- **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**
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AstraZeneca

Clinical Study Protocol	
Drug Substance	saxagliptin
Study Code	D1680C00016
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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

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

This protocol version includes Addendum 1.0 dated 3 Aug 2017.

VERSION HISTORY

Version 5.0 14 February 2020
Minor typographical errors have been corrected in the protocol. Protocol synopsis (Statistical methods) The actual non-inferiority margin for the study primary objective is clarified as 10% of the overall baseline mean LVEDV index across all treatment groups. Section 2. (Study objectives) Primary objective was not changed but added further clarification to the NI margin. Section 8.1 Added that combination of stratification levels and/or variables or dropping of variables could be done for imputation models, (in addition to analysis models which was specified originally). Section 8.2. (Sample size estimate) clarification that the 6.5 value used for the NI margin in this section is an estimate used for sample size calculation purposes and is not necessarily the NI margin that will be applied in the analysis (which will be 10% of the overall baseline mean). Section 8.5 (Method of statistical analysis) To more closely follow past health authority recommendations, a change to the handling of missing data has been made. Instead of complete case analysis, multiple imputation will be done. Clarification on how the non-inferiority margin will be tested is also added. Section 8.5.6 (Sensitivity analysis) Sensitivity analyses methodology for the primary endpoint described.
Version 4.0 13 June 2018
Study timelines, number of sites and countries updated. Minor typographical errors and house style issues have been corrected throughout the protocol. Protocol Synopsis updated according to the revised protocol. List of abbreviations and definitions was updated to cover new abbreviations added in the revised CSP wording.

Exploratory objective regarding PKs collection updated to reflect that the number of PKs collected may be higher than 150.

Section 1.3 (Study Design): NT-proBNP inclusion level lowered to >300 pg/mL, central laboratory HbA1c range deleted as no longer needed for inclusion criteria, pre-screening/screening period extended to 28 days, wording on requirement to perform blood sampling before change in diuretics removed.

Figure 1 (Study flow chart): The flow chart updated to reflect the revised study design.

Section 3.1 (Inclusion criteria): Section updated to reflect revised study design: definition of documented, controlled T2DM revised; NT-proBNP lowered to >300 pg/mL; HF medications requirements updated; removal of normal sinus rhythm requirement on the qualifying ECG.

Section 3.2 (Exclusion criteria): Criterion #2 on atrial fibrillation added with the adjustment in criteria numbering. Criterion #3 modified by adding claustrophobia or unwillingness to undergo the required MRI imaging that may preclude the ability to perform an MRI scan of acceptable quality; criteria 4 and 5 changed to reflect shortened (to 8 weeks) exclusion period after receipt of incretin therapy and/or therapy with TZD; criteria 10 and 11 updated with shortened exclusion period to 3 months before screening after MI/stroke/TIA and other procedures/surgeries; criterion 17 wording updated to reflect Addendum 1,0 dated 3 Aug 2017; criterion 22 changed.

Section 3.3 (Patient pre-screening, enrollment and randomization): procedure requiring blood collection for HbA1c measurement removed from pre-screening/screening period;

Section 3.8 (Restrictions): change in exclusion period for prohibited medications listed from 3 months to 8 weeks before randomization reflected.

Section 3.9. (Discontinuation of investigational product): Clarification on procedures regarding discontinuation of investigational product added.

Section 3.10.2 (Withdrawal of the informed consent): Clarification on procedures in case of withdrawal of consent added.

Table 2 (Study Plan): Table adjusted to reflect revised study design.

Section 4.1 (Pre-screening/Enrollment/screening period): (Pre) screening period changed from 21 to 28 days; procedure requiring blood collection for HbA1c measurement removed from pre-screening/screening period.

Section 4.1.1 (Pre-screening Informed Consent Form and Informed Consent Form): HbA1c laboratory test removed from the risks described in pre-screening ICF.

Section 4.1.7 (Clinical laboratory test): HbA1c removed from the pre-screening procedures.

Section 4.1.8 (Electrocardiogram (ECG)): clarification on the wording regarding assessment of ECG.

Section 4.1.9.1. (Urine pregnancy test): Week number added to visit number to be consistent with the visit descriptions throughout the CSP wording.

Section 4.2.1. (Scheduled telephone contacts): Week number added to visit number to be consistent with the visit description throughout the protocol.

Section 5.1.3.1. Clarification added that patients with HbA1c interference issue can be included in the study.

Table 4 (Blood sample volume): Blood volume updated due to removal of Hb1Ac testing at prescreening Visit, removal of biomarkers back-ups and recalculation of blood volume based on the lab manual.

Section 5.2.2.1 (Complete physical examination): Week number added to visit number to be consistent with the visit descriptions throughout the CSP wording.

Section 5.2.2.2. (Brief physical examination): Week number added to visit number to be consistent with the visit descriptions throughout the CSP wording

Section 5.3 (Pharmacokinetics) and section 5.3.1. (Collection of samples) – updated wording to reflect that the number of PKs collected may be higher than 150.

Section 5.6.4. (Withdrawal of Informed Consent for donated biological samples): Clarification added regarding procedures on withdrawal of consent for donated biological samples.

Section 7.7.1.1(Diuretics) removed.

Section 7.7.3 (Concomitant treatment): List of strong CYP 3A 4/5 inhibitors updated.

Section 8.3 (Definition of analysis set): Full analysis set definition updated with secondary efficacy analysis.

Section 8.3.1. (Efficacy analysis set): Definition of FAS ad PP updated. Clarification added that important protocol deviations will be defined in statistical analysis plan.

Section 8.3.2. (Safety analysis set): Definition of safety analysis set updated.

Section 8.3.3 (PK Analysis set): Updated wording to reflect that the number of PKs collected may be higher than 150.

Section 8.4.2 (Secondary efficacy variables). Definition of variables updated in more detail.

Section 8.5 (Methods for statistical analyses): Definition of statistical methods updated.

Section 8.5.1 (Analysis of the primary variable(s)): Methods for primary analysis updated.

Section 8.5.3. (Exploratory analyses): Wording added that subjects without central value of HbA1c will be removed from exploratory analysis.

Section 8.5.7: (Safety analysis) Definition of safety analysis updated.

Section 9.4. (Data management by AstraZeneca): AZ Drug Dictionary replaced with WHO Drug Dictionary.

Section 10.4.1(Pre-screening Informed Consent) updated to reflect removal of central testing of HbA1c at prescreening.

List of Appendixes updated: Added new Appendix C (Criteria for Diagnosis of Diabetes Mellitus); Appendix on NYHA reclassified as Appendix D.

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered, and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

AstraZeneca

PROTOCOL SYNOPSIS

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

International Co-ordinating Investigator

PPD

PPD **University of Michigan School of Medicine**

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United States

This protocol version includes Addendum 1.0 dated 3 Aug 2017.

Study site(s) and number of subjects planned

This study will be conducted at approximately 90 sites in 9 countries.

Approximately 330 patients will be randomized in equal proportions (110 patients per group) to treatment with saxagliptin, sitagliptin or placebo.

Study period		Phase of development
Estimated date of first subject enrolled	Q1 2017	Phase 4
Estimated date of last subject completed	Q3 2019	

Study design

This is a 24 week, multicenter, randomized, double-blind, parallel group, placebo-controlled study to investigate the effects of saxagliptin and sitagliptin on cardiac dimensions and function in patients with type 2 diabetes (T2DM) mellitus and heart failure (HF).

Objectives

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 Magnetic Resonance Imaging (MRI) at 24 weeks

Secondary Objectives:	Outcome Measure:
Evaluate the effects of saxagliptin compared to placebo on left ventricular end systolic volume (LVESV) index, left ventricular ejection fraction (LVEF), and left ventricular mass (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 N-terminal prohormone of brain natriuretic peptide (NT-proBNP) after 24 weeks of treatment	• Change from baseline in NT-proBNP after 24 weeks of treatment.

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 [CV death, myocardial infarction (MI), stroke, and hospitalization for heart failure (hHF)]

Exploratory Objectives:	**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 glycosylated hemoglobin (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 also 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 sparse pharmacokinetic (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

Target subject population

The target population includes male and female patients aged 18 years and older with documented type 2 diabetes mellitus and with a prior diagnosis of heart failure. 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.

Patients must have an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2 at screening to qualify for enrollment. The proportion of randomized patients with an eGFR of ≥30 and <50 mL/min/1.73 m^2 will be limited to 30% and randomization will be stratified to randomize a maximum of 99 patients (maximum 33 for each treatment group). Patients whose

eGFR falls below 30 mL/min/1.73 m^2 must be permanently discontinued from the study after an initial result is confirmed on repeat testing.

Patients must have a diagnosis of Type 2 DM based on current ADA guidelines.

Duration of treatment

In this study, sites will perform a pre-screening assessment prior to the enrollment visit to determine if patients meet eGFR inclusion criteria. All potentially eligible patients will be enrolled for screening, provide Informed Consent, and undergo screening for all applicable inclusion/exclusion criteria. Patients can enter screening as soon as laboratory results for eGFR are available, provided the patient meets the inclusion/exclusion criteria. The total duration of the pre-screening and screening periods should not exceed 28 days.

Patients with a recent (within 1 month) laboratory results for eGFR that meet the protocol mandated criteria can enter the screening period directly without pre-screening procedures needing to be performed.

Patients who do not qualify for the protocol based upon their pre-screening or screening results may have additional attempts to qualify. There may be no more than 3 attempts in total. If the patient failed to qualify during screening period (including, but not limited due to study supplies, equipment failure, unforeseen personal events that mandate missed screening visits, or out-of-range laboratory/clinical tests), the patient may potentially be re-screened. These cases should be discussed with the AstraZeneca Monitor and documented in the Investigator Study File (ISF). The Investigator may use his/her judgment regarding the interval between screening periods. The Investigator must track all attempts in the form of a log at the site. Screening will be followed by a 24-week randomized treatment period. Patients who complete the treatment period will be asked to return for an end-of-study visit at Week 28.

Investigational product, dosage and mode of administration

For patients randomized to treatment with saxagliptin, saxagliptin 5mg tablets and sitaglipitin placebo capsules will be administered orally once daily for a 24-week treatment period for patients with an eGFR ≥50 mL/min/1.73 m^2. For patients with an eGFR <50 mL/min/1.73 m^2, the dose of saxagliptin will be adjusted to 2.5 mg.

For patients randomized to treatment with sitagliptin, sitagliptin 100 mg capsules and saxagliptin placebo tablets will be administered orally once daily for a 24-week treatment period for patients with an eGFR ≥50 mL/min/1.73 m^2. For patients with an eGFR <50 mL/min/1.73 m^2, the dose of sitagliptin will be adjusted to 50 mg.

Saxagliptin placebo tablets and sitagliptin placebo capsules will be administered orally once daily for a 24-week treatment period for patients randomized to receive placebo.

Statistical methods

To demonstrate non-inferiority of saxagliptin compared to placebo for the change from baseline to Week 24 in LVEDV index with an assumed non-inferiority margin of 6.5 mL/m^2 , (This is

an estimate of the NI margin from publication [Foster et al]) and 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 have a missing endpoint assessment, a total of approximately 330 patients (110 patients in each of the 3 treatment groups) must be randomized in a 1:1:1 ratio to saxagliptin, sitagliptin, and placebo. Note, that the actual NI margin for the study will be calculated as 10% of the overall baseline mean LVEDV index across all treatment groups. Non-inferiority will be demonstrated if the upper bound of the 95% confidence interval for the difference in treatments (saxagliptin minus placebo) is less than the NI margin.

Randomization will be stratified by eGFR status and SGLT-2 inhibitor use, based on potential impact on the primary endpoint.

For purely administrative reasons, the randomization will also be stratified by regional drug distribution center to improve the efficiency of drug allocation.

LVEDV index and other continuous variables collected at only one visit during randomization treatment period (LVESV index, LVEF, and LVM by MRI, etc.) will be analyzed using analysis of covariance (ANCOVA) for the change from baseline at Week 24, with terms for treatment group, eGFR category (<50, ≥50 mL/min/1.73 m^2), SGLT-2 inhibitor use, region, and baseline value as covariates in the model. Point estimates and 95% confidence intervals will be calculated for the adjusted mean changes within each treatment group as well as for the differences in adjusted mean changes between treatment groups.

NT-proBNP and other continuous variables collected at more than one visit during randomized treatment period (biomarkers, HbA1c, body weight, percent change of plasma volume by Strauss formula, blood pressure, etc.) will be analyzed using a mixed-model repeated-measures (MMRM) approach with terms for treatment group, eGFR category (<50, ≥50 mL/min/1.73 m^2), SGLT-2 inhibitor use, region, baseline value, time (each relevant visit), the interaction of treatment and time, and the interaction of baseline value and time in the model. Point estimates and 95% confidence intervals will be calculated for the adjusted mean changes within each treatment group, as well as for the differences in adjusted mean changes between treatment groups. Biomarkers or data with extremely skewed distribution may be log transformed prior to ANCOVA or MMRM analysis.

Plasma concentrations of saxagliptin, 5-hydroxy saxagliptin and sitagliptin will be used to develop exploratory PK/PD models, which may be reported separately from the clinical study report.

The efficacy analyses will be performed based on the full analysis set (FAS). No multiplicity control will be applied for the statistical comparisons.

Safety analyses for the double-blind treatment period will be performed using the safety analysis set, including data after the addition of glycemic concomitant medication or change of heart failure concomitant medication. Safety analyses will include, where appropriate, descriptive

statistics, counts, and percentages for AEs and other safety measures. No formal statistical tests will be performed for safety endpoints.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ACE inhibitor	Angiotensin converting enzyme inhibitor
AE	Adverse event
ALT	Alanine transaminase
AF	Atrial fibrillation/flutter
ANCOVA	Analysis of covariance
ARB	Angiotensin receptor blocking
AST	Aspartate transaminase
eCRF	electronic Case Report Form
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
CV	Cardiovascular
CVD	Cardiovascular disease
DAE	Discontinuation of Investigational Product due to Adverse Event
DCCT	Diabetes Control and Complications Trial
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
DPP4	Dipeptidyl peptidase-4
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ETD	Early Treatment Discontinuation
FA	Full analysis
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GLP-1	Glucagon-like peptide-1
HF	Heart failure

Abbreviation or special term	Explanation
HFrEF	Heart Failure with reduced Ejection Fraction
hHF	hospitalization for heart failure
HbA1c	glycosylated hemoglobin
hs-CRP	high-sensitivity C-reactive protein
CCI	[redacted]
HR	Hazard Ratio
ICH	International Conference on Harmonisation
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational Product
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LSLV	Last Subject Last Visit
LVEF	Left Ventricular Ejection Fraction
LVEDV	Left Ventricular End Diastolic Volume
LVESV	Left Ventricular End Systolic Volume
LVM	Left ventricular mass
MACE	Major adverse cardiovascular event
MRA	Mineralocorticoid receptor antagonist
MMRM	Mixed-model repeated-measures
MRI	Magnetic Resonance Imaging
NGSP	National Glycohemoglobin Standardization Program
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association
OAE	Other Significant Adverse Event
OGTT	Oral glucose tolerance test
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per protocol
PV	Plasma volume

Abbreviation or special term	Explanation
RCV	Red blood cell volume
SAE	Serious adverse event
S_{cr}	Serum creatinine
SD	Standard deviation
SGLT-2	Sodium-glucose cotransporter 2
SMC	Safety Monitoring Committee
SU	Sulfonylurea
TECOS	Trial Evaluating Cardiovascular Outcomes with Sitagliptin
T2DM	Type 2 diabetes mellitus
TZD	Thiazolidinedione
TB	Total Bilirubin
CCI	[redacted]
VIVIDD	Vildagliptin in Ventricular Dysfunction Diabetes
WBDC	Web Based Data Capture
WHO	World Health Organization

1 INTRODUCTION

1.1 Background and rationale for conducting this study

Type 2 Diabetes mellitus (T2DM) is a chronic progressive disease, characterized by hyperglycemia and an increased risk of microvascular and macrovascular complications. CV disease is by far the greatest cause of death in individuals with diabetes (Skyler et al 2009). Diabetes is also a significant and often underappreciated risk factor for the development of heart failure. Diabetics are 2.5-fold more likely to develop HF than patients without diabetes, (Nichols et al 2004). The pathogenesis of heart failure among patients with diabetes is multifactorial with coronary artery disease, hypertension, diabetic cardiomyopathy, and extracellular fluid expansion playing major contributory roles (Foster et al 1998, Gilbert and Krum 2015).

Therapeutic options for treatment of T2DM in patients with heart failure are more limited, as there is uncertainty about the safety of many diabetes therapies in these patients. There is a need for carefully performed studies to characterize the safety of newer therapies in patients with known HF.

Saxagliptin

Saxagliptin is a highly potent, selective, reversible, and competitive dipeptidyl peptidase-4 (DPP4) inhibitor. DPP4 is the enzyme responsible for the inactivation of glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP). By inhibiting the enzyme DPP4, saxagliptin potentiates active endogenous GLP-1 concentrations, augmenting the physiological mechanism of insulin secretion and decreasing glucagon release, thereby reducing postprandial and fasting glucose levels in patients with T2DM. The clinical development program for saxagliptin supports its efficacy in a wide range of patients with T2DM, as monotherapy, as add-on therapy (to metformin, a sulfonylurea, a thiazolidinedione (TZD), or insulin), and as initial therapy in combination with metformin. Saxagliptin has a well-established safety profile, with a low risk of hypoglycemia and weight neutrality (Hirshberg et al 2014). Details on the efficacy and safety of saxagliptin can be found in the ONGLYZA™ prescribing information and Investigator Brochure.

Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (the SAVOR study)

SAVOR was designed to investigate the cardiovascular safety of saxagliptin. It was a multicenter, randomized, double-blind, placebo-controlled study in 16492 patients with type 2 diabetes who had a history of, or were at risk for, cardiovascular events that followed patients for a median of 2.1 years. SAVOR enrolled 2105 patients (12.8%) with a prior history of heart failure; 2576 (15.6%) had impaired renal function (eGFR ≤50 mL/min). The SAVOR study met its primary safety objective by demonstrating saxagliptin was non-inferior to placebo for the primary composite MACE endpoint of CV death, non-fatal MI, or non-fatal ischemic stroke; hazard ratio (HR) 1.00 (95% CI 0.89, 1.12). However, superiority of saxagliptin versus placebo on the composite MACE endpoint was not demonstrated (p=0.986). For the secondary composite endpoint of non-fatal MI, non-fatal stroke, CV death, hospitalization for heart failure (hHF), hospitalization for unstable angina, or hospitalization for coronary revascularization, no statistically significant treatment differences were observed between saxagliptin and placebo (HR 1.02 [95% CI 0.94, 1.11]; nominal p=0.662 for a difference between the 2 treatment groups). However, for the hHF component of the secondary composite endpoint, more events were observed with saxagliptin treatment compared with placebo (3.5% [289/8280 patients] versus 2.8% [228/8212 patients]; HR 1.27; 95% CI 1.07, 1.51; nominal p=0.007). There is no definitive mechanism to explain the hHF findings in SAVOR. No signal for heart failure was observed in preclinical studies, other studies in the clinical development program, or in post-marketing surveillance.

No heart failure signal was observed in TECOS (Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin). TECOS was a multicenter, randomized, double-blind, placebo-controlled study in 14671 patients with type with T2DM and established CV disease. Sitagliptin was non-inferior to placebo for the primary composite outcome of CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina (HR 0.98 [95% CI 0.88 to 1.09]; p=0.99 for superiority; p<0.001 for non-inferiority). Rates of hHF did not differ between the 2 groups (HR 1.00 [95% CI 0.83 to 1.20]; p=0.98, Green et al 2015). Reasons for the lack of a heart failure signal in TECOS, compared with SAVOR, may relate to differences in patient populations, the type of background care provided, the

capturing and adjudication of hHF events, differences among DPP4 inhibitors, or play of chance.

1.1.1 Rationale for the study design, doses, treatment and control groups

Because no mechanism for the increase in hHF observed in SAVOR has been identified, the current study is planned to investigate whether treatment with saxagliptin might affect cardiac dimensions, cardiac function, changes in plasma volume, and relevant blood and urine biomarkers.

This is a 24-week, randomized, double-blind, parallel-group, placebo-controlled, multicenter study. Approximately 330 patients with T2DM and HF will be randomized in equal proportions (110 patients per group) to treatment with saxagliptin, sitagliptin, or placebo. The study's primary objective is to exclude a meaningful increase in left ventricular end diastolic (LVEDV) index of greater than 10% for saxagliptin compared with placebo using magnetic resonance imaging (MRI). The rationale for choosing this endpoint is based on the findings of the Vildagliptin in Ventricular Dysfunction Diabetes (VIVIDD) study. VIVIDD was an echocardiographic study performed in patients with HF and LVEF <40%. The study met its primary endpoint of non-inferiority between vildagliptin versus placebo for a change in LVEF over 52 weeks, but unexpectedly found that treatment with vildagliptin was associated with a significant increase in LVEDV and a trend towards an increase in left ventricular end systolic volume (LVESV, McMurray et al 2013). For the present study, LVEDV index will be the primary endpoint and cardiac MRI, rather than echocardiography, has been chosen for the assessment of the primary endpoint because of its high accuracy and reproducibility (Grothues et al 2002).

Events of hHF occurred at a consistent rate throughout the SAVOR study. However, most of the difference in the rate of events between saxagliptin and placebo accrued in the first 6 to 9 months of treatment, with little increase in this difference afterward. The MRI primary endpoint analysis will be conducted at 24 weeks (by which time over three-fourths of the hHF events in SAVOR had occurred) to also investigate the potential for remodelling changes to occur.

In addition to the saxagliptin and placebo arms, there is another active antidiabetic treatment arm sitagliptin. Sitagliptin has been chosen as a reference DPP4 inhibitor that has not been associated with an increase in hHF in TECOS.

Sitagliptin

Sitagliptin is an orally active DPP4 inhibitor that is marketed as JANUVIA™ (Merck & Co) for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. Details on the efficacy and safety of sitagliptin can be found in the JANUVIA™ prescribing information.

1.2 Benefit/risk and ethical assessment

As stated in Section 1.1, an excess in heart failure hospitalizations was observed in the SAVOR trial. However, a mechanism to explain these findings has yet to be identified and an increase in hospitalization for heart failure was not observed in the TECOS study with sitagliptin. Saxagliptin and sitagliptin are effective anti-diabetic agents that have been extensively studied in clinical trials, are approved worldwide, and have substantial postmarketing experience with well-established safety profiles. For information on saxagliptin, please consult the respective Investigator Brochure; for sitagliptin, please refer to its Product Label.

Benefits related to participation in this trial include close follow-up of a patient's diabetes and treatment with anti-diabetes agents that are both efficacious and well tolerated. While one of the three possible treatments is placebo, patients will continue to be treated with their current anti-glycemic regiments as background therapy. Furthermore, appropriate rescue therapy for worsening glycemic control should be implemented if required, as recommended in Section 7.7.2.1.

Although the findings from SAVOR suggest that saxagliptin therapy could potentially result in an increased risk for hospitalization for heart failure, patients in this study will be closely monitored for signs and symptoms of worsening heart failure with frequent study visits. In SAVOR, therapy with saxagliptin was not associated with an increase in CV death, myocardial infarction, or stroke, even among patients with baseline risk factors for hHF. As previously discussed, sitagliptin has not been associated with an increase in hHF.

Further, study data on cardiac function, biomarkers, and plasma volume may result in improved patient management, on both an individual and population basis.

1.3 Study Design

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 abnormal 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. The calculated sample size is expected to yield approximately 88 patients per group with complete data (ie, patients with a nonmissing primary endpoint assessment). In this study, sites will perform a pre-study screening assessment prior to enrollment visit to screen for eGFR criteria. Patients must have an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2 at pre-screening to qualify for enrollment. Following Informed Consent, all potentially eligible patients will be enrolled and undergo screening for all applicable inclusion/exclusion criteria. The pre-screening value of eGFR can be used to qualify a patient for randomization.

Patients can enter screening as soon as laboratory pre-screening results for eGFR are available provided the patient meets the inclusion/exclusion criteria. The total duration of the pre-screening and screening periods should not exceed 28 days.

Patients with a recent (within 1 month) eGFR value will be allowed to enter the screening directly without pre-screening procedures performed.

Patients who do not qualify for the protocol based upon their pre-screening or screening results may have additional attempts to qualify. There may be no more than 3 attempts in total. If the patient failed to qualify during screening period (including, but not limited due to study supplies, equipment failure, unforeseen personal events that mandate missed screening visits, or out-of-range laboratory/clinical tests), the patient may potentially be re-screened. These cases should be discussed with the AstraZeneca Monitor and documented in the Investigator Study File (ISF). The investigator may use his/her judgment regarding the interval between screening periods. The Investigator must track all attempts in the form of a log at the site. Re-screened patients should re-sign informed consent on the re-screening visit. All procedures from screening period should be repeated.

The study will comprise a pre-screening period (optional – see section 3.3) and screening period that in total should not exceed 28 days, 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 treatment period will be asked to return for an end-of- study visit at Week 28. The schedule of study assessments is shown in Table 2.

Study treatment will be administered once daily, according to randomized treatment allocation. For patients with an eGFR ≥50 mL/min/1.73 m^2, 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 m^2, the doses of the active treatments will be adjusted as follows: saxagliptin 2.5 mg and sitagliptin 50 mg.

MRI to evaluate cardiac dimensions, and function will be performed at baseline (<= 7 days prior to randomization), and at 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.

Changes in plasma volume will be measured using the Strauss formula, as has been utilized in the EPHESUS study (Kalra et al 2002; Strauss et al 1951; Rossignol PR et al 2011).

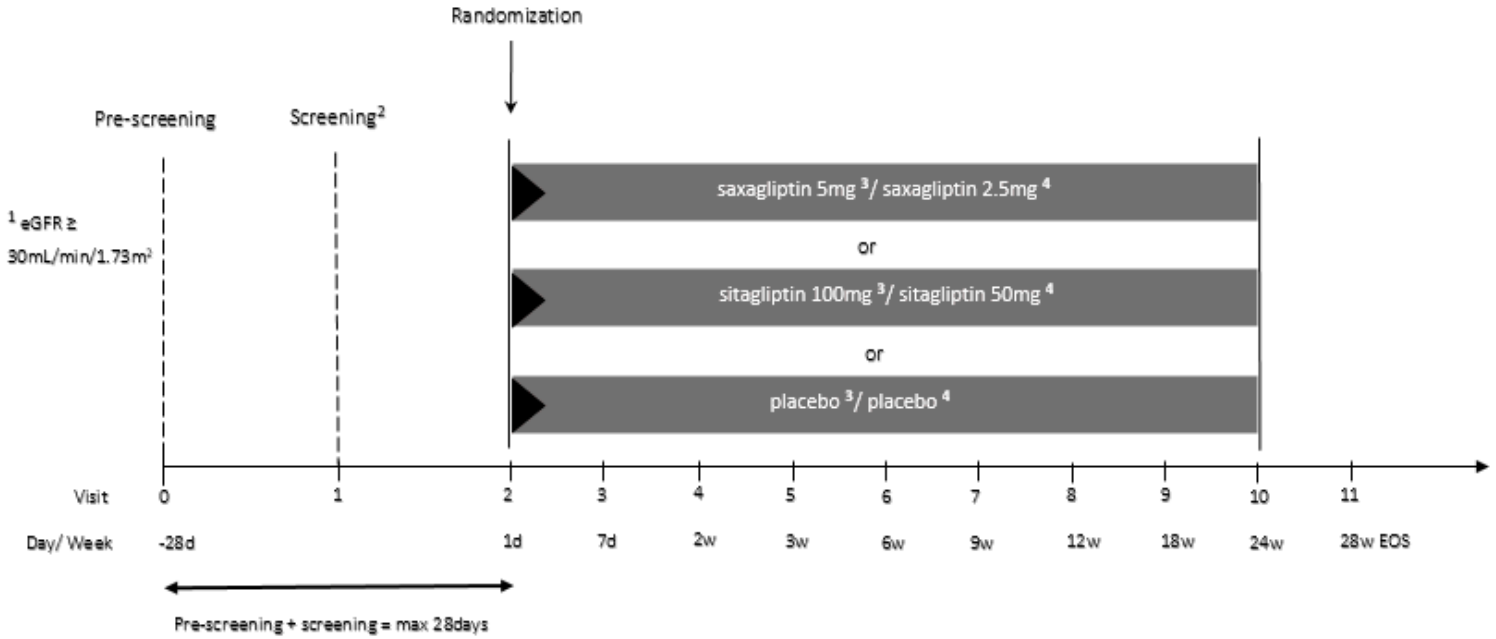
During the study, patients will continue to receive their usual, stable treatment regimens for diabetes and HF as prescribed by their physicians. Medications for diabetes and HF, including diuretic dose, should continue unchanged, unless there is a change in the patient's clinical status. Changes in diabetes and HF medications, including dose, must be recorded in the electronic case report form (eCRF). In cases where doses of medications, including diuretics, require adjustment, patients should be encouraged to remain in the trial and

complete all regularly scheduled study assessments. If a patient discontinues early from the study, he or she should be asked, at the discretion of the treating physician, to return to the study site as soon as possible but no later than 7 days from the last IP dose. All endpoint (Week 24/ETD) assessments, including cardiac MRI, and blood and urine biomarker assessments, must be performed at this visit. The patient should also be asked to return 4 weeks later for end of study (Week 28) assessments. If the patient is unable or unwilling to return, a phone follow-up should be conducted.

Table 1 Recruitment information

Category	Number of patients
Expected number of screened patients	660
Expected number of randomized patients	330
Expected number of complete primary endpoint data	264
Expected screen failures including pre-screened patients (%)	50
Expected non-evaluable rate of incomplete primary endpoint data (%)	20

Figure 1 Study flow chart



[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 labortory pre-screening result for eGFR is available and it is determined that the value meet the inclusion/exclusion criteria

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

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

2 STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To exclude an increase in 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

2.2 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

2.3 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)]

2.4 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

3 PATIENT SELECTION, PRE-SCREENING, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. Provision of informed consent prior to any study specific procedure (Pre-screening ICF and Informed Consent collected at screening)

2. Male or female, aged ≥18 years at the time of consent

3. Documented, controlled T2DM, as defined by:

   – Diagnosis of Type 2 DM based on current ADA guidelines (Appendix C)

     Treatment with stable doses of antidiabetic medications that have not increased or decreased for ≥8 weeks before screening

   – For patients taking insulin, the investigator must query the patient at pre-screening or screening regarding his/her usual total daily insulin dose (all types combined) during the previous 8 weeks. Insulin dosages during pre-screening and screening should not vary by more than ±20% on more than two occasions

   – Dosage reductions of insulin and sulfonylurea agents may be considered at randomization to minimize the possibility of hypoglycemia

     • Any reductions in the dosage of insulin and sulfonylurea agents will be at the discretion of the investigator

     • For patients treated with insulin, consider a reduction in dose of 20% at randomization

     • For patients receiving sulfonylurea agents, consider a reduction in dose of 50% or discontinue if on a dosage that is considered low at randomization

4. HFrEF demonstrated by all 3 of the following criteria:

   – History of HF and LVEF ≤45% within the last 6 months (echocardiogram, MRI, left ventriculography, or other accepted methodology). Patients without a recent assessment of LV function will undergo a local echocardiogram at the time of screening to determine ejection fraction

   – Elevated NT-proBNP (>300 pg/mL) during screening

   – Patients should receive background standard of care for HFrEF and be treated according to locally recognized guidelines as appropriate. Guideline-recommended medications should be used at recommended doses unless contraindicated or not tolerated. Therapy should have been individually optimized and stable for >or = 4 weeks (this does not apply to diuretics-see NB below) before screening visit and include (unless contraindicated or not tolerated):

   – an ACE inhibitor, or ARB, or sacubitril/valsartan

   – and

- a beta-blocker
- and
- if considered appropriate by the patient's treating physician; a mineralocorticoid receptor antagonist (MRA)
- NB: Most patients with heart failure require treatment with a diuretic to control sodium and water retention leading to volume overload. It is recognized that diuretic dosing may be titrated to symptoms, signs, weight, and other information and may thus vary. Each patient should, however, be treated with a diuretic regimen aimed at achieving optimal fluid/volume status for that individual

5. Stable HF, with no evidence of volume overload (no rales, jugular venous distention, peripheral edema) at screening

6. Women of childbearing potential (WOCBP):

- Must be using appropriate birth control to avoid pregnancy throughout the study and for up to 4 weeks after the last dose of investigational product
- Must have a negative serum or urine pregnancy test within 72 hours prior to the start of investigational product
- Must not be breastfeeding

3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. MRI contraindications: all implanted defibrillators; implanted pacemakers and other devices/implants that in the judgment of the investigator preclude an MRI evaluation

2. Patients with atrial fibrillation/flutter, or any rhythm that would impact on MRI imaging quality would be excluded. Patients with a prior history of atrial fibrillation or paroxysmal atrial fibrillation may be eligible for entry into the study based on the investigator's judgment related to the frequency of AF events and the patient's overall condition

3. Body mass index >45 kg/m^2 or any condition, including, but not limited to known claustrophobia, that may preclude the ability to perform an MRI scan of acceptable quality, or unwillingness to undergo MRI imaging

4. Receiving incretin therapy (DPP4 inhibitors, GLP-1 mimetics), or having received incretin therapy within the previous 8 weeks of randomization

5. Receiving therapy with a TZD or having received TZD therapy within the previous 8 weeks of randomization

6. Type 1 diabetes mellitus

7. History of unstable or rapidly progressing renal disease

8. A central lab eGFR value <30 mL/min/1.73 m^2 on pre-screening or screening

9. New York Heart Association (NYHA) Class IV HF

10. Myocardial infarction, stroke, transient ischemic attack, or coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]) within the past 3 months of screening

11. Inoperable aortic or mitral valvular heart disease. Recent (within 3 months) or planned valvular heart procedure

12. Heart failure secondary to restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, and hypertrophic obstructive cardiomyopathy

13. Previous cardiac transplantation or transplantation indicated or expected within 6 months of randomization

14. Contraindications to saxagliptin therapy as outlined in the saxagliptin Investigator's Brochure, or to sitagliptin therapy as outlined in the sitagliptin prescribing information

15. Current treatment with strong cytochrome P450 (CYP) 3A4/5 inhibitors

16. Involvement in the planning and/or conduct of the study (applies to both AZ staff and/or staff at the study site)

17. Previous enrollment which disqualifies patient from re-enrollment based on the rules in Section 4.1 of the protocol, or previous randomization in the study

18. Participation in another clinical study with an investigational product during the last 30 days

19. Patients either employed by or immediate relatives of the Sponsor

20. Known human immunodeficiency virus (HIV) infection

21. Severe hepatic disease, including chronic active hepatitis. Positive serologic evidence of current infectious liver disease, including patients who are known to be positive for hepatitis B viral antibody IgM, hepatitis B surface antigen, or hepatitis

C virus antibody; or aspartate transaminase (AST) or alanine transaminase (ALT) >3X the upper limit of normal; or total bilirubin (TB) >2 mg/dL

22. Active malignancy requiring treatment at the time of Visit 1(with the exception of successfully treated basal cell or treated squamous cell carcinoma).

23. Pregnant, positive pregnancy test, planning to become pregnant during clinical trial or breast feeding

24. History of any clinically significant disease or disorder which, in the opinion of the investigator, may put the patient at risk because of participation in the study, may influence the results, or may limit the patient's ability to participate in or complete the study

25. Unable or unwilling to provide written informed consent

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient pre-screening, enrollment and randomization

Investigators must keep a record of patients who entered pre-screening in the form of a log with assigned code associated with the Lab Kit used for pre-screening procedures. The pre-screening visit will not be captured in the eCRF. The investigator shall also keep a log of all patients who entered screening. Patients with a recent (within 1 month) eGFR value (the Scr value used for the eGFR calculation should be accurate to two decimal places) will be allowed to enter the screening directly without pre-screening procedures performed and only the main informed consent form will be signed. See section 4.1.1.

Patients who do not qualify for the protocol based upon their pre-screening or screening results may have additional attempts to qualify. There may be no more than 3 attempts in total. If the patient failed to qualify during screening period (including, but not limited due to study supplies, equipment failure, unforeseen personal events that mandate missed screening visits, or out-of-range laboratory/clinical tests), the patient may potentially be re-screened. These cases should be discussed with the AstraZeneca Monitor and documented in the Investigator Study File (ISF). The investigator may use his/her judgment regarding the interval between screening periods. The Investigator must track all attempts in the form of a log at the site. Re-screened patients should re-sign informed consent on the re-screening visit. All procedures from screening period should be repeated.

The Investigators will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed. Separate, specific ICFs will be collected before pre-screening and screening procedures.

2. Assign the patient a unique pre-screening code associated with Lab Kit used for pre-screening procedures.

After positive verification of pre-screening criteria, the investigator will assign potential patients a unique enrollment number via IVRS/IWRS beginning with 'E#' during screening.

3. Determine patient eligibility. See Sections 3.1 and 3.2

   At the randomization visit, once the patient is confirmed to be eligible, the Principal Investigator or suitably trained delegate will:

4. Assign the eligible patient a unique randomization number via IVRS/IWRS.

If a patient withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused.

Randomization codes will be assigned strictly sequentially as patients become eligible for randomization.

3.4 Procedures for handling incorrectly enrolled or randomized patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment.

Where a patient does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Eligible patients will be randomized to receive either saxagliptin or sitagliptin orally once daily or matching placebo in a 1:1:1 (saxagliptin, sitagliptin, placebo) ratio using the IVRS/IWRS system.

Randomization will be stratified by eGFR status and SGLT-2 inhibitor use, based on potential impact on the primary endpoint.

For purely administrative reasons, the randomization will also be stratified by regional drug distribution centre to improve the efficiency of drug allocation.

The proportion of randomized patients with an eGFR of ≥30 and <50 mL/min/1.73 m^2 will be limited to 30% or a maximum of 99 patients.

For patients with an eGFR ≥50 mL/min/1.73 m^2, 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 m^2, the doses of the active treatments will be adjusted as follows: saxagliptin 2.5 mg and sitagliptin 50 mg.

If a patient is discontinued from the study, his/her randomization or enrollment number will not be reused, and the patient will not be allowed to re-enter the study. Randomized patients who discontinue early from the study will not be replaced.

3.6 Methods for ensuring blinding

Investigational product (IP, also referred to as 'study drug' in this protocol) will be labelled using a unique material kit ID, which is linked to the randomization code. The IVRS/IWRS will assign the bottles of study material to be dispensed to each patient. This is a double-blind study wherein each patient will receive either the active drug or matching placebo. The active drug and placebo tablets and capsules will be identical and presented in identical packaging to ensure blinding of the medication.

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment allocation for each randomized patient, will be available to the investigator(s) or pharmacists from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each center.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

The following personnel will be unblinded as to the exact content of investigational treatments

(ie, the randomization code):

- Personnel carrying out the packaging and labelling of investigational treatment
- Personnel generating the randomization list.
- Personnel analyzing the pharmacokinetic samples.
- Personnel overseeing the overall supply chain.

No other personnel involved in the conduct of the study may have access to this information, which will be maintained in a secure location until after clean file and database lock have been declared. The sole exception will be in the event the PI determines knowledge of investigational treatment allocation to be essential for appropriate clinical management of a patient.

The randomization list will be kept in a secure location until the end of the study.

3.8 Restrictions

The following restrictions apply while the patient is receiving study drug and for the specified times before and after:

Once screened and qualified for entry, patients will be instructed as follows:

- Fast for at least 8 hours prior to the randomization visit and each study site visit at which fasting plasma glucose is obtained (Weeks 6, 12, and 24, as well as Week 18 if the patient was rescued at Week 12), ie, no food or beverage except water, until glycemic assessments scheduled for that day are performed. Allowed medications can be taken with water only*. Delay administering the IPs (as applicable) on the day of the clinic visit and bring study medication to each study site visit*
- Refrain from alcohol intake and intense exercise 24 hours prior to each visit and recommend not to use tobacco/nicotine within 12 hours prior to each visit*
- Do not donate blood for the duration of the study and for 3 months following the last study visit
- Comply with prescribed dosing regimen to preserve study integrity and ensure patient safety
- Discuss any new prescriptions and over-the-counter or herbal/nutritional therapies with the investigator, as concomitant use could result in alterations to their glycemic control and may place them at risk for significant hypoglycemic episodes
- Women must immediately contact the investigator if they suspect they might be pregnant and if they have changed or plan to change their birth control method.

*If a patient comes to a visit without having followed the above instructions, then the patient should be re-scheduled for the entire visit (if possible within the allowed time-window). The Sponsor or designee should be contacted if the investigator is informed of any restriction violations.

Women of childbearing potential (including perimenopausal women who have had a menstrual period within 1 year) must practice, and be willing to continue to practice,

appropriate birth control. As applicable, all methods must be in effect before the patient takes the first dose of study medication.

All concomitant medications should be captured on the electronic case report form (eCRF).

The following medications are prohibited from up to 8 weeks prior to study randomization and during randomized treatment:

- Incretin therapy (DPP4 inhibitors, GLP-1 mimetics)
- Therapy with thiazolidinedione agents (TZDs)
- Strong CYP3A4/5 inhibitors (see section 7.7.3)
- Background therapy with stable dosages of SGLT-2 inhibitors is permitted in patients qualifying for the study and can continue during the randomized treatment period. SGLT-2 inhibitors cannot be initiated or their dosages modified during randomized treatment or used as rescue therapy

3.9 Discontinuation of investigational product

Patients may be discontinued from investigational product (IP) in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment. Patients who choose to discontinue study treatment are expected to continue in the study until the end of the study as described in the Section 3.9.1 of the protocol.
- Safety reasons as judged by the investigator or by AstraZeneca representative
- Adverse Event
- Severe non-compliance with the study protocol as judged by the investigator and/or AstraZeneca
- Pregnancy (discontinue IP and notify AstraZeneca representative). See Section 6.6
- eGFR < 30 mL/min/1.73m^2
  - if at any time the patient´s eGFR (calculated by MDRD) falls below 30 mL/min/1.73m^2 and is confirmed at a repeated calculation (the re-test should be scheduled within 7 days), the patient should be discontinued from IP
- ALT and/or AST >3 x ULN and TB >2 x ULN
- ALT and/or AST >5 x ULN for ≥14 consecutive days, at any time after initial confirmatory results

- ALT and /or AST >8 x ULN

- Incorrectly enrolled patients (see Section 3.4)

Cases in which patients are incorrectly randomized (ie, the patient does not meet the required inclusion/exclusion criteria for the study), should be discussed with AstraZeneca representative prior to any actions being taken (see Section 3.4).

3.9.1 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue investigational product or withdraw from the study (ie, investigational product and assessments – see Section 3.10), without prejudice to further treatment. A patient who decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s).

All patients that are randomized will be followed until the end of the study. If a patient temporarily discontinues from study medication, it is the intention that the scheduled study visits, data collection and procedures continue according the study protocol until the study ends.

If a patient permanently discontinues from the study medication, he or she should be asked, at the discretion of the treating physician, to return to the study site as soon as possible, but not later than 7 days from last IP dose. All endpoint (Week 24/ETD) assessments, including cardiac MRI, and blood and urine biomarker assessments, must be performed at this visit. All study drugs should be returned by the patient. The patient should also be asked to return 4 weeks later for end of study (Week 28) assessments. If the patient is unable or unwilling to return, a follow up by phone call should be conducted. Adverse events will be collected throughout the treatment period and SAEs will be collected up to 4 weeks after the end-of-study visit or an Early Treatment Discontinuation Visit (see Section 6.3.1).

Only if a patient has explicitly refused to attend any visit or to have any future contact, including telephone follow up, then the patient is considered to have withdrawn informed consent (see Section 3.10.2).

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as ‘Screen Failure’ (ie. patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomized patients).

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment.

A patient who desires to withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any adverse events (AE). The investigator will follow up AEs outside of the clinical study. If a patient expresses a desire to withdraw from the study, modified follow up options, including telephone follow up, should be offered as an alternative. The patient will also be asked if they agree to the use of previously donated, stored biological samples for the purposes of research (see Section 5.6.4). Once withdrawal of consent is confirmed, no further patients visits or contact can occur.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of Executive Committee and AstraZeneca, trial patients are placed at undue risk because of clinically significant findings that:

- Meet individual stopping criteria or are otherwise considered significant
- Are assessed as causally related to study drug
- Are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

4 STUDY PLAN AND TIMING OF PROCEDURES

Table 2 Study plan

Study procedure	**Pre-screening[a]**	**Screening[a]**		**Randomization**	**Randomized treatment period**								**End-of-study visit**	**For details See Protocol Section**
Study week (W) or day (D)	**D --28 to -1**		**D -7[l]**	**D1**	**D7**	**W2**	**W3**	**W6**	**W9**	**W12**	**W18**	**D-7[l] Before visit 10**	**W24 / Early Treatment Discontinuation(ETD)[b]**	**W28**	
Visit window				**±0 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**		**±5 days**	**±5 days**	
Visit number	**0**	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**		**10**	**11**	
Site visit	**X**	**X**	**X[l]**	**X**		**X**		**X**		**X**	**X**	X[l]	**X**	**X**	
Telephone follow-up					**X**		**X**		**X**						
Informed consent	X	X													4.1.1, 10.4
Demography		X													4.1.2
Medical/surgical history		X													4.1.3
Prior/concomitant treatments		X		X	X	X	X	X	X	X	X		X	X	4.1.4, 7.7.1
Inclusion/exclusion criteria		X		X											3.1, 3.2
Echocardiogram for assessment of left ventricular function[c]		X													

Table 2 Study plan

Study procedure	**Pre-screening[a]**	**Screening[a]**		**Randomization**	**Randomized treatment period**								**End-of-study visit**	**For details See Protocol Section**
Study week (W) or day (D)	**D --28 to -1**		**D -7[l]**	**D1**	**D7**	**W2**	**W3**	**W6**	**W9**	**W12**	**W18**	**D-7[l] Before visit 10**	**W24 / Early Treatment Discontinuation(ETD)[b]**	**W28**	
Visit window				**±0 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**		**±5 days**	**±5 days**	
Visit number	**0**	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**		**10**	**11**	
Site visit	**X**	**X**	**X[l]**	**X**		**X**		**X**		**X**	**X**	X[l]	**X**	**X**	
Telephone follow-up					**X**		**X**		**X**						
Magnetic resonance imaging (MRI)			X[d] (max 7 days before visit 2)									X[d] (max. 7 days before visit 10)			5.1.1.1
Complete physical examination (with focus on signs and symptoms of heart failure)		X		X						X			X		5.2.2.1
Brief physical examination (with focus on signs and symptoms of heart failure)						X		X			X			X	5.2.2.2
Height		X													5.2.3

Table 2 Study plan

Study procedure	**Pre-screening[a]**	**Screening[a]**		**Randomization**	**Randomized treatment period**								**End-of-study visit**	**For details See Protocol Section**
Study week (W) or day (D)	**D --28 to -1**		**D -7[l]**	**D1**	**D7**	**W2**	**W3**	**W6**	**W9**	**W12**	**W18**	**D-7[l] Before visit 10**	**W24 / Early Treatment Discontinuation(ETD)[b]**	**W28**	
Visit window				**±0 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**		**±5 days**	**±5 days**	
Visit number	**0**	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**		**10**	**11**	
Site visit	**X**	**X**	**X[l]**	**X**		**X**		**X**		**X**	**X**	X[l]	**X**	**X**	
Telephone follow-up					**X**		**X**		**X**						
Vital signs and body weight		X		X		X		X		X	X		X	X	5.1.3.2, 5.2.3
Clinical laboratory tests (standard hematology and clinical chemistry)		X		X				X		X			X		4.1.7, 5.2.1
Calculation of eGFR[f]	X	X[k]		X				X		X			X		4.1.6, 4.1.7
Glycosylated hemoglobin (HbA1c)				X						X			X		4.1.7, 5.1.3.1
FPG								X		X	X[e]		X		4.2.2
NT-proBNP		X		X				X		X			X		5.1.2.1

Table 2 Study plan

Study procedure	Pre-screening[a]	Screening[a]		Randomization	Randomized treatment period								End-of-study visit	For details See Protocol Section
Study week (W) or day (D)	D --28 to -1		D -7[l]	D1	D7	W2	W3	W6	W9	W12	W18	D-7[l] Before visit 10	W24 / Early Treatment Discontinuation(ETD)[b]	W28	
Visit window				±0 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days		±5 days	±5 days	
Visit number	0	1		2	3	4	5	6	7	8	9		10	11	
Site visit	X	X	X[l]	X		X		X		X	X	X[l]	X	X	
Telephone follow-up					X		X		X						
CCI [redacted]				X				X		X			X		
Blood biomarkers (plasma or serum)[g,]				X				X		X			X		5.6
CCI [redacted] [redacted] [redacted] g,				X				X		X			X		5.1.3.3, 5.6
Pharmacokinetic sampling[h]								X		X			X		5.3
Plasma volume measurement (Strauss formula)				X				X		X			X		8.4.4
Urinalysis		X													5.2.1

Table 2 Study plan

Study procedure	**Pre-screening[a]**	**Screening[a]**		**Randomization**	**Randomized treatment period**								**End-of-study visit**	**For details See Protocol Section**
Study week (W) or day (D)	**D --28 to -1**		**D -7[l]**	**D1**	**D7**	**W2**	**W3**	**W6**	**W9**	**W12**	**W18**	**D-7[l] Before visit 10**	**W24 / Early Treatment Discontinuation(ETD)[b]**	**W28**	
Visit window				**±0 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**		**±5 days**	**±5 days**	
Visit number	**0**	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**		**10**	**11**	
Site visit	**X**	**X**	**X[l]**	**X**		**X**		**X**		**X**	**X**	X[l]	**X**	**X**	
Telephone follow-up					**X**		**X**		**X**						
Serum pregnancy test (women of childbearing potential)[i]		X													4.1.9.2
Urine pregnancy test (women of childbearing potential)[i]				X		X		X		X	X		X		4.1.9.1
Hepatitis B and C test		X													3.2
New York Heart Association (NYHA) Functional Classification		X													3.2

Table 2 Study plan

Study procedure	**Pre-screening[a]**	**Screening[a]**		**Randomization**	**Randomized treatment period**								**End-of-study visit**	**For details See Protocol Section**
Study week (W) or day (D)	**D --28 to -1**		**D -7[l]**	**D1**	**D7**	**W2**	**W3**	**W6**	**W9**	**W12**	**W18**	**D-7[l] Before visit 10**	**W24 / Early Treatment Discontinuation(ETD)[b]**	**W28**	
Visit window				**±0 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**		**±5 days**	**±5 days**	
Visit number	**0**	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**		**10**	**11**	
Site visit	**X**	**X**	**X[l]**	**X**		**X**		**X**		**X**	**X**	X[l]	**X**	**X**	
Telephone follow-up					**X**		**X**		**X**						
12-lead electrocardiogram		X													4.1.8
Drug dispensing				X				X		X	X				
Collection of unused study drug								X		X	X		X		
Compliance assessment						X		X		X	X		X		7.5
Adverse event (AE) review (AEs, AEoSI, and serious AEs)		X[j]		X	X	X	X	X	X	X	X		X	X[j]	6

[a] Patient can be enrolled to screening as soon as laboratory pre-screening result for eGFR is available and it is determined that the value meet the inclusion/exclusion criteria. Total duration of pre-screening and screening periods should not exceed 28 days. Up to 3 (in total) pre-screening/screening attempts are permitted.

b If a patient permanently discontinues from the study medication, he or she should be asked, at the discretion of the treating physician, to return to the study site as soon as possible but no later than 7 days from the last IP dose. All endpoint (Week 24/ETD) assessments, including an MRI and blood and urine biomarker assessments, must be performed at this visit. All study drugs should be returned by the patient.

c If no LV assessment has been performed within the 6 months prior to screening. If required, the test can be performed locally.

d RANDOMIZATION: The MRI must be performed before randomization and drug dispensing but no more than 7 days prior to Day 1. The MRI scan of acceptable quality must be confirmed before the patient is randomized and takes study medication. If a repeat MRI is required, it may be performed within 7 days of the prior scan and the randomization visit should be rescheduled if necessary to allow confirmation of quality before randomization and dosing.
WEEK 24: An MRI scan of acceptable quality must be confirmed before the visit occurs. Therefore, the MRI can be performed in advance of the planned visit but no more than 7 days. If a repeat MRI is required, it may be performed within 7 days of the prior scan. If necessary, the Week 24 visit should be re-scheduled until after the MRI has been qualified as acceptable and the patient should continue study medication.
cMRI assessment must be performed and approved according to Investigator Site Operations Manual and Image Acquisition Guideline.
A urine pregnancy test must be performed in women of child bearing potential before each MRI.

e A fasting plasma glucose at week 18 will only be required for individuals who require 'rescue' therapy at Week 12

f eGFR will be calculated by the central laboratory.

g Ideally to be obtained at the same time of day throughout the study, but max. ±6 hours' time window is acceptable. Biological samples (urine and blood) will be collected and will be analyzed for exploratory biomarkers to assess correlations with study endpoints and effects of study drug. The biomarkers assessed in the study include NT-proBNP, CCI [redacted]. Additional blood and urine samples may be assayed either during the study or stored for potential future analyses of other renal, cardiac, inflammatory, and metabolic disease-specific biomarkers. Those measurements, as well as other potential relevant biomarkers, will be performed at Sponsor`s discretion.

h Blood samples will be obtained at each visit indicated for analysis of trough plasma drug concentrations. Therefore, on these days, patients must take their study medication at the study site, after a pre-dose blood sample is collected. At Week 6 and 24 blood samples for PK analysis will be collected pre-dose only, while at Week 12 the blood samples will be collected pre-dose and at 30, 60, 120, and 180 minutes post dose for determination of plasma concentration – time profiles. In all cases, the time of day and date of the dose given prior to the trough sample being drawn and on the visit day at Week 12 must be recorded.

i A serum pregnancy test must be performed at screening. Urine pregnancy tests must be performed before the MRI and at Week 24 (or the final visit, if the patient discontinues early), and at all other on-site visits during the randomized treatment period.

j SAEs only - SAEs are collected from screening until follow-up at Week 28.

k eGFR must be obtained at screening visit, if no central laboratory value was obtained during pre-screening due to presence of recent local laboratory values (within 1 month) in patient medical history.

l Procedure that needs to be performed before the visit at the site – see Section 5.1.1.1

4.1 Pre-screening/Enrollment/screening period

The study will comprise a pre-screening and screening periods of up to 28 days. Study procedures and timing required during enrollment/screening period are indicated in the Study Plan, Table 2.

At pre-screening and screening, consenting patients are assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be enrolled in the study.

All patients will be required to provide consent to supply biological samples for entry into this study. This consent is included in the main patient informed consent form.

Patients who do not qualify for the protocol based upon their pre-screening or screening results may have additional attempts to qualify. There may be no more than 3 attempts in total. If the patient failed to qualify during screening period (including, but not limited due to study supplies, equipment failure, unforeseen personal events that mandate missed screening visits, or out-of-range laboratory/clinical tests), the patient may potentially be re-screened. These cases should be discussed with the AstraZeneca Monitor and documented in the Investigator Study File (ISF). The investigator may use his/her judgment regarding the interval between screening periods. The Investigator must track all attempts in the form of a log at the site. Re-screened patients should re-sign informed consent on the re-screening visit. All procedures from screening period should be repeated

4.1.1 Pre-screening Informed Consent Form & Informed Consent Form (ICF)

The Pre-screening informed consent for Protocol D1680C00016 is an abbreviated document that explains the risks associated with the screening laboratory tests for eGFR performed to assess qualification to the study. This document will provide only general information about the study, without the need to provide any specific details about the study procedures, and risks or benefits from study participation. The Pre-screening ICF will also document the patient's consent to return to the enrollment visit (Visit 1) in case they are considered eligible for the study.

For any patient that undergoes the pre-screening procedure and is considered eligible to participate in the study, the full Informed Consent for Protocol D1680C00016 will be provided at the enrollment (Visit 1) See section 10.4.

4.1.2 Demography

Demographic characteristics such as age, gender, race, and ethnicity will be collected. Date of birth will be collected if allowed by local regulations.

4.1.3 Medical/surgical history

A complete medical/surgical history will be performed at screening and will include current medical conditions, past or present, and any diseases or disorders. Surgical procedures within the previous 5 years will be collected at screening.

4.1.4 Prior/concomitant treatments

At screening, all concomitant medications will be recorded. All new concomitant medication started during the treatment period must be reported. See Section 7.7 for more information on concomitant medications.

4.1.5 Inclusion/Exclusion criteria

Patients will be assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be enrolled in the study.

4.1.6 Estimated glomerular filtration rate (eGFR)

Estimated GFR will be calculated from serum creatinine (S_{cr}) according to the Modification of Diet in Renal Disease (MDRD) formula and the eGFR value will be provided with accuracy to two decimal places.

Estimated GFR will be calculated using the MDRD formula (Levy et al 2006):

eGFR (mL/min/1.73 m^2) = 175 x $(S_{cr})^{-1.154}$ x $(Age)^{-0.203}$ x 1.212 (if African American) x (0.742 if female)

For the purpose of eGFR calculation the creatinine value will be provided with accuracy to two decimal places.

The eGFR will be used for verification of patient eligibility criteria during pre-screening, and will also be calculated at randomization and visit 6 (week 6), visit 8 (week 12) and visit 10 (week 24). It will also be used to determine the dosage of saxagliptin and sitagliptin at randomization and the need for dose adjustment during the treatment period. Please refer to Section 7.2.

Patients who, during the course of the study, develop eGFR <50mL/min/1.73m^2 based on the central laboratory serum creatinine value, will be scheduled for a follow-up visit (within 7 days) to obtain a second central laboratory serum creatinine value and to repeat the calculation of eGFR. If the repeat eGFR is still <50mL/min/1.73m^2, the patient's dose of IP will be adjusted. The patient must be invited for an additional visit to receive the down-titrated IP within 3 days after results arrival at the site.

The dose adjustments will be to 2.5 mg saxagliptin, 50 mg sitagliptin, or matching placebo. Once reduced to 2.5 mg saxagliptin, 50 mg sitagliptin or placebo, there will be no further dose-adjustment even if the eGFR subsequently increased sufficiently to meet initial requirements for the 5 mg saxagliptin and 100 mg sitagliptin dosing regimen. The IVRS/IWRS will be used to allocate the adjusted IP.

If at any time the patient´s eGFR falls below 30 mL/min/1.73m^2 and confirmed at a repeated calculation (the re-test should be scheduled within 7 days), the patient should be discontinued from IP, see Section 3.9.1.

4.1.7 Clinical laboratory test

At the pre-screening visit only the creatinine (for eGFR calculation) will be measured.

At screening a laboratory panel (standard hematology and clinical chemistry) will be obtained.

Pre-screening/screening values will be used at the randomization visit. Please refer to section 5.2.1, and Study Plan, Table 2.

All samples will be processed by a central laboratory and results will be reported back to the clinic.

4.1.8 Electrocardiogram (ECG)

A 12-lead ECG will be taken locally to assess the cardiac rhythm (supine position, standard ECG with a paper speed of 25 mm/second covering at least 6 sequential beats) after the patient has been lying down resting for at least 5 minutes, at the screening Visit 1 only.

4.1.9 Pregnancy test

4.1.9.1 Urine pregnancy tests

Urine pregnancy test must be performed in women of child bearing potential at Visits 2 (Day 1), 4 (Week 2), 6 (Week 6), 8 (Week 12), 9 (Week 18), and 10 (Week 24). At Visits 2 (Day 1), and 10 (Week 24), or the final visit, if patient discontinues early), the pregnancy test must be performed before the MRI. Women of child bearing potential must have a negative pregnancy test within 72 hours prior to the start of the investigational product. A positive urine pregnancy test should be confirmed by a serum pregnancy test.

4.1.9.2 Serum pregnancy test

At the Screening Visit, a serum pregnancy test will be collected from all women of child-bearing potential only.

4.2 Treatment period

The study will comprise a 24-week randomized treatment period. The last dose of study medication is to be taken at the Week 24 (Visit 10) after the required pre-dose blood samples are obtained. Patients who complete the study medication will be asked to return for an end-of-study visit at Week 28 (Visit 11). Patients discontinued from the treatment prematurely will be asked to return to the study site as soon as possible but not later than 7 days from the last IP dose (See section 3.9.1).

Patients will be randomized at Visit 2 (Day1) and receive either saxagliptin, sitagliptin, or matching placebo.

The assessments required during the treatment period are detailed in the Study Plan, (Table 2).

4.2.1 Scheduled telephone contacts

Visits 3 (Day 7), 5 (Week 3), and 7 (Week 9) will be conducted by phone. The responses regarding concomitant medications, AEs and SAEs will be transferred into the eCRF. Patients will be asked about signs and symptoms of heart failure.

4.2.2 Fasting plasma glucose (FPG)

FPG will be analyzed by a central laboratory according to the procedures described in the Laboratory Manual which will be distributed to each study site during site initiation.

If the FPG (value from central laboratory) meets rescue limits (See section 7.7.2), the patient should be brought back within 3-5 days for an unscheduled confirmatory visit to confirm the high FPG and assess eligibility for rescue during the double-blind treatment period.

4.3 End of Study Visit

Study procedures and timing required during End of Study (Visit 11) are indicated in the Study Plan, Table 2.

If a patient discontinues early from the study, he or she should be asked to return to the study site as soon as possible (see Section 3.9.1). All endpoint (Week 24, Visit 10/ETD) assessments, including a cardiac MRI, and blood and urine biomarker assessments, must be performed at this visit. The patient should also be asked to return 4 weeks later for end of study (Week 28) assessments. If the patient is unable or unwilling to return, a phone follow up should be conducted.

5 STUDY ASSESSMENTS

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

5.1 Efficacy assessments

5.1.1 Primary Efficacy Variable

5.1.1.1 Magnetic Resonance Imaging (MRI)

MRI is the primary assessment to evaluate cardiac dimensions and function. MRI will be performed at baseline and Visit 10 (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.

Baseline MRI must be performed before randomization and drug dispensing but no more than 7 days prior to Day 1. The MRI scan of acceptable quality must be confirmed before the patient is randomized and takes study medication. If a repeat MRI is required, it may be performed within 7 days of the poor-quality scan query received, and the randomization visit should be rescheduled if necessary to allow confirmation of quality before randomization and dosing.

At Week 24 an MRI scan of acceptable quality must be confirmed before the visit occurs. Therefore, the MRI can be performed in advance of the planned visit but no more than 7 days. If a repeat MRI is required, it may be performed within 7 days of the poor-quality scan query received. If necessary, the Week 24 visit should be re-scheduled until after the MRI has been qualified as acceptable and the patient should continue study medication.

The cMRI assessment must be performed and approved according to Investigator Site Operations Manual and Image Acquisition Guideline.

A urine pregnancy test must be performed before each MRI in women of child bearing potential.

The cardiac MRI will be reviewed locally by a qualified physician for incidental findings. Any incidental findings of potential clinical significance should be communicated directly to the investigator and then evaluated and handled by the investigator as per standard medical practice. Investigations and treatments required as follow up to MRI incidental findings are not covered by this study protocol and the costs will not be paid by AstraZeneca.

5.1.2 Secondary Efficacy Variable

5.1.2.1 N-terminal prohormone of brain natriuretic peptide (NT-proBNP)

NT-proBNP is primarily used to help detect, diagnose, and evaluate the severity of heart failure, as well as the response to therapy, and will be analyzed by a central laboratory according to the procedures described in the Laboratory Manual which will be distributed to each study site during site initiation.

5.1.3 Exploratory Efficacy Variable

5.1.3.1 HbA1c

HbA1c is the assessment for the determination of glycemic efficacy and will be analyzed by a central laboratory according to the procedures described in the Laboratory Manual which will be distributed to each study site during site initiation. In cases where the central measurement of HbA1C in not possible due to hemoglobin variants not compatible with the central assay, no value will be centrally collected.

5.1.3.2 Body weight

The patient's body weight will be recorded in kilograms (kg) to one decimal place, with light clothing and no shoes. All readings should be recorded as accurately as possible and the same scale should be used for all assessments for a given patient. The same scale should be used throughout the study, and calibrated on a regular basis as recommended by the manufacturer.

5.1.3.3 CCI

CCI

5.2 Safety assessment

The investigator will evaluate all enrollment and safety laboratory reports and will sign and date the review. Any out-of-range laboratory results should be assessed for clinical significance and reported as AEs accordingly. The investigator should follow all clinically significant laboratory abnormalities occurring during the study that were not present at baseline. These abnormalities should be evaluated with additional tests, if necessary, until the underlying cause is diagnosed or resolution occurs. The diagnosis and resolution date must be reported to the Sponsor.

Samples will be collected according to the schedules presented in the Study Plan (Table 2).

The instructions for collection, processing, packaging, and shipping of the samples will be detailed in the Laboratory Manual.

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the Study Plan (Table 2).

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The detailed methods for specimen collection, handling, processing, shipping and storage will be supplied in the Investigator's Laboratory Manual provided by the Central Laboratory. The date, time of collection and sample ID will be recorded on the appropriate eCRF.

The clinical chemistry, hematology and urinalysis will be performed at a central laboratory. The samples will be processed by a central laboratory and results will be reported back to the clinic.

All samples should be taken by adequately trained study personnel and handled in accordance with instructions in the Laboratory Manual.

The following laboratory variables will be measured:

Table 3 Laboratory Safety Variables

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	

The investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at center as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.6

5.2.1.1 Volume of blood

Total mandatory blood volume in the study is approximately 260.5 mL.

Table 4 Blood sample volume

Visit	Safety (mL)	FPG	PK analysis (mL)	Blood biomarkers (mL)
Pre-Screening	2.5			
Screening	15*			
Day 1	5.5			43
Week 6	5.5	2 (1 x 2 mL)	3 (1 x 3 mL)	43
Week 12	5.5	2 (1 x 2 mL)	15 (5 x 3 mL)	43
Week 18*		2 (1 x 2 mL)		
Week 24	5.5	2 (1 x 2 mL)	3 (1 x 3 mL)	43

Visit	Safety (mL)	FPG	PK analysis (mL)	Blood biomarkers (mL)
SUBTOTAL (mandatory)	**39.5**	**8**	**21**	**172**

PK = pharmacokinetics, FPG = fasting plasma glucose, * will only be required for individuals who require 'rescue' therapy at Week 12

*Including blood biomarker (NT-proBNP)

5.2.2 Physical examination

5.2.2.1 Complete physical examination

A complete physical examination will be performed at screening and include an assessment of the following: general appearance, skin inspection, lymph nodes, thyroid, abdomen, musculoskeletal/extremities, CV system, lungs, and reflexes. The results of the complete physical examination will be recorded for the screening visit, randomization visit (Day 1), visit 8 (Week 12), and visit 10 (Week 24). The baseline physical examination is performed at the screening visit (Visit 1).

5.2.2.2 Brief physical examination

The brief physical examination will focus on signs and symptoms of heart failure at Visit 4 (Week 2), 6 (Week 6), 9 (Week 18), and End-of-Study Visit (Week 28).

5.2.3 Vital signs

Vital signs will be assessed following the study plan (see Table 2). Weight will be measured as part of vital signs. The patient's weight will be recorded in kilograms, to 1 decimal place, with light clothing and no shoes. The patient's height will be recorded in centimeters, with no shoes. Height will be measured as part of vital signs at Visit 1 only.

Pulse and seated BP will be measured twice (5 minutes apart) before any blood sampling is done using a standardized cuff adapted to the size of the patient's arm after the patient has been sitting and resting for least 5 minutes. For timings of assessments see Table 2.

5.2.4 Other safety assessments

5.2.4.1 CV Events Adjudication Committee

An independent Events Adjudication Committee will be appointed and will adjudicate all CV events (including hHF). The committee members will not have access to individual treatment codes for any patient or clinical efficacy and safety event. The precise responsibilities and procedures applicable for the Committee will be detailed in a separate Adjudication Manual.

For all CV events identified for adjudication, the investigator will complete the appropriate modules of the eCRF and provide source documentation. Guidance for reporting CV events is provided in the Event Reporting Manual.

5.3 Pharmacokinetics

5.3.1 Collection of samples

In a subset of at least 150 patients, blood samples for determination of saxagliptin, 5-hydroxy saxagliptin, and sitagliptin in plasma will be taken at the times presented in the study plan (Table 2).

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Patients should be instructed to provide the exact time of the dose taken the previous day. This information and the time of the sample draw will be entered into CRF.

5.3.2 Determination of drug concentration

Samples for determination of drug concentration in plasma will be analyzed by Covance on behalf of AstraZeneca, using an appropriate bioanalytical method.

The randomization code will be provided to ensure that only samples from patients who were on active study treatment are analyzed. Samples from patients not dosed with the relevant active study treatment will only be analyzed on a 'for cause' basis, for example, if there is suspicion that a patient has been dosed incorrectly.

The treatment allocation information will be kept in a secure location until the end of the study.

Full details of the analytical method used will be described in separate bioanalytical reports.

5.3.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic (PK) samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft bioanalytical report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the Clinical Study Report but separately in a Bioanalytical Report.

Any residual sample remaining after PK analysis has been performed may be used for exploratory biomarker research and characterization of metabolites.

5.4 Pharmacodynamics – Not applicable

5.5 Pharmacogenetics – Not applicable

5.6 Biomarker analysis

The patients' consent to the use of biological samples is mandatory. Biological samples (urine and blood) will be collected and will be analyzed for exploratory biomarkers to assess correlations with study endpoints and effects of study drug. The biomarkers assessed in the study include NT-proBNP, CCI , given their association to CV risk. Additional blood and urine samples may be assayed either during the study or stored for potential future analyses of other renal, cardiac, inflammatory, and metabolic disease-specific biomarkers. Those measurements, as well as other potential relevant biomarkers, will be performed at Sponsor`s discretion and for the purpose of this protocol only.

5.6.1 Storage, re-use and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the last subject's last visit, after which they will be destroyed. The results of this biomarker research will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

5.6.2 Labelling and shipment of biological samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix B 'IATA 6.2 Guidance Document'.

5.6.3 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each center will keep full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate). The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered by the AstraZeneca Biobank team during the entire life cycle.

5.6.4 Withdrawal of Informed Consent for donated biological samples

If a patient insists on withdrawing consent from the study, the local investigator will confirm with the patient whether previously donated biological samples can still be used for the purposes of research. In the absence of expressed consent for their use, the biological samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples is an integral part of the study, then the patient is withdrawn from further study participation.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is properly documented and is notified immediately to AstraZeneca.
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

6 SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.1.1 AEs of special interest

The following are considered to be AEOSI:

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

6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed previously.

For further guidance on the definition of a SAE, see Appendix A to the Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse events will be collected from time of first administration of investigational product throughout the double-blind treatment period (Visit 10, Week 24).

Serious Adverse Events will be collected from signature of screening informed consent, throughout the double-blind treatment period and until the end-of-study visit (Visit 11, Week 28).

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collect for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- AE caused patient's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)

- Description of AE

The maximum intensity of an AE will be rated according to the following definition:

- Mild (awareness of sign of symptom but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

The investigator will assess causal relationship between investigational product and each adverse event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal, relationship will also be assessed for other medication and study procedures and additional study drug. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix A to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: Have you had any health problems since the previous visit/you were last asked, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarized in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values/vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the investigator/study site personnel how to proceed.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug and the EU Summary of Product Characteristics (SPC) for the active comparator product (including any AstraZeneca comparator).

6.5 Overdose

For the purpose of this study, an overdose is defined as a dose of study medication in excess of that specified in the CSP (ie, more than 1 tablet per day of either study drug).

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its active metabolite are removed by hemodialysis (23% of dose over 4 hours). The Product Label for sitagliptin states the drug is modestly dialyzable.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within a day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

6.6.2 Paternal exposure

There is no restriction on fathering children or donating sperm during the study

6.7 Management of IP related toxicities – Not applicable

6.8 Study governance and oversight

6.8.1 Executive Committee

The Executive Committee will be responsible for the overall study design, including the development of the protocol and any protocol amendments, supervision, interpretation, and reporting (presentations at international congresses and publications in peer reviewed journals) of the study. The Executive Committee will make recommendations to AstraZeneca regarding recruitment and conduct of the study. The Executive Committee will be comprised of the International Co-ordinating Investigator (ICI) and designated academic leaders with expertise in the fields of heart failure and Type 2 DM. The precise responsibilities and procedures applicable for the Committee will be detailed in a separate committee charter.

6.8.2 Safety Monitoring Committee (SMC)

An independent SMC will be appointed and will make recommendations to the Executive Committee and to AstraZeneca.

The SMC will be responsible for safeguarding the interests of the patients in the study by assessing the safety of the intervention during the study, and for reviewing the overall conduct of the clinical study. The SMC will make recommendations to AstraZeneca with regard to early stopping or modifications of the study.

The SMC will have access to the individual treatment codes and will be able to merge these with the collected study data while the study is ongoing.

The Executive Committee and AstraZeneca will not be made aware of the treatment codes until after clean file and database lock are declared. Similarly, all summary output reviewed at each SMC meeting will be held in confidence by the SMC members until the end of the study when clean file and database lock are declared. The precise responsibilities and procedures applicable for the Committee will be detailed in a separate committee charter.

7 INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Table 5 Identity of investigational product

Investigational product	Dosage form and strength	Manufacturer
Saxagliptin	Plain, yellow, biconvex, round, film-coated tablet; 5 mg	AstraZeneca
Saxagliptin	Plain, yellow, biconvex, round, film-coated tablet; 2.5 mg	AstraZeneca
Sitagliptin	Gray capsule 100 mg (containing two 50 mg commercial Januvia® tablets)	AstraZeneca
Sitagliptin	Gray capsule 50 mg (containing one 50 mg commercial Januvia® tablet)	AstraZeneca
Placebo to match saxagliptin 2.5mg/5mg	Plain, yellow, biconvex, round, film-coated tablet	AstraZeneca
Placebo to match sitagliptin	Gray capsule	AstraZeneca

The IPs will be supplied by AstraZeneca. Primary packaging of the IP will be carried out by AstraZeneca or their designee in accordance with Good Manufacturing Practice (GMP).

The tablets may contain lactose, which may cause discomfort in lactose-intolerant individuals.

7.2 Dose and treatment regimens

Study treatment will be administered once daily, according to randomized treatment allocation. For patients with an eGFR ≥50 mL/min/1.73 m^2, the doses of the active treatments are as follows: saxagliptin 5 mg and sitagliptin 100 mg. For patients whose eGFR decreases to <50 mL/min/1.73 m^2, the doses of the active treatments will be adjusted as follows: saxagliptin 2.5 mg and sitagliptin 50 mg.

Patients whose eGFR falls below 30 mL/min/1.73 m^2 must be discontinued from the study following confirmation of the initial result.

Patients will receive:

- One saxagliptin 5 mg tablet and one sitaglipitin placebo capsule administered orally once daily for a 24 week treatment period for patients with an eGFR ≥50 mL/min/1.73m^2. For patients with an eGFR ≥30 to <50 mL/min/1.73m^2, the dose of saxagliptin will be adjusted to one 2.5 mg tablet

or

- One sitagliptin 100 mg capsule and one saxagliptin placebo tablet administered orally once daily for a 24-week treatment period for patients with an eGFR ≥50 mL/min/1.73m^2. For patients with an eGFR ≥30 to <50 mL/min/1.73m^2, the dose of sitagliptin will be adjusted to one 50 mg capsule

or

- One saxagliptin placebo tablet and one sitagliptin placebo capsule administered orally once daily for a 24-week treatment period as a control.

Patients who, during the course of the study, develop renal impairment (eGFR <50 mL/min/1.73m^2 on 2 consecutive tests at least 1 week apart) will have their dose adjusted to 2.5 mg saxagliptin, 50 mg sitagliptin, or matching placebo. Once reduced to 2.5 mg saxagliptin, 50 mg sitagliptin or placebo, there will be no further dose-adjustment even if the estimated GFR subsequently increased sufficiently to meet initial requirements for the 5 mg saxagliptin, 100 mg sitagliptin or placebo dosing regimen. The IVRS/IWRS will be used to allocate the adjusted IP.

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

The label will include the following information: Name of the Sponsor, Study Code, For Clinical Trial use only, and/or any other market specific requirements. The label will also state keep out of the reach of children.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottles specifies the appropriate storage.

7.5 Compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the Case Report Form. This information plus drug accountability for all study drugs will be used to assess compliance with the treatment.

Each time study drug is dispensed, compliance will be reinforced. When study drug is returned, compliance will be assessed based on returned tablet counts. Compliance should be between ≥80% and ≤120%. The investigator (or designee) will record the amounts of study medication dispensed and returned at each site, as well as document reasons for noncompliance, in the source document. The dates of all study medication dosing, including interruptions, missed doses or overdose, must be recorded on the eCRF. If the patient is not compliant with recording study drug doses during the study period, non-compliance should be

noted as a protocol deviation and the Sponsor should be notified. The patient may continue in the study, but should be counselled on the importance of taking their study medication and applicable ancillary medications as prescribed.

7.6 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the patient.

Study site personnel, if applicable, or the AZ monitor will account for all study drugs received at the site, unused study drugs, and for destruction according to local procedure. Certificates of delivery, destruction should be signed.

7.7 Concomitant and other treatments

Background, rescue medication, and post-study treatment will not be provided by the Sponsor.

7.7.1 Concomitant treatment

Therapy with the patient's stable series of medications for T2DM and heart failure will continue during the duration of the trial.

For patients taking insulin, the investigator must query the patient at pre-screening or screening regarding his/her usual total daily insulin dose (all types combined). Dosage reductions of insulin and sulfonylurea agents may be considered at randomization to minimize the possibility of hypoglycaemia. For patients treated with insulin, consider a reduction in dose of 20% at randomization.

For patients receiving sulfonylurea agents, consider a reduction in dose of 50% or discontinue if on a dosage that is considered low at randomization.

Any reductions in the dosage of insulin and sulfonylurea agents will be at the discretion of the investigator.

Other medication than that described above, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator and recorded in the appropriate sections of the Case Report Form.

Concomitant herbal or nutritional therapies must also be entered into the eCRF.

7.7.2 Rescue medication

The Sponsor will not supply rescue medication during the study. Patients should continue receiving study medication while receiving rescue therapy. If rescue therapy fails, further therapy will be given at the discretion of the investigator.

7.7.2.1 Glycemic rescue medication

During the double-blind treatment period of the trial, patients may be eligible for the addition of open-label rescue medication to their blinded treatment regimen in order to treat ongoing hyperglycemia, based upon central laboratory FPG values and repeat, confirmatory FPG criteria (Table 6).

For participants with sustained hyperglycemia as outlined in Table 6, increased doses of background medication or additional agents, not listed in the exclusions, may be used according to local guidelines.

Patients with a central laboratory FPG value meeting the lack of glycemic control criterion at a pre-specified visit will be scheduled for a follow-up visit (within 3-5 days) to obtain a second central laboratory FPG value. If the repeat central laboratory FPG value still meets the criterion, the patient will receive rescue medication.

If a patient has a local, or unplanned FPG value meeting the lack of glycemic control criterion, then a central laboratory FPG value should be obtained as soon as possible. If the central laboratory FPG value meets the criterion, the patient will receive rescue medication.

Table 6 Lack of Glycemic Control Criteria for Initiation of Open-Label Rescue Medication

Visit label	Central Laboratory FPG
Up to and including Week 6	FPG >270 mg/dL (15.0 mmol/L)
After Week 6 up to Week 12	FPG >240 mg/dL (13.3 mmol/L)
At Weeks 12 to Week 24	FPG >200 mg/dL (11.1 mmol/L)

7.7.3 Prohibited medications

Other than study medication, and rescue medication as described in Section 7.7.2, the use of the following medications during randomized treatment is prohibited:

- Incretin therapy (DPP4 inhibitors, GLP-1 mimetics)
- While background therapy with stable dosages of SGLT-2 inhibitors is permitted in patients qualifying for the study and can continue during the randomized treatment period, SGLT-2 inhibitors cannot be initiated or their dosages modified during randomized treatment or used as rescue therapy
- Therapy with thiazolidinedione agents (TZDs)
- Strong CYP3A4/5 inhibitors.

The list of strong CYP 3 A4/5 inhibitors includes, but not limited to: boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, diltiazem, elvitegravir/ritonavir, grapefruit juice*, idelalisib, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, paritaprevir/ritonavir, ombitasvir, dasabuvir, posaconazole, ritonavir, saquinavir/ritonavir, telaprevir, tipranavir/ritonavir, troleandomycin, voriconazole.

*The effect of grapefruit juice varies widely among brands and is concentration-, dose- and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).

Patients should continue their usual diabetes medication (other than prohibited medications listed above) and their usual HF medications (including diuretics, ACE inhibitors, or ARB agents, beta blockers, and aldosterone antagonists). The diabetes and HF treatment regimens should remain stable during the study unless a change is required due to a change in the patient's clinical status. Any changes (dose adjustments, additions, deletions) must be recorded.

8 STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

All personnel involved with the analysis of the study will remain blinded until database lock and protocol violators identified.

Analyses will be performed by AstraZeneca or its representatives.

The SAP will be signed off before review of any potential treatment revealing data is undertaken and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data. If one or more stratification cells has sparse or no data, then, for purposes of the imputation and analysis models, stratification levels and/or variables may be combined or variables may be dropped from the models.

8.2 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 efficacy assessment will claim non-inferiority 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. (See below)

A total of 330 (110 each arm) eligible patients will be randomized in a 1:1:1 ratio to:

- Arm 1: Saxagliptin
- Arm 2: Sitagliptin
- Arm 3: Placebo

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, 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.

8.3 Definitions of analysis sets

The primary and secondary efficacy analyses will be performed based on the full analysis set. The Safety analysis will be performed based on the safety analysis set.

8.3.1 Efficacy analysis sets

The full analysis set (FAS) will include all randomized patients who take at least one dose of the study medication. Patients will be analyzed according to the treatment groups to which they are randomized.

The per-protocol (PP) analysis set is a subset of the FAS set that includes patients without important protocol deviations that might affect the primary analyses. Patients will be analyzed according to the treatment randomized. The criteria for important protocol deviations will be defined in the statistical analysis plan. The criteria for important protocol deviations will be established after protocol deviation reviews, before the data have been unblinded.

8.3.2 Safety analysis set

The safety analysis set will include all randomized patients who have received at least 1 dose of study treatment. Patients will be analyzed according to the treatment actually received.

8.3.3 PK analysis set

The PK analysis set will include a subset of at least 150 patients (approx. 50 per treatment group) for whom evaluable pharmacokinetic data are calculated (with no major protocol deviations or violations thought to significantly affect the pharmacokinetics of the drug).

PK data will be reported separately from the clinical study report.

8.4 Outcome measures for analyses

8.4.1 Primary efficacy variable

Change from baseline in LVEDV index measured by MRI at 24 weeks, saxagliptin compared to placebo.

8.4.2 Secondary efficacy variables

- Change from baseline in LVESV index, LVEF, and LVM measured by MRI after 24 weeks, saxagliptin compared to placebo
- Change from baseline in NT-proBNP after 24 weeks, saxagliptin compared to placebo.

8.4.3 Safety variables

- Incidence of AEs/SAEs/ AEs of special interest
- Collection of clinical chemistry/hematology parameters
- Vital signs
- Physical examination
- Incidence of independently adjudicated events (death, myocardial infarction, stroke, and hHF).

8.4.4 Exploratory variables

- Change from baseline in LVEDV index, LVESV index, LVEF, and LVM-measured by MRI at 24 weeks, sitagliptin compared to placebo
- Change from baseline in NT-proBNP after 6, 12, and 24 weeks
- Percent change from baseline in plasma volume using Strauss formula after 6, 12, and 24 weeks

$$\%\ \text{change in plasma volume} = 100 \times \frac{hemoglobin\ (before)}{hemoglobin\ (after)} \times \frac{1 - hematocrit\ (after)}{1 - hematocrit\ (before)} - 100$$

- 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 Weeks 6, 12, and 24
- Plasma concentration in PK samples
  - Saxagliptin and its major metabolite, 5-hydroxy saxagliptin
  - Sitagliptin

8.5 Methods for statistical analyses

The full analysis set (FAS) will be used for the primary and secondary efficacy analyses. Efficacy analyses will also be conducted using the PP analysis set. All primary and secondary analyses will be performed using values regardless of rescue or discontinuation of the study treatment. When patients have their final MRI measurements done at an ETD visit rather than at Week 24, these measurements will be used as the endpoint. Sensitivity analyses for the primary and secondary variables will be performed using analyses that do not assume the data are missing at random and incorporate patients randomized and treated but with only baseline data.

All statistical comparisons will be tested at the alpha level of 0.05 (two-sided) level. No multiplicity control will be applied for the statistical comparisons.

8.5.1 Analysis of the primary variable (s)

The primary analysis for LVEDV index, mean change from baseline at Week 24, will be performed using analysis of covariance (ANCOVA), with terms for treatment group, eGFR category (<50, ≥50 mL/min/1.73 m^2), SGLT-2 inhibitor use, region, and baseline value as covariates in the model. A multiple imputation approach will be used to impute the missing values of LVEDV at Week 24 for all FAS subjects with a nonmissing baseline value. Point estimates and 95% confidence intervals will be calculated for the adjusted mean changes within each treatment group, as well as for the differences in adjusted mean changes between treatment groups. The NI margin for the study will be calculated as 10% of the overall baseline mean LVEDV index across all treatment groups. Non-inferiority will be demonstrated if the upper bound of the 95% confidence interval for the difference in treatments (saxagliptin minus placebo) is less than the NI margin.

8.5.2 Analysis of the secondary variable(s)

Continuous variables collected at only one visit during randomization treatment period (cardiac dimension and function LVEDV index, LVESV index, LVEF, and LVM by MRI, etc), will be analyzed using the same analysis of covariance (ANCOVA) approach used for the primary variable.

Continuous variables collected at more than one visit during randomization treatment period, (NT-proBNP, etc), will be analyzed using a mixed-model repeated-measures (MMRM) approach with terms for treatment group, eGFR category (<50, ≥50 mL/min/1.73 m^2), SGLT-2 inhibitor use, region, baseline value, time (each relevant visit), the interaction of treatment and time, and the interaction of baseline value and time in the model. Biomarkers or data with extremely skewed distributions may be log transformed prior to ANCOVA or MMRM analysis.

Point estimates and 95% confidence intervals will be calculated for the adjusted mean changes within each treatment group as well as for the differences in adjusted mean changes between treatment groups. No multiplicity control will be applied for the statistical comparisons.

8.5.3 Exploratory analyses

For continuous variables (percent change of plasma volume by Strauss formula, blood pressure, HbA1c (using values prior to rescue), body weight, and biomarkers, etc) collected at multiple visits post-baseline, the same MMRM approach will be used. For continuous variables (LVEDV index, LVESV index, LVEF, and LVM, etc.) collected at one visit post-baseline, the same ANCOVA model described for the primary variable will be used although multiple imputation of missing data may not be used.

Plasma concentrations of saxagliptin, 5-hydroxy saxagliptin, and sitagliptin will be used to develop exploratory PK/PD models, which may be reported separately from the clinical study report.

In cases where the central measurement of HbA1C is 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.

8.5.4 Subgroup analysis

Details of the subgroup analysis will be specified in Statistical Analysis Plan. The treatment effect on the adjusted mean change from baseline in LVEDV index measured by MRI at 24 weeks will be examined in the following subgroups:

- Baseline HbA1c (<7.0%, 7.0% to 9.0%, and >9.0%)
- Gender (male, female)
- Age (<65, ≥65 years)

- Duration of T2DM
- eGFR (<50, ≥50 mL/min/1.73 m^2)
- SGLT-2 inhibitor use
- Region
- Baseline NYHA classification (I, II, III).

8.5.5 Interim analysis – Not applicable

8.5.6 Sensitivity analysis

Multiple sensitivity analyses for the primary endpoint will be performed including analyses that do not assume the data are missing at random and incorporate patients randomized and treated but with only baseline data. Details will be stated in the SAP.

8.5.7 Safety analysis

Safety analyses for the double-blind treatment period 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. Safety analyses will include, where appropriate, descriptive statistics, counts, and percentages for AEs and other safety measures. No formal statistical tests will be performed.

Descriptive statistics will be calculated for demographic and other baseline characteristics.

The number and percent of patients with at least one adverse event will be summarized for each treatment group, including summaries of AEs, SAEs, AEs leading to discontinuation, AEs of special interest, and adjudicated CV events, including hHF. Summaries will include the number of patients with events by specified system organ classes and preferred terms. Additionally, the incidence of adverse events and frequency of recurring adverse events will be summarized for each treatment group for both frequent events (occurring in at least 5% of patients) and for selected adverse events of special interest.

Values and changes from baseline at each scheduled time point for clinical laboratory parameters and vital signs, including seated blood pressure and heart rate, will be summarized by treatment group using descriptive statistics. The number and percent of patients with laboratory values meeting marked abnormality criteria will be summarized for each treatment group. Other safety assessments, including serum creatinine and eGFR by MDRD, will be summarized by treatment group using descriptive statistics of values and changes from baseline at each scheduled time point.

Additional analyses for adverse events and laboratory marked abnormalities may be performed excluding data after the addition of glycemic rescue concomitant medication.

9 STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the EDC systems utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts). The monitor should ensure that all CV endpoints are captured and that adjudication packages are complete.
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

9.2.1 **Source data**

Refer to the Clinical Study Agreement for location of source data.

9.2.2 Study agreements

The Principal Investigator at each center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.2.3 Archiving of study documents

The investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study'.

The study is expected to start in Quarter 1 2017 and to end by Quarter 3 2019.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with saxagliptin.

9.4 Data management by AstraZeneca

Data management will be performed by AstraZeneca Data Management Center staff according to the Data Management Plan.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the WHO Drug Dictionary. Classification coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre.

The data collected through third party sources will be obtained and reconciled against study data.

Data queries will be raised for inconsistent, implausible, or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed, and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Serious Adverse Event (SAE) Reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratories to AstraZeneca.

10 ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

An Ethics Committee (EC)/IRB should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable EC/IRB, and to the study site staff.

The opinion of the EC/IRB should be given in writing. The investigator should submit the written approval to AstraZeneca before enrollment of any patient into the study.

The EC/IRB should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC/IRB annually.

Before enrollment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, EC/IRB, and Principal Investigators with safety updates/reports according to local requirements.

Each Principal Investigator is responsible for providing the EC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

10.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

10.4.1 Pre-screening Informed Consent

The pre-screening informed consent is an abbreviated document that explains the risks associated with the pre-screening laboratory test (eGFR) performed to assess qualification to the study.

This document will provide only general information about the study, without the need to provide any specific details about the study procedures, and risks or benefits from study participation.

For any patient that undergoes the pre-screening procedure and is considered eligible to participate in the study, the full informed consent will be provided at the enrolment visit.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Executive Committee and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 10.3.

If a protocol amendment requires a change to a center's Informed Consent Form, AstraZeneca and the center's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

10.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

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