which includes the two ongoing large EMPEROR outcome trials and the two EMPERIAL exercise capacity trials (with more than 10,000 patients being followed up as of May 2020), the frequencies of overall adverse events (AE), severe AE, serious AE, and AE leading to treatment discontinuation reported in patients without T2D were similar or lower than the ones reported in patients with T2D, consistent with the known safety reporting described in the IB.

As of May 2020 based on blinded data review from the EMPEROR outcome trials, no new safety concerns has been raised in population without T2D.

An independent data monitoring committee (DMC) will be assigned to monitor the trial. The DMC will evaluate the unblinded data for potential safety signals on a quarterly basis. They will also analyse, at the DMC chair's discretion, unblinded data at any point during the trial if data from other studies of empagliflozin or other SGLT2-inhibitors reveal previously unknown risks. Please refer to Section 8.7 for details.

Patients will be treated according to standard of care and trial medication will be given on top of standard therapy. The investigator will also be able to change concomitant therapy to ensure sufficient standard of care for underlying conditions, such as hypertension and diabetes mellitus. Therefore, the placebo controlled trial design should not constitute a risk for the population in this trial.

Patients with current or planned use of an SGLT2-inhibitor at baseline are excluded. Moreover, in enrolled patients, if a strong need to treat with an SGLT2-inhibitor develops during the trial according to the investigator (anticipated in some T2D patients), trial medication can be discontinued and the patient can instead be treated with open-label empagliflozin or another SGLT2-inhibitor. Follow-up of the patient will continue as per the intention-to-treat principle.

Risk evaluation in relation with COVID-19

Patients with serious underlying medical conditions such as chronic heart disease and T2D are at higher risk for severe illness from coronavirus disease 2019 (COVID-19). Therefore, in case of local high risk of COVID-19 infection, on-site visits should be avoided as much as possible. In the event of restriction to visit the investigator site, a remote visit can be performed. This change is meant to keep the integrity of the trial and it will not affect the benefit-risk of empagliflozin.
There is no indication that empagliflozin may increase the risk of COVID-19 infection. As with any acute illness, empagliflozin during COVID-19 infection has the potential to increase the risk of ketoacidosis. The risk of ketoacidosis in case of acute illness is adequately addressed in the IB.

1.4.3 Discussion

A significant unmet need on patient and health care level related to excess risk of HF and mortality remains in patients with acute MI, and especially in those with high-risk features. Multiple pre-clinical and clinical trials have provided a strong rationale for the evaluation of efficacy and safety of empagliflozin in this population although clinical equipoise remains as all prior large scale trials with empagliflozin, and other SGLT2-inhibitors, have excluded patients with an acute or recent MI. In neighboring populations, empagliflozin has already demonstrated benefits on mortality and HF paired with a well established safety profile. The intended trial population for this trial is not considered to be at higher risk from a safety viewpoint as compared to previously or currently studied populations, thus allowing for a more streamlined trial approach, which includes focused safety reporting (serious adverse events and adverse events of special interest with respect to empagfliflozin and the post-MI setting), remote follow-up and blinded investigator event review instead of centralized adjudication, ultimately enabling continued evidence generation in an area of high unmet medical need.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this event-driven trial is to demonstrate the superiority of empagliflozin 10 mg once daily versus placebo, in addition to standard of care, for the reduction of the composite endpoint of time to first heart failure hospitalisation or all-cause mortality in high-risk patients hospitalised for acute MI.

2.1.2 Primary endpoint(s)

The primary endpoint is the composite of time to first heart failure hospitalisation or all-cause mortality, calculated from date of randomisation.

2.1.3 Secondary endpoint(s)

Key secondary endpoints, which are part of the confirmatory testing strategy, are:
- Total number of HHF or all-cause mortality
- Total number of non-elective CV hospitalisations or all-cause mortality
- Total number of non-elective all-cause hospitalisations or all-cause mortality
- Total number of hospitalisations for MI or all-cause mortality

Other secondary endpoints, not part of the confirmatory testing strategy, are:
- Time to CV mortality

All time-to-event endpoints are calculated from date of randomisation. CV mortality will include death of unknown cause. Non-elective hospitalisations include hospitalisations with unknown attribute of urgency.

2.2 FURTHER OBJECTIVES AND FURTHER ENDPOINTS

2.2.1 Further objectives

Further objectives are to evaluate additional details on efficacy and safety.

2.2.2 Further endpoints

- 30-day all-cause hospitalisation calculated from date of discharge or randomisation, whichever comes latest, as a binary variable
- Number of days alive and out of hospital within the first 90 days, 6 months, 9 months and 12 months after randomisation
- Time to first renal replacement therapy or renal transplantation

- Time to first revascularisation
- Time to first HHF
- Time to all-cause mortality
- Time to first non-elective CV hospitalisation or all-cause mortality
- Time to first non-elective CV hospitalisation
- Time to first non-elective all-cause hospitalisation or all-cause mortality
- Time to first non-elective all-cause hospitalisation
- Time to first hospitalisation for MI or all-cause mortality
- Time to first hospitalisation for MI

All time-to-event endpoints are calculated from date of randomisation.

A complete list of further endpoints will be given in the trial statistical analysis plan (TSAP).

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This is a streamlined, randomised, double-blind, parallel group, placebo controlled, multi-national and multicentre trial. The key streamlining elements in the trial consist of mainly remote follow-up, focused safety collection, and blinded investigator review of events in place of centralized adjudication.

Trial participants have an acute type 1 MI and will be identified, screened and randomised within 14 calendar days of hospital admission. Patients who were admitted for other causes but have an acute MI in-hospital can also be included but randomisation still has to occur within the 14 days of admission. For all patients, early randomisation prior to hospital discharge is strongly encouraged.

Preliminary identification of potentially eligible patients can occur at any time during the hospitalisation, i.e. from hospital admission or in the cardiac catheterisation lab, to discharge. As an exception, identification of potential participants could also be performed after discharge, if still within the 14 day time window. For suitable patients, trial information will be provided and informed consent obtained before screening. In this trial, information related to the eligibility criteria will typically be available as part of clinical routine in the patient health care records. Before randomisation, a physical examination will be performed. Any blood samples will be analysed locally and as part of clinical routine. In case of initial ineligibility, patients may be re-screened at a later time point, as they can become eligible later during the same index hospitalisation.

Patients who fulfill the eligibility criteria will undergo individual randomisation to either empagliflozin 10 mg daily or matching placebo once daily in addition to usual standard of care. Usual standard of care is to be provided according to local, national and international guidelines and recommendations relevant for the management of acute MI and associated risk factors and comorbidities. Screening and randomisation can be performed on the same day.

The trial is event-driven and all randomised patients will remain in the trial until the total number of patients with investigator reported primary endpoint events is projected to reach a target of 532. Estimated trial duration is approximately 26 months with a recruitment period of approximately 21 months. Consequently, individual treatment may range between approximately 5 and 26 months. The actual length of the recruitment may be extended beyond 21 months and the follow up may be adjusted to achieve the 532 primary endpoint events. The estimated total trial duration and length of the double-blind treatment period for each patient will vary accordingly. See also Section 3.3.

The number of primary endpoint events will be monitored continuously during the trial. As soon as the available data reliably suggests that the total number of patients with a primary endpoint event will be reached within a given timeframe, the trial team will initiate required actions to stop the trial. From this time point on, all patients are expected to perform their last visit (EoS visit) within the proposed time schedule, “called Close-out period”, communicated

via an investigator letter (see Section 6.2.3). The Close-out period will end when the last visit of the last patient in the whole trial takes place.

Outline of 1:1 randomisation and follow-up schedule

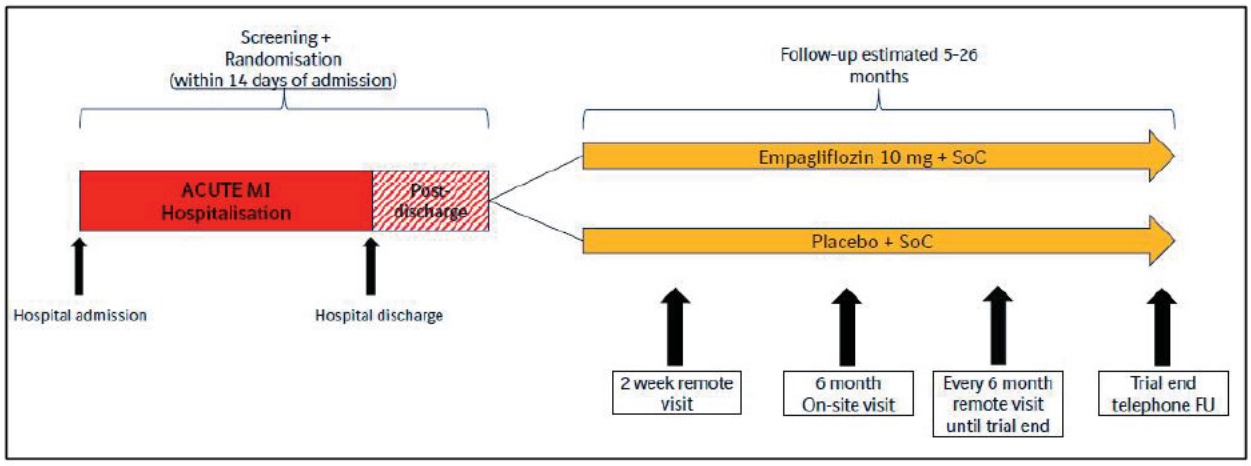

Figure 3.1: 1 Trial Design

All trial visits after randomisation, with the exception of the on-site 6-month visit, will be conducted remotely by means of telephone and/or web-based. During these visits, information on safety and outcome events, adherence to trial medication and specific concomitant medications will be collected.

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

This trial will be conducted in a streamlined setting. The main aim with this approach is to reduce the burden of extensive data collection for both patients and sites, allowing for more effective enrolment and facilitation of protocol adherence, while maintaining high data quality and collection of relevant safety information.
The key streamlining features of the trial are: 1. Majority of follow-up is conducted remotely; 2. Safety collection focused on SAEs, selected AESIs, and AEs leading to discontinuation; 3. Blinded investigator review and reporting of events (no central adjudication).

The primary support for a streamlined trial design results from the established extensive safety profile of empagliflozin in neighboring populations, including but not limited to T2D with chronic CV disease in the EMPA-REG OUTCOME trial (BI trial number 1245.25), chronic HF in patients with/without T2D in the EMPERIAL trials (BI trial numbers 1245.167 and 1245.168), worsening HF in patients with/without T2D in the EMPA RESPONSE-AHF trial (BI trial number 1245.166). Thus, the safety data collection in the present trial is focused on safety events that are serious, of special interest, or leading to trial medication discontinuation.

This in turn allows for the mainly remote follow-up procedures as there is no need for in-trial blood sampling, a physical examination or any other procedure that requires the patient to

visit the study site. However, one in-person visit at 6 months serves as an opportunity for a longer interaction with the patient to address any trial related topics at length, comprehensive concomitant medication collection, and to provide additional supplies of trial medication. For the remote follow-up, all relevant trial information will be collected in a structured questionnaire and/or interview. If requested by a trial participant or deemed necessary by the investigator at any time, an on-site trial visit can be conducted, either in place of or in addition to a pre-specified remote visit. Similarly, as in any clinical trial, study sites should be ready to address any concerns, questions or event reporting from patients outside the pre-specified follow-up time points.

All endpoints will be reviewed by the trained and blinded investigators, incorporating clinical judgment and objective pre-defined event criteria structured in the CRF. No central adjudication of the endpoints will be performed. A meta-analysis of 47 randomised controlled trials has demonstrated that treatment effect estimates were not different whether investigator reported or adjudicated events were used as a basis for the analysis, especially in trials where investigators were blinded [P20-00872]. Moreover, further support to use investigator reports instead of central adjudication comes from the SHIFT study, a chronic HF trial where there was approximately 85% confirmation of investigator-reported HHF events by central adjudication [R20-0249].

Patients should be receiving appropriate care as defined by their physician or practitioner for all cardiovascular conditions according to the prevailing guidelines. For the acute MI, this may include, but is not limited to, myocardial revascularization, medication with anti-platelet agents, beta-blockers, RAAS-inhibitors and cholesterol lowering agents. Finally, adequate treatment, prevention and follow-up of relevant CV and non-CV comorbidities, including diabetes mellitus, must also be ensured.

For details regarding the choice of a placebo control refer to Section 1.4.2.

3.3 SELECTION OF TRIAL POPULATION

Approximately 5000 patients will be randomised into the trial. Approximately 450 sites are planned across multiple countries. Additional back-up countries and sites may be initiated, if deemed necessary.

The trial is event-driven and all randomised patients will remain in the trial until the total number of patients with investigator reported primary endpoint events will reach a target of 532. If the accumulated blinded data suggests a slower accrual of primary outcome events over calendar time than projected (i.e. target 532 events needed with a planned number of 5000 patients randomised), the number of patients randomised may be increased up to 6500, or trial duration may be prolonged.

Recruitment of T2D will be monitored on a regional level. Capping on a regional level may be applied to achieve a contribution of each region to the categories of patients with and without T2D.

Further, monitoring will be conducted with respect to proportions of patients included in the following two subgroups: patients included based on LVEF 35-<45% without signs/symptoms/treatment of congestion; and patients randomised post-discharge; with the aim of either group not corresponding to more than 1/3rd of total trial population. The final decision on capping will be based on the recommendation from the EC during the recruitment period.

Recruitment of patients for this trial is competitive, i.e. screening will stop at all sites at the same time once a sufficient number of patients has been screened to deliver the required number of randomised patients. Investigators will be notified about screening completion and will not be allowed to screen additional patients thereafter. The recruitment period may be extended for individual countries, if necessary, to achieve their reasonable contribution to the global trial population. For the same reason, recruitment may be ended in individual countries or regions.
Re-screening (if a patient is not eligible initially) is allowed once. In case of re-screening, the patient should first be declared a screening failure in the eCRF and the Interactive Response Technology (IRT) with the original patient number. Upon re-screening, the IRT system will allocate a new screening number for the patient.

If a patient is randomised in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of randomisation), the sponsor/CRO should be contacted immediately.

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) irrespective of whether they have been treated with trial medication or not.

3.3.1 Main diagnosis for trial entry

In order to qualify for trial entry, patients must be hospitalised with a spontaneous acute MI (AMI) defined as MI with a primary etiology of an acute coronary artery disease pathology (e.g., plaque rupture/erosion, in-stent restenosis, stent thrombosis) rather than MIs caused by supply-demand mismatch (e.g., sepsis, arrhythmia, anemia, or other condition). Patients with an in-hospital spontaneous AMI are also eligible. In addition, patients should further be selected based on an elevated risk of HHF and mortality defined as signs/symptoms/treatment of congestion, and/or a left ventricular ejection fraction <45% and one additional enrichment criterion will be requested (see Section 3.3.2). Patients must be randomised no later than 14 calendar days after hospital admission. Early randomisation, prior to discharge, is strongly encouraged. Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

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

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

3. 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) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information and in Section 4.3.2.3.

4. Diagnosis of spontaneous AMI: STEMI or NSTEMI with randomisation to occur no later than 14 calendar days after hospital admission. For patients with an in-hospital MI as qualifying event, randomization must still occur within 14 days of hospital admission.

   Spontaneous AMI is defined as MI with a primary etiology of an acute coronary artery disease pathology (e.g., plaque rupture/erosion, in-stent restenosis, stent thrombosis) rather than MI caused by supply-demand mismatch (e.g., sepsis, arrhythmia, anemia, or other condition).

   Spontaneous AMI is established when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia due to primary coronary event. Under these conditions, the following criteria have to be met for the diagnosis of spontaneous AMI:
   Detection of rise and/or fall of cardiac enzymes (cardiac troponin, cTn or the MB fraction of creatinine kinase, CKMB) with at least one value above the 99th percentile of the upper reference limit (URL) or the local laboratory MI diagnosis cut-off value, together with evidence of myocardial ischemia with at least one of the following:
   - Ischemic discomfort or other ischemia symptom(s)
   - Electrocardiogram (ECG) characteristics of STEMI or NSTEMI including new or presumably new significant ST-segment-T wave (ST-T) changes
   - Newly developed pathological Q waves or left bundle branch block (LBBB) in the ECG
   - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiologyIdentification of a coronary thrombus by angiography

5. High risk of HF, defined as **EITHER**
   a) Symptoms (e.g. dyspnea; decreased exercise tolerance; fatigue), or signs of congestion (e.g. pulmonary rales, crackles or crepitations; elevated jugular venous pressure; congestion on chest X-ray), that require treatment (e.g. augmentation or

[1] A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Tubal ligation is NOT a method of permanent sterilisation. A woman who underwent tubal ligation is still considered as WOCBP. However tubal ligation is considered as a method of highly effective birth control.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

initiation of oral diuretic therapy; i.v. diuretic therapy; i.v. vasoactive agent; mechanical intervention etc.) at any time during the hospitalization.

OR

b) Newly developed LVEF < 45% as measured by echocardiography, ventriculography, cardiac CT, MRI or radionuclide imaging during index hospitalisation.

6. In addition at least one of the following risk factors:
   - Age ≥ 65 years,
   - Newly developed LVEF < 35%,
   - Prior MI (before index MI) documented in medical records,
   - eGFR < 60 ml/min/1.73m^2 (using CKD-EPI formula based on creatinine from local lab at any time during index hospitalisation),
   - Atrial fibrillation (persistent or permanent ; if paroxysmal, only valid if associated with index MI),
   - Type 2 diabetes mellitus (prior or new diagnosis),
   - NT-proBNP ≥1,400 pg/mL for patients in sinus rhythm, ≥2,800 pg/mL if atrial fibrillation; BNP ≥350 pg/mL for patients in sinus rhythm, ≥700 pg/mL if atrial fibrillation, measured at any time during hospitalisation,
   - Uric acid ≥7.5 mg/dL (≥446 µmol/L), measured at any time during hospitalisation,
   - Pulmonary Artery Systolic Pressure [or right ventricular systolic pressure] ≥40 mmHg (non-invasive [usually obtained from clinically indicated post-MI echocardiography] or invasive, at any time during hospitalisation),
   - Patient not revascularized (and no planned revascularization) for the index MI (Includes e.g. patients where no angiography is performed, unsuccessful revascularization attempts, diffuse atherosclerosis not amenable for intervention; but does NOT include if revascularization was not performed due to nonobstructive coronary arteries),
   - 3-vessel coronary artery disease at time of index MI,
   - Diagnosis of peripheral artery disease (extracoronary vascular disease, e.g. lower extremity artery disease or carotid artery disease).

3.3.3 Exclusion criteria

1. Diagnosis of chronic HF prior to index MI.
2. Systolic blood pressure ≤ 90 mmHg at randomisation.
3. Cardiogenic shock or use of i.v. inotropes in last 24 hours before randomisation.
4. Coronary Artery Bypass Grafting planned at time of randomisation.
5. Current diagnosis of Takotsubo cardiomyopathy.
6. Any current severe (stenotic or regurgitant) valvular heart disease.
7. eGFR < 20 ml/min/1.73m2 (using CKD-EPI formula based on most recent creatinine from local lab during index hospitalisation) or on dialysis.
8. Type I diabetes mellitus.
9. History of ketoacidosis.

10. Current use or planned treatment with an SGLT-2 inhibitor or combined SGLT-1 and 2 inhibitor. Discontinuation of a SGLT-2 inhibitor or combined SGLT-1 and 2 inhibitor for the purposes of enrolment in the trial is not permitted.
11. Contraindication for using empagliflozin or any other SGLT-2 inhibitor.
12. Any physical or mental condition significantly affecting the patient's ability to participate in the Investigator's opinion.
13. Any other clinical condition that would jeopardise patient's safety while participating in this study, or may prevent the patient from adhering to the trial protocol in the Investigator's opinion.
14. Presence of any other disease than the acute MI or its immediate complications with a life expectancy of <1 year in the opinion of the investigator.
15. Current or previous randomisation in one of the empagliflozin heart failure trials (i.e. trials 1245.110, 1245.121, 1245-0167, 1245-0168, 1245-0204) or currently enrolled in another investigational device or drug trial, or less than 30 days since ending another investigational device or drug trial, or receiving other investigational treatment(s). Patients participating in purely observational trial will not be excluded.
16. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.

3.3.4 Withdrawal of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see Sections 3.3.4.1 and 3.3.4.2 below.

This is a long-term outcome trial and an excessive withdrawal rate can have a severe negative impact on the scientific value of the trial. The Intention To Treat (ITT) analysis requires that all randomised patients be followed until trial end even if the trial medication was temporarily interrupted, discontinued or never started. Therefore, every effort should be made to keep the patients in the trial: if possible on treatment, or at least to collect important trial data. Patients are encouraged to notify the site in cases of treatment discontinuation even outside regular follow-up time points, in order for a timely discussion and decision on whether treatment should be reinstated, re-evaluated or permanently stopped. Requests from patients for on-site visits should also be accommodated.

If a patient is withdrawn from the trial the sponsor/CRO should be informed immediately about each individual case.

Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the options for follow-up of patients in case of withdrawal.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and eCRF. If applicable, consider the requirements for Adverse Event collection reporting (please see Sections 5.2.1.2.1 and 5.2.1.2).

3.3.4.1 Discontinuation of trial treatment

A patient should discontinue trial treatment if:

- If it is the patient's wish, without need for justification.
- The patient has repeatedly demonstrated non-compliance with important trial procedures and, in the opinion of both the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- The patient needs to take a concomitant medication that interferes with the investigational medicinal product. Please see Section 4.3.2.
- The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events, other diseases, or pregnancy).

In all cases where a patient has discontinued trial medication, the possibility to restart therapy should be considered if medically justified. With the exception of short and temporary interruptions, patients are encouraged to contact site whenever and as soon as they discontinue trial medication so that a timely assessment of the potential to restart therapy can be performed by the investigator or designee. If the patients do not notify the site, the assessment must be performed in conjunction with the regular follow-up visits. For further information, please see Section 4.1.4.

If the patient nonetheless discontinues trial treatment prematurely, every effort should be made for the patient to take part in the regularly scheduled trial visits and have all trial procedures performed except those pertaining to drug intake. It is also expected that every effort should be made to follow-up on the collection of all SAEs, AESIs and endpoint events to have a complete dataset without missing data. If a patient is not willing to return for the on-site visit after 6 months (visit 4), then this visit should be conducted by phone.

Patients that are not actively taking trial medication may be less motivated to adhere to the scheduled trial visits. In potential cases where a patient is no longer willing to complete all follow-up measures, the following sequence of options should be considered and discussed if allowed by local regulations:

Option 1	Conduct all remaining trial visits remotely using phone (direct contact) + medical records review
Option 2	Conduct yearly trial visits and EoS Visit remotely using phone (direct contact) + medical records review
Option 3	Conduct all remaining trial visits remotely using web-based application (only) and EoS Visit using phone (direct contact) + medical records review
Option 4	Conduct the EoS Visit only using phone (direct contact) + medical records review
Option 5	No direct contact with the patient, indirect collection of information only, e.g. medical records review

Vital status should be collected at the EoS during the Close-out period for all patients if allowed by local regulations.

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

If a patient becomes pregnant during the trial, the trial medication will be stopped, the patient will be followed up during the trial and until birth or termination of the pregnancy (see further details in Section 5.2.1.2).
If new efficacy/safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all patients or take any other appropriate action to guarantee the safety of the trial patients.

3.3.4.2 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision. This is a long-term outcome trial and an excessive withdrawal rate can have a severe negative impact on the scientific value of the trial.
If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 3.3.4.1 above. In the event of patient withdrawal from trial participation, all assessments should occur at the patient's EoS visit with completion of the eCRF.

Vital status should be collected during the Close-out period for patients that withdraw consent from trial participation, if allowed by local regulations.

3.3.4.3 Patients lost to follow-up

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

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

3.3.4.4 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. New efficacy or safety information invalidating the earlier positive benefit-risk-assessment, please see Section 3.3.4.1.
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

Further follow up of patients affected will occur as described in Section 3.3.4.1.
The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The trial medication will be provided by Boehringer Ingelheim Pharma GmbH & Co.KG.

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Test product 1

Substance:	Empagliflozin
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim GmbH & Co. KG
Unit strength:	10 mg
Posology:	1 tablet once daily
Method and route of administration:	Oral

Table 4.1.1: 2 Test product 2

Substance:	Placebo matching empagliflozin 10 mg
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim GmbH & Co. KG
Unit strength:	Not applicable
Posology:	1 tablet once daily
Method and route of administration:	Oral

4.1.2 Selection of doses in the trial and dose modifications

Empagliflozin 10 mg and 25 mg are approved for the treatment of T2D.
In the EMPA-REG-OUTCOME trial both doses were administered to patients with T2D and showed to be equally effective in reducing CV mortality, all-cause mortality, and HHF.
In a subgroup analysis, empagliflozin improved the outcome of CV mortality and HHF with a similar magnitude in patients with low or high levels of HbA1c at baseline and irrespective of the dose of empagliflozin [P18-10152]. This indicates the risk reduction for this outcome is independent of the degree of glycaemic control at baseline, suggesting that these benefits can be achieved with the 10 mg dose similar to the 25 mg dose in the non-diabetic population.
The mechanism of action is supported by studies in healthy volunteers where both doses were associated with a glucosuria of about 50g per day.

Given the lower exposure with empagliflozin 10 mg and similar general safety, and similar observed CV, HHF and mortality effects for both doses, empagliflozin 10 mg once daily has been selected as the dose in this trial.
For further details see current version of the IB [c01678844].

4.1.3 Method of assigning patients to treatment groups

After the assessment of all inclusion and exclusion criteria, each eligible patient will be randomised to receive empagliflozin 10 mg or matching placebo according to a randomisation plan in a 1:1 ratio. The assignment will occur in a blinded fashion at visit 2a via IRT stratified by established T2D (yes, no) and region (North America, Latin America, Europe, Asia). Note that the medication number is different from the patient number (the latter is generated during screening via the IRT System).

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

Patient assignment to a treatment group will be determined by a computer generated random sequence. Access to the randomisation code will be controlled and documented - for further details please refer to Section 4.1.5.1 and 4.1.5.2. For information on capping, please refer to Section 3.3.

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

4.1.4 Drug assignment and administration of doses for each patient

Patients who qualify will be randomised to treatment groups as described in Section 4.1.3.
Trial medication will be dispensed by the investigator in a double-blind manner.

IRT will be used to allocate trial medication to patients. At Visit 2a patients will be assigned one medication kit for a 6 months treatment period and 6 weeks of reserve. At Visit 4 patients will be assigned medication kits for a 6, 12 or 18 months treatment period, depending on

when the randomisation took place – see Table 4.1.4: 1. Each medication kit contains 6 weeks of reserve.

During the COVID-19 pandemic, there might be situations that would not allow a patient to come to the site for Visit 4. If the investigator judges it as favourable and safe to continue trial medication, trial medication might be shipped from the site to the patient (for more details see Section 6.2.2).

Additional medication kits can be assigned to patients, e.g. in the event of treatment prolongation. The trial medication may then be shipped by courier from site to patient, if legally acceptable according to local regulations.

Treatment starts on the day of Visit 2a and ends on the EoS visit (or in the event of premature discontinuation, the time when the permanent withdrawal takes place). For further details regarding packaging please refer to Section 4.1.6. For return of trial medication please refer to Section 6.2.3.

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

To ensure a dose interval of about 24 hours, the medication should be taken in the morning at approximately the same time every day including the days of study visits. 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.

In case trial medication was discontinued for a temporary reason or by the patient without a medical indication, trial treatment can be resumed at any time until EoS. Trial medication should be restarted if and as soon as medically justified (see also Section 3.3.4.1 and 4.3.1).

Table 4.1.4: 1 Dispense of medication kits – visualising amount and timing of dispense depending on the randomisation of the patient

Trial duration months	1 - 3			4 - 6			7 – 9			10 - 12			13 - 15			16 – 18			19 - 21			22 - 26	
Patients examples	Randomisation period																					Follow-up period*	
Randomised month 1	X	-	-	-	3X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Randomised month 3		X	-	-	-	3X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Randomised month 7					X	-	-	-	2X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Randomised month 10							X	-	-	-	2X	-	-	-	-	-	-	-	-	-	-	-	-
Randomised month 13									X	-	-	-	X	-	-	-	-	-	-	-	-	-	-
Randomised month 16											X	-	-	-	X	-	-	-	-	-	-	-	-

(*) If the trial is prolonged (beyond 26 months) additional medication kits can be assigned
X = Medication kit(s) dispensed

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

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

The access to the randomisation code will be kept restricted until its release for analysis.

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

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator via IRT. Emergency unblinding should be rare and it must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page.

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 for processing in the Pharmacovigilance database system and not be shared further.

The patient could continue trial medication after unblinding.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

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

4.1.7 Storage conditions

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

If the storage conditions are found to be outside the specified range, the Clinical Research Associate (CRA) (as provided in the list of contacts) must be contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the Institutional Review Board (IRB) / Independent Ethics Committee (IEC),
- Availability of a signed and dated clinical trial contract between the sponsor/CRO 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,
- For USA: Availability of FDA Form 1572.

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics.

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor/CRO or warehouse / drug distribution centre or alternative disposal of unused products.
If applicable, the sponsor 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 medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor or appointed CRO, the investigator or designee must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 TREATMENT COMPLIANCE

The patients are requested to bring all remaining trial medication including empty package material with them when attending any on-site visits. The site personnel will register the medication kits (a pill count will not be performed).

At every trial visit (on-site and remote) patients will be asked if they have complied to the trial treatment regimen.
If the patients indicate non-adherence to the trial medication the investigator or designee will carefully interview the patient, assess and address reasons for non-adherence, and repeat information about importance of treatment compliance and the purpose/conduct of the trial.

Randomised patients will not be discontinued for poor compliance without prior discussion between the investigator and the monitor.

4.3 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.3.1 Other treatments and emergency procedures

The use of medication for the treatment of MI and HF will be at the discretion of the Investigator and/or other treating physician, and should be in accordance with local, national and international guidelines.
All concomitant (additional) medications and other therapies should be recorded on the appropriate pages of the electronic Case Report Form (CRF).

Sequence and timing of initiation of concomitant therapies in relation to trial medication is left at the discretion of the investigator. However, initiation of RAAS inhibitor(s) and trial medication within 24 hours of each other is not recommended. For further details see the ISF.

During potential episodes of fluid loss, for instance due to gastrointestinal illness, careful monitoring of volume status, concomitant blood pressure therapies and electrolytes is recommended and temporary interruption of the trial medication should be considered until the fluid loss is corrected.

Concomitant antidiabetic medications should be adjusted individually as clinically indicated by the patient's usual diabetes care provider. Additional guidance is provided in the IB. Restrictions of antidiabetic background therapy are described in Section 4.3.2.

Hypoglycaemia
Patients with and without T2D experiencing repeated or severe symptoms such as nervousness, sweating, intense hunger, trembling, weakness and palpitations should contact the investigator or another healthcare professional, as these symptoms might be suggestive of hypoglycaemia. In the case of hypoglycaemia, 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.

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

Cases of DKA have been reported in patients treated with empagliflozin, including fatal cases. In a number of reported cases, the presentation of the condition was atypical with only moderately increased blood glucose values; below 14 mmol/l (250 mg/dl).

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

Patients should be assessed and treated for ketoacidosis immediately according to local guidelines if these symptoms occur, regardless of blood glucose level. If ketoacidosis is

suspected, the trial medication should be discontinued, the patient should be evaluated, and prompt treatment should be initiated.

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

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

There are no trial specific emergency procedures to be followed.

4.3.2 Restrictions

4.3.2.1 Restrictions regarding concomitant treatment

The use of any SGLT-2 inhibitors or combined SGLT-1 and 2 inhibitors during the trial, is prohibited as long as the patient is taking trial medication and up to 7 days after last trial medication intake.

If the patient is in need of an SGLT-2 inhibitor or combined SGLT-1 and 2 inhibitors during the trial, this may be given at the discretion of the investigator, and can be initiated at minimum 7 days after trial medication discontinuation. The patient will still remain in the trial.

4.3.2.2 Restrictions on diet and life style

None. For diet and risk of ketoacidosis refer to Section 4.3.1.

4.3.2.3 Contraception requirements

WOCBP participating in the trial must use a highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly if their sexual partner is a man able to father a child. Acceptable methods meeting these criteria is provided below and in the patient information.

- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable)
- Intrauterine device or intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomised partner
- True sexual abstinence

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

The investigator is responsible for reviewing the endpoints. Investigators are blinded to trial treatment and will receive dedicated training on event review prior to trial initiation. Investigators assigned to the trial after initiation will also undergo event review training for subsequent qualification. Hospitalisation for HF will be reviewed by the investigators based on clinical judgement and objective criteria assessed in relevant source documents and documented in a structured eCRF.

For the all-cause mortality component of the primary endpoint, only the date of death will be required. Investigators will further be requested to categorize deaths as CV or non-CV mortality based on best available information, clinical judgment and guidance in the eCRF. Investigators will also be requested to categorize hospitalisations into elective and non-elective hospitalisations. MI events will be collected in the eCRF as reported by the investigator.

Detailed information with event criteria and instructions how to report the endpoint events is available in the event review charter (access through the eDC and in the ISF).

5.2 ASSESSMENT OF SAFETY

5.2.1 Assessment of adverse events

5.2.1.1 Definitions of AEs

5.2.1.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following should also be considered as an AE:

- 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 exist prior to randomisation, they will be considered as baseline conditions and should be collected in the CRF.

5.2.1.1.2 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 prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- 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.

5.2.1.1.3 AEs considered “Always Serious”

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

The latest list of “Always Serious AEs” can be found in the eDC system. A copy of the latest list of “Always Serious AEs” will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.1.2.
Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in Section 5.2.1.2.

5.2.1.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor/CRO within the same timeframe that applies to SAEs, please see Section 5.2.1.2.1.

The following are considered as AESIs:

Contrast induced acute kidney injury (AKI)
Contrast induced AKI in this trial is defined as a creatinine increase of >44 µmol/L (0.5 mg/dl) or >25% increase within 72 hours of contrast administration, in the absence of alternative more likely explanations. In the report the investigator will be asked to provide supporting information (creatinine values and time points in relation to contrast

administration) as available. It is important to note that lab values alone do not automatically fulfil the definition above and that clinical judgment should be applied.

Ketoacidosis

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

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

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

Events leading to lower limb amputation

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

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

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

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

Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- an elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or in samples drawn within 30 days of each other, or,
- aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.

No central laboratory assessments are planned in this trial for liver enzymes or serum bilirubin.
Based on local laboratory data, if any of the above abnormalities are reported during the course of the trial this constitute a hepatic injury alert. The patients showing these local laboratory 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 available laboratory results (ALT, AST, total bilirubin), the investigator should make sure these parameters are analysed, by performing appropriate local laboratory blood tests. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

5.2.1.1.5 Causal relationship of AEs

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between the adverse event and the given trial medication, 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 reduced).

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.

- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.1.2 Adverse event collection and reporting

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

- From randomisation onwards until the individual patient's end of trial (EoS) participation:
  -all AESIs (serious and non-serious)
  -SAEs
  -AEs leading to discontinuation of trial medication for at least 7 consecutive days (serious and non-serious)

The EoS visit coincides with individual patient's last day of trial medication administration with the exception of patients with early treatment discontinuation.

- After the individual patient's EoS:
  -the investigator does not need to actively monitor the patient for new AEs but must report all SAEs and AESIs up to EoS + 7 days.

  After this EoS + 7 days period the investigator then should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call.

All AEs should be reported into the eCRF as long as the site has access to the EDC system. After that, the reporting pursues on the BI paper SAE form (see Section 5.2.1.2.1).

The rules for Adverse Event Reporting exemptions still apply, please see Section 5.2.1.2.3.
Vital Status Data Collection
Patients who discontinue trial medication prematurely, who agree to be contacted further but do not agree to physical visits, should be followed up as described in Section 3.3.4.1, withdrawal from trial treatment.

5.2.1.2.1 AE reporting to the sponsor/CRO and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the SAE or AESI in the AE- and SAE eCRF pages immediately (within 24 hours). The same timeline applies if follow-up information becomes available. In specific occasions, the

investigator could inform the sponsor/CRO upfront via telephone. This does not replace the requirement to complete the SAE eCRF page.

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

In exceptional cases when the eDC is unavailable for longer than 24 hours, the following applies:
The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the existing SAE or AESI, on the BI paper SAE form via fax immediately (within 24 hours) to the sponsor's/CRO's unique entry point (country specific contact details will be provided in the ISF).
Once the eDC is available again, information from the BI SAE form should be entered in the applicable eCRF pages.

5.2.1.2.2 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/CRO'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/CRO's unique entry point on the Pregnancy Monitoring Form for Clinical Studies (Part B).
The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (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 Studies is to be completed. If there is an SAE and/or AESI associated with the pregnancy the SAE page must be completed in addition.

5.2.1.2.3 Exemptions to SAE reporting

Protocol specified exempted events listed below should be collected immediately on the appropriate eCRF page only.
Primary and secondary end point components to be exempted irrespective of their causality assessment by the investigator, to protect the integrity of the trial:

- Hospitalisation for heart failure
- Myocardial infarction
- Other CV events
- CV mortality

In addition, the following SAEs that are occurring at some frequency independent of drug exposure in the trial population are exempted from expedited reporting, and should be collected on the appropriate eCRF page(s) only. These events are known consequences of the underlying disease and it is not possible, based on a single case, to conclude that there is a reasonable possibility that the investigational drug caused these events.

- Post procedural haemorrhage
- Gastrointestinal haemorrhage
- Haematuria
- Non-cardiac chest pain
- Respiratory tract infection including Respiratory tract infection bacterial, Respiratory tract infection fungal and Respiratory tract infection viral, excluding COVID-19 infection
- Pneumonia, excluding COVID-19 pneumonia
- Syncope

All the above stated events should be considered exempted only if the event does not qualify as AESI.

Regardless of relationship to trial medication, these events will not be reported by the sponsor/CRO to regulatory agencies or IECs in an expedited manner unless they qualify as an AESI (for definition of AESI, see Section 5.2.1.1.4) with fulfilment of expedited regulatory safety reporting requirements.

Although the primary endpoint of the trial includes non-CV mortality (all-cause mortality), the sponsor/CRO is of the opinion that certain non-CV fatal cases may potentially constitute new safety information about empagliflozin (e.g., fatal hepatic AE, fatal serious cutaneous AE).

Therefore, non-CV SAEs, including cases of non-CV mortality, will be required to be immediately reported by the investigator to the sponsor/CRO. For further information on reporting and timelines see Section 5.2.1.2.1.

An independent DMC will monitor the safety data in the trial on an ongoing basis. Reported SAEs that are protocol exempted events will be collected in the CRFs and evaluated by the DMC. These events will not be collected on the SAE CRF for expedited review or reporting.

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

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

5.3 OTHER ASSESSMENTS

Physical examination including vital signs
A physical examination, including at minimum an evaluation of the cardiovascular and pulmonary system and assessment of vital signs (blood pressure and pulse rate), will be performed at Visit 2a/randomisation. If available in the local medical records, the most recent height and weight information from the index hospitalisation can be used, or should otherwise be measured.

Local laboratory tests
The most recent serum creatinine before randomisation must be collected from local laboratory at baseline to derive eGFR based on the using the CKD-EPI equation (see below).

CKD-EPI equation
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 CKD-EPI equation considers the race as an adjustment factor, therefore the race must be known for accurate estimation.

The following laboratory tests from the index hospitalisation before randomisation should be entered in the eCRF if available:

- NT-proBNP (highest value)
- BNP (highest value)
- Uric acid (highest value)
- Haemoglobin (most recent value)
- Potassium (most recent value)
- HbA1c (most recent value)
- LDL cholesterol (most recent value)

5.4 APPROPRIATENESS OF MEASUREMENTS

The measures conducted at baseline reflect the current clinical practice across the different countries.
All measurements performed during this trial are standard measurements and will be performed in order to monitor safety aspects, and to determine empagliflozin efficacy and safety in an appropriate way.
The primary and secondary endpoints are accepted for evaluation of efficacy and safety of an oral drug administered to patients with MI and/or HF, and they are widely used in respective pivotal phase III MI and HF trials.

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

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the Flow chart. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule.

The remote visits will be conducted by means of mobile/web-based application, telephone or telemedicine (Telehealth). The site personnel will discuss the different options with the patient during the screening to ensure the patients' preferences are met. Patients are allowed to switch between the different remote contact options.

Patients using the mobile/web-based application to complete the questionnaire will receive push-notifications to remind of their upcoming visits. If the questionnaire has not been completed within the defined visit window site/call center personnel will be alerted and proceed to call the patient.

In cases where the patients using mobile/web-based application have indicated potential occurrence of an endpoint event, safety related or medication adherence issue, the site personnel will contact the patient via telephone for additional information.

In conjunction with all visits, remote or on-site, site personnel will additionally screen local medical records for endpoint events, SAEs and AESIs.

Should the patient during the structured interview or via the mobile/web-based application indicate that a safety related issue has occurred, site personnel will collect relevant information, e.g. from medical records needed for reporting the event/endpoint.
The investigator is responsible for reviewing the endpoints. For further information see Section 5.1 and the event review charter.

The site personnel will refer to the investigator if the patient seeks medical advice or requires medical attention.

If requested by the patient or deemed necessary by the investigator at any time, an on-site trial visit can be conducted, either in place of or in addition to a pre-specified remote visit. Similarly, as in any clinical trial, trial sites should be ready to address any concerns, questions or event reporting from patients outside the pre-specified follow-up time points.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

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

6.2.1 Screening period

No trial procedures should be performed unless the patient has consented to taking part in the trial.

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

The investigations for the main diagnosis for inclusion are to be completed and documented per standard of care as a prerequisite to consideration for trial participation. Patients will be included in the trial based on patient interview and available information in the medical records.

Relevant medical history/baseline conditions will be documented using pre-specified categories as given in the eCRF.

If the patient meets the entry criteria, Visit 2a/randomisation must occur within 14 days of hospital admission and investigators should strive for randomisation prior to hospital discharge. If the patient does not meet the entry criteria following Visit 1/screening procedures, the patient should be registered as a screen failure in IRT.

A physical examination, including collection of vital signs will be performed at Visit 2a/randomisation. Selected local laboratory tests will be collected if available as indicated in Section 5.3.

6.2.2 Treatment period(s)

Randomisation can occur at the same day as the screening visit.
After a final check of all in- and exclusion criteria, eligible patients will be randomised at Visit 2a using IRT. All Visit 2a assessments must be performed before the first dose is taken in hospital.

For patients that are still hospitalised after Visit 2a assessment of safety, endpoints and updates of concomitant medication will take place at Visit 2b/ day of hospital discharge.

WOCBP will receive a pregnancy test to bring back home in order to perform the test at the EoS Visit.

Visit 3, to be performed 14 days after randomisation, will be conducted remotely by means of telephone or via mobile/web-based application. Thereafter, visits every 6 months after randomisation will be scheduled as specified in the Flow Chart. Information on safety and endpoint events, and adherence to trial medication will be collected at all visits.

Information on concomitant therapy will be collected up to and including Visit 4.

Information on specific concomitant medication (SGLT-2 inhibitor (or combined SGLT-1 and SGLT-2 inhibitor)) will be collected on all visits.

Visit 4, 6 months after randomisation is an on-site visit. Patients should bring their trial medication with them at this visit in order for site personnel to confirm treatment adherence. Trial medication for the remaining treatment period will be dispensed at this visit and allocation of new kit number(s) will be managed through the IRT.

In exceptional cases, e.g. during the COVID-19 pandemic, if it is not recommended to conduct Visit 4 at the trial site, it may be performed at patient's home or remotely (via telephone and/or internet based means of communication). In the event of a remote Visit 4 trial medication may be shipped by courier from site to patient, if legally acceptable according to local regulations and considered safe for patient to continue treatment.
It is important that any remote Visit 4 is discussed with and approved by the sponsor/CRO to ensure delivery of trial medication fulfil the trial specific and country-specific requirements.

The remaining visits will be conducted remotely, but on-site visits replacing remote visits or arranged as additional visits should be arranged if requested by patient or considered deemed necessary by investigator.

At any time during the treatment period the investigator is allowed to adjust and optimise the medical therapy according to local and international guidelines.

If any additional therapy is considered necessary for the patient's welfare during the treatment period it may be given at the discretion of the Investigator (see also restrictions in Section 4.3.2).

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

6.2.3 Trial completion and Follow-up period

All patients still in the trial at the time when the required number of primary outcome events are expected to be reached will be contacted via telephone by the investigator or designee. The proposed time schedule for this last remote visit will be communicated via an investigator letter to the sites.

During the EoS Visit occurrence of safety and endpoint events will be assessed, and adherence to trial medication and use of specific concomitant medication will be recorded. Patients on trial medication will be asked to stop their trial medication and to return the unused drugs to the site per agreement with the site personnel.

During the 7 days following EoS patients are asked to report any AESIs, SAEs including endpoint events to the investigator or designee.

After the patients have completed the trial standard of care should be provided according to local, national and international guidelines and recommendations.

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

6.2.4 Early discontinuation of trial medication and trial termination

If trial medication is prematurely discontinued, the reason for discontinuation must be collected and reported if applicable. Patients who discontinue trial medication prematurely should continue to follow scheduled visits until EoS. For patients reluctant to attend the scheduled visits after prematurely discontinuing trial medication, the importance of further trial assessments should be emphasized and discussed.

Please refer to Section 3.3.4.1 for detailed procedures to be followed in case a patient wants to stop trial medication.
In case of early trial termination (e.g. based on recommendation by the DMC), a reasonable timeframe to stop the trial (perform last patient visits) will be defined and communicated to the investigators.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

Eligible patients will be randomised to receive empagliflozin or matching placebo in a 1:1 ratio, stratified according to established T2D status (yes, no) and geographical region (North America, Latin America, Europe, Asia). The primary endpoint is the composite of time to first HHF or all-cause mortality. The statistical model will be a Cox proportional hazards model adjusting for stratification factors as well as further baseline covariates known to be prognostic for the primary endpoint, see Section 7.2.2. The hazard ratio and its confidence limits will be determined for evaluating superiority of empagliflozin to placebo.

The key secondary endpoints are defined as:

1. Total number of HHF or all-cause mortality
2. Total number of non-elective CV hospitalisations or all-cause mortality
3. Total number of non-elective all-cause hospitalisations or all-cause mortality
4. Total number of hospitalisations for MI or all-cause mortality

7.1 NULL AND ALTERNATIVE HYPOTHESES

A hierarchical testing procedure will be applied from the primary endpoint to the set of key secondary endpoints 1 and 2. If, and only if, the primary endpoint is significant at α=5% (two-sided) and shows superiority of empagliflozin versus placebo, then a Hochberg step-up procedure [R20-0113] will be applied to test the family of two key secondary endpoints of

- Total number of HHF or all-cause mortality
- Total number of non-elective CV hospitalisations or all-cause mortality

at α=5% (two-sided). If the null hypotheses for both of these two key secondary endpoints can be rejected and both show superiority of empagliflozin versus placebo, only then the third key secondary endpoint of:

- Total number of non-elective all-cause hospitalisations or all-cause mortality

will be tested at α=5% (two-sided). The fourth key secondary endpoint

- total number of hospitalisations for MI or all-cause mortality

will only be tested if all the hypotheses for the primary and key secondary endpoints 1, 2 and 3 have been rejected and all show superiority of empagliflozin versus placebo. This ensures strong control of the family-wise error rate, see Figure 7.1: 1.

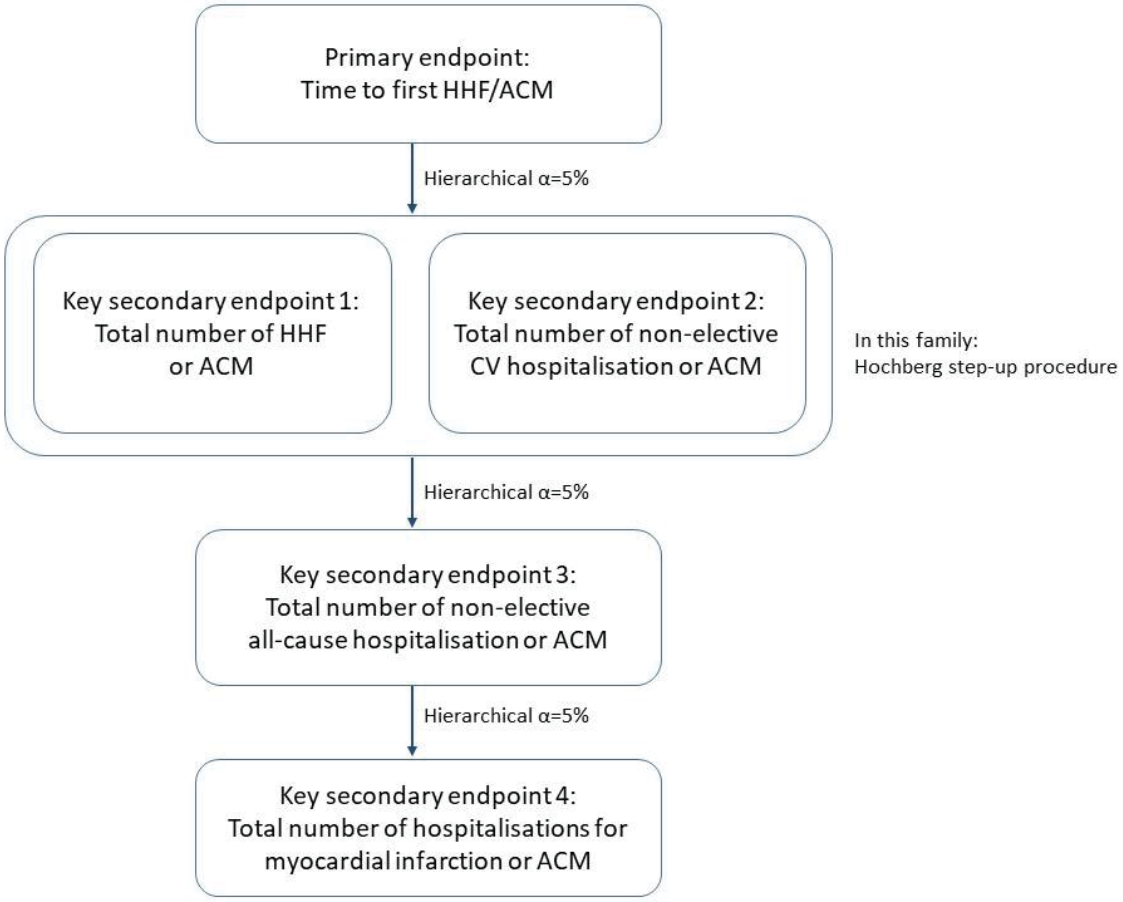

Figure 7.1: 1 Multiple testing strategy

For all primary and key secondary endpoints, superiority for empagliflozin versus placebo will be evaluated with a two-sided test in the following structure:

Null hypothesis: There is no difference regarding the risk of the endpoint in question between empagliflozin versus placebo

Alternative hypothesis: There is a difference regarding the risk of the endpoint in question between empagliflozin versus placebo

Two-sided 95% confidence intervals will be given for the hazard ratio (HR) (primary endpoint) and rate ratio (key secondary endpoints).

The Hochberg step-up procedure controls family-wise error rate at 5% for the family of the two key secondary endpoints, if there is a non-negative correlation for the two endpoints of 1) total number of HHF or all-cause mortality, and 2) total number of non-elective CV hospitalization or all-cause mortality. This is assumed to hold true as the total number of HHF is a subset of all non-elective CV hospitalizations.

Other secondary endpoints will be evaluated in an exploratory manner.

The trial is considered positive, if the null hypothesis of the primary endpoint can be rejected and the result is more favorable for empagliflozin versus placebo (HR<1).

7.2 PLANNED ANALYSES

7.2.1 General considerations

The primary efficacy analysis will be based on the randomised set (RS) including all randomised patients. Analyses will be performed according to the intention-to-treat principle, with the use of all available data (on and off treatment) through the trial. This equates a treatment-policy estimand. Supplementary analyses investigating a hypothetical estimand using on-treatment data only will be specified below.

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

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

Baseline will be defined as the last available measurement before randomisation.

Important protocol deviations will be defined in a separate document.

7.2.2 Primary endpoint analyses

The primary endpoint will be analysed using a Cox proportional hazards model [R07-4680] with treatment, T2D at baseline (yes vs no), geographical region (North America, Latin America, Europe, Asia), age at baseline (continuous), eGFR (CKD-EPI) at baseline (<45 vs 45-<60 vs 60-<90 vs >=90 ml/min/1.73m2), LVEF at baseline (<35% vs ≥35%), persistent or permanent atrial fibrillation at baseline (yes vs no), prior MI at baseline (yes vs no), peripheral artery disease (PAD) at baseline (yes vs no) and smoking at baseline (current vs non-current) as covariates. Breslow's method for dealing with ties will be used. The hazard ratio for the effect of treatment (empagliflozin versus placebo) and its 95% confidence limits will be estimated and presented with the two-sided p-value for the null hypothesis of equality based on the Wald chi-squared statistic.

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

To detect any heterogeneity in the treatment effect among patients with established T2D and without established T2D, a subgroup analysis will be performed by including the status of established T2D by treatment interaction term into the Cox model.

Standard subgroup analyses of the primary endpoint include e.g. geographical region, age, sex, race, LVEF and eGFR. More details will be specified in the TSAP.

A sensitivity analysis will be provided using only on-treatment data. This analysis will be based on the Treated Set (TS) only including any events up to 7 days after treatment discontinuation. Patients who do not have an event during the trial will be censored at the individual day of discontinuation of trial medication +7 days or the last day that the patient was known to be free of the event, whichever is earliest.

7.2.3 Secondary endpoint analyses

Comparisons between treatment groups regarding the key secondary endpoint of total number of HHF or all-cause mortality will be performed using a negative binomial regression model. The negative binomial model will include factors for treatment and all covariates specified for the primary endpoint analysis model. The analysis will be adjusted for differences in observation time. Regression coefficients together with 95% confidence intervals will be used to quantify the effect of treatment, comparing empagliflozin to placebo.

The key secondary endpoints of total number of non-elective CV hospitalisations or all-cause mortality, total number of non-elective all-cause hospitalisations or all-cause mortality and total number of hospitalisations for MI or all-cause mortality will be analysed in the same way as the total number of HHF or all-cause mortality.

Time to CV mortality will be analysed using a Cox proportional hazards model with the same covariate adjustment as for the primary endpoint.

7.2.4 Further endpoint analyses

Comparisons between treatment groups regarding the binary endpoint variable 30-day all cause hospitalisation will be performed using a logistic regression model adjusting for the same covariates as in the primary analysis model. The likelihood-ratio test will be used to test for the difference between treatments. Adjusted odds ratios together with 95% confidence intervals will be used to quantify the effect of treatment, comparing empagliflozin with placebo as the reference.

The continuous endpoint days alive and out of hospital until day 90 after randomisation will be analysed descriptively. Days alive and out of hospital until 6 months, 9 months and 12 months after randomisation will be analysed using the same approach.

Time-to first event endpoints will be analysed in the same way as the primary endpoint.

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

7.2.5 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events

with an onset between start of treatment and end of the 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 (TS) will be included in the safety analysis and treatment will be analysed as randomised. 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 REP. Adverse events that start before first trial medication intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

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

Adverse events of special interst as identified by the investigator will be tabulated by primary SOC and PT. Adverse events of special interest are:

- Contrast induced AKI
- Ketoacidosis
- Events leading to Lower limb amputation
- Hepatic injury

The details of these analyses will be specified in the TSAP.

7.2.6 Interim Analyses

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

7.3 HANDLING OF MISSING DATA

There will be no imputation of data for safety data or time-to-event efficacy endpoints. Missing data for time-to-event and all key secondary endpoints will be handled by censoring and under missing-at-random assumption. Patients discontinuing the treatment prematurely will still be followed for the primary endpoint, all-cause mortality and all other endpoints including the key secondary endpoints.

7.4 RANDOMISATION

Patients will be randomized in blocks to double-blind treatment via interactive response technology (IRT). Approximately equal number of patients will be randomised to receive empagliflozin 10 mg or placebo using a 1:1 ratio. Randomisation will be stratified by

- Established T2D (yes, no)
- Geographical region (North America, Latin America, Europe, Asia)

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.

7.5 DETERMINATION OF SAMPLE SIZE

The trial is intended to show a reduction in the composite endpoint of time to first event of HHF or all-cause mortality with empagliflozin versus placebo. A Cox proportional hazards model will be used to analyse the primary endpoint. The trial is designed to achieve a power of 85% for a two-sided test at level α=5% if the analysis is performed at the number of accumulated events in Table 7.5: 1. The calculation assumes to show superiority of empagliflozin versus placebo based on a 1:1 randomisation ratio.

The expected hazard ratio for the comparison of empagliflozin versus placebo is 0.75 based on results from EMPA-REG OUTCOME and other SGLT2-inhibitor studies [P16-01253, R19-3125]. To account for drop-in to active SGLT2-inhibitor treatment, the assumed overall hazard ratio is 0.77 and requires at least 532 primary outcome events to show superiority with a power of 85% based on two-sided α=5 % and 1:1 randomisation ratio.

The initial determination of sample size to reach the anticipated 532 primary outcome events is as follows:

The yearly event rate in the placebo group is assumed to be 12.5% based on previous similar trial populations and including that the standard of care changed over time with better prognosis to date [R20-0260, R20-0257, R20-0201]. Assuming a yearly event rate of 12.5% in the placebo arm and 9.77% in the empagliflozin arm, accounting for 1% yearly drop out, an estimated 12 months recruitment and an estimated minimum follow-up of 12 months, a number of 3312 patients would need to be randomised to provide the 532 primary outcome events.

Table 7.5: 1 sumarizes the total number of patients and events needed assuming different event rates and hazard ratios. The calculations were performed using the Freedman formula.

Table 7.5: 1 Total number of events and sample sizes required to show superiority with 85% power, 2-sided α=5%, 1:1 randomisation ratio for different hazard ratios

Power	HR	Total number of events needed	Event rate Placebo at 1 year (%)	Event rate Empa at 1 year (%)	Total sample size for 2 treatment groups
85%	0.75	440	12.5%	9.53%	2772
	0.77	**532**	**12.5%**	**9.77%**	**3312**
	0.80	726	12.5%	10.1%	4454

Calculations consider a trial drop out rate of 1% per year, a 12 months recruitment period and an estimated follow-up of at least 12 months.

Sample size calculation was performed using ADDPLAN version 6.

During trial conduct the recruitment progress was slower than initially planned and associated event accumulation was slower than anticipated. Therefore the decision was taken to increase the sample size to 5000 patients based on blinded study data to avoid a substantial prolongation of overall study duration. The required number of primary outcome events of 532 is not affected by this decision.

With 5000 randomised patients and assuming a yearly event rate of 12.5% in the placebo arm and 9.77% in the empagliflozin arm, accounting for 1% yearly drop out and an estimated 21 months recruitment, an estimated minimum follow-up of 5 months would provide the 532 primary outcome events. Calculations consider a non-linear recruitment over time and were performed with RPACT version 3.0.4.

The event rate and recruitment progress will be assessed in a blinded manner and in an on-going basis to keep track of the progress of the trial. If reliable event predictions suggests a slower accrual of primary outcome events over calendar time than projected (i.e. a target of 532 events needed with a planned number of 5000 patients randomised), the number of patients randomised may be increased up to 6500, or trial duration may be prolonged.

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

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC / EU regulation 536/2014 and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as “protocol deviation”.
Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

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

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

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

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 / 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 or delegate obtains written consent of the patient’s own free will with the informed consent form after confirming that the patient understands the contents. The

investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.
Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's/CRO's instructions.
The consent and re-consenting process should be properly documented in the source documentation.

If trial conduct needs to be adjusted during the COVID-19 pandemic, the patient must be made aware of any modifications and informed consent needs to be obtained prior to the implementation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial participant protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.
Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.
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/CRO. 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 the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.
The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

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

The trial design is streamlined with extra work for collaborating site personnel being kept to a minimum. Only essential data will be collected with the focus being on readily identifiable and important clinical outcomes.

The primary data collected will be from carefully structured interviews.

The following data will be recorded directly on the eCRF (i.e. no prior written or electronic record of data), and to be considered to be source data:
- Data entered by the patient in the mobile/web-based application
- Data collected from the structured telephone interview

Additional medical information will be sought for Enpoints, SAEs and AESIs, and may include the collection of records held the study site, other hospitals, or the patient's own doctors, or from electronic sources and registries.

For the eCRF, data below 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
- AEs leading to treatment discontinuation, SAEs, AESIs and events exempted from expedited reporting (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 investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will

be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor/CRO will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial site(s):
The trial site(s) must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).
Sponsor/CRO:
The sponsor/CRO 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.
Exemptions from expedited reporting are described in Section 5.2.1.2.3.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook.
Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:
Personalised 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 at the site 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 the 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 Completed").The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT 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.

Database Lock (DBL) milestone is accomplished after quality review, query resolution, treatment unblinding, data transformation and determination that the data is ready for analysis.

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

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

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

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).
A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

An Executive Committee (EC) consisting of independent experts (including the Coordinating Investigator of this trial) and sponsor representatives will be established to support the sponsor in designing the trial and successful execution. The composition of the EC will be documented in the Trial Master File (TMF). The tasks and responsibilities will be agreed in contracts between the EC members and the sponsor and also summarised in an EC charter. The EC will assess the baseline characteristics of the patients in an ongoing blinded manner and if needed, may take appropriate steps, which may include restrictions to enrolment for certain subpopulations.

A National Coordinator Committee (NCC) will be established and will consist of the leading expert(s) in each of the participating countries. The NCs will support the sponsor/CRO in the successful execution of the trial. The NCC will have an advisory function in the trial. The tasks and responsibilities will be agreed in contracts between the NCC member and the CRO.

A Data Monitoring Committee (DMC) will be established. Members of the DMC are independent of BI, they are physicians experienced in the treatment of the disease under investigation and a statistician. The DMC will evaluate safety data. While DMC members may be unblinded, measures are in place to ensure the blinding for everyone else involved in the trial. Regular DMC meetings will be held at specified intervals. The DMC will recommend continuation, modification or termination of the trial as detailed in the DMC charter. DMC recommendations as well as the final BI decision will be reported to the appropriate Regulatory Authorities (RAs)/ Health Authority (Has), IRBs/ECs, and to investigators as requested by local law. The tasks and responsibilities of the DMC are specified in a charter.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

The CRO will have access to the BI web portal Clinergize to access documents provided by the sponsor for distribution to the investigators.

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

- manage the trial in accordance with applicable regulations and applicable BI- and CRO SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate oversight of vendors.

The organisation of the trial in the participating countries will be performed by a CRO with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

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

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

An IRT vendor will be used in this trial. Details will be provided in the IRT manual made available in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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10. APPENDICES

Not applicable

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		20 Apr 2022
EudraCT number **EU number**		2019-001037-13
BI Trial number		1245-0202
BI Investigational Medicinal Product(s)		Jardiance®, empagliflozin
Title of protocol		EMPACT-MI: A streamlined, multicentre, randomised, parallel group, double-blind placebo-controlled superiority trial to evaluate the effect of EMPAgliflozin on hospitalisation for heart failure and mortality in patients with aCuTe Myocardial Infarction
Global Amendment due to urgent safety reasons		N/A
Global Amendment		X
Section to be changed		Synopsis: Chair and co-chair Executive Committee
Description of change		Address of Chair changed
Rationale for change		Chair moved location
Section to be changed		Synopsis: Total number of patients randomised; Number of patients on each treatment; Duration of treatment; Statistical methods
Description of change		Increased sample size and adjusted recruitment and treatment duration
Rationale for change		The recruitment was slower than initially planned and associated event accumulation was slower than anticipated. Therefore the decision was taken to increase the sample size to avoid a substantial prolongation of overall trial duration
Section to be changed		Synopsis: Main inclusion and exclusion criteria
Description of change		Details are added to Inclusion criterion No. 4 and to the risk factor Pulmonary Artery Systolic Pressure
Rationale for change		Details are added for clarification
Section to be changed		Flow Chart: Footer No. 7 and 10
Description of change		Details how to follow-up patients completing the treatment period as planned and those prematurely discontinuing are added
Rationale for change		Further clarification required on patient management and data collection during the study and at study end

Section to be changed		1.4.2; Table 1.4.2 :1
Description of change		Removal of text related to LLA which erroneously referred to text in ICF in column Mitigation Strategy. Rationale for risk updated in column Summary of data
Rationale for change		To harmonize the content in the protocol with the ICF and the updated information in the IB
Section to be changed		3.1 and Figure 3.1: 1
Description of change		a) Recruitment and treatment duration are updated b) Details how to manage patients completing the study are added
Rationale for change		a) The recruitment was slower than initially planned and associated event accumulation was slower than anticipated. Therefore the decision was taken to increase the sample size to avoid a substantial prolongation of overall trial duration. The recruitment and treatment period were adjusted accordingly. b) Further clarification was required on patient management at the end of study
Section to be changed		3.3
Description of change		a) Increased sample size and adjusted recruitment and treatment duration b) Removal of the 25% cap of patients with established T2D c) Allow for extension or shortening of recruitment period on country level or regional level
Rationale for change		a) The recruitment was slower than initially planned and associated event accumulation was slower than anticipated. Therefore the decision was taken to increase the sample size to avoid a substantial prolongation of overall trial duration. The recruitment and treatment period were adjusted accordingly b) Strengthening generalisability of trial results to overall population including type 2 diabetes c) To achieve reasonable contribution and distribution across countries and regions
Section to be changed		3.3.1 and 3.3.2
Description of change		a) Details to clearly describe the main diagnosis for the trial are added in section 3.3.1 and in inclusion criterion No. 4. b) Right ventricular systolic pressure is added to the risk factor Pulmonary Artery Systolic Pressure
Rationale for change		Details are added for clarification
Section to be changed		3.3.4.1 and 3.3.4.2

Description of change		Details explaining how to follow-up patients are added
Rationale for change		Further clarification required on patient management and data collection during the study and at study end
Section to be changed		4.1.4; Table 4.1.4 :1
Description of change		The table visualising the amount and timing of dispense of medication kit are adapted to reflect the revised treatment period
Rationale for change		Changes to the treatment period require modification to the table
Section to be changed		4.3.2.3
Description of change		Removed text in brackets mentioning partner of participating WOCBP
Rationale for change		Removed for clarification
Section to be changed		6.1
Description of change		Description of call centers are removed
Rationale for change		Call centers are not used in this study
Section to be changed		7.5
Description of change		Increased sample size and adjusted recruitment and treatment duration
Rationale for change		The recruitment was slower than initially planned and associated event accumulation was slower than anticipated. Therefore the decision was taken to increase the sample size to avoid a substantial prolongation of overall trial duration. The recruitment and treatment period were adjusted accordingly.
Section to be changed		9.1
Description of change		Reference to definition of T1 MI removed
Rationale for change		Definition of T1 MI replaced by detailed description of spontaneous AMI
Section to be changed		9.2
Description of change		Reference to trial 1245-0171 added
Rationale for change		Reference to results in the trial 1245-0171 made in section 1.4.2

APPROVAL / SIGNATURE PAGE

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Document Name: clinical-trial-protocol-version-02

Title: EMPACT-MI: A streamlined, multicentre, randomised, parallel group, double-blind placebo-controlled superiority trial to evaluate the effect of EMPAgliflozin on hospitalisation for heart failure and mortality in patients with aCuTe Myocardial Infarction

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	20 Apr 2022 11:37 CEST
Approval		20 Apr 2022 11:39 CEST
Author-Trial Statistician		20 Apr 2022 12:14 CEST
Approval-Therapeutic Area [redacted]		20 Apr 2022 19:26 CEST
Verification-Paper Signature Completion		25 Apr 2022 14:57 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed