- **Protocol number: D1680C00016**
- **Document title: A 24-Week, Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Study to Investigate the Effects of Saxagliptin and Sitagliptin in Patients with Type 2 Diabetes Mellitus and Heart Failure**
- **NCT number: NCT02917031**
- **Version number: 1.0**
- **Date of the document: 14 October 2020**

AstraZeneca

Statistical Analysis Plan

Study Code	D1680C00016
Edition Number	1.0
Date	13 October 2020

MEASURE-HF

MEchAniStic evalUation of glucose-loweRing strategiEs in patients with Heart Failure

A 24-Week, Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Study to Investigate the Effects of Saxagliptin and Sitagliptin in Patients with Type 2 Diabetes Mellitus and Heart Failure

MEASURE-HF

MEchAniStic evalUation of glucose-loweRing strategiEs in patients with Heart Failure

A 24-Week, Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Study to Investigate the Effects of Saxagliptin and Sitagliptin in Patients with Type 2 Diabetes Mellitus and Heart Failure

Study Statistician

PPD

Date

MEASURE-HF

MEchAniStic evalUation of glucose-loweRing strategiEs in patients with Heart Failure

A 24-Week, Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Study to Investigate the Effects of Saxagliptin and Sitagliptin in Patients with Type 2 Diabetes Mellitus and Heart Failure

AZ Study Statistician

PPD _____ Date _____

AZ Global Project Statistician

PPD _____ Date _____

TABLE OF CONTENTS PAGE

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
AEoSI	Adverse events of special interest
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AST	Aspartate transaminase
BMI	Body mass index
BP	Blood pressure
BPPS	Biomarkers per protocol set
BSA	Body surface area
cm	centimetre
CRF	Case report form
CV	Cardiovascular
CVD	Cardiovascular disease
ECG	Electrocardiogram
EPS	Enrolled Patients Set
ETD	Early treatment discontinuation
FAS	Full Analysis Set
FPG	Fasting plasma glucose
Hb	Hemoglobin
HbA1c	Hemoglobin A1c
Hct	Hematocrit
hHF	Hospitalization for Heart failure
HF	Heart failure
HR	Heart rate
IP	Investigational Product
IWRS	Interactive Web Response System
LOCF	Last-Observation-Carried-Forward
LVEDV	Left Ventricular End Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
LVESV	Left Ventricular End Systolic Volume
LVM	Left ventricular mass
MAR	Missing at random
MNAR	Missing not at random
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic Resonance Imaging
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association
PDs	Protocol deviations
PK	Pharmacokinetic
PPS	Per Protocol Set

Abbreviation or special term	Explanation
PT	Preferred Term
PV	Plasma Volume
IPDs	Important Protocol deviations
SAE	Serious adverse event
SAF	Safety Analysis Set
SAS	Statistical Analysis Software
SCAR	Severe cutaneous adverse reaction
SD	Standard deviation
SE	Standard error
SGLT-2	Sodium-glucose cotransporter 2
SI	International System of Units
SOC	System Organ Class
SU	Sulfonylurea
T2DM	Type 2 Diabetes mellitus
VIVIDD	Vildagliptin in Ventricular Dysfunction Diabetes

AMENDMENT HISTORY

Date	Brief description of change
Date of signature	New document

INTRODUCTION

This is a multicenter, randomized, double-blind, parallel group, placebo-controlled study to investigate the effects of saxagliptin on cardiac dimensions and function, in patients with T2DM and HF with reduced systolic function from both ischemic and non-ischemic causes.

Approximately 330 patients with documented LVEF ≤45% and NT-proBNP >300 pg/mL will be randomized in equal proportions (110 patients per group) to treatment with saxagliptin, sitagliptin, or placebo.

MRI to evaluate cardiac dimensions, and function will be performed at baseline (≤ 7 days prior to randomization), and Week 24 (≤7 days Prior to Week 24) for all study patients. The Week 24 MRI will provide the primary endpoint data. The MRI evaluations will be performed according to a standard protocol and will be centrally read by a core laboratory.

An independent Events Adjudication Committee will be appointed and will adjudicate all CV events (including hHF).

Analysis of PK data is not part of this statistical analysis plan and will be reported separately from the clinical study report.

This Statistical Analysis Plan is based upon the
Clinical Study Protocol, Version 5.0 (10 February 2020)

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

Primary Objective:	Outcome Measure:
To exclude an increase in left ventricular end diastolic volume (LVEDV) index of greater than 10% of the overall baseline value (non-inferiority margin) in patients with T2DM and HF treated with saxagliptin for 24 weeks, compared to placebo	Change from baseline in LVEDV index measured by MRI at 24 weeks

1.1.2 Secondary objectives

Secondary Objective:	Outcome Measure:
Evaluate the effects of saxagliptin compared to placebo on LVESV index, LVEF, and LVM after 24 weeks in patients with T2DM and HF	Change from baseline in LVESV index, LVEF, and LVM measured by MRI at 24 weeks
Evaluate the effects of saxagliptin compared to placebo on NT-proBNP after 24 weeks of treatment	Change from baseline in NT-proBNP after 24 weeks of treatment

1.1.3 Safety objectives

Safety Objective:	Outcome Measure:
To assess the safety and tolerability of saxagliptin and sitagliptin treatment in patients with T2DM and HF	• Incidence of adverse events (AEs), serious adverse events (SAEs), AEs of special interest • Collection of clinical chemistry/hematology parameters • Vital signs • Physical examination • Incidence of independently adjudicated Cardiovascular (CV) events [death, myocardial infarction (MI), stroke, and hospitalization for heart failure (hHF)]

1.1.4 Exploratory objectives

Exploratory Objective:	Outcome Measure:
Evaluate the effects of sitagliptin compared to placebo on LVEDV index, LVESV index, LVEF, and LVM after 24 weeks of treatment in patients with T2DM and HF	Change from baseline in LVEDV index, LVESV index, LVEF, and LVM measured by MRI at 24 weeks
Evaluate the effects of saxagliptin at Weeks 6 and 12 and sitagliptin at 6, 12, and 24 weeks, compared to placebo on NT-proBNP	Change from baseline in NT-proBNP after 6, 12, and 24 weeks
Evaluate the effects of saxagliptin and sitagliptin, on plasma volume at 6, 12, and 24 weeks	Percent change from baseline in plasma volume using the Strauss formula after 6, 12, and 24 weeks
Evaluate the effects of saxagliptin and sitagliptin on changes from baseline body weight compared to placebo at 12 and 24 weeks	Change from baseline in body weight at 12 and 24 weeks
Evaluate the effects of saxagliptin and sitagliptin on changes from baseline HbA1c compared to placebo at 12 and 24 weeks	Change from baseline in HbA1c at 12 and 24 weeks

Collect and analyze blood and urine samples for changes from baseline in CCI [redacted] at 6, 12, and 24 weeks. Samples will be collected for additional biomarkers that may be analyzed at the Sponsor's discretion	Change from baseline of blood and urine biomarker values at 6, 12, and 24 weeks
Collect PK samples for analysis of plasma concentrations of saxagliptin and its major metabolite, 5-hydroxy saxagliptin; , and sitagliptin for PK/pharmacodynamic (PD) modelling at 6, 12, and 24 weeks in a subset of at least 150 patients	Plasma concentration in PK samples • Saxagliptin and its major metabolite, 5-hydroxy saxagliptin • Sitagliptin

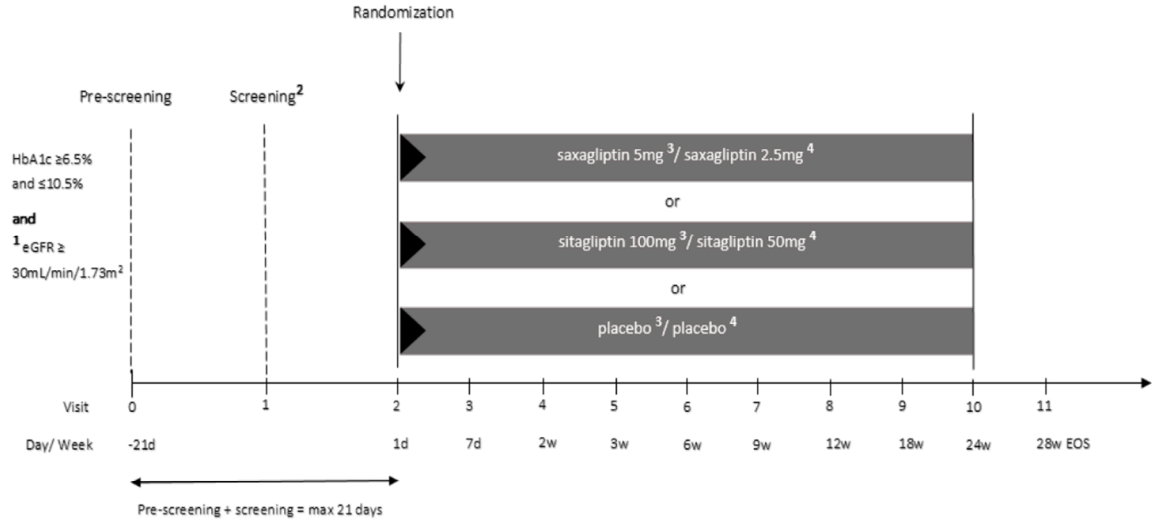
1.2 Study design

Study D1680C00016 is a 24-week, multicenter, randomized, double-blind, parallel group, placebo-controlled study to evaluate study objectives and safety of therapy with saxagliptin, and sitagliptin, compared to placebo in adult patients with T2DM and HF with abnormal systolic function from both ischemic and non-ischemic causes, who have a diagnosis of Type 2 DM based on current ADA guidelines and documented LVEF ≤45% and NT-proBNP >300 pg/mL.

Approximately 330 patients will be randomized in equal proportions (110 patients per group) to treatment with saxagliptin, sitagliptin, or placebo. For patients with an eGFR ≥50 mL/min/1.73 m2, the doses of the active treatments are as follows: saxagliptin 5 mg and sitagliptin 100 mg. For patients with an eGFR <50 mL/min/1.73 m2, the doses of the active treatments will be adjusted as follows: saxagliptin 2.5 mg and sitagliptin 50 mg.

The study will comprise pre-screening and screening periods, a 24-week randomized treatment period and a 4-week follow up period. After randomization, patients will visit the study site for study assessments at Weeks 2, 6, 12, 18, and 24. Follow-up telephone calls will be conducted at Day 7, Week 3, and Week 9. Patients who complete the study will be asked to return for an end-of-study visit at Week 28. The schedule of study assessments is shown in Study flow chart (Figure 1) in the clinical study protocol.

Figure 1 - Study Design



[1] The proportion of randomized patients with an eGFR of ≥30 and <50 mL/min/1.73 m2 will be limited to 30% (max of 99 patients)

[2] A patient can be enrolled to screening as soon as laboratory pre-screening results for HbA1c and eGFR are available and it is determined that the values meet the inclusion/exclusion criteria

[3] For patients with estimated GFR ≥ 50mL/ min/ 1.73m²

[4] For patients with estimated GFR < 50 mL/ min/ 1.73 m²

1.3 Number of patients

Approximately 330 patients with T2DM and HF with abnormal systolic function from both ischemic and non-ischemic causes, who have a diagnosis of Type 2 DM based on current ADA guidelines will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups (110 patients each arm):

Arm 1: Saxagliptin

Arm 2: Sitagliptin

Arm 3: Placebo

Sample size estimate

The comparison of saxagliptin versus placebo in LVEDV index is used to estimate sample size. The mean change from baseline in LVEDV index at Week 24 will be assessed comparing saxagliptin versus the placebo treatment group. The MRI analysis will claim non-inferiority for the LVEDV index if the upper bound of the 95% confidence interval (CI) for the adjusted mean treatment difference between saxagliptin and placebo is less than the non-inferiority margin, which will be taken as 10% of the overall (all treatments combined) baseline mean value. For purposes of the sample size calculation, this number will be assumed to be 6.5 mL/m^2.

To demonstrate non-inferiority of saxagliptin compared to placebo for the change from baseline to Week 24 in LVEDV index within a non-inferiority margin of 6.5 mL/m^2, assuming a standard deviation (SD) of 15 mL/m^2, and at a 1-sided significance level of 0.025, approximately 88 patients will be needed in each treatment group to provide approximately 80% power (given a true difference of zero between saxagliptin and placebo). Assuming that 20% of patients will be missing an endpoint assessment, a total of approximately 330 patients (110 patients in each of the 3 treatment groups) must be randomized.

The non-inferiority margin estimate for the sample size calculation for LVEDV index is based on data from Foster et al 1998 [1], where the baseline LVEDV index is 65 ±13 (mean ±SD) mL/m^2. To exclude an increase in LVEDV index (relative to placebo) of greater than 10% of the baseline, the change seen with vildagliptin in LVEDV in the VIVIDD study, the non-inferiority margin for these calculations is equivalent to 6.5 (65 × 0.10) mL/m^2.

2. ANALYSIS SETS

2.1 Definition of analysis sets

There are six analysis (population) sets defined below for this study. Analysis sets will be finalized prior to unblinding of the study.

2.1.1 Enrolled patients set

The enrolled patients set (EPS) will consist of all patients who sign informed consent. This data set will be used to summarize the patient disposition data.

2.1.2 Full analysis set

The full analysis set (FAS) will be defined as all randomized patients who take at least one dose of the study medication. Analysis of the FAS will be based on the randomized treatment.

2.1.3 Per protocol set

The per protocol set (PPS) will be defined as all FAS patients without any important protocol deviation (IPD) that might affect the analyses for the primary and secondary MRI endpoints for the whole patient profile including baseline. Patients with any IPD affecting post-baseline MRI values will partially be excluded from the per protocol MRI analyses for their post-baseline measurements.

Treatment exposure less than 20 weeks

The clinical study protocol defines the analysis parameters for patients after a study treatment of 24 weeks. Patients who discontinued the study treatment earlier than 20 weeks after their individual first dose will be considered having a major impact on the primary endpoint, and will therefore also be partially excluded from the per protocol MRI analyses for their post-baseline measurements.

The criteria for important protocol deviations are detailed in Appendix 3.

2.1.4 Biomarkers per protocol set

The Biomarkers per protocol set (BPPS) will be defined as all FAS patients without any important protocol deviation (PD) that might affect the analyses for the secondary endpoint for N- Terminal Pro-Brain Natriuretic Peptide for the whole patient profile including baseline. Patients with any IPD affecting post-baseline NT-proBNP values will partially be excluded from the per protocol analyses for their post-baseline measurements.

The criteria for important protocol deviations are detailed in Appendix 3.

2.1.5 Safety analysis set

The safety analysis set (SAF) will be defined as all randomized patients who received at least one dose of study medication. This data set will be used to summarize safety data (AE, SAE, AEoSIs, adjudicated events, vital signs and laboratory parameters), and patient demography and their baseline data as well.

If there is a difference between the SAF and FAS, baseline and demography data will also be presented for the FAS.

Data in this data set will be analysed based on randomised treatment, except in cases where a patient received a different treatment for the entire course of his/her participation in the treatment period. In this case, safety data for such a patient will be analysed based on the first treatment the patient actually received.

2.1.6 PK analysis set

The PK analysis set will include all randomized patients for whom any plasma concentrations data were recorded.

2.2 Violations and deviations

IPDs are defined as those important deviations from the protocol likely to have an impact on the study objectives and/or safety of study treatments.

Protocol deviation monitoring

During study conduct, protocol deviations will be closely monitored and identified from two sources:

- IMPACT monitoring – These are manually entered protocol deviations identified by the monitor during study conduct.
- Programmed protocol deviations – These are deviations generated by execution of programs written using the predefined deviator descriptions in the SAP, see Appendix 3

The reports or information collected from IMPACT monitoring report will be reviewed and assessed periodically during study conduct by AZ study team and documented in EXCEL spreadsheet.

Protocol deviation reporting

Protocol deviations will be reviewed in a blinded fashion by the study team prior to database lock. All decisions to exclude patients and/or data from the Full Analysis Set (to form the Per-Protocol Analysis Set) will be made prior to the unblinding of the study and agreed by the study team. Protocol deviations that are determined to affect the primary analysis results are deemed IPDs.

Appendix 3 specifies the criteria for IPDs for patients to be excluded from the per protocol analysis. Patients having IPDs will be summarized and listed by treatment group and overall. The list of protocol deviations (including IPDs) will be compiled separately and finalised prior to DBL.

Potential Unblinding of treatment code to AstraZeneca Monitors

Mid March 2018 The Global Study Team made an incidental finding: Unblinding data was shown in the IWRS system where the Study Drug Accountability is recorded. It was possible to see the actual treatment allocation in the returned/accounted bottle after drilling down two levels in the module. This module was only accessible to AZ Monitors and the Global Operational Study Team. No AZ Monitors have reported that the unblinded information has been visible. This module was reportedly used only rarely during study conduct. Paper logs were used instead. Access to the module was removed immediately upon discovery of the flaw in the module. In response to queries no investigator or staff has claimed to have seen unblinded codes. The Quality issue has been investigated and managed according to AZ SOPs on how to handle a Quality Issue. A CAPA has been established.

The integrity of the study is not at risk because the primary and secondary endpoint data were not biased as the adjudicators do not get clinical data and so are still blinded to treatment. However, a subgroup analysis will be performed by the status of the patients being potentially unblinded or not, see section 4.2.6. Patients, who were randomized before the date of the corrective action on 15 March 2018 are stated as being potentially unblinded. The remaining patients were not unblinded.

3. PRIMARY AND SECONDARY VARIABLES

3.1 General principles taken for analysis variables

3.1.1 Study Day Definition

For the purposes of the data summaries, Study Day 1 is defined as the first date of study treatment. For patients who were randomized but no actual treatment data is available, the

Day 1 will be the date of randomization. For visits (or events) that occur on or after first date of study treatment, study day is defined as:

(date of visit [event] - first date of study treatment + 1).

For visits (or events) that occur prior to first date of study treatment, study day is defined as:

(date of visit [event] - first date of study treatment).

There is no Study Day 0.

For listings (such as for AEs/SAEs that include the derivation of "days since last dose"), this is defined as:

(event date - date of last dose).

Events that occur on the same day as the last dose of study treatment will therefore be described as occurring zero days from the last dose of study treatment.

3.1.2 Duration of Type 2 Diabetes

Duration of T2DM is calculated as the number of years from T2DM diagnosis date to informed consent date:

(consent date - diagnosis date +1) / 365.25.

The duration of diabetes will be included in the baseline diabetes characteristics listing.

If the date T2DM was diagnosed is missing or partially missing, the following rules will take effect:

- Missing day, but month and year are present: the day will be imputed as the 15th day of the month.
- Missing day and month, but year is present: the day and month will be imputed as 30th June of the year (provided that the imputed date is less than the consent date).
- Missing year, but day and month are present: No imputations will occur, and the patient will be excluded from all summaries related to duration of T2DM.
- Missing day, month and year: No imputations will occur, and the patient will be excluded from all summaries related to duration of T2DM.
- If any such imputed date falls after the consent date, then the diagnosis date will be taken as equal to the consent date.

These durations, even if partially imputed, will be listed. However, only the portion of the date of diagnosis actually observed, rather than imputed dates, will be displayed in listings.

3.1.3 Definition of Baseline Measurements

Unless otherwise stated, for each patient, baseline value of a parameter is defined as the last available assessment on or prior to the date of the first dose of the study medication.

Composed parameters will be derived from corresponding assessments as recorded at the same timepoint.

3.1.4 Change from Baseline

Change from baseline to any Week t is defined as follows:

$$C_{Week\ t} = M_{Week\ t} - M_{baseline},$$

where:

- $C_{Week\ t}$ is the change from baseline at Week t,
- $M_{Week\ t}$ is the measurement at Week t,
- $M_{baseline}$ is the measurement at baseline.

3.1.5 Visit Assignment Windows

For all assessments recorded by visit and considered as obtained during the treatment period, the data records will be assigned to calculated visit windows (using study day) as described in Table 1 below. A data record refers to a unique set of assessments as specified with the Table 2 in the CSP, as recorded on a visit. Single missing assessments in a data record will not be substituted by non-missing assessments from other data records.

Inclusion of a data record within the visit window will be based on the actual date and not the intended date of the visit. The window for the visits following baseline (including unscheduled visits) will be constructed in such a way that the upper limit of the interval falls half way between the two visits, see Table 1 - Visit Assignment Windows.

If a patient has more than one data record included within a window, the assessment closest to the target day will be used. In case of ties between observations located on different sides of the target day, the earlier assessment will be used. In case of ties located on the same side of the target day (i.e. more than one value for the same day but different time), the value with the earlier entry date/time will be used.

In case of two or more measurements for laboratory data with identical dates and times (including possibly missing times), the average value will be derived and in case that the record is assigned for the respective analysis visit the average value will be used for analysis. This will be done both for cases with multiple baseline values or with multiple post-baseline values with the same date and time.

Early termination visits will be assigned to their respective visit assignment window.

The visits not considered as obtained during the treatment period will be reported as recorded, without re-assignment, e.g. end-of-study visit at Week 28.

Table 1 - Visit Assignment Windows

Assessment	Visit	Week	Target Day	Day Range
Vital signs, Body weight, Pregnancy testing				
Day 1/Baseline	2		1	1 [a]
Week 2	4	2	15	2 to 29
Week 6	6	6	43	30 to 64
Week 12	8	12	85	65 to 106
Week 18	9	18	127	107 to 148
Week 24	10	24	169	from 149 onwards [b]
Safety laboratory, eGFR, Plasma volume, PK sampling, NT-proBNP, Biomarkers				
Day 1/Baseline	2		1	1 [a]
Week 6	6	6	43	2 to 64
Week 12	8	12	85	65 to 127
Week 24	10	24	169	from 128 onwards [b] [c]
FPG				
Week 6	6	6	43	2 to 64
Week 12	8	12	85	65 to 106
Week 18	9	18	127	107 to 148
Week 24	10	24	169	from 149 onwards [b]
HbA1c				
Day 1/Baseline	2		1	1 [a]
Week 12	8	12	85	2 to 127
Week 24	10	24	169	from 128 onwards [b]
MRI				
Day 1/Baseline	2		1	1 [a]
Week 24	10	24	169	any post-baseline assessment [d]

[a] Study Day 1 is defined as date of study treatment.

[b] Safety laboratory data as defined in Table 2 - Chemistry and hematology assessmentsTable 2, and vital signs obtained up to and including 4 days (30 days for liver function laboratory tests) after the last dosing date will be used for assignment to the analysis visit windows. Data obtained outside of this range will not be assigned to an analysis visit.

[c] For the biomarkers (NT-proBNP, CCI [redacted]) any post-baseline value is supposed to be mapped to the visit windows. For multiple values within the Week 24 window, the one will be selected, which was recorded:

1. On treatment;
2. In case of more than one value is on treatment, then the one closest to the target date (on day 128);
3. In case of no on-treatment value in Week 24 window, the one closest to the end of treatment date will be chosen.

All Laboratory data for the biomarker endpoints will be used for assignment to the analysis windows with no exclusions because of rescue or treatment discontinuation.

[d] Any post-baseline MRI recording is supposed to be selected for analysis. In case of multiple post-baseline MRIs, the one will be selected, which was recorded:

1. On treatment;
2. In case of more than one MRIs on treatment, then the one closest to the target date (on day 169);
3. In case of no on-treatment MRI, the one closest to the end of treatment date will be chosen.

If ties still exist after these rules are applied, then the above rules for picking values closest to target will be used for the remaining values under consideration.

3.1.6 Handling missing data

Missing data for the primary and secondary MRI analyses will be imputed using multiple imputation. Partial dates will also be imputed. For other values, missing data will not be imputed and will be treated as missing.

The primary, secondary, and exploratory analyses will be performed based on full analysis set (FAS) on observed data, regardless of rescue or discontinuation of the study treatment. When patients have their final MRI measurements done at ETD visit rather than at Week 24, these measurements will be used as the endpoint (effectively, a last observation carried forward (LOCF) analysis).

Multiple imputation will generally be performed for the analyses of the MRI parameters based on the MAR assumption, and on MNAR assumption for the primary endpoint as sensitivity analysis.

3.1.6.1 Imputation of partial dates

Concomitant Medication Dates

Start and stop date of all concomitant medications are collected on the CRF. In order to classify medication as prior, current or concomitant, partial, missing or invalid start and stop dates will be imputed where possible as follows:

- If the reported start date is missing or invalid and the informed consent date is not missing or invalid, then the imputed start date is set equal to the informed consent date. If the consent date is missing or invalid and the birth date is not missing or invalid, then the imputed start date is set equal to the birth date. If the start date, the consent date and the birth date are all invalid or missing, then the imputed start date is set equal to missing.
- If the reported start date is partially entered, then the imputed start date is set equal to the earliest possible reported start date based on the partial entered reported start date.
- If the reported end date is missing, continuing, unknown or invalid, then the imputed end date is set equal to the most recent database extraction date or date of database lock.
- If the reported end date of the medication is partial, then the imputed end date is set equal to the last possible reported end date based on the partial entered reported end date.

Imputed dates will not appear on the listings of non-study medication.

Adverse Events Onset Date

In the case an AE onset date is missing or partially missing, an imputation needs to be done to determine if the event is to be classified as occurring during the treatment period according to the rules in section 4.2.5.1.

If an onset date is completely missing (or the year is missing), the derived onset date will be calculated as the first non-missing valid (actual) date from the following list (in order of precedence):

- First active study medication date
- Consent date
- If a valid non-missing date is not available for any of these dates, the derived onset date will be set to missing.

If an onset date is incomplete, the derived onset date will be calculated using the following algorithm:

Calculate a surrogate date as the first non-missing valid date from the following list (in order of precedence):

- First active study medication date
- Consent date

- If a valid non-missing date is not available for any of these dates, the surrogate date will be set to missing.

Based on the information provided, set the initial derived date to the earliest possible date. If only a year is provided, set the derived date to January first of that year. If a year and month is provided, set the derived date to the first day of that month.
If the surrogate date is non-missing then:

- If the derived date is on or after the surrogate date use the derived date as calculated
- If the derived date is prior to the surrogate date and the surrogate date is consistent with the partial data provided for the onset date, use the surrogate date as the derived date
- If the derived date is prior to the surrogate date and the surrogate date is not consistent with the partial data provided for the onset date then set the derived onset date to be the latest possible date based on the partial onset date information provided. If only a year is provided, set the derived date to December 31st of that year. If a year and month is provided, set the derived date to the last day of that month.

If all dates used to determine the surrogate date are missing, then based on the information provided, set the derived date to the earliest possible date. If only a year is provided, set the derived date to January first of that year. If a year and month is provided, set the derived date to the first day of that month.

A missing or incomplete end date of an AE will not be imputed.

3.1.7 Study periods

Screening Period: the Screening Period includes all data recorded on a date before the date of Day 1.

Treatment Period: the start of the Treatment Period is the date of Day 1. The end of the Treatment Period is the date of Visit 10 (Week 24) or the date of last dose for subjects who prematurely and permanently discontinued.

For subjects who were lost to follow up during the Treatment Period without a recorded date of last dose, the end of the Treatment Period is the date of last known visit date (including contact visits), or the date of discontinuation, whichever is the latest.

3.2 Primary endpoint

The primary endpoint is the change from baseline in LVEDV index at 24 weeks of treatment measured by MRI to evaluate the effects of saxagliptin compared to placebo.

3.3 Secondary endpoints

The following secondary variables will be analyzed to evaluate the effects of saxagliptin compared to placebo:

- Change from baseline in LVESV index, LVEF, and LVM at 24 weeks of treatment measured by MRI;
- Change from baseline in NT-proBNP after 24 weeks of treatment.

3.4 Exploratory endpoints

The following exploratory endpoints will be analyzed:

- Change from baseline in LVEDV index, LVESV index, LVEF, and LVM measured by MRI at 24 weeks to evaluate the effects of sitagliptin compared to placebo;

- Change from baseline in NT-proBNP after 6, and 12 weeks to evaluate the effects of saxagliptin compared to placebo;
- Change from baseline in NT-proBNP after 6, 12, and 24 weeks to evaluate the effects of sitagliptin compared to placebo;

- Percent change from baseline in plasma volume using the Strauss formula after 6, 12, and 24 weeks;
- Change from baseline in body weight at 12 and 24 weeks;
- Change from baseline in HbA1c at 12 and 24 weeks;
- Change from baseline of blood and urine biomarker values at 6, 12, and 24 weeks;
- Plasma concentration in PK samples for:
    - Saxagliptin and its major metabolite, 5-hydroxy saxagliptin; and
    - Sitagliptin.

  For analysis of PK data see section 4.2.7 PK analysis

3.5 Safety variables

The safety data, which will be collected for this study comprises: AEs/SAEs, AEoSIs, CV events, physical examination, clinical chemistry/hematology parameters, and vital sign measurements.

3.5.1 Adverse Events

All AEs and SAEs occurring during the study will be recorded. Details such as start and stop date of AE, action taken and outcome will be recorded.

The incidences of CV events will independently be adjudicated according to the categories of:

- CV Death,
- Myocardial infarction (MI),
- Stroke, and
- Heart failure.

For heart failure events the status about hospitalization (hHF), and/or urgent outpatient visits will be recorded.

The following AEs will be recorded and considered as adverse events of special interest (AEoSI):

- Hypersensitivity reactions,
- Severe cutaneous adverse reactions (SCAR),
- Decreased lymphocyte count,
- Pancreatitis,
- Cardiac failure (including confirmed adjudicated cardiac failure events),
- Renal impairment/renal failure.

3.5.2 Vital sign

Vital sign measurements in this study will include sitting systolic and diastolic BP and heart rate (HR). Vital signs should be measured from Visit 1 after the patient rests for approximately 5 minutes and with the patient in a sitting position, and again as per the schedule of event defined in protocol at the Visits 2, 4, 6, 8, 10 for the Weeks 2, 6, 12, 18, and 24 after randomization. The Pulse and seated BP will be measured twice (5 minutes apart).

3.5.3 Physical examination

Physical examination findings from general appearance, skin inspection, lymph nodes, thyroid, abdomen, musculoskeletal/extremities, CV system, lungs, and reflexes observed at screening will be recorded with the medical history, whereas the findings which are new or aggravated compared to baseline will be recorded with the adverse events data. Therefore, no specific analysis for findings by body system from the physical examination will be performed.

3.5.4 Laboratory Safety Variables

The following laboratory variables will be recorded during this study and summarized using descriptive statistics:

Table 2 - Chemistry and hematology assessments

Hematology/Hemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
B-Hemoglobin (Hb)	S/P Glucose
B-Hematocrit (Hct)	S/P HbA1c
	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count	S/P-Alkaline phosphatase (ALP)
B-Platelet count	S/P-Aspartate transaminase (AST)
	S/P-Alanine transaminase (ALT)
Urinalysis	S/P-Albumin
U-Hb/Erythrocytes/Blood	S/P-Potassium
U-Protein/Albumin	S/P-Sodium
U-Glucose	S/P-Creatine kinase (CK)
U-Ketones	

Hematology and Clinical Chemistry assessments will be performed according to the Study Plan (Table 2) in the clinical study protocol, whereas Urinalysis is performed during the screening period only.

4. ANALYSIS METHODS

4.1 General principles

Continuous data will be summarized in terms of the number of observations, mean, standard deviation (SD), standard error (SE), upper quartile, median, lower quartile, minimum and maximum unless otherwise stated. In addition, 95% confidence interval for the mean (percent) change from baseline will be calculated for continuous primary, secondary, and exploratory variables. They will be presented by treatment group and time point where applicable. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database and the SE will be reported to three more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Descriptive summaries of categorical variables will consist of frequencies and percentages for each treatment group and overall, where applicable.

Descriptive summaries of change from baseline in categorical variables will be provided using shift tables. Frequencies and percentages of patients within each treatment group will be generated for levels of cross-classifications of baseline and the on-treatment value of the parameter. The on-treatment value can either be the value at a certain time point, or e.g. for laboratory tests, the minimum/maximum value in the direction of toxicity, which has been

observed during the treatment period. Treatment group differences will not be assessed in summaries of shifts.

To demonstrate non-inferiority of saxagliptin compared to placebo the change from baseline in LVEDV index at Week 24 will be assessed and claimed non-inferiority if the upper bound of 95% confidence interval (CI) for the adjusted mean treatment difference between saxagliptin and placebo is less than 10% of the overall baseline value.

The non-inferiority margin estimate for the sample size calculation for LVEDV index is based on data from Foster et al 1998 [1], where the baseline LVEDV index is 65 ±13 (mean ±SD) mL/m^2. To exclude an increase in LVEDV index (relative to placebo) of greater than 10% of the baseline, the change seen with vildagliptin in LVEDV in the VIVIDD study, the non-inferiority margin for these calculations is equivalent to 6.5 (65 × 0.10) mL/m^2.

4.2 Analysis methods

4.2.1 Patient disposition

A clear accounting of the disposition of all patients who enter the study will be provided, from screening to study completion. Summaries of patient disposition will be presented by treatment and overall (column), while summaries in the EPS (when applicable) will be presented only by overall (column) using FAS. The following patient disposition summaries will be provided:

- Number and percentage of patients who complete the study and who withdraw from the study, further classified by reasons for withdrawal from the study (as recorded on patient's disposition page on the CRF) (Analysis Population: FAS).

- Number and percentage of patients in the EPS, FAS, PP and SAF populations will be presented on their own as well as by country, study centre and overall (row) (Analysis Population: EPS).

- Number and percentage of screen failure-patients (i.e., patients enrolled but not randomized), further classified by reasons for screen failure (Analysis Population: EPS).

4.2.2 Demographics and other baseline characteristics

Demographic and baseline patient characteristics will be listed and summarized for the SAF. If the FAS differs from the SAF, the analysis will be repeated for the FAS. All summaries of continuous characteristics will be based on non-missing observations. For categorical characteristics, percentages will be calculated out of the total number of patients in the data set, overall and by treatment group, where applicable (i.e., each denominator includes the number of patients with missing/unknown values for the characteristic).

4.2.2.1 Demography data

Standard descriptive statistics will be presented for the continuous variables of:

- Age (years);
- Weight (kg);
- Height (cm);
- Body mass index (BMI) (kg/m^2), calculated as: weight/(height)^2;
- Baseline BSA.

The baseline BSA will be calculated using the formula as defined by Mosteller [3]:

$$\text{BSA (m}^2\text{)} = \sqrt{\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3600}}$$

The total frequency counts and percentages of patients will be presented for the categorical variables of:

- Sex (grouped as male, female);
- Age group (years) (grouped as <65 years, ≥65 years, ≥75 years);
- Race (grouped as White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, or Other);
- Ethnic group (grouped as Hispanic/Latino, Non-Hispanic/Latino);
- Body mass index (kg/m2) (grouped as Normal (<25 kg/m2); Overweight (≥25 kg/m2 - ≤30 kg/m2), Obese (>30 kg/m2));
- Geographic Region, as defined in Table 3:

Table 3 - Geographic regions

Geographic Region	Countries
North America	USA
South America	Chile
Asia Pacific	South Korea/ Republic of Korea, Thailand
Central Europe	Hungary, Romania, Bulgaria
Eastern Europe	Russia, Ukraine

4.2.2.2 Other baseline characteristics

As applicable, standard descriptive statistics, and total frequency counts and percentages of patients will be presented, as follows:

Baseline disease characteristics

- Duration of type 2 Diabetes (years)
- Duration of type 2 Diabetes (grouped as < 3years, ≥ 3 and ≤ 10 years, > 10 years);
- Baseline HbA1c (%)
- Baseline HbA1c (grouped as <7.0%, 7.0% to 9.0%, and >9.0%);
- eGFR (mL/min/1.73 m^2)
- eGFR (grouped as <50 and >=50 mL/min/1.73 m^2);
- SGLT-2 inhibitor use (grouped as Yes/ No);
- Baseline NYHA classification (grouped as I, II, III, IV);
- CCI ;
- CCI
- LVEF (%)
- LVEF (grouped as <= 45%, > 45%)
- LVEF (grouped as <= 65%, > 65%)
- LVEF (grouped as <40, >=40 - <50, >=50 - <60, >=60%)
- Sinus rhythm (grouped as Yes, No)
- Main etiology (grouped as Non-Ischemic, Ischemic, Valvular, Arrythmia, Unknown, Other);
- NT-proBNP (pg/mL).
- Serum Potassium (mmol/L);
- Sodium (mmol/L);
- Haemoglobin (g/L);

The baseline disease characteristics will also be presented by subgroups of LVEF at baseline at <=45%, > 45%, and <=65%, > 65%.

Baseline LVEDV index

For determination of the non-inferiority margin for the primary endpoint the baseline LVEDV index will be summarized by treatment group and overall.

4.2.2.3 Medical History

Diabetes-related medical history, surgical, and general medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients will be summarized for the FAS by system organ class (SOC) and preferred term (PT).

The number and percentages of patients with diabetes complications (grouped as Any, Retinopathy, Neuropathy Autonomic, Neuropathy Peripheral, Nephropathy, Angiopathy, Other) will be presented.

All medical history will be listed.

4.2.2.4 Prior Medications

Previous medications, including any medication (other than study medication) taken prior and discontinued before the date of the first dose of study treatment (Day 1) will be summarized.

Missing and partial date handling of start and stop dates of previous medications is described in section 3.1.6.1 above. The actual WHO Drug Dictionary version from the date of database lock will be used to code the non-study medication.

4.2.2.5 Elapsed time between randomization and final MRI measurements

The elapsed time between baseline MRI measurements and final MRI measurements will be summarized as patient-24-weeks of follow up time, see also section 4.2.4.3.

4.2.3 Extent of Exposure and Treatment Compliance

4.2.3.1 Extent of Exposure – Study and Glycemic Rescue Medications

The extent of exposure to each study medication during the treatment period is defined as:

treatment end date – treatment start date +1

The extent of exposure to each study medication will be summarized using the SAF for the treatment period, where the number and percent of patients with an extent of exposure within specified day ranges (1-7, 8-30, 31-60, 61-90, 91-120, 121-180, > 180 days) will be presented by treatment group.

The mean, standard deviation (SD), median and range of the number of days of exposure to each study medication will also be presented. Summaries will be presented for both methods including and excluding periods of treatment interruptions (defined by record of 0 tablets of study medications on the CRF).

All glycemic rescue medication use during the treatment period will be summarized and listed by treatment group.

A listing of patients by packaging/batch number of study medication will also be generated.

4.2.3.2 Extent of Exposure – Concomitant Medications

Concomitant medications include any medication taken at any time point during the treatment period regardless if the medication started during or prior to, but continued into the treatment period.

Concomitant medications will be summarized using the SAF dataset by drug class and (generic) drug name. A summary table by drug class and generic drug name will be generated for each of the following:

- all concomitant medication
- all concomitant anti-diabetic medication
- all concomitant heart failure related medication

The type of medication in terms of common concomitant, anti-diabetic, and heart failure related medication will be derived from the CRF module assigned to the respective type of medication. Missing and partial date handling of start and stop dates of concomitant medications is described in section 3.1.6.1 above.

For grouping of subjects taking, and not taking insulin and/or SUs (sulfonylurea agents) these medications will be identified from the anti-diabetic drugs by the ATC-codes: A10A for Insulin and A10BB for use of SUs.

4.2.3.3 Measurement of Treatment Compliance

Percent treatment compliance is calculated during treatment period for each study medication and overall. For each study treatment and overall, percent compliance is defined as follows:

$$\frac{\text{Number of doses actually administered}}{\text{Number of doses planned}} * 100$$

Where the number of doses planned is calculated as the number of days of the duration of the treatment period based on 1 tablet/day or 1 capsule/day during this period for saxagliptin and sitagliptin respectively:

$$\text{end date} - \text{start date} + 1$$

The overall compliance rate refers to both 1 tablet/day and 1 capsule/day for the number of days during the treatment period:

$$(\text{end date} - \text{start date} + 1) * 2$$

The number of doses actually administered is calculated as: Total number of tablets or capsules dispensed - total number of tablets or capsules returned based on the CRF accountability pages.

A patient is considered compliant if percent overall compliance is $\geq 80\%$ and $\leq 120\%$. The number and percent of patients being compliant during the treatment period and a summary for the percent study treatment compliance rates will be displayed for the SAF per study treatment.

4.2.3.4 Heart failure related medication at start of study treatment

This analysis includes heart failure related medications taken prior to and continued at date of first dose of investigational product (Day 1). The medications will be summarized using the SAF dataset by drug class.

The type of medication in terms of heart failure related medication will be derived from the CRF module assigned to the respective type of medication. Missing and partial date handling of start and stop dates of concomitant medications is described in section 3.1.6.1 above.

4.2.4 Analyses of study objectives

Summary statistics will be presented for each primary, secondary and exploratory variable as described in section 4.1, as well as the statistical analyses as described below.

This study is designed to demonstrate non-inferiority of saxagliptin compared to placebo for LVEDV index in the change from baseline to Week 24 within a non-inferiority margin of 10% of the overall baseline mean value in LVEDV index from FAS.

For a given MRI, values for the set of 4 left ventricular heart function parameters will be obtained from three different readers. For each parameter, the average of all values provided by the readers will be used for analysis.

The patient's LVEDV index (mL/m²) value will be derived from LVEDV (mL) as measured at baseline and week 24/ETD visit divided by the baseline BSA (m²), as

$$\text{LVEDV index } (\text{mL}/\text{m}^2) = \frac{\text{LVEDV (mL)}}{\text{BSA } (\text{m}^2)}$$

LVESV index (mL/m²) value will similarly be derived, as

$$\text{LVESV index } (\text{mL}/\text{m}^2) = \frac{\text{LVESV (mL)}}{\text{BSA } (\text{m}^2)}$$

For the derivation of the baseline BSA (m²) see section 4.2.2.2 Other baseline characteristics.

The analyses for the MRI parameters on the full analysis set (FAS) will be performed based including all patients in the FAS having a non-missing baseline value. For the selection of MRI image readings for analysis see section 3.1.5.

Multiple imputation

Multiple imputation for Week 24 will be applied for all MRI analyses for FAS and PPS under the MAR assumption using the linear regression model:

$$Y = \text{intercept} + ß_1\tau + ß_2\kappa_1 + ß_3\kappa_2 + ß_4\kappa_3 + ß_5M_{baseline}$$

where

- Y is the observed change from baseline,
- κ_1 is eGFR category (<50, ≥50 mL/min/1.73 m2),
- κ_2 is SGLT-2 inhibitor use (yes, no),
- κ_3 is the region,
- τ_i is treatment group,
- $M_{baseline}$ is the baseline measurement,

This will be implemented by use of the MONOTONE REG option in PROC MI including baseline as independent variable, and with:

- NIMPUTE=200 steps;
- SEED=512.

The results from the analyses will be combined for statistical inference using Rubin's rules from the SAS procedure MIANALYZE.

The remaining non-MRI endpoints will be analyzed based on observed data. No imputation will be applied on missing data.

Per protocol analysis

For the analyses of the MRI parameters for the per protocol set (PPS) the post-baseline measurements are required to be within 14 days after the last study treatment. MRI measurements more than 14 days after the last study medication will be set to missing and not considered in the windows. Missing final MRI values generated as a result of this will be imputed by use of the multiple imputation method as described above. Additionally, any other patients with missing final MRI data (but not missing baseline MRI data) generated by application of the per protocol criteria, (see Appendix 3) will be imputed using the same methodology. Missing baseline MRI values will not be imputed. All subjects in the per protocol population with a non-missing baseline value (after exclusions of data from application of the PP criteria) will be included in the primary per protocol analyses.

Maintain model convergence

The models will include stratification variables as fixed categorical effects. If the model does not converge or effects are not estimable then stratification levels will be combined or stratification variables will be dropped according to the following sequence:

1. Region will be combined as: Europe (Central Europe + Eastern Europe) vs others;
2. If the model still does not converge or if any effects are not estimable, the region variable will be dropped from the model;
3. If the model still does not converge or if any effects are not estimable, the variable for SGLT-2 use will be dropped from the model and instead the model will include the combined regions Europe/Others and eGFR status;
4. If the model still does not converge or if any effects are not estimable, then region variable will be dropped from the model and the model will include only the eGFR status variable;
5. If the model still does not converge or if any effects are not estimable, then eGFR status variable will be dropped from the model and no adjustments will be made for stratification variables.

4.2.4.1 Primary outcome variable

For the evaluation of the effects of saxagliptin compared to placebo in the change from baseline in LVEDV index at 24 weeks of treatment measured by MRI an analysis of covariance (ANCOVA) will be performed. The SAS procedure PROC MIXED will be used. The preferred model will include the fixed categorical effects of treatment, eGFR category (<50, ≥50 mL/min/1.73 m2), SGLT-2 inhibitor use, region, and the continuous fixed covariates of baseline measurement.

The following model will be used:

$$C_{ij} = \text{intercept} + ß_1\,[M_{baseline,ij}] + \tau_i + \kappa_{1,m} + \kappa_{2,q} + \kappa_{3,r} + \text{error}_{ij}$$

where

- C_{ij} is the change from baseline for patient j in treatment group i,
- $ß_1$ is the slope coefficient for the baseline measurement,
- $\kappa_{1,m}$ is the mean effect of eGFR category (<50, ≥50 mL/min/1.73 m2),
- $\kappa_{2,q}$ is the mean effect of SGLT-2 inhibitor use (yes, no),
- $\kappa_{3,r}$ is the mean effect of the region,
- $M_{baseline,ij}$ is the baseline measurement of patient j in treatment group i,
- τ_i is the mean effect of treatment group i,
- error_{ij} is the error term for patient j in treatment group i.

The model will be calculated including all three treatment groups, and will provide least-squares mean estimates, SE and 2-sided 95% confidence intervals for the change from baseline per treatment group and for the differences between the treatment groups. For the primary endpoint the results per treatment groups saxagliptin and placebo and for their difference will be presented. For the treatment difference the corresponding nominal p-value will also be presented on a descriptive level.

4.2.4.2 Secondary variables

The secondary endpoints to evaluate the effects of saxagliptin compared to placebo in the changes from baseline in LVESV index, LVEF, and LVM at 24 weeks of treatment measured by MRI the same model as described above for the primary endpoint will be applied.

For the change from baseline in NT-proBNP after 24 weeks of treatment a longitudinal repeated measures analysis using 'direct likelihood' will be performed. The SAS procedure PROC MIXED will be used. The preferred model will include the fixed categorical effects of treatment, eGFR category (<50, ≥50 mL/min/1.73 m2), SGLT-2 inhibitor use, region, week and treatment-by-week interaction as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction.

The following model will be used for analysis:

$$C_{ijk} = \text{intercept} + ß_1\,[M_{baseline,ij}] + \tau_i + \kappa_{1,m} + \kappa_{2,q} + \kappa_{3,r} + \alpha_k + (\alpha\,\tau)_{ik} + (\alpha\,M_{baseline})_{ijk} + \text{error}_{ijk}$$

where

- C_{ijk} is the change from baseline for patient j in treatment group i at time k,
- $ß_1$ is the slope coefficient for the baseline measurement,
- $\kappa_{1,m}$ is the mean effect of eGFR category (<50, ≥50 mL/min/1.73 m2),
- $\kappa_{2,q}$ is the mean effect of SGLT-2 inhibitor use (yes, no),
- $\kappa_{3,r}$ is the mean effect of the region,
- $M_{baseline,ij}$ is the baseline measurement of patient j in treatment group i,
- τ_i is the mean effect of treatment group i,
- α_k is the mean effect at time k
- $(\alpha\,\tau)_{ik}$ is the interaction term between treatment group i and time k.
- $(\alpha\,M_{baseline})_{ijk}$ is baseline measurement-by-week interaction term for patient j in treatment group i at time k, and
- error_{ijk} is the error term for patient j in treatment group i at time k.

An unstructured matrix for the within-patient error variance-covariance will be used. The denominator degrees of freedom will be calculated according to the Kenward-Roger method.

In case of non-convergence of the preferred model or memory space issues, the following back-up models are defined:

- The first backup model is the same as the preferred model but the Kenward-Roger method will be replaced by Satterthwaite approximation.
- The second backup model is the same as the preferred model but without the term for baseline measurement-by-week interaction.

The second back-up model will only be provided if the first back-up model does not converge or has memory issues.

For the selection of NT-proBNP measurements for analysis see section 3.1.5.

The models will be calculated including all three treatment groups, and will provide least-squares mean estimates, SE and 2-sided 95% confidence intervals for the change from baseline at all time points within and between treatments. For the secondary endpoints the results per treatment groups saxagliptin and placebo and for their difference will be presented. For the treatment difference the corresponding nominal p-value will also be presented on a descriptive level.

For the analysis of the NT-proBNP for the biomarkers per protocol set (BPPS) the post-baseline measurements are required to be within 14 days after the last study treatment. Measurements more than 14 days after the last study medication will not be included into the analysis.

4.2.4.3 Sensitivity analysis

Sensitivity analyses will be conducted for the primary endpoint for FAS using the same model and multiple imputation as described above. The multiple imputation will be done for the MNAR assumption by adding to each of the imputed values for the saxagliptin group, the non-inferiority margin of 10% of the overall baseline value.

Additional sensitivity analyses will be conducted on the primary and secondary MRI endpoints using post-baseline MRI values of at least 20 weeks (140 days) but no more than 28 weeks (196 days) of follow up before the MRI measurements. The analysis will use the same ANCOVA approach, including multiple imputation, as the primary analysis. Post-baseline MRI values outside this range will be set to missing and imputed using MAR multiple imputation.

Another set of sensitivity analyses will be conducted on the primary and secondary MRI endpoints adjusting the change in the MRI endpoints for follow-up time between the initial and final MRI. A rate of change in the MRI endpoints will be expressed per patient-24-weeks of follow up time, as:

$$\text{Adjusted MRI endpoint} = \frac{MRI\ endpoint}{Patient\text{-}24\text{-}weeks\ of\ follow\ up\ time}$$

Whereas:

$$\text{Patient-24-weeks of follow up time} = \frac{Date\ of\ post\text{-}baseline\ MRI\ -\ Date\ of\ baseline\ MRI}{168}$$

The analysis will use the same multiple imputation and ANCOVA approach as the primary analysis. Scatter plots will be provided, presenting the changes in the MRI values from baseline to Week 24 versus the patient-24-weeks of follow up time.

Furthermore, the primary endpoint for the full analysis set will be analyzed for sensitivity based on the actual strata eGFR category (<50, ≥50 mL/min/1.73 m2), and SGLT-2 inhibitor use, as derived from the clinical data.

For the sensitivity analyses, least squares mean estimates and 2-sided 95% confidence intervals for changes from baseline within and differences in change from baseline between treatments will be provided. For the treatment differences the corresponding nominal p-values will also be presented on a descriptive level.

4.2.4.4 Exploratory variables

The following exploratory endpoints will be analyzed using the same models as described above for the primary and secondary variables, as applicable (using MMRM for variables with multiple post-baseline measurements and ANCOVA for those with a single scheduled post-baseline measurement).:

- Change from baseline in LVEDV index, LVESV index, LVEF, and LVM measured by MRI at 24 weeks to evaluate the effects of sitagliptin compared to placebo;

- Change from baseline in NT-proBNP after 6, and 12 weeks to evaluate the effects of saxagliptin compared to placebo;
- Change from baseline in NT-proBNP after 6, 12, and 24 weeks to evaluate the effects of sitagliptin compared to placebo;

- Percent change from baseline in plasma volume after 6, 12, and 24 weeks based on the Strauss formula as defined in Strauss et al 1951 [2]:

$$\%\ \text{Change in PV} = 100 * \frac{Hb_{baseline}}{Hb_{post-baseline}} * \frac{1 - Hct_{post-baseline}}{1 - Hct_{baseline}} - 100$$

A baseline covariate for the model will be derived according to Hakim RM [5]:

$$\text{Baseline PV} = 1 - Hct_{baseline}(ratio) * \text{a} + \text{b} * Weight_{baseline}(\text{kg})$$

Whereas:

$$\text{a} = \begin{cases} 1530, male \\ 864, female \end{cases}$$

$$b = \begin{cases} 41, male \\ 47.9, female \end{cases}$$

The modelling will be performed twice, one without, and one with applying of the Baseline PV covariate.

- Change from baseline in body weight at 12 and 24 weeks;
- Change from baseline in HbA1c at 12 and 24 weeks;
  (In case where the central measurement of HbA1C was not possible due to hemoglobin variants not compatible with the central assay, no value will be centrally collected and these subjects will be excluded from the HbA1c analysis);
- Change from baseline of blood and urine biomarker values at 6, 12, and 24 weeks;

For the exploratory analyses, least squares mean estimates and 2-sided 95% confidence intervals for changes from baseline within and differences in change from baseline between treatments will be provided. For the treatment differences the corresponding nominal p-values will also be presented on a descriptive level.

4.2.4.5 Percent Change from Baseline in NT-proBNP and Biomarkers

In case of skewed distribution for NT-proBNP and the Biomarkers (CCI [redacted]) the MMRM models will be applied as described above for the logarithms (ln) of the post- to pre-treatment ratios, and the logarithms of the baseline measurements. The results from PROC MIXED (adjusted means and the confidence intervals) will be back-transformed to the percentage scale using the formula:

$$Percentage = 100 * (e^{result} - 1).$$

The estimate of the difference versus PLAC and the confidence interval will be transformed to the ratio by: $ratio = e^{estimate}$.

4.2.5 Safety analyses

Safety analyses will be performed using the Safety analysis set, including data after the addition of glycemic rescue concomitant medication or change of heart failure concomitant medication.

4.2.5.1 Adverse Events

Adverse Events (AEs) will be classified by Primary SOC and PT according to MedDRA.

In summaries by SOC and PT, AEs will be sorted by overall decreasing frequency within each SOC and PT within the saxagliptin group. In summaries by PT, AEs will be sorted by decreasing frequency of each PT within the saxagliptin group.

For summaries presenting the incidence rates per 100 patient years, this will be calculated by number of patients with AEs divided by the total number of days under study treatment across all patients per treatment group, multiplied by 365.25 multiplied by 100.

All Adverse Events

An overall summary of adverse events occurred during the study and during the treatment period at patient level, including AEs, SAEs, death, severe events, treatment-related events, events leading to the discontinuation of study medication, events leading to death will be presented. All AEs (serious and non-serious) occurred during the study and during the treatment period will be summarized by SOC and PT. In addition, a patient listing of all reported AEs will be produced. This will include displaying events that occurred prior to the start date of treatment period, if any. All AEs (serious and non-serious) will also be summarized by treatment group, where applicable.

Adverse Events and SAEs with an onset from Day 1 of treatment up to and including 4 days and 30 days respectively, after the last dose date in the treatment period will be considered as treatment emergent. Adverse events leading to discontinuation with onset on or after Day 1 will generally be considered as treatment emergent.

In addition, the following summaries will be provided for the treatment period:

- Most common adverse events and incidence rates per 100 patient years by preferred term and treatment group (i.e., reported by ≥ 5 % of patients in any treatment group);
- Adverse events by system organ class, preferred term, intensity and treatment group;
- Adverse events related to study medication by system organ class, preferred term and treatment group;
- Proportion of patients with adverse events by SOC and PT in subgroups of patients defined by age category (< 65 and ≥ 65 years), gender and race.

No formal comparisons will be made between treatments. No formal statistical testing will be performed, only summary statistics will be provided.

Adverse Events of Special Interest

Number of adverse events of special interest and their incidence rates per 100 patient years will be tabulated. The event categories of AEoSI for this study may include, but are not limited to:

- Hypersensitivity reaction;
- Severe cutaneous adverse reaction (SCAR) (explicitly including bullous pemphigoid);
- Decreased lymphocyte count (lymphocytopenia);
- Pancreatitis;
- Cardiac failure (including confirmed adjudicated cardiac failure events);
- Renal impairment/renal failure.

For identification of the AEoSI the Sponsor provides a set of the specific Standard and Customized MedDRA queries.

Separate summaries similar to those produced for AEs/SAEs will be provided for AEoSI.

4.2.5.2 Serious Adverse Events

All adverse events, which are indicated as serious in the CRF, will be summarized for the number of patients with at least one serious adverse event by treatment group.

4.2.5.3 Adverse Events adjudicated as CV Deaths, heart failure, MIs, strokes

An overall summary will be presented showing death cases, and adverse events related to: heart failure, MIs, and strokes as recorded in the CRF and adjudicated as:

- CV Death;
- Heart Failure;
- Cardiac Ischemic Event (MIs);
- Cerebrovascular Event (strokes).

In case of adjudication of an event in more than one category (e.g. a heart failure event with fatal outcome adjudicated as both a heart failure event and cardiovascular death event) the event will be counted once within each category.

4.2.5.4 Hospitalization with heart failure

A summary will be presented showing number of patients who experienced a hospitalization with heart failure by the primary reason for the hospitalization, as:

- Heart failure
- Acute coronary syndrome
- Pneumonia
- Other infection
- Other cause.

4.2.5.5 Deaths

All deaths recorded on the disposition page, the AE page, or SAE page (with a death date, cause of death, outcome or SAE categorization present) of the CRF will be captured and included in the analyses. Any deaths that occur during the study will be described in depth as narrative in the CSR. A listing of all deaths that occur during the study will be produced.

4.2.5.6 Clinical laboratory variables

The clinical laboratory values and changes from baseline at each scheduled time point will be summarized by treatment group using descriptive statistics, for laboratory tests as described in in the CSP, see

Table 4 below. All other tests will be included in patient listings, only.

The summaries will be presented using SI units in general and for the conventional units, as listed in Appendix 1.

Laboratory data obtained after the start of study medication dosing up to and including 4 days (30 days for liver function laboratory tests) after the last dosing date will be considered as obtained during the treatment period.

Table 4 - Laboratory Safety Variables

Hematology/Hemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
B-Hemoglobin (Hb) B-Hematocrit (Hct) B-Leukocyte count B-Leukocyte differential count B-Platelet count	S/P Glucose S/P HbA1c S/P-Creatinine S/P-Bilirubin, total S/P-Alkaline phosphatase (ALP) S/P-Aspartate transaminase (AST) S/P-Alanine transaminase (ALT)
Urinalysis	S/P-Albumin
U-Hb/Erythrocytes/Blood U-Protein/Albumin U-Glucose U-Ketones	S/P-Potassium S/P-Sodium S/P-Creatine kinase (CK)

The number and percentage of patients with laboratory values outside normal range will be summarized by shift tables from baseline to the post-baseline maximum and minimum value during the treatment period for each treatment group.

Laboratory values meeting marked abnormality criteria, as defined in Appendix 2, will be summarized for each treatment group. The marked abnormalities will be analyzed overall for any post-baseline data, regardless the baseline values are available for the parameters.

To apply for a worst-case scenario for missing data, for patients having missing pre-treatment values the respective portion of the marked abnormality criterion will be assumed as fulfilled.

For liver safety, a summary of proportion of subjects with elevated liver test including elevated AT (ALT and/or AST) and total bilirubin (see Appendix 2 for definition) will be provided. No comparison vs. baseline is required to include these elevations in the summary.

For laboratory test values that have been received with an operator sign as a part of the result (>, ≥, <, or ≤), the operator sign will be stripped and the resulting numeric value will be used for data analysis. The raw value with operator will remain in the database as such in the electronic record and will be displayed in listings.

Baseline urinalysis results will be presented by means of frequency and percentage.

4.2.5.7 Vital signs

Vital signs measurements in terms of systolic blood pressure, diastolic blood pressure, and heart rate will be recorded according to the Study Plan (Table 2) in the clinical study protocol by two readings and average reading.

The average values and changes from baseline of the average values will be summarized for each scheduled time point by treatment group using descriptive statistics.

Vital signs measurements obtained after the start of study medication dosing up to and including 4 days after the last dosing date will be considered as obtained during the treatment period.

4.2.6 Subgroup analyses

Primary and secondary variables

The subgroup analyses of the primary variable (change from baseline in LVEDV index) will be performed on the primary analysis model for the comparison of SAXA vs. PLAC for the full analysis set on the subgroups as defined by the following variables:

- Baseline HbA1c (<7.0%, 7.0% to 9.0%, and >9.0%);
- Gender (male, female);
- Age (<65, ≥65 years);
- Duration of T2DM (< 3 years, ≥ 3 and ≤ 10 years, > 10 years);
- eGFR (<50, ≥50 mL/min/1.73 m^2);
- SGLT-2 inhibitor use (Yes/ No);
- Geographic Region (North America, South America, Asia Pacific, Central Europe, Eastern Europe);

- Baseline NYHA classification (I, II, III, IV);
- Patient status of potentially unblinded, see section 2.2 for the paragraph Potential Unblinding of treatment code to AstraZeneca Monitors.

In addition subgroup analyses of the primary and secondary variables (change from baseline in LVEDV index, LVESV index, LVEF, LVM, NT-proBNP after 24 weeks) will be performed on the subgroups of LVEF at baseline (<=45%, > 45%) for the treatment comparison of SAXA vs. PLAC for both, full analysis set and per protocol set, and for SITA vs. PLAC for the full analysis set using the same models as defined for the primary and secondary analyses in section 4.2.4 and 4.2.4.2, as applicable.

Similarly, analysis for LVEDV index will be performed on the subgroups of LVEF at baseline (<=65%, > 65%) for the treatment comparison of SAXA vs. PLAC for the full analysis set.

Point estimates and 95% confidence intervals will be calculated for the adjusted changes within each treatment group as well as for the differences in adjusted changes between treatment groups. For the treatment differences the corresponding nominal p-values will also be presented on a descriptive level. For each subgroup analysis, the median p-values for the interaction tests will be reported along with the results obtained from Rubin's rules. In case that the subgroup classification was derived from a continuous variable, the continuous variable will be submitted with the treatment interaction term to a separate model to obtain the interaction p-value.

If problems with convergence or estimability occur for the subgroup analyses, the effects in the model will be modified or dropped according to the modification rules as defined in section 4.2.4.

Adverse events

The overall summary for adverse events adjudicated as CV Deaths, heart failure, MIs, strokes, as defined in section 4.2.5.3, and the summary of the number of patients who experienced a hospitalization with heart failure by the primary reason, as described in section 4.2.5.4 will separately be presented per LVEF subgroup at baseline (<=45%, > 45%).

4.2.7 PK analysis

Analysis of PK data is not part of this statistical analysis plan and will be reported separately from the clinical study report. The plasma concentrations will be listed. Not any transition of the concentration data to numeric analysis variables will be performed.

5. INTERIM ANALYSES (NOT APPLICABLE)

6. CHANGES OF ANALYSIS FROM PROTOCOL

No updates were made from the clinical study protocol.

7. REFERENCES

1 Foster RE, Johnson DB, Barilla F, Blackwell GG, Orr R, Roney M, et al. Changes in left ventricular mass and volumes in patients receiving angiotensin-converting enzyme inhibitor therapy for left ventricular dysfunction after Q-wave myocardial infarction. Am Heart J 1998;136: 269-75.

2 Strauss et al 1951
Strauss MB, Davis RK, Rosenbaum JD, Rossmeisl EC. Water dieresis produced during recumbency by the intravenous infusion of isotonic saline solution. J Clin Invest 1951;30:862– 8.

3 Mosteller RD 1987
Simplified calculation of body-surface area.
N Engl J Med. Oct 22; 317(17):1098

4 Maceira et al. 2010
Reference left atrial dimensions and volumes by steady state free precession cardiovascular magnetic resonance.
Journal of Cardiovascular Magnetic Resonance 2010 12:65.

5 Hakim RM
Daugirdas JT, Blake PG, Ing TS, eds. Handbook of dialysis, 3rd ed.
Philadelphia: Lippincott, Williams and Wilkins; 2001. p 236.

6 SAS
SAS/STATS® User Guide, Version 9.4, Cary, North Carolina, SAS Institute Inc.

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: d1680c00016-sap-ed-1		
Document Title:	Statistical Analysis Plan Edition 1.0	
Document ID:	CCI [redacted]	
Version Label:	2.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
22-Oct-2020 15:31 UTC	PPD	Content Approval
22-Oct-2020 15:24 UTC	PPD	Content Approval
22-Oct-2020 15:24 UTC	PPD	Author Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.