ICH E3 STRUCTURED CLINICAL STUDY REPORT

Non-Commercial Sponsor - EMMY–Trial

Study title	Impact of Empagliflozin on cardiac function and biomarkers of heart failure in patients with acute Myocardial infarction (EMMY-Trial) – a phase III Study
Name of test drug	Empagliflozin 10 mg (Jardiance®) / Placebo
Indication studied	Patients with acute myocardial infarction
Study design	Investigator initiated, prospective, randomised, multicentre, double-blind, placebo-controlled phase III trial
Sponsor	Medical University of Graz Auenbruggerplatz 2-4 8036 Graz / Austria
Protocol identification/number	HS 2017-01
Development phase of study	Phase III
Study initiation date *first patient enrolled*	17th May 2017
Date of early study termination	not applicable
Study completion date *last patient completed*	03rd May 2022
Name and affiliation of principal or coordinating investigator	Univ.-Prof. PD Harald Sourij, MD, MBA Medical University of Graz Department of Internal Medicine Division of Endocrinology and Diabetology Auenbruggerplatz 15 / 8036 Graz / Austria ✉ ha.sourij@medunigraz.at ☎ +43 316 385 81310
Author of the study report	Peter Pferschy, M.Sc., B.Sc., RN Medical University of Graz Department of Internal Medicine Division of Endocrinology and Diabetology Auenbruggerplatz 15 / 8036 Graz / Austria ✉ peter.pferschy@medunigraz.at ☎ +43 316 385 78030
GCP statement	EMMY was conducted in accordance with the guidelines laid down by the International Conference on Harmonization for Good Clinical practice (ICH GCP E6 guidelines).
Report date	21st October 2022

Signature of Chief Investigator responsible for clinical study report submission:

_____ _____

Univ.-Prof. PD Harald Sourij, MD, MBA Date

Note: This clinical study report contains confidential information.

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1. SYNOPSIS

Name of Sponsor/Company	Medical University of Graz Auenbruggerplatz 2-4 8036 Graz Austria
Study medication	***Active substance:*** Empagliflozin 10 mg ***Commercial name:*** Jardiance® ***Manufacturer:*** Boehringer Ingelheim RCV GmbH & Co KG, Biberbach an der Riss, Germany
Study title	Impact of Empagliflozin on cardiac function and biomarkers of heart failure in patients with acute Myocardial infarction (EMMY-Trial) – a phase III Study
Chief Investigators	Univ.-Prof. PD Harald Sourij, MD, MBA Medical University of Graz Department of Internal Medicine Division of Endocrinology and Diabetology Auenbruggerplatz 15 / 8036 Graz / Austria ✉ ha.sourij@medunigraz.at ☎ +43 316 385 81310 Assoc.-Prof. Dirk von Lewinski, MD Medical University of Graz Department of Internal Medicine Division of Cardiology Auenbruggerplatz 15 /8036 Graz / Austria ✉ dirk.von-lewinski@medunigraz.at ☎ +43 316 385 80684
Study Centers	1) Graz / Auenbruggerplatz 15 / A-8036 Graz 2) Graz II / Göstinger Straße 22 / A-8020 Graz 3) Vienna / Währinger Gürtel 18-20 / A-1090 Vienna 4) Vienna II / Juchgasse 25 / A-1030 Vienna 5) Feldkirch / Carinagasse 47 / A-6807 Feldkirch 6) Klagenfurt / Feschnigstraße 11 / A-9020 Klagenfurt 7) Schwarzach / Kardinal Schwarzenbergplatz 1 / A-5620 Schwarzach 8) Salzburg / Müllner Hauptstraße 48 / A-5020 Salzburg 9) Eisenstadt / Johannes von Gott Platz 1 / A-7000 Eisenstadt 10) St. Pölten / Dunant-Platz 1 / A-3100 St. Pölten
Publications *references*	**Tripolt NJ, et al.;** Impact of EMpagliflozin on cardiac function and biomarkers of heart failure in patients with acute MYocardial infarction-The EMMY trial. Am Heart J. 2020 Mar;221:39-47. (https://doi.org/10.1016/j.ahj.2019.12.004) **von Lewinski D, et al.;** Empagliflozin in acute Myocardial Infarction: the EMMY trial. Eur Heart J. 2022 Aug 29:ehac494. (https://doi.org/10.1093/eurheartj/ehac494)
Studied period *years*	five

Objectives	***Primary objective:*** The primary objective is to investigate the impact of empagliflozin on NT-proBNP in patients with myocardial infarction within 6 months after randomization. ***Secondary objectives:*** - short term changes of NT-proBNP levels - short term and intermediate term changes in echocardiography parameters - change in levels of ketone body concentrations - change in HbA1c levels - change in body weight - number of hospital re-admissions due to heart failure or other causes - duration of hospital stay - all-cause mortality ***Safety objectives:*** - all-cause mortality - number of serious adverse events - number of severe hypoglycemic events (i.e. requiring third party assistance) - number of genital infections - number of ketoacidotic events - changes in liver function parameters (AST, ALT, GGT) - changes in renal function parameters (creatinine, eGFR)
Methodology	In this academic, multicentre, double-blind trial, patients with acute myocardial infarction accompanied by a large creatine kinase elevation (>800 U/L) were randomly assigned to empagliflozin 10 mg or matching placebo once-daily within 72 hours of percutaneous coronary intervention. The primary outcome was the N-terminal pro-hormone of brain natriuretic peptide (NT-proBNP) change over 26 weeks. Secondary outcomes included changes in echocardiographic parameters.
Number of patients *planned and analysed*	476 planned and analysed
Diagnosis and main criteria for inclusion	1) Acute myocardial infarction (MI) with evidence of significant myocardial necrosis defined as a rise in creatine kinase >800 U/l and a troponin T- or I-level >10x ULN. In addition at least 1 of the following criteria must be met: - Symptoms of ischemia - ECG changes indicative of new ischemia (new ST-T changes or new LBBB) - Imaging evidence of new regional wall motion abnormality 2) 18 – 80 years of age 3) Informed consent has to be given in written form 4) eGFR > 45 ml/min/1.73m^2 5) Blood pressure before first drug dosing: systolic >110mmHg 6) Blood pressure before first drug dosing: diastolic >70mmHg

	7) First intake of study medication ≤72h after myocardial infarction after performance of a coronary angiography
Main criteria for exclusion	1) Any other form of diabetes mellitus than type 2 diabetes mellitus, history of diabetic ketoacidosis 2) Blood pH < 7.32 3) Known allergy to SGLT-2 inhibitors 4) Haemodynamic instability as defined by intravenous administration of catecholamine, calcium sensitizers or phosphodiesterase inhibitors 5) >1 episode of severe hypoglycemia within the last 6 months under treatment with insulin or sulfonylurea 6) Females of child bearing potential without adequate contraceptive methods (i.e. sterilization, intrauterine device, vasectomized partner or medical history of hysterectomy) 7) Acute symptomatic urinary tract infection or genital infection 8) Patients currently being treated with any SGLT-2 inhibitor (dapagliflozin, canagliflozin, empagliflozin) or having received treatment with any SGLT-2 inhibitor within the 4 weeks prior to the screening visit
Test product, dose and mode of administration	Empagliflozin, 10mg once daily orally administered
Duration of treatment *weeks*	26
Reference therapy, dose and mode of administration:	Placebo, once daily orally administered
Statistical methods	Baseline characteristics were summarized using descriptive statistics with mean and standard deviation for continuous measures and frequency tables for categorical variables. Categorical variables were compared using Chi-squared or Fisher's exact tests, and continuous variables using an unpaired *t*-test or its non-parametric equivalent (Wilcoxon rank-sum test) where the normality assumption was violated. The primary endpoint (change in NT-proBNP from baseline to week 26) was analysed in the intention-to-treat (ITT) population using a robust linear mixed effect model (LMEM) (1) in which the dependent variable was log-transformed NT-proBNP and the fixed effects were treatment, visit, treatment-by-visit interaction, the stratification factors sex and presence/absence of type 2 diabetes, and baseline NT-proBNP concentration. For the primary analysis no missing data were imputed. At week 26, estimated mean values and mean differences between treatment groups were derived from the robust LMEM using marginal means (or least squares means). Their associated P-values and two-sided 95% confidence intervals were derived from the robust LMEM using bootstrap techniques (2). To claim superiority of empagliflozin over placebo, the primary efficacy analysis was required to demonstrate a statistically significant treatment at week 26 at a 5% alpha level with a two-sided test.

Summary – Conclusions	In patients with a recent myocardial infarction, empagliflozin was associated with a significantly greater NT-proBNP reduction over 26 weeks, accompanied by a significant improvement in echocardiographic functional and structural parameters.
Efficacy Results	Baseline median (interquartile range) NT-proBNP was 1,294 (757–2,246) pg/ml. NT-proBNP reduction was significantly greater in the empagliflozin group, compared with placebo, being 15% lower (95% confidence interval (CI) -4.4% to -23.6%) after adjusting for baseline NT-proBNP, sex and diabetes status (p=0.026). Absolute left ventricular ejection fraction improvement was significantly greater (1.5%, 95% CI 0.2% to 2.9%, p=0.029), mean E/e' reduction was 6.8% (95% CI 1.3% to 11.3%, p=0.015) greater, and left ventricular end-systolic and end-diastolic volumes were lower by 7.5 ml (95% CI 3.4 to 11.5 ml, p=0.0003) and 9.7 ml (95% CI 3.7 to 15.7 ml, p=0.0015), respectively, in the empagliflozin group, compared with placebo.
Safety Results	Seven patients were hospitalised for heart failure (three in the empagliflozin group). Other predefined serious adverse events were rare and did not differ significantly between groups. Two patients died within 5 days after enrolment in trial secondary to large MIs and subsequent cardiogenic shock. One participant died 149 days after enrolment due to bronchial carcinoma.
Funding	This 'Investigator Initiated Study' (IIS) was financially supported by Boehringer Ingelheim. The funder was not involved in the preparation of the protocol, the conduct of the study, or the analysis of the results.
Date of report	21st October 2022

2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACC	American College of Cardiology
ACE-I	Angiotensin-Converting-Enzyme Inhibitors
ADA	American Diabetes Association
AE	Adverse Event
AESI	Adverse Event of Special Interest
AHA	American Heart Association
ALT	Alanine Transaminase
ARB	Angiotensin Receptor Blockers
ASE	American Society of Echocardiography
AST	Aspartate Aminotransferase
CABG	Coronary Artery Bypass Graft
CI	Confidence Interval
DKA	Diabetic Ketoacidosis
DSUR	Development Safety Update Report
EACVI	European Association of Cardiovascular Imaging
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GLP1-RA	Glucagon-Like Peptide-1 Receptor Agonist
HDL	High-Density Lipoprotein
HFmrEF	Heart Failure with mildly reduced Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
HFSA	Heart Failure Society of America
HHF	Hospitalisation for Heart Failure
IB	Investigator Brochure
HbA1c	Hemoglobin A1C
IEC	Independent Ethics Committee
IIS	Investigator Initiated Study
IMI	Institute of Medical Informatics, Statistics and Documentation
ISF	Investigator Site File

IRB	Institutional Review Board
ITT	Intention To Treat
ICH	International Council for Harmonisation
IQR	Interquartile Range
KIMCL	Clinical Institute for Medical and Chemical Laboratory Diagnostics
LBBB	Left Bundle Branch Block
LDL	Low-Density Lipoprotein
LMEM	Linear Mixed Effect Model
LVEDV	Left Ventricular End-Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
LVESV	Left Ventricular End-Systolic Volume
MACE	Major Adverse Cardiovascular Event
MI	Myocardial Infarction
MICE	Multiple Imputation with Chained Equation
MRA	Mineralocorticoid receptor antagonists
NT-proBNP	N-Terminal prohormone of Brain Natriuretic Peptide
PCI	Percutaneous Coronary Intervention
PI	Principal Investigator
PP	Per Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SGLT2i	Sodium–Glucose co-Transporter 2 Inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAPSE	Tricuspid Annular Plane Systolic Excursion
TMF	Trial Master File
T2DM	Type 2 Diabetes Mellitus
ULN	Upper Limit of Normal
WMSI	Wall Motion Score Index

3. ETHICS

3.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Prior to the enrolment of subjects, the leading Ethics Committee at the Medical University of Graz provided written approval of the conduct of the study at named sites, the protocol, any amendments, case report form, the patient informed consent form and any other written information that were provided to the subjects. All centers received institutional review board approval from their own ethics committees.

3.2 List of IECs or IRBs

Table 1: List of consulted IECs during the Study

Role	State	IEC
Leading Ethics Committee	Styria	Ethics Committee Medical University Graz Auenbruggerplatz 2 /8036 Graz
Local Ethics Committee	Burgenland	Ethics Committee of Burgenland Josef-Hyrtl-Platz 4 / 7000 Eisenstadt
	Carinthia	Ethics Committee of Carinthia Feschnigstraße 11 /9020 Klagenfurt
	Lower Austria	Ethics Committee of Lower Austria Landhausplatz 1 / 3109 St. Pölten
	Upper Austria	Ethics Committee Johannes Kepler University Wagner-Jauregg Weg 15 / 4020 Linz
	Salzburg	Ethics Committee of Salzburg Michael-Pacher-Straße 36 / 5020 Salzburg
	Vorarlberg	Ethics Committee of Vorarlberg Römerstraße 15 / 6900 Bregenz
	Vienna	Ethics Committee Medical University Vienna Borschkegasse 8b / 1090 Wien Ethics Committee of the city of Vienna Thomas-Klestil-Platz 8 / 1030 Vienna

3.3 Ethical Conduct of the Study

The EMMY trial was conducted in full conformity with the 1964 Declaration of Helsinki and all subsequent revisions, as well as in accordance with the guidelines laid down by the International Conference on Harmonization for Good Clinical Practice (ICH GCP E6 guidelines).

3.4 Patient Information and Consent

Clinic staff of the intensive care unit informed patients about the possibility of being enrolled in this study. No study-related procedures were undertaken before obtaining informed consent. The study team explained the study procedures in detail and asked the participant about their willingness to participate in this research

study. After informed consent was signed and obtained, participants were given a signed copy of the informed consent. Subjects unable to provide written informed consent were not included in this study.

4. INVESTIGATORS AND STUDY ADMINITRATIVE STRUCTURE

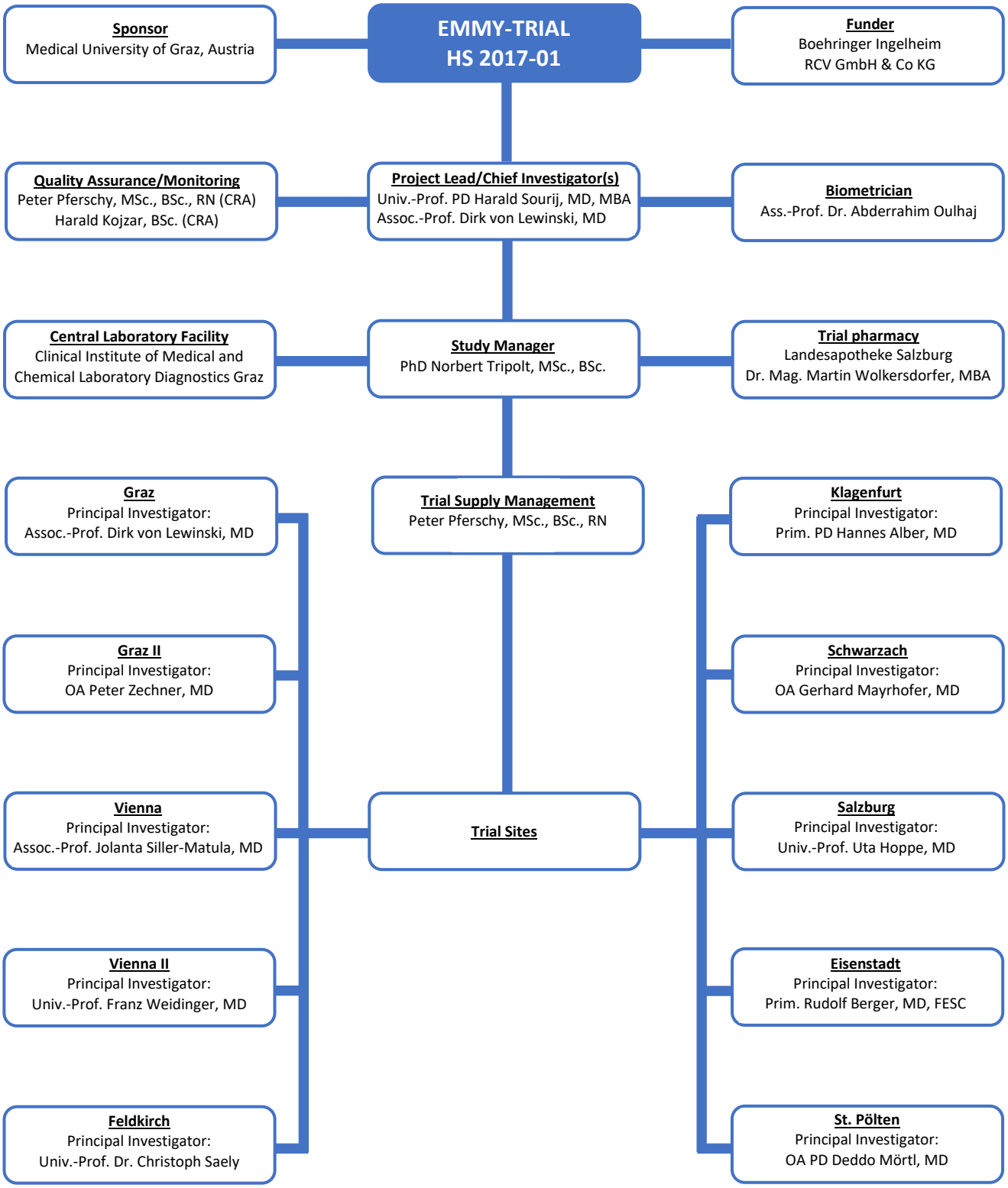

Figure 1: Investigators and study administrative structure

5. INTRODUCTION

In chronic heart failure with reduced ejection fraction (HFrEF), sodium–glucose co-transporter 2 inhibitors (SGLT2i) have been shown to reduce the risk of hospitalisation for heart failure (HHF) as well as all-cause mortality and cardiovascular mortality (3-6). Recent evidence also indicates beneficial effects of initiating treatment after acute heart failure (7). In addition, empagliflozin was the first drug shown prospectively in the EMPEROR-Preserved trial to improve the primary outcome of HHF and cardiovascular death in heart failure patients with mildly reduced (HFmrEF) or preserved ejection fraction (HFpEF) (8). The use of SGLT2i for HFrEF was recently recommended in the European and American heart failure guidelines as part of first-line therapy (9, 10), with the more recent AHA/ACC/HFSA guidelines also advocating SGLT2i use in patients with HFmrEF and HFpEF (10). Sodium–glucose co-transporter inhibitors appear to exhibit cardioprotective effects attributable to metabolic (11) and anti-inflammatory (12) mechanisms, as well as modification of myocardial signal transduction by inhibition of Na_+/H_+ exchanger (13, 14). Strikingly, onset of the beneficial cardiovascular effects observed in cardiovascular outcome trials emerged within a few weeks of treatment initiation and have been shown to be independent of glycaemic status (4, 8). The question as to whether early SGLT2i initiation following MI is effective and safe is of key importance, since ischaemic heart disease with a subsequent MI is a major cause of incident heart failure with a 15% event rate (symptomatic heart failure and/or reduced ejection fraction) within 12 months (15, 16).

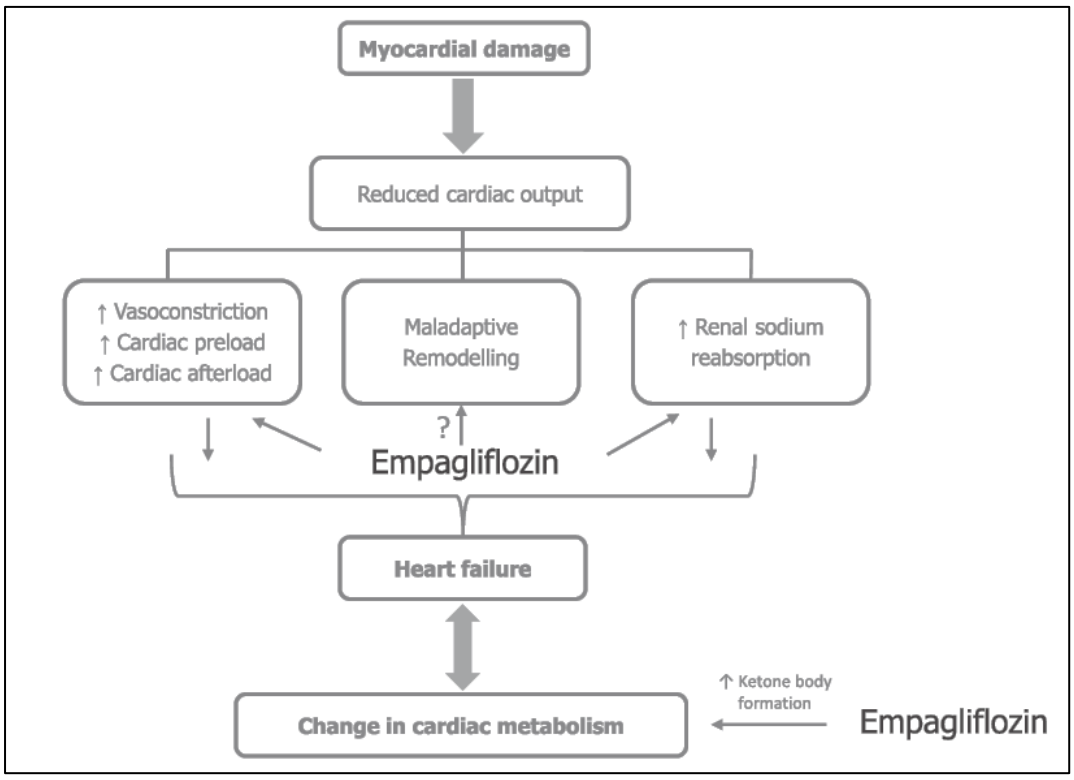

Figure 2: Potential beneficial mechanisms of empagliflozin

6. STUDY OBJECTIVE

Empagliflozin in patients with acute myocardial infarction (EMMY-trial) was designed, to investigate whether empagliflozin treatment given in addition to guideline-recommended post-MI therapy (17), and initiated within 72 hours after percutaneous coronary intervention (PCI) in people with a large acute MI, with or without diabetes, would result in a larger decline in N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and larger improvement in ejection fraction.

7. INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan-Description

EMMY is a multicentre, randomized, double-blind, placebo-controlled, phase 3 trial designed to evaluate the effect of empagliflozin 10 mg once daily per os for 26 weeks on cardiac function and biomarkers for heart failure in patients with acute MI. Ten Austrian sites enrolled a total of 476 patients to evaluate the overall study hypothesis. The primary objective of the EMMY trial was to investigate the impact of empagliflozin on biomarkers of heart failure in patients with MI with and without type 2 diabetes mellitus (T2DM) within 6 months after the event. The study flow chart is illustrated in Figure 3.

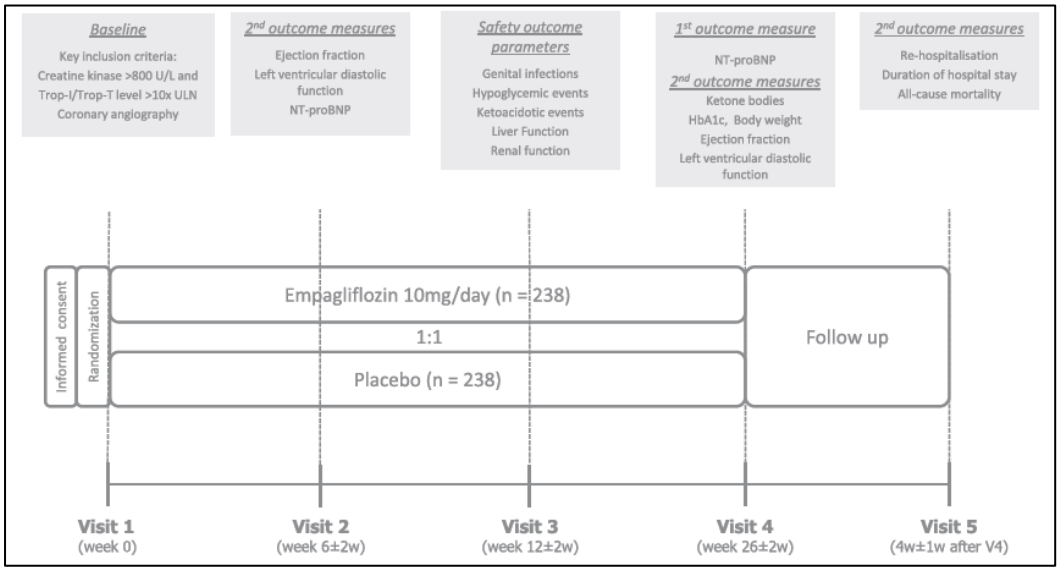

Figure 3: Study Flow Chart

Patients with confirmed acute MI were assessed for eligibility. In order to increase the likelihood of a beneficial treatment effect with empagliflozin, inclusion criteria contained parameters indicating severe myocardial necrosis. These included maximal creatine kinase after acute MI of more than 800 U/l and high-sensitive troponin T-level (or troponin I-level) after MI of more than 10-fold the upper limit of normal

(according to local laboratory). These chosen cut-offs are based on previous studies. After given written informed consent prior to study entry, the screening process started and all patients eligible for the trial were randomized into one of the two arms of the study via Randomizer Software (Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, http://www.randomizer.at), which was programmed with a randomization schedule provided by an independent statistician. The randomization was stratified by site, T2DM and by sex. Only the subject number and subject initials were recorded in the CRFs. The local investigator maintained a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified. A summary of all visits and procedures is outlined in Table 2.

Table 2: Visits and procedures

RCT	STUDY PERIOD				
	Baseline (Visit 1)	Visit 2	Visit 3	Visit 4	Follow-up (Visit 5)
TIMEPOINT	0	9 ± 4 weeks after baseline	12 ± 2 weeks after baseline	26 ± 2weeks after baseline	30 ± 1 week after baseline
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Randomization	X				
Allocation	X				
INTERVENTIONS:					
Empagliflozin (intervention group)	◆	—	—	◆	
Placebo (control group)	◆	—	—	◆	
ASSESSMENTS:					
Demographic Data	X				
Anthropometric measurements	X	X	X	X	
Vital signs (Blood pressure, heart rate)	X	X	X	X	
Medical History	X				
Concomitant medication	X	X	X	X	
Physical examination	X	X	X	X	
Adverse Events					X
Dispense medication	X				
Drug accountability				X	
Laboratory					
NT-proBNP (local)	X	X	X	X	
Liver function parameters (AST, ALT, GGT)	X	X	X	X	
Renal function parameters (creatinine, eGFR)	X	X	X	X	
Biobank sampling	X	X		X	
Investigations					
Cardiac ultrasound	X	X	X	X	
Electrocardiogram (ECG)	X				

In the case of a requirement to unblind study medication, one of the chief investigators had to be informed to discuss unblinding. The unblinding list was held by the Institute of Medical Informatics, Statistics and Documentation (IMI), Medical University of Graz, which was not involved in study investigations.

7.2 Selection of Study Population

A total of 476 patients were enrolled and randomised to empagliflozin 10 mg/day (n=237) or matching placebo (n=239) at 10 trial sites.

7.2.1 Inclusion/Exclusion criteria

Patients aged 18 to 80 years with a confirmed acute large MI (creatine kinase >800 U/L), a high- sensitivity troponin T-level (or troponin I-level) >10-fold the upper limit of normal, and an estimated glomerular filtration rate >45 ml/min/1.73 m2 were eligible for inclusion. Those with diabetes mellitus other than type 2, a blood pH <7.32, haemodynamic instability, acute symptomatic urinary tract infection or genital infection, an ongoing SGLT2i treatment or an SGLT2i treatment within 4 weeks prior to enrolment, were excluded. The detailed inclusion and exclusion criteria are listed in Table3. Patients were enrolled within 72 hours after a PCI for acute MI. Before randomisation, patients were required to be hemodynamically stable (defined as no use of hemodynamically active intravenous drugs) and have had a blood pressure ≥110/70 mmHg.

Table 3: Detailed listing of inclusion and exclusion criteria

Inclusion criteria
1) 'Acute myocardial infarction with evidence of significant myocardial necrosis defined as a rise in creatine kinase >800 U/L and a troponin T-level (or troponin I-level) >10× ULN. In addition at least 1 of the following criteria must be the met:
- Symptoms of ischemia
- ECG changes indicative of new ischemia (new ST-T changes or new LBBB)
- Imaging evidence of new regional wall motion abnormality
2) 18–80 years of age
3) Informed consent has to be given in written form
4) eGFR >45 mL/min per 1.73m^2
5) Blood pressure before first drug dosing: $RR_{systolic}$ >110 mmHg
6) Blood pressure before first drug dosing: $RR_{diastolic}$ >70 mmHg
7) First intake of study medication ≤72 h after myocardial infarction after performance of a coronary angiography
Exclusion criteria
1) Any other form of diabetes mellitus than type 2 diabetes mellitus, history of diabetic ketoacidosis
2) Blood pH <7.32
3) Known allergy to SGLT-2 inhibitors
4) Hemodynamic instability as defined by intravenous administration of catecholamine, calcium sensitizers or phosphodiesterase inhibitors
5) >1 episode of severe hypoglycemia within the last 6 months under treatment with insulin or sulfonylurea
6) Females of child bearing potential without adequate contraceptive methods (i.e. sterilization, intrauterine device, vasectomized partner; or medical history of hysterectomy)
7) Acute symptomatic urinary tract infection (UTI) or genital infection
6) Patients currently being treated with any SGLT-2 inhibitor (dapagliflozin, canagliflozin, empagliflozin) or having received treatment with any SGLT-2 inhibitor within the 4 weeks prior to the screening visit

7.3 Treatment

Empagliflozin is a sodium-glucose cotransporter 2 inhibitor (SGLT2i), a glucose lowering drug that inhibits reabsorption of glucose in the proximal tubule. The study dose was 10 mg once daily in the morning, taken with or without food. Each tablet contains 10 mg Empagliflozin or Placebo. The pharmaceutical form is a round, pale yellow, biconvex, bevel-edged film coated tablet debossed with "S10" on one side and the Boehringer Ingelheim logo on the other. Patients were advised to take precautions to avoid hypoglycemia while driving and using machines, in particular when empagliflozin was used in combination with a sulfonylurea and/or insulin. To preserve the status of a double-blind trial the pharmacy (Landesapotheke Salzburg, Austria) packed the medication as 26 weeks supplies for study participants and labelled study medication according to current regulatory requirements. Neither the patients nor the researchers knew which patient was receiving which medication. In case of a requirement to unblind study medication, one of the chief investigators needed to be informed to discuss the unblinding. The unblinding list was held by the IMI, Medical University of Graz, which was not involved in study investigations. If a dose was missed, it should have been taken as soon as the patient remembered. A double dose should not be taken on the same day. Subjects were advised to follow the study protocol and return all used and unused containers to the site at study visit 4 (week 26). The study team dispensed the study drug only to subjects entered into the study, under the direction of the PI or sub-investigators authorized to receive or dispense it. The study drugs were not dispensed or supplied to any person not authorized to receive it. Each time a study drug was dispensed, it was documented in the sponsor provided log (EMMY Investigational Drug Accountability Record) as to the amount dispensed, to whom it is dispensed, and the date and signature or initials of the person who dispensed the drug. Subjects were advised to follow the study protocol and as appropriate to protocol returned all used and unused containers to the site at study visit 4 (week 26). The study drug had to be kept locked in a secure area. For this study drug no particular storage temperature conditions were required. Unused supplies of the study drug were returned to the sponsor in accordance with sponsor requirements. Returned, unused study medication were destroyed on behalf of sponsor. This process was documented via 'EMMY Investigational Drug Disposal/Destruction Records' as well as 'EMMY IMP Destruction Forms'.

7.4 Efficacy and Safety Variables

The primary endpoint was the change in NT-proBNP levels from randomisation to week 26. Secondary endpoints included changes in NT-proBNP levels from randomisation to week 6, changes in left ventricular ejection fraction (LVEF) from randomisation to weeks 6 and 26, as well as echocardiographic parameters for diastolic dysfunction, left ventricular end-systolic volume (LVESV), left ventricular end-diastolic

volume (LVEDV), changes in ketone body and glycated hemoglobin concentrations and body weight. Additional exploratory endpoints were hospitalisations due to heart failure or other causes, duration of hospital stay and all-cause mortality. Key safety outcomes were the incidence of serious adverse events (SAEs), severe hypoglycaemic events, number of genital infections, number of ketoacidosis events, and acute liver or renal injury. Hospitalisations during follow-up were adjudicated by an independent adjudication committee prior to unblinding.

Table 4: Trial objectives

PRIMARY OBJECTIVE - To investigate the impact of Empagliflozin on NT-proBNP (a heart failure biomarker) in patients with myocardial infarction within 6 months after randomization. SECONDARY OBJECTIVES - Short term changes in NT-proBNP levels - Short term and intermediate term changes in echocardiography parameters - Change in levels of ketone body concentrations - Change in HbA1c levels - Change in body weight - Number of hospital re-admissions due to heart failure or other causes - Duration of hospital stay - All-cause mortality SAFETY OBJECTIVES - All-cause mortality - Number of serious adverse events - Number of severe hypoglycaemic events (i.e. requiring third party assistance) - Number of genital infections - Number of ketoacidotic events - Changes in liver function parameters (AST, ALT, GGT) - Changes in renal function parameters (creatinine, eGFR)

7.4.1 Description of procedures and measurements

NT-proBNP measurement

Although NT-proBNP levels were measured in each local lab, the parameter for the analysis of the primary endpoint was also measured centrally. NT-proBNP biomarker samples were shipped to the Biobank of the Medical University of Graz and stored at −80°C. At the end of the trial, samples were analyzed at the Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Austria (KIMCL) on the Elecsys proBNP platform (Roche Diagnostics, Mannheim, Germany) with chemiluminescence technology.

Echocardiography

Echocardiography was performed in accordance with the current guidelines of the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE) using locally available

ultrasound devices (18-20). The protocol required the performance of 2D, Doppler echocardiography and M-mode imaging. Left ventricular wall thickness and chamber diameters were assessed and left ventricular mass index was calculated using the linear method (modified Devereux formula, Cube formula) indexed by body surface area. Left ventricular end-diastolic and endsystolic volumes were assessed in both apical two- and four- chamber views. Ejection fraction was calculated using the biplane method of disks summation (modified Simpson's rule). Regional systolic dysfunction was classified using the wall motion score index (WMSI). Peak transmittal inflow velocities (E and A) and peak early diastolic mitral ring velocities (lateral and septal e`) were measured as parameters of left ventricular diastolic function. Right ventricular function was evaluated using Tricuspid Annular Plane Systolic Excursion (TAPSE). Left atrial volume index was calculated from left atrial dimensions using the biplane method. Colour flow Doppler, continuous and pulsed wave Doppler were used to quantify valvular diseases. Right atrial pressure conditions were estimated by the diameter of the inferior vena cava. Since not all sites were able to provide loops for core lab analyses, we decided to use local data for secondary outcome analyses.

Medical history and physical examination

A medical history documentation was performed at the screening visit to record illnesses, disorders and medications. This information was updated on all follow-up visits. Physical examination was performed at the screening visit (study visit 1) according to local procedure. During this visit the physician performed a physical examination with focus on cardiac, lung and abdominal examination. Any abnormal clinical significant finding was recorded on the working sheet as well as in the electronic Case Report Form (eCRF). Any changes in subsequent visits as compared to the screening visit, which fulfils the criteria of an Adverse Event (AE), had to be recorded as an AE. Any changes in concomitant illness were recorded as changes in medical history. Any changes in medications were recorded in the eCRF.

ECG

An ECG was performed at the screening visit. The ECG was interpreted, signed and dated by the investigator before randomisation.

Vital signs

Pulse was recorded at all visits after resting for five minutes in a sitting position. Systolic and diastolic blood pressure were measured in sitting position at all visits.

Body weight and height

Weight was measured at all visits. The same and calibrated pair of scales should have been used preferably throughout the trial. Height was recorded at the screening visit. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Routine biochemistry

Blood samples were obtained at all visits after an 8 hour fast and processed by the local laboratory using standard methods for routine tests. Patients were allowed to take their regular morning medications but were asked that they do not take any of their diabetes medications on the morning of their study visit.

Blood sample collection and plasma extraction for biobanking

Blood was collected via venous puncture into 16ml serum, 6ml EDTA and 4ml sodium citrate vacutainers and centrifuged. Plasma was transferred into tubes and stored at a minimum of -25°C locally. In regular intervals, these samples were shipped on dry ice to the Biobank of the Medical University of Graz, where they were stored at -80°C up to the analyses. NT-proBNP was measured centrally for visits one and three in batches from these stored biomarker samples.

7.4.2 Benefit-Risk Assessment

Empagliflozin was studied in subjects with T2DM and demonstrated cardiovascular benefit in terms of reduction of a 3-point major adverse cardiovascular event (MACE) composite endpoint as well as of hospitalization for heart failure. However, it has not been studied shortly after myocardial infarction yet. Given that the drug is not causing hypoglycemic events per se, hypoglycemia appeared not to be a major issue in subjects without diabetes, that were studied in this trial as well. When empagliflozin is used together with sulfonylurea or insulin, hypoglycemia might occur and therefore participants were instructed to reduce concomitant antihyperglycemic medication accordingly. Fungal genital infections are the most common side effect of empagliflozin and participants were informed about this and instructed on prevention measures. Rarely, serious infections of the genitals and the area around the genitals have been reported. This infection, called necrotizing fasciitis of the perineum, is also referred to as Fournier's gangrene. In people with T2DM, the risk for ketoacidosis is increased, in particular in situations such as insulin deficiency, alcohol abuse, exsiccosis or infections.

7.4.3 Primary efficacy outcome

Mean NT-proBNP concentrations decreased in both groups during the study, but to a significantly greater extent in the empagliflozin group compared with placebo. Mean 26-week NT-proBNP was 15% (95% CI -4.4 to

-23.6%) lower in the empagliflozin group compared with placebo, after adjusting for baseline NT-proBNP concentration, sex and diabetes status (p=0.026). The greater reduction with empagliflozin was already evident by 12 weeks (p=0.021) (Figure 4). The greater NT-proBNP reduction with empagliflozin was confirmed in sensitivity analyses using multiple imputation for missing data (-14.9%; 95% CI -12.5% to -17.3%) with an absolute week 26 NT-proBNP change of -16.1% (95% CI -2.0% to -28.1%). Figure 2B (empagliflozin group) and 2C (placebo group) demonstrate that the reduction in NT-proBNP is evident across the entire spectrum of baseline NT-proBNP.

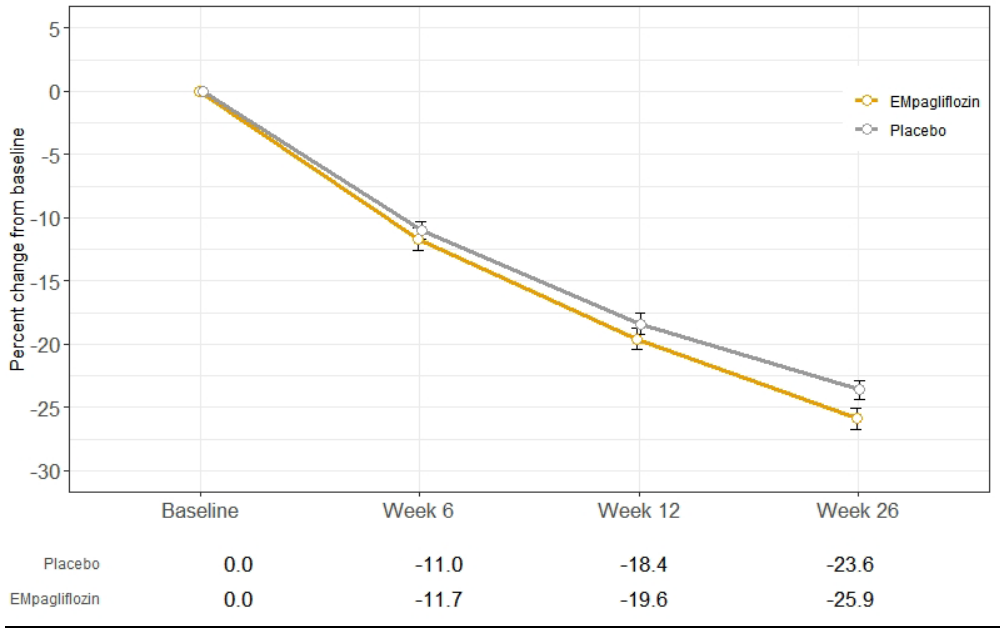

Figure 4: *NT-pro BNP percentage change from baseline to week 26 for both groups*

7.4.4 Secondary efficacy and safety outcomes

Secondary outcomes are shown in Table 5. Left ventricular systolic and diastolic function improved in both groups over the course of the trial. LVEF increased by absolute 1.5% (95% CI 22 0.2% to 2.9%; p=0.029) more in the empagliflozin than in the placebo group. The greater increase was already significant by 6 weeks (1.7%, 95% CI: 0.35% to 3.05%; p=0.014). Left ventricular diastolic function, as assessed by E/e`, also changed during the trial with significantly greater improvement in the empagliflozin group at 26 weeks, being 6.8% (95% CI 1.3% to 2 11.3%, p=0.015) lower compared with placebo.

Table 5: *Secondary outcome measures*

	Empagliflozin				Placebo			
	Baseline	Week 26	Absolute change	Percent change	Baseline	Week 26	Absolute change	Percent change
LV-EF	47.6 (7.8)	52.3 (9.0)	4.7 (8.4)	11.1 (19.5)	48.8 (8.5)	51.4 (8.4)	2.8 (8.3)	7.6 (18.3)
E/e'	9.4 (2.9)	8.2 (2.2)	-1.3 (2.6)	-9.7 (26.2)	9.7 (3.2)	8.7 (2.9)	-0.7 (3.0)	-3.5 (30.7)
LVESV	63.7 (22.4)	61.6 (23.8)	-3.6 (19.3)	-2.2 (30.5)	61.6 (23.6)	65.7 (27.8)	4.30 (23.0)	12.1 (41.5)
LVEDV	118 (32.7)	123 (35.9)	3.4 (29.7)	5.9 (30.2)	117 (33.9)	130 (42.7)	13.5 (35.2)	14.8 (34.0)

LV-EF left ventricular ejection fraction, LVESD left ventricular end systolic volume, LVEDV left ventricular end

Echocardiographic parameters reflecting structural cardiac changes significantly improved in the empagliflozin group: LVESV (-7.5 ml; 95% CI -11.5 to -5 3.4 ml, p=0.0003) and LVEDV (-9.7 ml; 95% CI -15.7 to -3.7 ml, p=0.0015) were smaller in the empagliflozin group compared with the placebo group (Figure 5C and 5D).

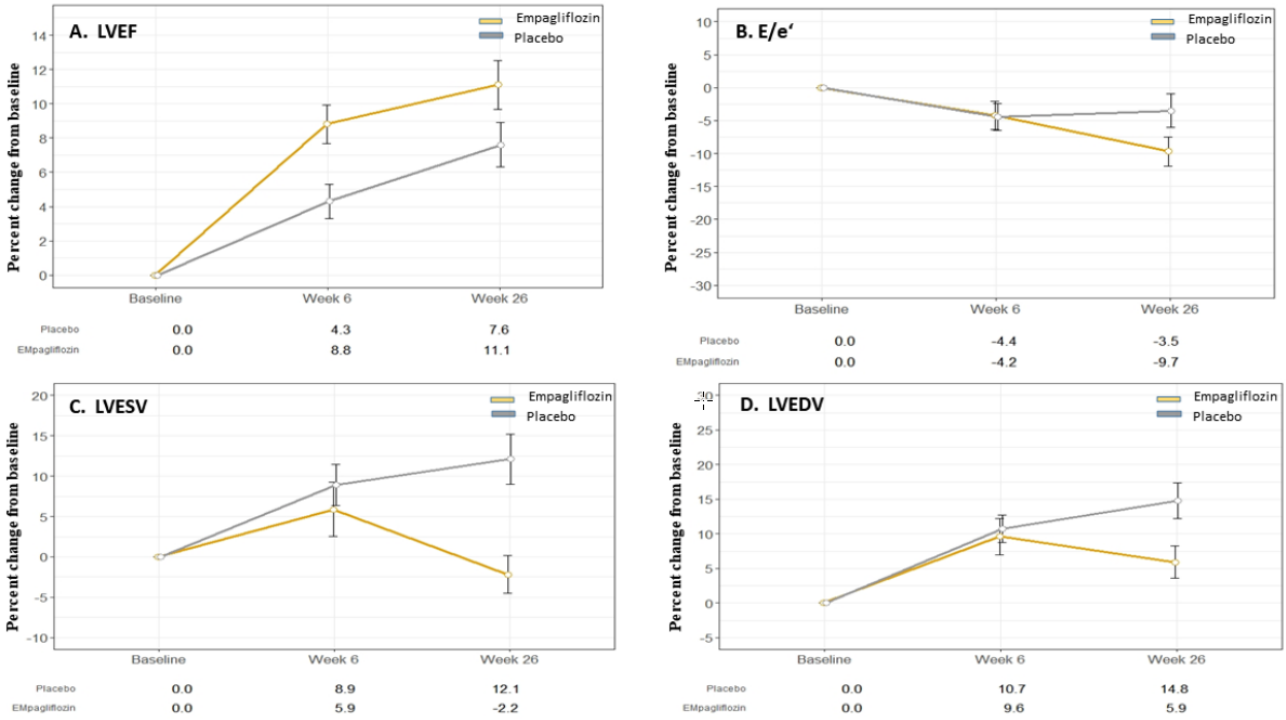

Figure 5: Changes in echocardiographic parameters from baseline to week 26 for both groups

Ketone body (beta-hydroxybutyrate) concentrations showed a significantly greater increase in the empagliflozin group, compared with placebo (Δ = 23.4%; 95% CI: 5.9% to 42.4%), p=0.0066), that was more pronounced at 26 weeks (Δ = 41.9%; 95% CI 21.8% to 63.8%, p<0.0001). Body weight decreased more in the empagliflozin group (Δ = -1.76 kg; 95% CI -3.27 to -0.25 kg, 11 p=0.022). Within the small subgroup of participants with diabetes, there was no significant between-group difference in the degree of HbA1c lowering at week 26 (p=0.11). Duration of hospital stay due to acute MI did not differ between groups with a median (IQR) duration of 6.0 (3–9) days in the empagliflozin and 6.0 (3–9) days in the placebo group (p=0.40).

Serious Adverse Event (SAE) rates did not differ between the empagliflozin and the placebo groups. A total of 72 SAEs were registered over the study period. 63 participants (69 events) were hospitalised, out of which seven participants were hospitalised for heart failure (three in the empagliflozin group, four in placebo group). Three deaths occurred during the study, all in the empagliflozin group. Two participants died within 5 days after enrolment in the trial secondary to large MIs and subsequent cardiogenic shock. One participant died 149 days after enrolment due to lung cancer. All three fatalities were considered by the adjudication committee prior to unblinding to be unrelated to study medication. Other safety

endpoints such as the number of genital infections did not differ significantly between the empagliflozin and placebo group. Moreover, no amputations, no ketoacidosis and no severe hypoglycaemic episodes were reported throughout the follow-up.

7.5 Data Quality Assurance

This study captured and processed data using an eCRF (Clincase) which is a fully validated high quality electronic data capture system with an audit trail and controlled level of access. This eCRF was provided by the IMI of Graz, Austria. The biological materials obtained from the subject were identified by subject number, trial site and trial identification number. Appropriate measures such as encryption or deletion were enforced to protect the identity of human subjects in all presentations and publications as required by local/ regional and national requirements. The study was periodically monitored by a team of Clinical Trial Monitors who performed 100% source data verification (SDV). Initiation visits were completed at all trial centres prior to the recruitment of participants and consisted of review of protocol and trial documents, training with respect to trial procedures (informed consent, safety reporting, inclusion and exclusion criteria, laboratory manual, performance of study visits, comprehensive processing of essential trial documents and the investigator site file (ISF)), review of recruitment strategy, review of site facilities and equipment, review of GCP principles, essential document receipt, collection and filing, archiving and possible inspections. Copies of the trial specific procedure manuals and related documents were given to the investigators and study nurses. The monitoring plan describes in detail all monitoring procedures. During the course of the trial, the monitoring team periodically visited the trial sites to ensure that the protocol was adhered to, that all issues have been recorded and SDV was performed. The investigators ensured that the monitors were able to:

- inspect the site, the facilities, device management and materials used for the trial
- meet all members of the team involved in the trial, and ensure all staff working on the trial were experienced and appropriately trained and had access to review all of the documents relevant to the trial
- have access to the electronic case record forms and source data
- discuss with the investigator and site staff trial progress and any issues on a regular basis

The monitor ensured that:

- records were inspected for confirmation of existence, eligibility and integrity
- 100% of consent forms were reviewed along with all SAE's
- there was adherence to the protocol, including consistency with inclusion/exclusion criteria
- there was GCP and regulatory compliance

- trial documentation was complete and up to date (e.g. correct versions of documents being used, source data captured) and relevant documents were collected for the Trial Master File (TMF)
- the monitored eCRFs were completed correctly and accurately, and all entries correspond to data captured in source documents

The Monitor had to be given direct access to the source documents (original documents, data and records). Direct access included permission to examine, analyse, verify and reproduce and record reports that are important to evaluation of the clinical trial. All information dealt with during such visits were treated as strictly confidential. At the end of the trial, close out visits were performed by the monitor after the final participant visit has been completed and prior to database lock. During this visit the monitor verified that all trial close out activities were completed – all queries resolved, missing data completed, monitoring completed, archiving arrangements in place, ISF completed and TMF documents collected, and end of trial notification.

7.6 Statistical Methods Planned in the Protocol and Determination of Sample Size

7.6.1 Description of procedures and measurements

Previous data showed that NT-proBNP levels decreased by about 50% within 6 months after acute myocardial infarction. To detect a relative 40% larger reduction in NT-proBNP levels in the empagliflozin group as compared to the placebo group with a power of 80% and an alpha-level of 0.05% and assuming a correlation for NT-proBNP levels of 0.85, a sample size of 216 subjects in each group was necessary. To account for a dropout rate of about 10% each group consisted of 238 patients.

7.6.2 General Analysis Considerations

The trial ended after the last subject completed the follow-up telephone assessment (Study visit 5). All patients were reviewed by a clinician at their last on-site study visit (Study visit 4) in order to arrange return to appropriate routine clinical care pathways. The data analysis was performed after the finalization and approval of the Statistical Analysis Plan (SAP) document.

7.6.3 Intention to Treat Population (ITT)

The ITT population included all patients who were randomized and received at least one dose of the study medication (i.e. Empagliflozin or Placebo). The ITT population was used for the primary efficacy analysis.

7.6.4 Per Protocol Population (PP)

The PP population included all patients in the ITT population who completed week 26 evaluation without any major protocol violations. More specifically, the PP population included all patients in the ITT population excluding:

- Patients not fulfilling inclusion/exclusion criteria at baseline, which was identified after randomization and first treatment dosing but who remained in the trial as no safety concern was considered by the principal investigators
- Patients who did not complete week 26 evaluation
- Patients who took study medication for less than 75% of the study duration (study duration = 26 +/- 2 weeks)

7.6.5 Safety Population

All patients who were randomized and received at least one confirmed dose of study medication (i.e. Empagliflozin or Placebo) and provided any post-baseline safety information.

7.6.6 Covariates and Subgroups

All analyses, including the primary analysis, were adjusted for the variables used when stratifying the randomization. These variables were sex and T2DM status. Analysis was also adjusted for baseline levels of the dependent variables.

Subgroup analyses focused on the evidence for a difference in treatment effects using the interaction term. Subgroup-specific treatment effect estimates were presented only if the interaction effect was judged to be statistically significant. Interaction effects were investigated for the following variables:

- T2DM
- Previous cardiovascular events (MI or stroke)
- Previous MI
- History of heart failure
- Age
- Sex
- Renal function
- LV-EF
- Baseline levels of the dependent variable. Here the interaction was investigated using the original dependent variable and/or by categorizing this dependent variable into a clinically relevant number of categories. Percentiles were used if there were no prior clinical cut offs.

Because this study was not designed to detect site specific effects with specific power, all study center were grouped and analysed as a whole. However, we performed an exploratory analysis for study center effects with respect to each of the dependent variables.

7.6.7 Missing Data

Missing data was imputed for some efficacy analyses (sensitivity analyses). Missing values were imputed at all visits using Multiple Imputation with Chained Equation (MICE) approach. Ten imputed data sets with all visit values filled in were generated. The analysis was performed on each of the 10 imputed datasets, which produced estimates of treatment effect and the standard error of that estimate. Finally, the set of estimates and standard errors were analysed by the *mice* R package to produce overall (pooled) estimates, confidence intervals, and P-values for the treatment effect.

7.6.8 Interim Analyses and Data Monitoring

No interim analyses was planned for this study

7.6.9 Multiple Testing

There was no need to control for the overall type 1 error using multiple testing procedure since we have one single primary efficacy endpoint.

7.6.10 Summary of Study Data

All summary tables were structured with columns for each treatment and overall in the order (Overall, placebo, empagliflozin) and annotated with the total population size relevant to that table, including any missing observations. All continuous variables were summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation. The frequency and percentages (based on the non-missing sample size) of observed levels were reported for all categorical variables. Demographic and clinical characteristics to be summarized included all baseline variables. P-values were added to compare baseline characteristics between placebo and empagliflozin groups.

7.6.11 Treatment Compliance

Treatment compliance was assessed by remaining pill count. The pill count was controlled by the monitoring-team at on-site visits.

7.6.12 Efficacy Analyses

Efficacy analyses performed using the ITT population was considered as primary, whereas efficacy analyses performed using the PP population was considered as supportive.

7.6.13 Primary Efficacy Analyses

The primary efficacy endpoint was the change in NT-proBNP from baseline to week 26. This primary endpoint was analysed on the ITT population using a LMEM where the dependent variable is the NT-proBNP and the fixed effects are treatment, visit, treatment by visit interaction, the stratification factors Sex and T2DM and the level of NT-proBNP at baseline. In case of non-convergence problems other covariance structures, such as compound symmetry, were applied until the problem was resolved.

In this analysis, no missing data was imputed. It was handled by using the LMEM which assumes the data to be missing at random. At week 26, estimates of mean values, the mean differences between the treatment groups and the associated 2-sided 95% confidence interval were derived from the LMEM model through the use of estimated marginal means. To claim superiority of empagliflozin over placebo, this primary efficacy analysis had to show a statistically significant effect of treatment at an alpha level of 5% and two-sided test direction.

7.6.14 Secondary Efficacy Analyses

To support the interpretation of the primary efficacy analysis, some robustness and/or sensitivity analyses were performed on the primary efficacy endpoint. However, the conclusion of superiority for comparison of the primary endpoint between the two treatment groups was purely based on results of the primary efficacy analysis. Secondary efficacy analyses was performed to assess robustness of the results against missing data, analysis population, and the statistical model used.

Secondary Efficacy analysis I

To assess the sensitivity of primary efficacy analysis to missing data, analysis was also conducted on the ITT population with missing values being imputed at all visits using MICE approach. Ten imputed data sets with all visit values filled in were generated. The primary efficacy analysis was performed on each of the 10 imputed datasets, which produced estimates of treatment effect and the standard error of that estimate. Finally, the set of estimates and standard errors were analysed by MICE package to produce overall (pooled) estimates, confidence intervals, and P-values for the treatment effect.

Secondary Efficacy analysis II

In this analysis, we used the absolute change in NT-proBNP from baseline to week 26 as the primary endpoint. This endpoint was analyzed on the ITT population, with no imputation of missing values, and by using a multiple linear regression model where the dependent variable is the absolute change in NT-proBNP and the independent variables are treatment, Sex, T2DM and baseline level of NT-proBNP.

7.6.15 Analyses of Secondary Endpoints

The change from randomization to week 26 of all continuous secondary endpoints were analysed in the same way as the primary efficacy endpoint.

7.6.16 Safety Analyses

The safety section of the analysis contains a descriptive listing of the following tables:

- All-Cause Mortality: A table of all cases of deaths due to any cause, with number and frequency of such events in each arm/group of the clinical study.
- Serious Adverse Events, which occurred during this study: A table of all anticipated and unanticipated serious adverse events, grouped by trial site, SAE description, outcome, date of onset and treatment duration.

  This table will also include the reporting of cases of diabetic ketoacidosis.

7.6.17 Clinical Laboratory Evaluations

Summary statistics on laboratory measurements were tabulated. Baseline values, differences in normal ranges between sites were provided. The primary outcome, NTproBNP, was assessed at the KIMCL central lab in Graz, Austria. If measurement in the central lab were not possible (e.g. missing biomarker sample), NT-proBNP measurement from the local lab will be accepted for the analysis.

7.6.18 Reporting Conventions

P-values ≥0.001 were reported to 3 decimal places; p-values less than 0.001 were reported as “<0.001”. The mean, standard deviation, and any other statistics other than quantiles, were reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum used the same number of decimal places as the original data.

8. STUDY PATIENTS

8.1 Withdrawal criteria

Subjects could have been withdrawn from the study at the discretion of the Investigator or Sponsor due to a safety concern or if judged non-compliant with trial procedures. A subject had to be withdrawn from treatment of the following applies.

- Adverse event requires unblinding of the study medication
- Pregnancy or intention of becoming pregnant
- Intolerable adverse effects
- Major violation of the study protocol
- Occurrence of an exclusion criterion
- Other circumstances that would endanger the health of the subject if he/she were to continue his/her participation in the trial.

Additionally subjects could chooses to withdraw from the study at any time. Reasons for withdrawals and discontinuation of any subject from the protocol have to be recorded.

8.2 Disposition of Participants

A total of 476 patients were enrolled and randomised to empagliflozin 10 mg/day (n=237) or matching placebo (n=239). Twenty-six (5.5%) patients discontinued study medication 16 prematurely (14 empagliflozin, 12 placebo). Twelve (2.5%) participants withdrew informed consent and a total of 20 (4.2%) patients were lost to follow-up, with only two patients with unknown vital status at study end.

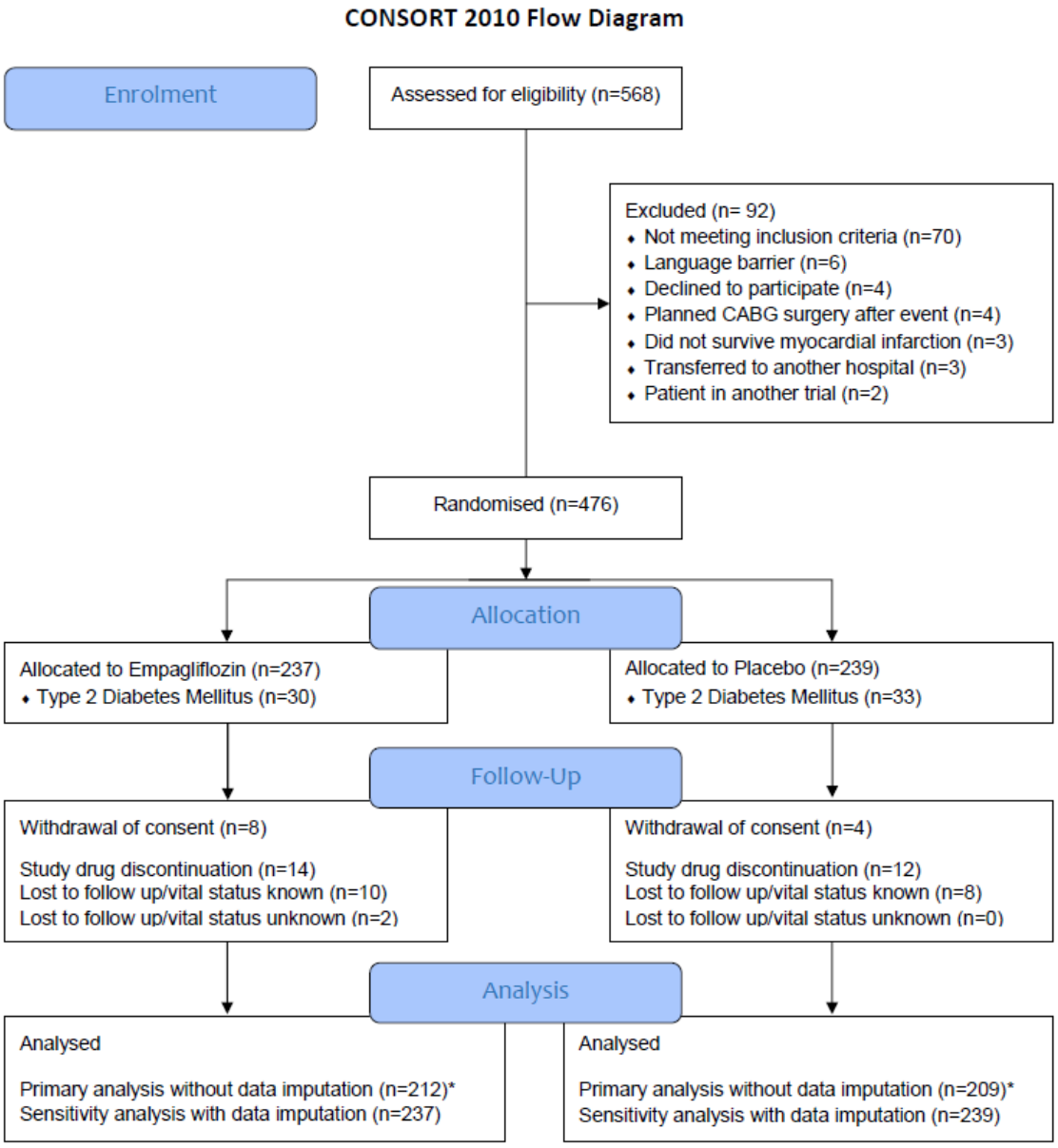

Figure 6: Disposition of study participants

8.3 Baseline Characteristics

Baseline characteristics were summarized using descriptive statistics with mean and standard deviation (SD) for continuous measures and frequency tables for categorical variables. Categorical variables were compared using Chi-squared or Fisher's exact tests, and continuous variables using an unpaired *t*-test or its non-parametric equivalent (Wilcoxon rank-sum test) where the normality assumption was 6 violated.

Table 6,: Participant baseline characteristics

Characteristic	Overall N = 476	Empagliflozin N = 237	Placebo N = 239	p-value[1]
Age (years), median (IQR)	57 (52–64)	57 (52–64)	57 (52–65)	0.78
Male, n (%)	392 (82)	195 (82)	197 (82)	0.97
Body mass index (kg/m2), median (IQR)	27.6 (25.1–30.3)	27.7 (25.3–30.3)	27.2 (24.9–30.2)	0.20
Systolic blood pressure (mmHg), median (IQR)	125 (117–131)	125 (116–131)	125 (118–131)	0.21
Diastolic blood pressure (mmHg), median (IQR)	78 (74–85)	78 (74–85)	78 (75–85)	0.60
Obesity, n (%)	138 (29)	68 (29)	70 (29)	0.89
Type 2 diabetes mellitus, n (%)	63 (13)	30 (13)	33 (14)	0.71
Hypertension, n (%)	199 (42)	92 (39)	107 (45)	0.19
Dyslipidaemia, n (%)	135 (28)	71 (30)	64 (27)	0.44
Smoking (active or former), n (%)	341 (72)	171 (72)	170 (72)	0.92
Coronary artery disease, n (%)	53 (11)	28 (12)	25 (10)	0.64
History of Stroke, n (%)	6 (1.3)	5 (2.1)	1 (0.4)	0.12
History of CABG, n (%)	2 (0.4)	1 (0.4)	1 (0.4)	>0.99
History of myocardial infarction, n (%)	23 (4.8)	14 (5.9)	9 (3.8)	0.28
Depression, n (%)	24 (5.0)	15 (6.3)	9 (3.8)	0.20
History of carcinoma, n (%)	24 (5.0)	11 (4.6)	13 (5.4)	0.69
Coronary angiography vessel status				
3-vessel disease	86 (18.1)	50 (21.1)	36 (15.0)	0.08
2-vessel-disease	162 (34.0)	82 (34.6)	80 (33.5)	0.80
1-vessel disease	228 (47.9)	105 (44.3)	123 (51.5)	0.12
Treatment				
ACE-I/ARB, n (%)	459 (96)	228 (96)	231 (97)	0.75
ARNI, n (%)	9 (1.9)	2 (0.8)	7 (2.9)	0.18
Beta-blocker, n (%)	457 (96)	223 (94)	234 (98)	0.078
MRA, n (%)	180 (38)	86 (36)	94 (39)	0.54
Loop diuretic, n (%)	51 (11)	27 (11)	24 (10)	0.61
Statin, n (%)	462 (97)	229 (97)	233 (97)	0.98
Ezetimibe, n (%)	59 (12)	29 (12)	30 (13)	0.94
Calcium channel blocker, n (%)	21 (4.4)	9 (3.8)	12 (5.0)	0.52
Aspirin, n (%)	474 (99.6)	235 (99)	239 (100)	0.50
Anticoagulation drugs, n (%)	37 (7.8)	16 (6.8)	21 (8.8)	0.41
Metformin, n (%)	41 (8.6)	21 (8.9)	20 (8.4)	0.84
DPP4-Inhibitor, n (%)	13 (2.7)	7 (3.0)	6 (2.5)	0.76
Sulfonylurea, n (%)	4 (0.8)	2 (0.8)	2 (0.8)	>0.99
GLP1-RA, n (%)	4 (0.8)	2 (0.8)	2 (0.8)	>0.99
Insulin, n (%)	11 (2.3)	5 (2.1)	6 (2.5)	0.78

Characteristic	Overall N = 476	Empagliflozin N = 237	Placebo N = 239	p-value[1]
Laboratory parameters				
NT-proBNP (pg/ml), Median (IQR)	1,294 (757–2,246)	1,272 (773–2,247)	1,373 (754–2,217)	0.91
eGFR, (ml/min/1.73m2) Median (IQR)	92 (78–102)	92 (78–101)	91 (78–102)	0.89
Hemoglobin A1c (%), Median (IQR)	5.60 (5.40–6.00)	5.60 (5.40–6.00)	5.70 (5.40–6.00)	0.87
Creatine kinase (U/l), Median (IQR)	1,673 (1,202–2,456)	1,668 (1,136–2,532)	1,701 (1,254–2,404)	0.71
Troponin T (ng/l), Median (IQR)	3,039 (2,037–4,856)	3,059 (2,082–4,775)	3,029 (1,980–4,856)	0.56
Total cholesterol (mg/dL), Median (IQR)	188 (162–223)	188 (163–225)	188 (162–220)	0.75
LDL-cholesterol, (mg/dl), Median (IQR)	120 (93–149)	118 (96–150)	121 (90–145)	0.82
HDL-cholesterol (mg/dl), Median (IQR)	44 (36–54)	44 (36–52)	43 (36–54)	0.77
Aspartate aminotransferase (U/l), Median (IQR)	204 (125–322)	203 (136–328)	212 (120–320)	0.67
Alanine aminotransferase (U/l), Median (IQR)	50 (37–72)	50 (37–75)	50 (38–68)	0.53
Gamma glutamyltransferase (U/l), Median (IQR)	31 (21–49)	29 (21–49)	32 (21–48)	0.84

[1] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

9. SAFETY EVALUATION

9.1 Adverse Events

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, including an exacerbation of a pre-existing condition, or disease temporally associated with the use of the trial device/procedure, whether or not considered related to the treatment. All adverse events that occurred during this study were recorded in the eCRF. 465 Adverse Events occurred during this trial (253 empagliflozin group; 212 placebo group). Safety endpoints such as recorded urinary tract infection adverse events or genital fungal infection adverse events did not differ significantly between the empaglifozin and placebo groups (Table 9).

9.1.1 Adverse Event Description

For the purposes of the study, AEs were followed up according to local practice until the event has stabilised or resolved, or the Follow-up Visit, whichever is the sooner. SAEs were recorded throughout the study.

9.1.2 Severity of Adverse Events

Mild: Awareness of event(s) or sign(s) but easily tolerated

Moderate: Discomfort enough to cause some interference with usual activity

Severe: Incapacitating or causing inability to carry out usual activity

9.1.3 Causality of Adverse Events

Medical judgment was used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship was recorded in the eCRF:

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.

No: There is no reasonable causal relationship between the investigational product administered and the AE.

9.2 Adverse Events of Special Interest

The term AESI (Adverse Event of Special Interest) 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 Pharmacovigilance Department of Boehringer Ingelheim within the same timeframe that applies to SAEs. Patients with AESIs had to be followed up appropriately, regardless of the origin of the laboratory data (e.g. central, local etc.). The Investigator should have considered which, if any, concomitant therapies should have be taken during evaluation. Discontinued treatments could have been reintroduced per Investigator discretion.

The following are considered as AESIs:

9.2.1 Hepatic injury

A hepatic injury was defined by the following alterations of hepatic laboratory parameters after randomisation:

- an elevation of AST and/or ALT ≥ 3 fold ULN combined with an elevation of total bilirubin ≥ 2 fold ULN measured in the same blood sample

- an isolated elevation of ALT and/or AST ≥ 5 fold ULN

These laboratory findings constitute a hepatic injury alert and the patients which showed these abnormalities need to be followed up according to medical judgement. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without laboratory results (ALT, AST, total bilirubin) available, the Investigator made sure these parameters were analysed, if necessary in an unscheduled blood test.

9.2.2 Decreased renal function

Decreased renal function was defined by a creatinine value showing a ≥ 2 fold increase from baseline and is above the ULN. For the AESI "decreased renal function" the Investigator had to collect an unscheduled laboratory sample for creatinine as soon as possible and hat to initiate follow-up laboratory tests of creatinine according to medical judgement.

9.2.3 Metabolic acidosis, ketoacidosis and diabetic ketoacidosis

In case of metabolic acidosis, ketoacidosis and diabetic ketoacidosis (DKA) further investigations were necessary according to the medical judgment and the clinical course until a diagnosis is made and/or the patient is recovered. DKA was defined by the diagnostic criteria in the table below, and as defined by the American Diabetes Association (ADA). Investigators were aware that not all criteria in the table below needed to apply for the diagnosis of DKA, and clinical judgment had also been taken into consideration. Due to its mechanism of action, empagliflozin may potentially modify the clinical presentation of DKA which may have occurred at lower plasma glucose levels than stated in the table below.

Table 7: Severity categories of diabetic ketoacidosis

	Diabetic ketoacidosis		
	Mild	**Moderate**	**Severe**
Plasma glucose (mg/dL)	>250	>250	>250
Arterial pH	7.25-7.30	7.00-7.24	<7.00
Serum bicarbonate (mEq/L)	15-18	10 to <15	<10
Urine ketones*	Positive	Positive	Positive
Serum ketones*	Positive	Positive	Positive
Effective serum osmolality (mOsm/kg)**	Variable	Variable	Variable
Anion gap***	>10	>12	>12
Alteration in sensoria or mental obtundation	Alert	Alert/drowsy	Stupor/coma

* Nitroprusside reaction method
** Calculation: 2[measured Na (mEq/L) + glucose (mg/dL)/18
*** Calculation: (Na+) – (Cl- + HCO3-) (mEq/L)

9.2.3 Events involving lower limb amputation

This definition includes amputation (i.e. resection of a limb through a bone), disarticulation (i.e. resection of a limb through a joint) and auto-amputations (i.e. 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). Each lower limb amputation, disarticulation, or auto-amputation had to be reported separately. The SAE report had to 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.

Table 8: Adverse Events overview

	Total	**Empagliflozin**	**Placebo**
Serious Adverse Events			
Death	3	3	0
Non cardiovascular death	1	1	0
Death from cardiovascular cause	2	2	0
Any Hospitalisation	63 (69)	31 (35)	32 (34)
Hospitalisation due to heart failure	7 (10)	3 (6)	4 (4)
Hospitalisation due to cardiovascular event	7 (7)	2 (2)	5 (5)
Adverse Events of Special Interest			
Hepatic injury	2	1	1
Renal injury	0	0	0
Metabolic acidosis and diabetic ketoacidosis	0	0	0
Event involving lower limb amputation	0	0	0
Other Adverse Events			
Urinary tract infection	18 (26)	11 (18)	7 (8)
Genital fungal infection	9 (9)	7 (7)	2 (2)

Given numbers are participants with adverse events (number of events); Renal injury: > 2-fold increase creatinine; Hepatic injury: AST/ALT ≥ 3-fold ULN with elevation of total bilirubin ≥ 2-fold ULN or AST/ALT elevation ≥ 5-fold ULN

SAE rates did not differ between the empagliflozin and the placebo groups. In total there were 72 SAEs with 63 participants hospitalised, out of which seven participants were hospitalised for heart failure (three in the empagliflozin group, four in placebo group). Three deaths occurred during the study, all in the empagliflozin group. Two participants died within 5 days after enrolment in the trial secondary to large MIs and subsequent

cardiogenic shock. One participant died 149 days after enrolment due to lung cancer. All three fatalities were considered by the adjudication committee prior to unblinding to be unrelated to study medication. Moreover, no amputations, no ketoacidosis and no severe hypoglycaemic episodes were reported throughout the follow-up.

9.3 Serious Adverse Events

An SAE is defined as any event that:

- results in death;
- is immediately life-threatening*;
- requires hospitalisation or prolongation of existing inpatient's hospitalisation**
- results in persistent or significant disability or incapacity;
- is a congenital abnormality or birth defect;

* "Life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission). Medical judgement had to be exercised in deciding whether an adverse event/reaction was serious in other situations. Important adverse events/reactions that were not immediately life-threatening, or did not result in death or hospitalisation but may have jeopardised a subject, or may have required intervention to prevent one of the other outcomes listed in the definition above had to be considered serious. Patients may have been hospitalised for administrative or social reasons during the study (e.g. days on which infusion take place, long distance from home to site). It was not necessary to report these and other hospitalisations planned at the beginning of the study as a SAE in case they have been reported at screening visit in the source data and have been performed as planned. Worsening of the underlying disease or of other pre-existing conditions had be recorded as an (S)AE in the (e)CRF.

- Changes in vital signs, ECG, physical examination, and laboratory test results
- Changes in vital signs, ECG, physical examination and laboratory test results were recorded as an (S)AE in the (e)CRF , if they are judged clinically relevant by the investigator.

9.3.1 Reporting of SAEs

The Sponsor had to report (i.e., from signing the informed consent onwards through the trial defined follow-up period) all SAEs and non-serious AEs which were relevant. For a reported SAE and AESI by fax or other secure method BI IIS SAE form has to be submitted to the Boehringer Ingelheim pharmacovigilance immediately (within twenty-four hours) or the next business day whichever is shorter. For each adverse event, the investigator provided the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator determined the expectedness of the investigational drug to the AEs as defined in the listed Adverse Events section of the Boehringer Ingelheim's Investigator Brochure for the Productor Boehringer Ingelheim Drug Information e.g. Summary of Product Characteristics (SmPC)/Investigator Brochure (IB) for the authorised Study Drug provided by Boehringer Ingelheim. The investigator does not need to actively monitor patients for adverse events once the clinical trial has ended. However, if the investigator becomes aware of an SAE(s) that occurred after the patient has completed the clinical trial (including any protocol specified follow-up period), it should be reported to Boehringer Ingelheim if investigator considers it as relevant to the BI study drug. The sponsor reported the SAEs to the ethics committee and the local authorities as well as Boehringer Ingelheim Pharmacovigilance in accordance with the aforementioned SAE reporting instructions via annual development safety update report (DSUR). Suspected unexpected serious adverse reaction (SUSAR) is designated as such according to Guideline 2001/20/EG. A serious adverse reaction was deemed unexpected when it is not listed in the corresponding basic document (SmPC, IB).

9.3.2 Line Listing of Serious Adverse Events

Table 9: Line listing of SAE

SAE #	Serious Adverse Event	Outcome	Date of Onset	Dates of Treatment (Treatment Duration) Treatment allocation	Comments
# 1	Suspect minor stroke; transient Ischaemic Attack (TIA)	Resolved	19th Aug 2017	2nd Aug 2017- 18th Aug 2017 (17d) Placebo	Hospitalised. History of arterial hypertension and diffuse coronary artery disease. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug (Empagliflozin/Placebo)
# 2	Planned myocardial scintigraphy	Resolved	28th Mar 2018	13th Feb 2018- 27th Mar 2018 (43d) Placebo	Hospitalised for planned myocardial scintigraphy. History of psoriasis and hyperlipidaemia. Multiple concomitant medications. Planned procedure for further diagnostic evaluation of baseline coronary artery

					disease. No causal relationship between hospitalization and investigational drug.
# 3	Ischemic mitral regurgitation	Resolved	07th Feb 2018	20th Nov 2017 – 07th Feb 2018 (79d) Placebo	Patient was hospitalized for shortness of breath, and was diagnosed with novel mitral regurgitation. On 17th Feb 2018 patient received a mitral valve replacement.
# 4	Angina pectoris	Not yet recovered	24th Jun 2018	04th Jun 2018 – not known Placebo	Hospitalised for planned myocardia scintigraphy. History of coronary artery disease, varicosis (surgical intervention 2007) and hyperlipidaemia. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
# 5	Myocardial infarction	Death	28th Jun 2018	22th Jun 2018 – 27th Jun 2018 (5 days) Empagliflozin	Large myocardial infarction with consecutive severe heart failure which resulted in death. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
# 6		Not yet recovered	04th Jul 2018	Not known – not known Placebo	Hospitalized for observation due to angina pectoris with chest pain and planned coronary angiography. History of coronary hypertension, benign prostatic hyperplasia and type 2 diabetes mellitus. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
# 7	Retroperitoneal haematoma	Resolved	09th Jun 2018	05th Jun 2018 – 09th Jun 2018 (5 days) Placebo	Hospitalized for angio CT due to retroperitoneal haematoma after femoral access percutaneous coronary intervention post baseline myocardial infarction. History of hypercholesterinaemia. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
# 8	Stress dyspnoea	Resloved	18th Jun 2018	5th Jun 2018 – not known Placebo	Hospitalized for echocardiography due to stress dyspnoea. Cardiac decompensation was diagnosed. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
# 9	Pulmonary embolism	Not yet recovered	30th Aug 2018	17th Jul 2018 – not known Empagliflozin	Hospitalized due to pulmonary embolism. Multiple concomitant medications.

					Investigator considers no causal relationship between event and investigational drug.
# 10	Cardiac decompen-sation	Resolved	17th Sep 2018	24th Aug 2018 – not known Empagliflozin	Hospitalized due to cardiac decompensation. History of hypertension, breast cancer, osteoporosis and cerebral microangiopathy. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
# 11	Ischaemic cardiomyo-pathy	Not yet recovered	26th Sep 2018	17th Aug 2018 – 26th Sep 2018 (40 days) Empagliflozin	Hospitalized due to angina pectoris symptoms. Coronary angiography was done due to diagnosed CAD stenosis. History of hypertension and type 2 diabetes mellitus. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
# 12	Elevated troponin I	Resolved	02nd Oct 2018	20th Sep 2018 – 02nd Oct 2018 (12 days) Empagliflozin	Hospitalized due to pain in the left arm with elevation of troponin I, ascribed to the initial myocardial infarction. History of hypertension and hyperlipidaemia. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
# 13	Cardiogenic shock	Death	19th Dec 2018	15th Dec 2018 – 19th Dec 2018 (4 days) Empagliflozin	Irreversible cardiogenic shock due to occlusion of a cardiac vessel leading to death. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
# 14	Myocardial infarction	Resolved	31st Jan 2019	06th Oct 2018 – not known Placebo	Hospitalized due to progress of coronary arterial disease which led to another myocardial infarction. History of hypertension. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
# 15	Cardiac decompen-sation	Resolved	10th Feb 2019	12th Sep 2018 – 10th Feb 2019 (151 days) Placebo	Hospitalized due to cardiac decompensation. History of hypertension, obstructive sleep apnoea syndrome, coronary heart disease and ischemic cardiomyopathy (NYHA III). Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
# 16	Nonsustained ventricular tachycardia	Resolved	15th Feb	10th Oct 2018 – no known	Hospitalized due to nonsustained ventricular tachycardia under ergometry. ICD implantation for secondary

			2019	Placebo	prophylaxis. History of hypertension, hyperlipidaemia and adiposity. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
# 17	Pulmonary carcinoma	Fatal	03-Jan-2019	24th Aug 2018 – not reported Empagliflozin	Hospitalised due to general weakness with lethal outcome. Death was most likely caused by pulmonary carcinoma. Multiple comorbidities. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
# 18	Non cardiac thoracic syndrome	Recovered	14th Apr 2019	26th Mar 2019 – 14th Apr 2019 (19 days) Placebo	Hospitalised due to acute thoracic pain. Multiple comorbidities. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
# 19	Atypical thorax pain	Recovered	18th May 2019	02nd May 2019 – 18th May 2019 (16 days) Placebo	Hospitalised due to atypical thorax pain with cardiac enzymes elevation. Multiple comorbidities. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
# 20	Vasovagal reaction	Recovered	29th Jul 2019	not reported – 29th Jul 2019 Placebo	Hospitalised due to vasovagal reaction regarding contrast agent for echocardiography (dizziness, sweating, nausea). Multiple comorbidities. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
# 21	Unstable angina pectoris	Recovered	18th Apr 2019	01st Oct 2018 – not reported Empagliflozin	Hospitalised due to unstable angina pectoris. Multiple comorbidities. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
# 22	Gastroenteritis	Recovered	23th Aug 2019	26th Jul 2019 – 23th Aug 2019 (28 days) Empagliflozin	Hospitalised due to gastroenteritis with epigastric pain. Multiple comorbidities. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
# 23	Syncope AV block intermittent	Not yet recovered	15th Aug 2019	08th Mar 2019 – 15th Aug 2019 (160 days) Placebo	Hospitalised due to syncope. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.

# 24	N-stemi	Recovered	01st Oct 2019	09th Apr 2019 – 30th Sep 2019 (174 days) Empagliflozin	Hospitalised due to a pathological myocardial scintigraphy, associated with coronary artery disease. Multiple comorbidities. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
# 25	Elective PCI due to proximal RCA-stenosis	Recovered	29th Oct 2019	13th May 2019 08th Nov 2019 (179 days) Empagliflozin	Hospitalised due to elective PCI of proximal RCA with implantation of DES (99% senosis). Multiple comorbidities. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
# 26	N-stemi	Recovered with sequelae	03rd Sep 2019	06th Jun 2019 – 29th Aug 2019 (84 days) Empagliflozin	Hospitalised due to angina pectoris symptoms. Multiple comorbidities. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
# 27	Angina pectoris symptoms	Recovered	17th Dec 2018	03rd Jul 2018 – not reported Empagliflozin	Hospitalised due to angina pectoris symptoms. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
# 28	Perforated appendicitis	Recovered	23th Dec 2019	17th Dec 2019 – not reported Placebo	Hospitalised due to perforated appendicitis. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
#29	Benign mass	Recovered	16th Jan 2019	17th Dec 2019 – not reported Placebo	Hospitalised due to benign mass of the pancreas with sonography. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
#30	Coronary artery stenosis	Recovered	18th Jun 2020	20th Dec 2019 – 18th Jun 2020 (181 days) Empagliflozin	Requires/prolongs hospitalisation due to DES RCA and CX stenosis. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
#31	Recurrent Angina pectoris	Recovered	22th May 2020	13th Dec 2019 – 22nd May 2020 (161 days) Placebo	Requires/prolongs hospitalisation due to recurring retrosternal feeling of pressure Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.

#32	STEMI anterior	Recovered	22th Jul 2020	19th Feb 2020 – not reported Placebo	Requires/prolongs hospitalisation due to STEMI anterior. Multiple comorbidities. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
#33	Hyperuricemia aggravation	Recovered	05th Mar 2020	11th Feb 2020 – 05th Mar 2020 (23 days) Empagliflozin	Requires/prolongs hospitalisation due to hyperuricemia aggravation. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
#34	Syncope Melaena	Recovered	05th Oct 2020	23th Jul 2020 – 04th Oct 2020 (73 days) Empagliflozin	Requires/prolongs hospitalisation due to syncope. Multiple concomitant medications. Investigator considers potential relationship between event and investigational drug.
#35	RCA stenosis	Recovered	28th Oct 2020	12th Sep 2020 – 28th Oct 2020 (46 days) Empagliflozin	Requires/prolongs hospitalisation due to a stenosis of RCA. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
#36	Pneumonia bilateral	Recovered	13th Nov 2020	05th Sep 2020 – 12th Nov 2020 (68 days) Empagliflozin	Requires/prolongs hospitalisation due to bilateral pneumonia. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
#37	Acute cholecystitis	Recovered	03rd Dec 2020	12th Sep 2020 – 02th Dec 2012 (81 days) Empagliflozin	Requires/prolongs hospitalisation due to acute cholecystitis. History of pneumonia and STEMI anterior. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
#38	Chest pain	Recovered	08th Jan 2021	13th Aug 2020 – 08th Jan 2021 (148 days) Empagliflozin	Requires/prolongs hospitalisation due to atypical angina pectoris with left-thoracic pain and radiation to the left arm. Multiple comorbidities. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
#39	Coronary artery disease	Recovered	19th Jan 2021	29th Dec 2020 19th Jan 2021 (21 days) Placebo	Requires/prolongs hospitalisation due to elective PCI. Multiple comorbidities. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.

# 40	Insult	Recovered	12th Feb 2021	28th Jan 2021 12th Feb 2021 (15 days) Placebo	Requires/prolongs hospitalisation due to new ischaemic stroke of left median cerebral artery. Multiple concomitant medications. Multiple comorbidities. Investigator considers no causal relationship between event and investigational drug.
#41	N-Stemi	Not yet recovered	09th Apr 2021	03rd Oct 2020 – 09th Apr 2021 (188 days) Placebo	Requires/prolongs hospitalisation due to loaboratory increase of hsT, CK, CK-MB, LDH, Myoglobin, NTpro BNP and ALT. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
#42	OSAS	Recovered	11th Jul 2017	29th Jun 2017 – 11th Jul 2017 (12 days) Placebo	Requires/prolongs hospitalisation due to elective admission at the sleeping laboratory for CPAP-adjustment of known OSAS. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
#43	Subileus	Recovered	23th Nov 2017	26th Sep 2017 – 23rd Nov 2017 (58 days) Placebo	Requires/prolongs hospitalisation due to unclear abdominal pain. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
#44	Recurrent VTs Electric Storm	Recovered	17th Apr 2021	14th Apr 2021 – 17th Apr 2021 (3 days) Empagliflozin	Requires/prolongs hospitalisation due to postischemic recurrent VTs and electric storm. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
#45	Severe OSAS	Recovered	17th Jan 2021	19th Nov 2020 – 17th Jan 2021 (59 days) Placebo	Requires/prolongs hospitalisation due to elective hospital admission for lung function testing in known severe OSAS. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
#46	Event 1: Planned elective ICD-implatation (isch. CMP) Event 2: acute heart failure/grand-mal fit	Event 1: Recovered Event 2: Recovered	Event1: 02nd May 2018 Event 2: 24th Apr 2018	Event 1: 18th Nov 2017 – 02nd May 2018 (165 days)	Event 1: Requires/prolongs hospitalisation due to planned elective ICD-implantation in known ischemic cardiomyopathy. No ICD-implantation because of size of thrombus.

				Event 2: 18th Nov 2017 – 24th Apr 2018 (157 days) Empagliflozin	Event 2: Requires/prolongs hospitalisation due to first time grand-mal tits with acute heart failure (indication for ICD-implantation). Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
#47	Acute heart failure	Recovered	02nd Mar 2018	18th Nov 2017 – 02nd Mar 2018 (104 days) Empagliflozin	Requires/prolongs hospitalisation due to progressive dyspnea. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
#48	Acute heart failure	Recovered	16th Mar 2018	18th Nov 2017 – 16th Mar 2018 (118 days) Empagliflozin	Requires/prolongs hospitalisation due to progressive dyspnea. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
#49	Acute heart failure	Recovered	26th May 2018	18th Nov 2017 – 04th May 2018 (167 days) Empagliflozin	Requires/prolongs hospitalisation due to progressive dyspnea and peripleural edema. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
# 50	ICD-implantation	Recovered	06th Jun 2018	18th Nov 2017 – unknown Empagliflozin	Requires/prolongs hospitalisation due to elective ICD-implantation. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
#51	Re-CA, st. p. LAD PTCA (22.01.2018)	Recovered	09th May 2018	23th Jan 2018 – 17th Jul 2018 (175 days) Empagliflozin	Requires/prolongs hospitalisation due to elective PCI. Multiple concomitant medications and hypertension. Investigator considers no causal relationship between event and investigational drug.
#52	Atrial flutter-ablation	Recovered	11th Jun 2018	30th Jan 2018 – unknown Placebo	Requires/prolongs hospitalisation due to elective atrial flutter ablation. Multiple concomitant medications and hypertension. Investigator considers no causal relationship between event and investigational drug.
#53	EVR from AIC dexter	Recovered	04th Dec 2018	10th Jul 2018 – unknown	Requires/prolongs hospitalisation due to ECR right leg AIC dexter. Multiple concomitant medications.

				Empagliflozin	Investigator considers no causal relationship between event and investigational drug.
#54	Incarcerated inguinal hernia	Recovered	Unkn. May 2021	23rd Oct 2020 – 22nd Apr 2021 (180 days) Empagliflozin	Requires/prolongs hospitalisation due to incarcerated inguinal hernia. Multiple concomitant medications and hypercholesterolemia. Investigator considers no causal relationship between event and investigational drug.
#55	Pneumonia	Recovered	23rd Jun 2021	14th Apr 2021 – 23rd Jun 2021 (70 days) Empagliflozin	Requires/prolongs hospitalisation due to dyspnoe and shortness of breath. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
#56	Acute goute attack	Recovered	24th Sep 2018	08th Mar 2018 – 22nd Aug 2018 (167 days) Empagliflozin	Requires/prolongs hospitalisation due to acute goute attack, known hyperuricemia. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
#57	Weber B fracture	Recovered	04th Aug 2018	10th Mar 2018 – 10th Aug 2018 (153 days) Placebo	Requires/prolongs hospitalisation due to surgery of a Weber-B fracture. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
#58	GI-bleeding	Recovered	20th Sep 2018	10th May 2018 – 20th Sep 2018 (133 days) Placebo	Requires/prolongs hospitalisation due to colon bleeding of unknown origin. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
#59	Re-steonsis of RCA	Recovered	13th Dec 2018	10th May 2018 – 31st Oct 2018 (174 days) Placebo	Requires/prolongs hospitalisation due to symptoms of intermittent AP. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
#60	Morphine intoxication	Recovered	02nd Aug 2018	14th June 2018 – 02nd Aug 2018 (49 days) Empagliflozin	Requires/prolongs hospitalisation due to sudden loss of consciousness and reduced general condition with somnolence. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.

#61	Angina pectoris	Recovered	20th Jul 2021	13th May 2021 – 20th Jul 2021 (68 days) Empagliflozin	Requires/prolongs hospitalisation due to new-onset angina pectoris. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
#62	Pneumonia	Recovered	11th Aug 2021	10th Jul 2021 – 11th Aug 2021 (32 days) Placebo	Requires/prolongs hospitalisation due to pneumonia. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
#63	Isch. CMP (st. p. VF)	Recovered	08th Dec 2018	31st Oct 2018 – 08th Dec 2018 (38 days) Empagliflozin	Requires/prolongs hospitalisation due to elective ICD implantation in ischemic CMP and status post ventricular fibrillation. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
#64	Acute cholecystitis	Recovered	14th Feb 2019	30th Jan 2019 – 14th Feb 2019 (15 days) Placebo	Requires/prolongs hospitalisation due to acute cholecystitis. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
#65	Parox. Afib. de novo	Not yet recovered	27th May 2019	09th May 2019 – 27th May 2019 (18 days) Placebo	Requires/prolongs hospitalisation due to new onset high heart rate and palpitations. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
#66	Gastrointestinal bleeding	Recovered	04th Sep 2021	10th Mar 2021 – 04th Sep 2021 (178 days) Placebo	Requires/prolongs hospitalisation due to sudden syncope at home with haematochezia. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
#67	Angina pectoris	Recovered	28th Jun 2019	05th Jun 2019 – 28th Jun 2019 (23 days) Empagliflozin	Requires/prolongs hospitalisation due to recurrent angina pectoris. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
#68	Suspected PCI stenosis (planned CAG)	Recovered	15th Aug 2021	16th March 2021 – 21st Mar 2021 (5 days) Empagliflozin	Requires/prolongs hospitalisation due to planned CAG. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.

#69	Ischemic CMP	Recovered	15th Aug 2021	14th April 2021 – 15th Aug 2021 (123 days) Empagliflozin	Requires/prolongs hospitalisation due to known ischemic CMP and st.p. VTs (electric storm). Elective DDD-ICD implantation. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
#70	DES in RCA (planned PCI)	Recovered	11th Nov 2021	22nd Sep 2021 – 11th Nov 2021 (56 days) Placebo	Requires/prolongs hospitalisation due to planned PCI + DES in RCA. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
#71	Epigastrial pain	Not yet recovered	15th Nov 2021	24th Jun 2021 – 15th Nov 2021 (144 days) Placebo	Requires/prolongs hospitalisation due to epigastrial pain. Elective DDD-ICD implantation. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.
#72	Angina pectoris	Recovered	22nd Dec 2021	30th Jun 2021 – 22nd Dec 2021 (175 days) Empagliflozin	Requires/prolongs hospitalisation due to recurrent angina pectoris symptoms. Multiple concomitant medications and comorbidities. Investigator considers no causal relationship between event and investigational drug.

9.3.3 Subjects who died during the trial

Table 10: Line listing of subjects who died during the reporting period of the trial

Case ID Trial Site	**Gender Age**	**Study Drug**	**Reason**
G-061 Univ. Klinikum Graz	M 75	Empagliflozin 10mg	Large myocardial infarction with consecutive severe heart failure which resulted in death. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
G-084 Univ. Klinikum Graz	M 54	Empagliflozin 10mg	Irreversible cardiogenic shock due to occlusion of a cardiac vessel leading to death. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.
G-071 Univ. Klinikum Graz	F 79	Empagliflozin 10mg	Hospitalised due to general weakness with lethal outcome. Death was most likely caused by pulmonary carcinoma. Multiple comorbidities. Multiple concomitant medications. Investigator considers no causal relationship between event and investigational drug.

10. CONCLUSION

The EMMY trial evaluated for the first time the efficacy and safety of empagliflozin therapy when initiated within 72 hours after PCI for a large acute MI. Early initiation of empagliflozin, given in addition to established guideline-recommended post MI therapy, led to a greater reduction in median NT-proBNP levels compared with placebo without clinically relevant adverse events. NT-proBNP is a well-established biomarker of neurohormonal activation, hemodynamic stress, and subsequent cardiovascular events. The substantial decline in NT-proBNP concentrations which occurs over time following large MI (21-23), is a robust predictor of subsequent cardiovascular outcomes. The effect of SGLT2i on NT-proBNP concentrations in heart failure trials is heterogeneous within different cohorts with reductions (24), a moderate decline (25), or no significant reduction compared with placebo despite significant improvement in left ventricular mass as observed in the EMPA-HEART trial (26). Given the beneficial effects on NT-proBNP concentrations in combination with functional (LVEF, diastolic function) and structural (LVESV, LVEDV) improvements seen in the EMMY trial, established SGLT2i clinical benefits might be even more pronounced after a large MI. The EMMY trial was not powered for hard clinical endpoints but there are two large outcome trials currently ongoing (EMPACT-MI and DAPA-MI) which may provide definitive data. In EMMY the beneficial effect of empagliflozin on NT-proBNP concentrations was accompanied by a greater increase in LVEF, compared with placebo. The degree of LVEF recovery in the weeks after a MI has been shown to complement and out-perform baseline LVEF alone when providing prognostic information such as risk of sudden cardiac death and all-cause mortality (27, 28). LVEF trajectories separated early in the EMMY trial with the mean increase in the empagliflozin group being twice the size compared with the placebo group by 6 weeks (+8.8% vs. +4.3%). The absolute ~1.5% difference in the 26-week LVEF change seen in the EMMY trial is comparable to a recent analysis of the BEST trial (29) which observed an average LVEF of 4.5 units (%) after 12 months. This analysis compared heart failure patients with LVEF improvement ≥ 5 units to all other patients and described a significantly better outcome in all endpoints analysed ranging from HHF to all-cause mortality for those with greater LVEF recovery. These differences were independent of the treatment group (bucindolol or placebo). Data in post-MI patients reveal comparable or even more favourable outcome in patients with LVEF recovery compared to those with unaltered LVEF at baseline, whereas those patients without LVEF recovery have significantly worse outcomes (30, 31). The highly significant prognostic value of LVEF recovery within the first 6 months has been confirmed in a cohort with >10 years of follow-up (32). Thus, differences in LVEF changes, as observed in the EMMY trial with empagliflozin, suggest there may well be beneficial effects on clinical outcomes. Diastolic function also improved in EMMY, in line with data showing SGLT2i to be the first pharmacological treatment to improve prognosis in HFpEF. This finding is further supported by the smaller increases in left ventricular volumes seen following MI in the empagliflozin group. Thus, biomarker as well as functional and structural outcome data in the EMMY trial point towards a potential positive impact on clinical outcomes. Increases in circulating ketone

levels and ketone oxidation with SGLT2i have been suggested to improve cardiac efficiency and/or the energy supply in energy starved myocytes in heart failure (11, 33, 34). Beta-hydroxybutyrate, the commonest ketone body, was significantly increased in the empagliflozin, compared with the placebo group, in EMMY after 12 and 26 weeks.

Strengths and limitations of the study

EMMY is the first trial to present data on early SGLT2i treatment after a large MI, predominately in patients without established diabetes. A smaller previous trial in Japan was limited to patients with diabetes, initiated SGLT2 inhibition after the acute phase, and focussed on sympathetic activity (35). EMMY demonstrates the significant benefit of SGLT2i with respect to heart failure markers as well as left ventricular functional and structural parameters in the trial population. Empagliflozin was shown to have beneficial effects, despite optimal guideline post-MI treatment with EMMY providing safety data in the cohort of 474 participants out of the 476 randomised 1 (only two participants were lost to follow up without known vital status). However, the sample size in this investigator-initiated trial was insufficient to power it for hard clinical endpoints. Large CVOTs are of particular importance in providing definitive data for patients with acute MI, as for example, positive outcome data in heart failure trials did not necessarily translate into positive outcomes in post-MI trials, as observed in PARADIGM-HF (36) and PARADISE-MI (37), although those undergoing PCI during the index event in PARADISE-MI (the population enrolled in EMMY) seemed to benefit from angiotensin receptor–neprilysin inhibition. The role of SGLT2i in acute MI patients will be clarified when the robust outcome data from the two ongoing SGLT2i CVOTs (EMPACT-MI [NCT04509674] and 10 DAPA-MI [NCT04564742]), which are powered for differences in the composite outcome of hospitalization for heart failure and cardiovascular or all-cause mortality, are reported. In EMMY, the proportions of female patients and those with diabetes were lower than anticipated. Of note, patients with diabetes more often did not achieve the >800 U/L creatine kinase threshold. For this analysis we used locally performed and analysed echocardiography data but loop recordings are available in a substantial subgroup of participants which will be looked at in subsequent analyses.

Among patients with an acute large MI, early initiation of empagliflozin given in addition to guideline-recommended post-MI treatment resulted in a significantly greater median NT-proBNP reduction than with placebo over 26 weeks. There were no significant differences with regard to safety endpoints such as hospitalisation, alterations of glucose metabolism, renal or liver function.

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