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Statistical Analysis Plan for EMPA-VISION

Version: 2.0
Date: 12th-March-2020

[redacted] Trial No.:TRG17-01
BI Trial No.: 1245.148
EudraCT No.: 2017-000376-28

EMPA-VISION: A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MECHANISTIC CARDIAC MAGNETIC RESONANCE STUDY TO INVESTIGATE THE EFFECTS OF EMPAGLIFLOZIN TREATMENT ON CARDIAC PHYSIOLOGY AND METABOLISM IN PATIENTS WITH HEART FAILURE

[PROTOCOL VERSION 3.0/DATE: 14TH AUGUST 2018]

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Prepared For: **Boehringer Ingelheim**
[Sponsor]

Revision History

Version	Date	Author(s) and Role	Summary of Changes/Comments
2.0	12 March 2020	[redacted] Lead Statistician	The main changes in this version are as follows: Section 1.4, details added for changes to the planned protocol analyses. [redacted] Analysis sets/populations in Section 3 have been renamed to match the clinical trial protocol. SAS code provided in Section 5.3 for the primary endpoint analyses Section 5.3.2, sensitivity analysis of primary endpoint including adopted using ANCOVA. Section 5.5, analysis model changed to ANCOVA. [redacted]

SAP Approval

Signature of Approval for Statistical Analysis Plan for *EMPA-VISION* [BI Trial No: 1245.148]:

Lead Statistician [redacted]

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LIST OF ABBREVIATIONS

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

GMP	Good Manufacturing Practice
GLM	General Linear Model
HAF	History of Atrial Fibrillation
[redacted]	[redacted]
HDL	High Density Lipoprotein
HF	Chronic Heart Failure
HHF	Hospitalisation for Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HR	Hazard Ratio
[redacted]	[redacted]
IB	Investigator's Brochure
ICD	Implantable Cardioverter Defibrillator
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IPV	Important Protocol Violation
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ITT	Intent to Treat
i.v.	Intravenous
[redacted]	[redacted]
LA	Left Atrial
LAEF	Left Atrial Emptying Function
LAVI	Left Atrial Volume Index
LDL	Low Density Lipoprotein
LGE	Late Gadolinium Enhancement
LPDD	Last Patient Drug Discontinuation
LV	Left Ventricular
LVAD	Left Ventricular Assist Device
LVEF	Left Ventricular Ejection Fraction
LVH	Left Ventricular Hypertrophy
LVMI	Left Ventricular Mass Index
MACE	Major Adverse Cardiovascular Event
MedDRA	Medical Dictionary for Drug Regulatory Activities
MI	Myocardial Infarction
MRA	Mineralocorticoid Receptor Antagonist
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NT-proBNP	N-terminal of the prohormone brain natriuretic peptide
NYHA	New York Heart Association Classification
PCr	Phosphocreatine
PP	Per Protocol
PPS	Per Protocol Set
PMRS	Proton Magnetic Resonance Spectroscopy
PSA	Prostate Specific Antigen
[redacted]	[redacted]
SAEs	Serious Adverse Events
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SBP	Systolic Blood Pressure
SD	Standard Deviation
SGLT-1	Sodium-glucose co-transporter 1
SGLT-2	Sodium-glucose co-transporter 2
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
T1DM	Type 1 Diabetes Mellitus

T2DM	Type 2 Diabetes Mellitus
TIA	Transient Ischaemic Attack
ULN	Upper Limit of Normal
WOCBP	Women of childbearing potential

1 Introduction

This Statistical Analysis Plan (SAP) describes the planned analyses and reporting of the Boehringer Ingelheim [BI Trial No: 1245.148 & EU Trial No: 2017-000376-28] Protocol No: 1245-148 "A randomised, double-blind, placebo-controlled, mechanistic cardiac magnetic resonance study to investigate the effects of empagliflozin treatment on cardiac physiology and metabolism in patients with heart failure": The EMPA-VISION Study Protocol version 3.0 dated 14th August 2018).

The purpose of this SAP is to outline the planned analyses that are to be performed on the data to support the completion of the Clinical Study Report (CSR) for protocol 1245-148. The SAP will be amended if substantial changes to the planned analyses, and in any case, will be finalized before the database lock for this study.

Exploratory post-hoc or unplanned analyses not necessarily identified in this SAP may be performed on these data as required. These analyses will be clearly identified in the CSR or the statistical report for the study. In addition, all the planned analyses identified or unplanned analyses not specified in this SAP may be included in the future manuscripts.

The reader of this SAP is encouraged also to read the clinical protocol for details on the conduct of this study, and the operational aspects of clinical assessments and the timing of the process of completing a patient in this study.

1.1 Study Objectives

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

1.1.1 Primary Objectives

The primary endpoint is the change from baseline (Randomisation) to week 12 (Day 84) in the PCr / ATP ratio in the resting state measured by ^{31}P MRS.

1.1.2 Secondary Objectives

There are no secondary endpoints defined in this trial.

[redacted]

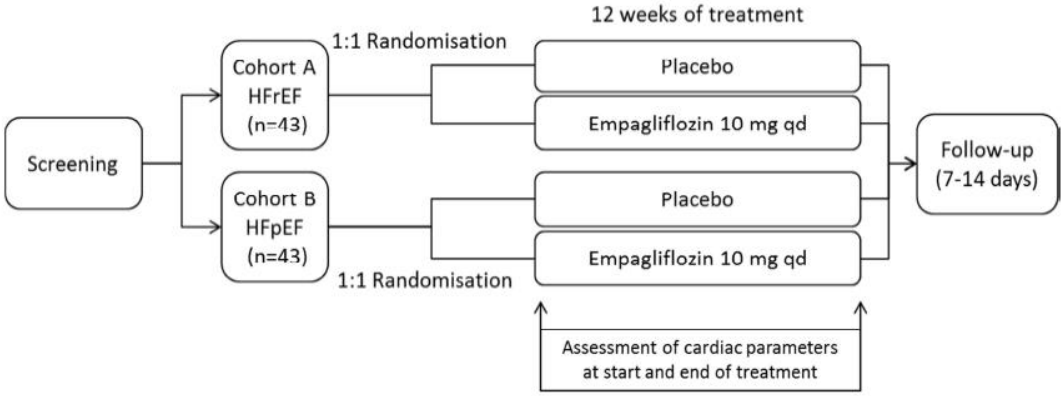
[redacted]

1.2 Study Design

1.2.1 OVERALL TRIAL DESIGN AND PLAN

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

Figure 1-1. Trial Design



1.2.2 Administrative structure of the trial

1.2.2.1 Clinical Event Committee for Diabetic ketoacidosis (DKA)

An independent external committee (CEC) will be established to adjudicate centrally and in a blinded fashion events suspected of DKA (for further details see Protocol (1245.148, version 3.0, dated 14th August 2018) Section 5.3.5.1). The CEC will evaluate whether pre-specified criteria for adjudication endpoints are met.

For any events that qualify for adjudication, study sites will be asked to provide clinical documentation such as laboratory values, discharge summaries etc. to support the external event adjudication. The tasks and responsibilities of the CEC will be specified in a charter. The CEC will maintain the adjudication results in writing.

1.2.2.2 **Hepatic external adjudication**

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

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

1.2.3 SELECTION OF TRIAL POPULATION

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

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the investigator site file (ISF) at the investigational site irrespective of whether they have been treated with an investigational drug or not.
Re-screening of patients who do not meet the inclusion/exclusion criteria will not be permitted, however, assessments may be repeated within the screening period and the latest assessment prior to randomisation must always be used to assess eligibility.

Cohort A will contain 43 patients with heart failure with reduced ejection fraction (HFrEF) and Cohort B will contain 43 patients with heart failure with preserved ejection fraction (HFpEF). Within each cohort patients will be randomised 1:1 to receive either empagliflozin or matching placebo. A drop-out rate of 30% is expected and the total sample size for a cohort may be increased if the drop-out rate is higher than expected (Protocol (1245.148) Section 7.7). Patients with T2DM will be eligible to enter the trial and are expected to account for 30-40% of randomised patients. There are no targets or restrictions on the recruitment of patients with T2DM but randomisation will be stratified according to history of diabetes (Yes/No) to ensure a balance between the arms (see also Protocol (1245.148) Section 7.1).

1.2.3.1 **Main diagnosis for trial entry**

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

Patients who do not meet all of the inclusion criteria or who meet any of the exclusion criteria are not eligible for study participation and are not eligible to receive study medication. Please refer to Protocol (1245.148, version 3.0, dated 14th August 2018) Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

1.2.3.2 **Inclusion criteria**

1. *Chronic heart failure diagnosed at least 3 months before informed consent*
2. *NYHA class II-IV at screening*
3. *Inclusion criterion no longer applicable*

4. *Age ≥ 18 years at screening*
5. *Male or female patients. Women of childbearing potential (WOCBP)[1] must be ready and able to use highly effective methods of birth control per ICH M3 (R2) [R09-1400] that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria are provided in the Protocol (1245.148) Section 4.2.2 and also in the patient information.*
6. *Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial*

Cohort A (HFrEF)

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

Cohort B (HFpEF)

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

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

1.2.3.3 Exclusion criteria

1. *Stroke or transient ischaemic attack (TIA) within 6 months prior to informed consent.*
2. *Any patients with myocardial scars and/or non-viable myocardium in the interventricular septum, unstable angina due to significant coronary artery disease (CAD), or major (in the opinion of the investigator) cardiovascular surgery.*
3. *Any contraindication for MRI, CPET and/or dobutamine stress test in accordance with the institution guidance, including implanted left ventricular assist device (LVAD), implantable cardioverter defibrillator (ICD), cardiac resynchronisation therapy (CRT) or any cardiac device.*
4. *Heart transplant recipient or listed for heart transplant*

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

5. *Cardiomyopathy based on infiltrative diseases (e.g. amyloidosis), accumulation diseases (e.g. haemochromatosis, Fabry disease), muscular dystrophies, cardiomyopathy with reversible causes (e.g. stress cardiomyopathy), hypertrophic obstructive cardiomyopathy or known pericardial constriction*
6. *Moderate to severe uncorrected valvular heart disease, obstructive or regurgitant, or any valvular heart disease expected to lead to surgery in the Investigator's opinion*
7. *Acute decompensated HF (exacerbation of chronic HF) requiring intravenous (i.v.) diuretics, i.v. inotropes or i.v. vasodilators, or LVAD or hospitalisation within 1 week prior to Visit 1 (Screening), or during screening period until Visit 2 (Randomisation)*
8. *Systolic blood pressure (SBP) ≥ 180 mmHg at screening. If SBP >150 mmHg and <180mmHg at screening, the patient is ineligible if receiving 3 or more antihypertensive drugs*
9. *Symptomatic hypotension and/or a SBP < 100 mmHg at Screening*
10. *Atrial fibrillation which is uncontrolled in the opinion of the investigator*
11. *Untreated ventricular arrhythmia with syncope documented within the 3 months prior to informed consent in patients without ICD*
12. *Diagnosis of cardiomyopathy induced by chemotherapy or peripartum within the 12 months prior to informed consent*
13. *Symptomatic bradycardia or second or third degree heart block in need of a pacemaker after adjusting beta-blocker therapy or any other negative inotropic agents, if appropriate*
14. *Chronic pulmonary disease requiring home oxygen, oral steroid therapy or hospitalisation for exacerbation within 12 months prior to informed consent, or significant chronic pulmonary disease in the Investigator's opinion, or primary pulmonary arterial hypertension*
15. *Indication of liver disease, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatase above 3 x upper limit of normal (ULN) as determined at screening*
16. *Impaired renal function, defined as estimated Creatinine Clearance < 30 mL/min (using Cockcroft-Gault formula) or requiring dialysis, as determined at screening*
17. *Haemoglobin < 10 g/dL at screening*
18. *Type 1 Diabetes Mellitus (T1DM)*
19. *History of ketoacidosis*
20. *Major surgery (major according to the investigator's assessment) performed within 3 months prior to informed consent, or scheduled major elective surgery (e.g. hip replacement) within 3 months after Visit 1*
21. *Gastrointestinal (GI) surgery or GI disorder that could interfere with absorption of trial medication in the investigator's opinion*
22. *Any documented active or suspected malignancy or history of malignancy within 6 months prior to informed consent, except appropriately treated basal cell carcinoma of the skin, in situ carcinoma of uterine cervix or low risk prostate cancer (patients with pretreatment PSA <10 ng/mL, and biopsy Gleason score of ≤ 6 and clinical stage T1c or T2a)*
23. *Presence of any other disease than heart failure with a life expectancy of <1 year in the investigator's opinion*
24. *Patients who must or wish to continue the intake of restricted medications (see Protocol (1245.148, version 3.0, dated 14th August 2018, Section 4.2.2) or any drug considered likely to interfere with the safe conduct of the trial*
25. *Patients with requirement for treatment with empaglifozin according to local standard of care*
26. *Treatment with any SGLT-2 inhibitor or combined SGLT-1 and 2 inhibitor within 1 week prior to informed consent or during screening period until Visit 2 (Randomisation)*
27. *Currently enrolled in another investigational device or drug study, or less than 30 days between randomisation and ending another investigational device or drug study, or*

receiving other investigational treatment(s). Patients participating in a purely observational trial will not be excluded.

28. *Known allergy or hypersensitivity to empagliflozin or other SGLT-2 inhibitors*
29. *Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable trial subject or unlikely to complete the trial*
30. *Women who are pregnant, breastfeeding, or who plan to become pregnant while in the trial*
31. *Any clinical condition that would jeopardise patients safety while participating in this trial, or may prevent the subject from adhering to the trial protocol*

1.3 Schedule of Study Assessments

1.3.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the Figure 1-2. Schedule of Assessment. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule calculated from the date of randomisation. The trial medication packs contain sufficient medication to allow for these time windows.

1.3.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Please refer to the Figure 1-2. Schedule of Assessment and Protocol (1245.148) Protocol (1245.148) Section 5 for details of the procedures performed at each visit.

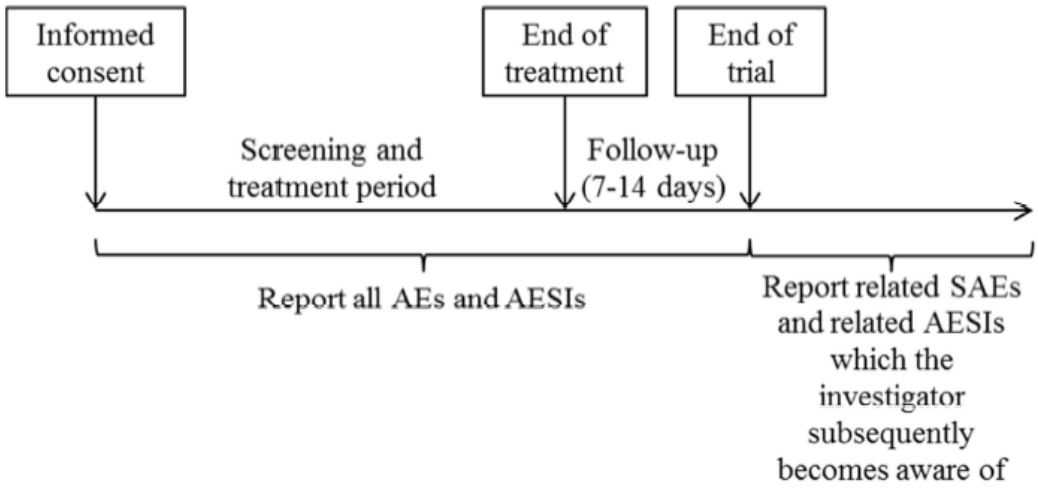
Figure 1-2. Schedule of Assessment

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

* The follow-up visit must be completed for all randomised patients, including those who withdraw prematurely (see *Protocol (1245.148)* Section 3.3.4.1), unless the patient has withdrawn consent to follow-up. The follow-up visit is expected to be performed via a telephone call, but a clinic visit may be performed at the discretion of the investigator.
** Patients must be fasting at Visits 2 and 4. See *Protocol (1245.148)* Section 6 for restrictions on the order of assessments during Visit 2 and Visit 4.

1 If echocardiogram and/or electrocardiogram is/are performed as part of standard care within 3 months prior to informed consent, and written results are available, the assessment does not need to be repeated during the screening visit and the existing scan(s) can be used to assess eligibility.
2 The following assessments do not need to be repeated at visit 2 if performed within the previous 7 days; Safety laboratory tests (urine and blood), Echocardiogram, Electrocardiogram, Vital signs, Weight.
3 At Visit 3 only a urine test for ketone bodies is required.
4 For women of childbearing potential either a urine or serum pregnancy test is required.
5 Daily dosing should continue until the last dose is taken on the day of Visit 4.
[redacted]

Figure 1-3. Requirements for Adverse Event Collection



1.3.2.1 **Screening period**

Following informed consent, the patient will undergo visit 1/screening assessments as indicated in the Figure 1-2. Schedule of Assessment. The assessments must all fall within the acceptable screening visit window but do not need to be performed on the same day. The patient should be registered in IRT as a screened patient.

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

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

Re-screening is not allowed in this trial. Screening assessments may be repeated as long as they fall within the screening visit window. If more than one screening assessment is available, the latest assessment prior to randomisation must be used to assess eligibility.
If the patient meets the eligibility criteria during screening (Visit 1), Visit 2 should be scheduled. Any baseline conditions which are present at Visit 1 should be reported in the eCRF.

1.3.2.2 **Treatment period**

Visit 2 (Randomisation)

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

If the patient is eligible for trial participation, the patient is randomised using IRT and treatment is allocated. The visit 2 assessments as listed in the Figure 1-2. Schedule of Assessment are then performed. Some assessments do not need to be repeated if performed during the last 7 days as part of the screening visit; see Figure 1-2. Schedule of Assessment for details.
The patient should be fasting in preparation for the blood sampling at this visit (no food or liquid except water for at least 6 hours prior to sampling). The following rules apply for the order of assessments at this visit;

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

Visit 3 (Day 15)

The patient will return to the clinic for visit 3 on day 15 ± 1 day of treatment. The purpose of this visit is to check patient safety, to check medication compliance and to perform limited assessments. Assessments to be performed are indicated in the Figure 1-2. Schedule of Assessment.

Visit 4 (Day 84)

Visit 4 will take place on Day 84 of treatment, which is also the last day of treatment. If the visit cannot be scheduled for Day 84, it should be scheduled as close as possible, but within 4 days and the patient should continue to take the medication daily until the day of the visit. All Visit 4 assessments must be performed within 48 hours of the last dose, regardless of which day this is. The patient should be asked to return all remaining medication during this visit.
The assessments to be performed at Visit 4 are indicated in the Figure 1-2. Schedule of Assessment. The patient should be fasting in preparation for the blood sampling at this visit (no food or liquid except water for at least 6 hours prior to sampling). The following rules apply for the order of assessments at this visit;

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

1.3.2.3 Follow up period and trial completion

A follow up visit (Visit 5) will be performed 7-14 days after the last dose of trial medication. The expectation is that this visit will be performed via a telephone call, but where appropriate, a clinic visit may be scheduled. The assessments to be performed at Visit 5 are indicated in the Figure 1-2. Schedule of Assessment.

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

1.3.2.4 Early discontinuation of trial medication

See Protocol (1245.148) Section 3.3.4.1 for procedures to be followed in case a randomised patient does not reach Visit 4 for any reason.

1.4 Changes to the Planned Analysis

The main statistical model defined in the protocol does not include baseline response as a covariate, as baseline response is usually predictive of response the following changes to the protocol have been introduced:

- A sensitivity analysis of the primary efficacy endpoint has been included that includes baseline in an analysis of covariance (ANCOVA) model. Note the main analysis of the primary efficacy endpoint remains as defined in the protocol (i.e. without the addition of baseline as a covariate).
- The analysis of variance (ANOVA) model will be replaced by an ANCOVA model for all applicable exploratory endpoints in order to fit baseline response as a covariate.

2 Endpoints

Absolute change (Δ): will be defined as the value obtained at Week 12 minus value obtained at Baseline [Δ = Week 12 (Value) -Baseline (Value)]. Positive value represents an increase from baseline. Negative value represents a decrease from Baseline.

2.1 Primary Endpoints

2.1.1 Definition and Derivation of Primary Endpoint

The primary endpoint is the change from the baseline to week 12 in PCr/ATP ratio in resting state measured by ^{31}PMRS after treatment with Empagliflozin or matching placebo.

2.1.2 Primary Hypothesis under Investigation

The null hypothesis is that for patients in each of the HFrEF and HFpEF cohorts, the change from the baseline to week 12 in PCr/ATP ratio in resting state measured by ^{31}P Magnetic Resonance Spectroscopy (MRS) after treatment with Empagliflozin is not different from matching placebo. The alternative hypothesis is that the change is different.

2.1.3 Handling of Outliers and Missing Data

For the primary outcome, patients who do not have a measurement taken at baseline and week 12 will be excluded from the primary analysis. For primary analyses, missing efficacy data will not be imputed.

Any outliers will be identified and documented prior to the database lock and unblinding. Cases that are visually "extreme" will be assessed for possible influence on the results and conclusions by comparing results from analyses with or without outliers. Any discrepant results from the two analyses will be reported and discussed in the CTR and publication manuscripts.

2.2 Secondary Endpoints

2.2.1 Definitions and Derivations of Secondary Endpoints

No secondary endpoints are defined for this trial.

2.2.2 Secondary Hypotheses under Investigation

No secondary hypotheses are defined for this trial.

[redacted]

[redacted]

3 Analysis Sets/Populations

The following analysis sets are defined in this trial.

3.1 Per-protocol Set (PPS)

The primary endpoint analysis will be performed using the per protocol (PP) set of patients having a valid PCr/ATP ratio measurements available at baseline and week 12, and not having an important protocol violation relevant to the primary endpoint. Protocol violations will be reviewed by the study team before the database lock to determine which violations disqualify a patient from the Per-Protocol analysis. A preliminary list of criteria that may disqualify a patient from the Per-Protocol analysis are presented in Section 9.2 in the SAP. The list is suggestive and subject to change at the final Blinded Report Planning Meeting (BRPM) pre-lock review.

3.2 Randomised Set (RS)

This set will include all subjects who are randomised to study treatment. The RS set will be employed for a sensitivity analysis to check for an unbiased estimation of the primary endpoint result if a substantial number of protocol violations resulted in a reduced sample size used for the primary endpoint estimates. The analysis of exploratory endpoints will be performed on the RS of patients with available data.

3.3 Treated set (TS)

All randomised and treated patients will be included in the safety analysis and safety summaries will be presented by actual treatment received.

4 General Issues for Statistical Analysis

Patients randomised into the incorrect stratum, cohort (HFrEF or HFpEF) and/or history of diabetes (Yes or No) will be analysed according to the stratum that they should have been randomised into.

The summary statistics and statistical estimates (effect sizes) will be presented to one decimal place greater than the raw data collected. All p-values will be rounded to 4 decimal places. All estimates of treatment effects will be presented with corresponding 95% confidence intervals.

For parameters which are known to follow a log-normal distribution (e.g. NT-proBNP and BNP), the geometric mean and geometric coefficient of variation will be used instead of the mean and standard deviation for any by visit descriptive summaries. Changes from baseline will be presented as geometric mean ratios.

4.1 Analysis Software

All statistical analyses will be conducted using SAS 9.4, software. All the statistical analyses outputs/results will be reviewed and validated by an independent DTU statistician.

4.2 Multiplicity, Multiple Comparisons and Interim Analyses

If recruitment is different between the cohorts such that one cohort's last patient out visit is considerably earlier than the last patient out of the other cohort, an interim analysis may be planned in order to report the data the completed cohort. For this interim analysis only the completed cohort will be unblinded.

A single hypothesis is being tested for each cohort for a single primary efficacy endpoint. The analysis of all other endpoints will be considered exploratory in nature with nominal p-values. All p-values will be two-sided at an alpha-level of 0.05.

[redacted]

5 Statistical Methodology

A table of contents for all outputs that will be produced along with supporting templates will be provided in separate documentation.

5.1 Disposition of Patients

All patients in the screened set (signed informed consent) will be included in the summary of patient disposition. Frequencies and percentages of the total number of patients screened, randomised, treated, prematurely discontinued treatment (along with reason for discontinuation) and status at trial completion will be summarised in tabular forms for each cohort and for both cohorts overall.

A summary of the frequency and percentage of patients by treatment group will be produced for the randomised, treated and per-protocol analysis sets. Summaries by cohort and overall will be produced.

5.2 Demographic and Baseline Characteristics

The screening demographic and the clinical characteristics will be tabulated and summarised by the treatment group. The demographic and baseline data will include gender, age, race, weight, height, SBP, DBP, T2DM, history of atrial fibrillation, alcohol use, smoking, heart rate, vital signs medical history, and other cardiac parameters (EF, BNP) measured at screening.

5.3 Primary Endpoint Analysis

5.3.1 Primary Efficacy Analysis

The primary efficacy endpoint of change from baseline to week 12 in PCr/ATP will be analysed for each cohort (HFrEF and HFpEF) separately, to test the hypothesis detailed in Section 2.1.2.

The analytical procedure will include a descriptive summary and a formal (inferential) statistical summary, ANOVA, for the primary endpoint hypothesis testing. Plots of individual patient changes from baseline to week 12 will be produced by treatment group and cohort, including the mean change also.

Formal analysis

The formal statistical analysis will employ an Analysis of Variance (ANOVA) model to test the primary hypothesis for each individual cohort using the following for the model inputs:

- Response (outcome) variable is defined as:
  The change (PCr/ATP absolute change) from baseline to week 12 is calculated for each patient by subtracting each patient's baseline PCr/ATP measurement from the 12 weeks measurement.

- Factors:
  Treatment (Empagliflozin vs. Placebo), History of diabetes (Yes/No) and History of atrial fibrillation *(Yes/No)*

The null hypothesis of no difference in change between the treatment and placebo groups will be tested by an ANOVA on the PCr/ATP ratio absolute change using treatment (empagliflozin vs. placebo), history of diabetes (yes vs, no) and history of atrial fibrillation (yes vs no) as fixed effects. If the treatment main effect is significant then we reject the null hypothesis.

The formal model will be specified in SAS as follows (equivalent to ANOVA):

PROC MIXED data=values cl method=reml covtest;
CLASS af diab trt;
MODEL endpt = af diab trt / ddfm=kr solution;
LSMEANS trt / cl diff om alpha=**0.05**;
RUN;

Though the primary endpoint is regarded to generally be normally distributed some model checking will be performed. The model adequacy assessment will be based on the normality of residuals, homogeneity of variance between groups and homoscedasticity. Any violation of the model assumptions will be investigated and ratified accordingly and will be reported in the clinical trial report.

[redacted]

5.4 Secondary Endpoint Analyses

Not applicable as no secondary endpoints defined for the study.

[redacted]

6 Safety and Tolerability Analysis

All safety and tolerability summaries will be produced on the treated set of patients.

6.1 Drug Exposure

Empagliflozin 10 mg for 12 weeks, see for the drug exposure and accountability plans throughout the trial (see also Protocol (1245.148) Section 4.0). Both empagliflozin and placebo exposure will be tabulated, duration of exposure will be calculated from the day of first exposure to the day of last exposure, ignoring any missed doses between. . Summaries of exposure by days and weeks will be produced. Cumulative dose (mg) will be summarized using descriptive statistics, where cumulative dose is the actual dose taken summed across all visits, missed days will be counted as 0 mg. The number of missed doses will also be tabulated.

6.2 Adverse Events and Tolerability

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e., all adverse events occurring between the start of treatment and end of the residual effect period, 7 days after the last dose of medication. Adverse events that start before first drug intake and deteriorate during the treatment period will also be considered as 'treatment-emergent'. All AEs will be listed, according to whether the AE start date occurred during the screening period, treatment period, or during the follow-up period.

The safety analyses will be purely descriptive statistics *(number and percentage, n (%))* and will be based on the current version of Dictionary of Drug Regulation (MedDRA) coding system and display in tables and data listings using SOC and preferred term. The analyses will be provided for each cohort and also pooled across all cohorts. No hypothesis testing is planned. An overall summary of AEs will be presented, in addition the following tables will be produced by MedDRA SOC and preferred term:

- All AEs
- AEs by severity
- Serious AEs
- Drug-related AEs
- AEs leading to treatment discontinuation

In addition a summary of all AEs by investigator-defined category and MedDRA preferred term will be produced, the following categories will be included:

- Hypoglycaemic event
- Genital infection
- Acute pyelonephritis
- Sepsis
- Urinary tract infection
- Bone fracture
- Hepatic injury
- Ketoacidosis (metabolic acidosis, ketoacidosis, diabetic ketoacidosis)
- Decreased renal function
- Other

Further details on the specific AEs of hypoglycaemia, genital infections, acute pyelonephritis, sepsis, bone fractures and ketoacidosis will be listed. Additional summaries of these specific AEs and other specific AEs (e.g. volume depletion) may be produced dependent upon the frequency of occurrence.

6.3 Laboratory Data

Descriptive statistics (Mean (SD) and Median (IQR)) of the laboratory data will be presented. The presentation will cover data collected at screening or baseline to week 12 (screening to treatment period). Summaries of actual values at baseline and last value on-treatment along with the change from baseline will be tabulated for the individual parameter. Baseline data will be taken as the last available laboratory measurement on or prior to the day of starting study treatment. The individual patient values profile over time will plotted. The marginal means of individual parameter will also be included in these plots. Laboratory values will be compared to their reference ranges at baseline and the last measurement on-treatment. Frequency tables will summarise the number of patients with potentially clinically significant abnormalities (as defined by BI project standards). Laboratory measurements taken up to 3 days after the last administration of randomised study treatment will be considered as on-treatment.

6.4 Vital Signs, Electrocardiogram, and Other Safety Assessments

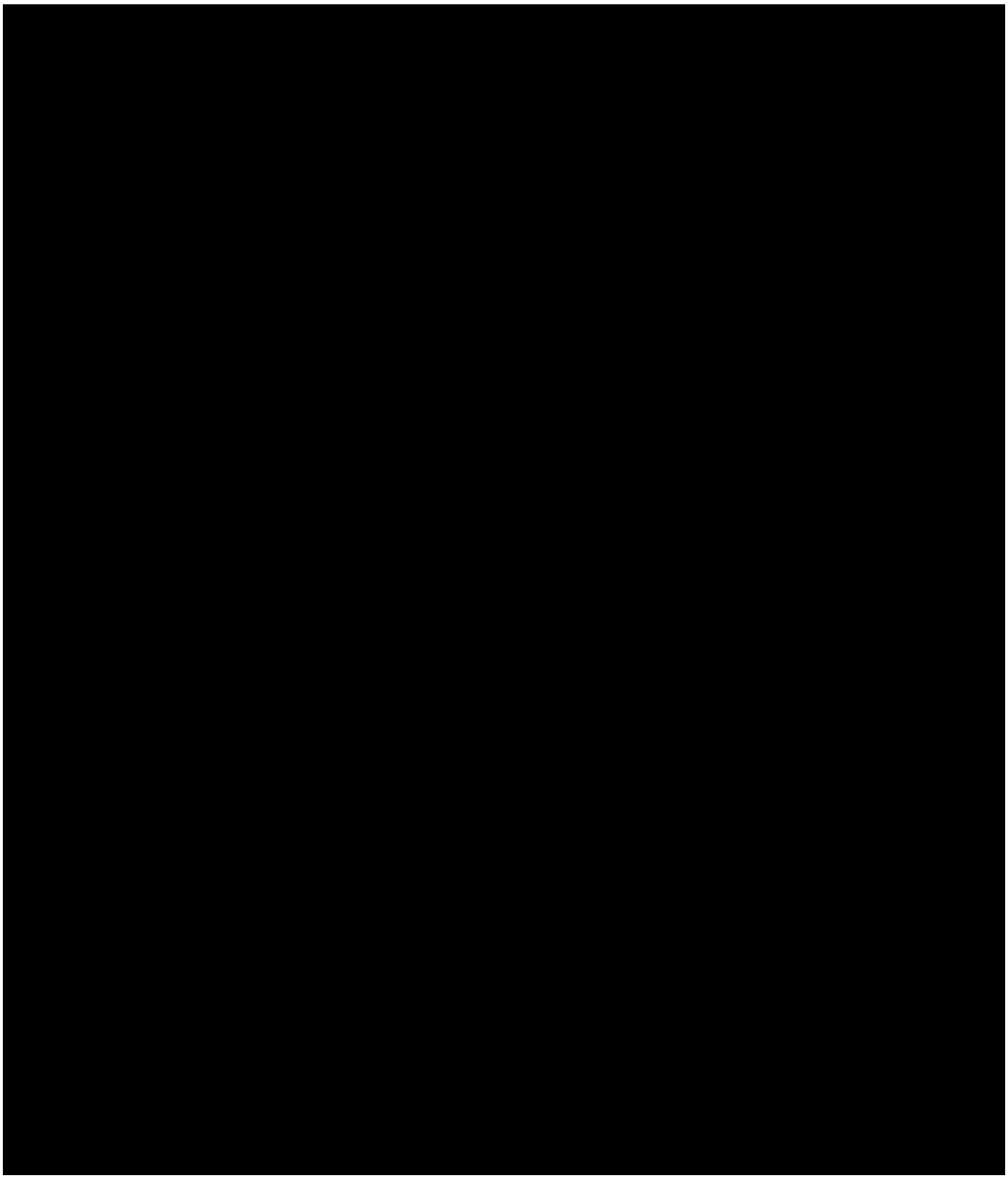
Vital signs, ECG and other safety assessments will be summarised descriptively.

7 Data Handling Conventions

7.1 Data Quality Assurance and Monitoring

For the data monitoring and quality assurance procedures for the study, see the study in Protocol (1245.148) Section 8.2 – Section 8.7

7.2 Data Transformations



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[redacted]

[redacted]

8 References

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9 Appendices

9.1 Appendix 1: Reporting Conventions

- *This section clarifies the reporting conventions adopted or utilized in the SAP related statistical operations that could be utilized in the reporting of the study.*
- *All tables, listings and figures will be presented in landscape orientation unless there is a specific reason to use portrait orientation.*

9.2 Appendix 2: Important Protocol Deviations (iPDs)

The IPDs listing below is taken from the Medical and Quality Review Plan document, Version 2.0, dated 27th February 2018, for Study 1245-0148. The listing is tentative and subject to a review before the data lock. The updated version of the IPDs listing in the Medical and Quality Review Plan document will be used for the statistical analyses and the CTR.

Category / Code		Description	Requirements	Excluded from
A		Entrance criteria not met		
A1		Target indication not met		
	A1.06	No chronic HF NYHA class II-IV	Inclusion criterion #2 violated	<None or PPS>
	A1.07	Conditions on ejection fraction (EF) violated	Inclusion criterion #7 for Cohort A, #10 for Cohort B violated	PPS
	A1.08	Conditions on NT-proBNP violated	Inclusion criterion #8 for Cohort A, #11 for Cohort B violated	PPS
	A1.09	Conditions on HF violated	Inclusion criterion #1 and #9 for Cohort A, or #1 and #12 for Cohort B violated	PPS
A2		Inclusion criteria not met		
	A2.02	Age out of range	Inclusion criterion #4 violated	None
	A2.08	Specific inclusion criterion for women of child-bearing potential violated	Inclusion criterion #5 violated	None
A3		Exclusion criteria not met		
	A3.44	Patient with unstable conditions	Exclusion criteria #1, #2, #4, #7, #11, #14, #15, #16 or #20 violated	None
	tba	All other in/exclusion criteria		Individual discussion
B		Informed consent		
	B1	Informed consent not available/not done	Informed consent date missing or inclusion criterion #6 violated	PPS
	B2	Informed consent too late	Informed consent date was after Visit 1	None
C		Trial medication and randomisation		
C1		Încorrect trial medication		

	C1.02	Incorrect trial medication taken	Medication from wrong treatment arm taken for more than 20% of the overall treatment duration Can only be finally judged after data base lock (DBL) since unblinding information is required.	None
C2		Randomisation not followed		
	C2.01	Treated without randomisation	Patient treated according to eCRF, but not randomised according to IVRS.	None
C3		Non-compliance		
	C3.01	Non-compliance with study drug intake	Overall study treatment compliance outside 80% and 120% (exclusive) or study treatment compliance below 80% Missing compliance will be considered iPD.	None
C4		Medication code broken		
	C4.01	Medication code broken at site without just cause	Medication code was broken for no valid reason. Final decision at the DBL meeting based on medical judgement.	None
D		Concomitant medication		
	D1.02	Use of other investigational drug	Review of eCRF for prohibited medication. Final decision at the DBL meeting based on medical judgement.	None
	D2.01	Use of protocol defined prohibited medication during treatment period	Use of SGLT-2 or combined SGLT-1 and 2 – inhibitors after randomization until the follow-up visit.	None
E		Missing data		
	E1.05	No baseline resting ^{31}P MRS result	No valid baseline PCr/ATP ratio at resting and dobutamine stress.	PPS
	E1.06	No baseline stress ^{31}P MRS result	No valid baseline PCr/ATP ratio at dobutamine stress.	PPS
F		Other		
	F1.02	Other PD related to safety only	Manually detected, safety related protocol deviations Final decision at the DBL meeting based on medical judgement.	None
	F1.03	Other PD related to primary endpoint	Final decision at the DBL meeting based on medical judgement.	PPS

	F1.04	Other PD related to patient rights	Manually detected protocol deviations related to patient rights Final decision at the DBL meeting.	None

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Approval-Biostatistics	[redacted]	21 Apr 2020 14:15 CEST

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Meaning of Signature	Signed by	Date Signed