AstraZeneca

Clinical Study Protocol	
Drug Substance	Saxagliptin/Dapagliflozin
Study Code	D1683C00005
Version	4.0
Date	4 August 2016

A Multi-Center, Randomised, Double-Blind, Active-Controlled, Parallel Group, Phase III Trial to Evaluate the Safety and Efficacy of Saxagliptin 5mg Co-administered with Dapagliflozin 5mg compared to Saxagliptin 5mg or Dapagliflozin 5mg all given as Add-on therapy to Metformin in Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on Metformin Alone

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CSPVERSION HISTORY

Version 4.0, 4 August 2016

Changes to the protocol are summarised below.

Section 1.1(Background and rationale for conducting this study) and Section 11 (List of references): References in the 3rd paragraph were modified.

Section 3.1 (Inclusion criteria):

- Fasting Plasma Glucose (FPG) in mmol/L was added to make it clear for all countries.
- Male condom with spermicidal gel is added as an acceptable method of birth control.

Section 3.2 (Exclusion criteria): The criteria 8 'a' was updated and mentioned as a separate bullet ‘b’ to **exclude any exposure of DPP-4 and SGLT-2 inhibitor within 8 weeks prior to enrolment** to be consistent with exclusion criteria 8 a on the timings for administration of any other antihyperglycaemic therapy.

Section 3.7 (Methods for Unblinding): 'pharmacist' is removed as Individual treatment codes will only be available to the Investigator from the IVRS/IWRS.

Section 3.9.2 (Study-specific discontinuation criteria): The note was added to withhold study medication when eGFR <60mL/min/1.73m^2 (by MDRD) until retest eGFR result are available only for randomisation visit, as dapagliflozin is contraindicated in patients with eGFR <60mL/min/1.73m^2.

Table 1 (Study Plan):

- The footnote 'k' was added to make it clear on rescue medication. Rescue medication should also be returned for rescued patients at Visit 4 and 5.
- The footnote 'h' was updated to make it clear on pregnancy testing. Visit window for enrolment visit was changed to be consistent with footnote 'c'.
- Return study medication was added to make it clear
- Study Medication Compliance Review marked for Visit 3 to be consistent with Section 7.6
- Collect unused study medication/supplies was removed to make it clear

Section 4.2.1 (Enrolment visit): Patient diary review was removed to be consistent with Table 1.

Section 4.3.2 (Treatment period visits): Item 12 was updated to be consistent with Table 1. Study medication will be dispensed and returned at Visit 4.

Section 6.3.1 (Time period for collection of adverse event): Discontinuation visit was deleted to be consistent with Table 1.

Section 6.3.7 (Hypoglycaemia): Reference in the 3rd paragraph were updated.

Section 6.4.1 (Adverse event of special interest): FDA has removed the post approval requirements for ONGLYZA (saxagliptin) for several AE's of special interest. Specifically these include Liver test abnormalities accompanied by jaundice or hyperbilirubinemia, Opportunistic infections and Severe hypersensitivity. Therefore, all these three events were all removed.

Section 7.6 (Compliance): The section is updated to be consistent with Table 1. Upper limitation ≤120% of that prescribed was added.

Section 7.9 (Concomitant and other treatment): Typographical error where 'or chronic' was deleted for glucocorticosteroid therapy to be consistent with exclusion criteria 8 'e'.

Appendix D (Algorithm on Management of Sustained Elevated Liver Safety Abnormalities): Patient must be discontinued from the study medication and not study is updated to be consistent with following paragraph and section 3.9.

Appendix F (Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law): Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law was added and List of appendices was updated in accordance with regulatory requirement on reporting of FDA requested events for saxagliptin.

Minor editorial and typographical errors are updated and not noted.

Version 3.0, 18 January 2016

Changes to the protocol are summarised below.

Protocol Synopsis: Estimated date of last patient completed is updated from 4Q 2016 to 2Q 2017.

Abbreviation: Liver Function Test (LFT) is added.

Section 3.1 (Inclusion criteria): To make it clear and consistent with Section 6.6.2 (Paternal exposure), "Sexually active fertile men must use effective birth control if their partners are

WOCBP" is removed.

Section 3.9.1 (General discontinuation criteria): The section was updated to clearly differentiate treatment discontinuation from study withdrawal by removing 'Lost to follow-up' since this is one of the reason for study withdrawal.

Section 5.2.4.3 (Diabetes Ketoacidosis) and Section 6.8.3 (DKA Adjudication): These sections are removed and will be updated after the review from FDA regarding the relevant text to be added in CSP.

Section 6.4.1 (Adverse events of special interest): The section was updated to include regulatory requirement on reporting of FDA requested events.

Section 6.6.1 (Maternal exposure): To make it clear that, If a patient becomes pregnant during the course of study all study medication should be discontinued immediately. Patient should be continued in the study as per original visit schedule. Hence, "The patient should be withdrawn from study and continue treatment of diabetes according to the standard of care" is removed.

Version 2.0, 08 January 2016

Changes to the protocol are summarised below.

Section 1.3 (Benefit/risk and ethical assessment): Per FDA request, information on ketoacidosis was added in the clinical study protocol.

Section 3.10 (Criteria for Withdrawal): Per FDA request, the clinical study protocol is updated to clearly differentiate treatment discontinuation from study withdrawal.

Section 3.9.1 (General discontinuation criteria): To make it clear and consistent with Section 3.10, bullet 3 is rephrased.

Section 3.11 (Discontinuation of the study): Additional reasons for discontinuation of the study are added in the clinical study protocol.

Section 4.1 (Screening visit): Retesting of HbA1c once, at screening visit is added.

Section 3.2 (Exclusion criteria): Bullet (f) of exclusion criteria no 12 is rephrased to be consistent with Section 4.1 as retesting of HbA1c is allowed under specific condition.

Section 3.10.1 (Screen failures): The section was rephrased to be consistent with Section 4.1 as patients are permitted to retest HbA1c once under specific condition.

Section 4 (Study Plan and Timing of Procedures): Table 1 is updated for HbA1c, footnote is

added to reflect the retesting of HbA1c at screening visit under specific condition.

Section 5.7 (Biomarker analysis): Typographical error in aliquots was corrected.

Section 7.4 (Labelling): Visit number removed as it will be added on the label when IP is dispensed by site personnel.

Section 8.1 (Statistical considerations): To be more clear and specific regarding SAP and its further amendments

Section 8.5.6 (Exploratory analysis): To be clear and specific on timing of collection of data for hypoglycaemia.

Version 1.0, 23 December.2015
Initial creation

This submission document contains confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

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 Multi-Center, Randomised, Double-Blind, Active-Controlled, Parallel Group, Phase III Trial to Evaluate the Safety and Efficacy of Saxagliptin 5mg Co-administered with Dapagliflozin 5mg compared to Saxagliptin 5mg or Dapagliflozin 5mg all given as Add-on therapy to Metformin in Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on Metformin Alone

International Co-ordinating Investigator

Study site(s) and number of patients planned

This will be a multi-center study conducted at approximately 120 sites across North America, EU and ROW. Approximately 900 patients will be randomised.

Study period		Phase of development
Estimated date of first patient enrolled	1Q 2016	III
Estimated date of last patient completed	2Q 2017	III

Study design

Study D1683C00005 is a 24-week, double-blind, randomised, active-controlled, multi-center, parallel-group study to evaluate safety and efficacy of saxagliptin 5mg co-administered with dapagliflozin 5mg, compared with either saxagliptin 5mg or dapagliflozin 5mg in patients who are inadequately controlled on ≥1500mg/day of metformin. After randomisation the patients will visit the clinic after 6, 12, and 24 weeks. Efficacy as well as safety assessments will be taken before randomisation and at each visit at the clinic.

In this study, sites will be allowed to perform a pre-study screening assessment (at Week -3) prior to enrolment visit to screen for HbA1c criteria. All potentially eligible patients will be enrolled, provide informed consent, undergo screening for all applicable inclusion/exclusion criteria, and submit laboratory samples at Enrolment (Visit 1, 2 weeks prior to randomisation). Patients should be treated with a stable, Maximum Tolerated Dose (MTD) of metformin monotherapy (≥1500mg/day) for at least 8 weeks prior to Enrolment, and remain on the same type and dose of metformin therapy for the duration of the study as the background therapy for all treatment arms indicated below:

1. Dapagliflozin (5mg orally once daily [QD]) plus placebo as an add-on to metformin (≥1500mg/day orally)

2. Dapagliflozin (5mg orally once daily [QD]) plus saxagliptin (5mg orally once daily [QD]) as an add-on to metformin (≥1500mg/day orally)

3. Saxagliptin (5mg orally once daily [QD]) plus placebo as an add-on to metformin (≥1500mg/day orally)

Study Objectives

Primary Objective:	**Outcome Measure:**
To demonstrate the superiority of the change from baseline HbA1c achieved with the co-administered saxagliptin 5mg and dapagliflozin 5mg to either agent individually after 24 weeks	Change from baseline HbA1c to week 24

Secondary Objective:	**Outcome Measure :**
To demonstrate the effect of the co-administered saxagliptin 5mg and dapagliflozin 5mg to either agent individually on proportion of patients achieving therapeutic glycaemic response with after 24 weeks	Proportion of patients achieving HbA1c < 7.0% at 24 weeks
To demonstrate the effect of the co-administered saxagliptin 5mg and dapagliflozin 5mg to either agent individually on fasting plasma glucose after 24 weeks	Change in fasting plasma glucose at 24 weeks.
To demonstrate the effect of the co-administered saxagliptin 5mg and dapagliflozin 5mg to saxagliptin 5mg on total body weight after 24 weeks	Change in total body weight at 24 weeks

Safety Objective:	Outcome Measure :
To evaluate the safety and tolerability of the co-administered saxagliptin 5mg and dapagliflozin 5mg to either agent individually after 24 weeks	Adverse Events (AEs)/ Serious AEs (SAEs) Vital signs Collection of clinical chemistry/hematology parameters

Target patient population

Approximately 900 patients with T2DM with inadequate glycaemic control receiving metformin at a MTD of ≥1500mg/day for at least 8 weeks prior to enrolment, will be randomised to 1 of 3 treatment groups.

Duration of treatment

Study duration will be at least 27 weeks, including a 1-week pre-study Screening period, a 2-week enrolment period, and a 24-week double-blind treatment period.

Investigational product, dosage and mode of administration

Dapagliflozin and matching placebo:

Dapagliflozin 5mg tablets or placebo matching dapagliflozin will be administered orally once daily for the 24-week double-blind treatment period.

Saxagliptin and matching placebo:

Saxagliptin 5mg tablets or placebo matching saxagliptin will be administered orally once daily for the 24-week double-blind treatment period.

Other Treatments:

Metformin:

For the duration of the study, patients should continue to administer the same type and dose of metformin therapy they were using at study entry (at a daily dose ≥1500mg). Metformin should be administered and stored according to product and country specific labelling.

Rescue therapy:

Patients who require rescue therapy will receive open label dapagliflozin 10mg plus saxagliptin 5mg as a first line treatment. Insulin can be given as a second line treatment at Investigators discretion.

Statistical methods

Efficacy analyses will be run for the Full Analysis (FA) population and for the Per Protocol (PP) population (Refer section 8.3.1) if more than 10% of patients from the FA population are excluded from the PP population for important protocol deviations.

All analyses will be done using values regardless of rescue/intensification of treatment or discontinuation of the study treatment. Sensitivity analyses will be conducted for the primary efficacy analysis excluding the data after rescue or more than 8 days after discontinuation of the study treatment.

The primary endpoint will be tested for saxagliptin plus dapagliflozin versus each of the individual agents simultaneously at the alpha = 0.05 level (two sided). The secondary endpoints then will be tested sequentially. Each comparison will be tested at the alpha = 0.05 (two-sided) level.

The primary efficacy analysis will be performed using a longitudinal repeated measures analysis CCI for the change from baseline at Week 24, with terms for treatment group, 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.

A sample size of 300 patients per group will provide at least 90% power to simultaneously detect a difference in mean change from baseline to week 24 in HbA1c of -0.30 (%) for both primary endpoint comparisons of saxagliptin plus dapagliflozin vs its components at the 2-sided alpha = 0.05 level. This assumes a common standard deviation of 1.0% and a 3% non-evaluability rate.

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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
AE	Adverse event
ADA	American Diabetes Association
ALK-P	Alkaline Phosphatase
ALT	Alanine transaminase
ALP	Alkaline phosphatase
ANA	Antinuclear Antibody
ANCOVA	Analysis of covariance
Anti-LKM	Anti-Liver/Kidney Microsomal Antibody
AST	Aspartate transaminase
β-HCG	β- human chorionic gonadotrophin
BMI	Body mass index
BP	Blood pressure
CDT	Carbohydrate deficient transferrin
CABG	Coronary Artery Bypass Grafting
CK	Creatine Kinase
CMV	Cytomegalovirus
CRO	Clinical Research Organization
CrCl	Creatinine Clearance
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CSP	Clinical Study Protocol
CTCAE	Common Terminology Criteria for Adverse Event
CV	Cardiovascular
DAE	Discontinuation of Investigational Product due to Adverse Event
DBP	Diastolic blood pressure
DGR	Dangerous Goods Regulations
DILI	Drug Induced Liver Injury
DNA	Deoxyribonucleic acid

Abbreviation or special term	Explanation
DPP-4	Dipeptidyl peptidase -4
EBV	Epstein-Barr Virus
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
E-code	Enrolment code
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EOT	End of Treatment
FA	Full Analysis
FDC	Fixed Dose Combination
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GGT	Gamma-glutamyl-transpeptidase
GLP-1	Glucagon-like peptide-1
GMP	Good Manufacturing Practice
GPV	AZ Global Pharmacovigilance
AZRand	AZ Randomisation system
Hb	Haemoglobin
HbA1c	Haemoglobin A1c
HIV	Human immunodeficiency virus
HR	Heart rate
HSV	Herpes Simplex Virus
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICH	International Conference on Harmonization
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.
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IP	Investigational Product
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System

Abbreviation or special term	Explanation
LADA	Latent Autoimmune Diabetes of Adults
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LOCF	Last-Observation-Carried-Forward
LIMS	Laboratory information management system
LSLV	Last Subject Last Visit
MCH	Mean Cell Haemoglobin
MCHC	Mean Cell Haemoglobin concentration
MCV	Mean Cell Volume
MAR	Missing at random
MDRD	Modification in Diet and Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MoA	Mechanisms of action
MTD	Maximum Tolerated Dose
NYHA	New York Heart Association
OAD	Oral antidiabetic
OAE	Other Significant Adverse Event
PGx	Pharmacogenetic research
PI	Principal Investigator
PP	Per Protocol
PPG	Postprandial glucose
PCI	Percutaneous Coronary Intervention
PT/INR	Prothrombin time
QD	Once daily
SA	Sickle cell trait
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SCSM	AZ Supply Chain Study Management
SGLT2	Sodium glucose co-transporter 2
SMA	Anti-Smooth Muscle Antibody

Abbreviation or special term	Explanation
SOPs	Standard operating procedures
SU	Sulphonylurea
T2DM	Type 2 diabetes mellitus
TB	Bilirubin, total
TIA	Transient ischemic attack
TIBC	Total iron binding capacity
TSH	Thyroid Stimulating Hormone
TZD	Thiazolidinediones
U/A	Urinalyses
ULN	Upper Limit of Normal
Vs	Versus
WBDC	Web Based Data Capture
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Type 2 diabetes mellitus (T2DM) is a chronic disease characterised by hyperglycaemia and an increased risk of microvascular and macrovascular complications. Given the progressive nature of T2DM, it is challenging to achieve and maintain tight glycaemic control and approximately 50% of T2DM patients fail to achieve the American Diabetes Association (ADA) goal for glycaemic control of haemoglobin A1c (HbA1c) of <7.0% (Hoerger et al 2008). Typically the treatment paradigm consists of a step-wise addition of different classes of antihyperglycaemic drugs, as most patients eventually require 2 or more agents to achieve or maintain glycaemic targets. Metformin, a biguanide, is the recommended drug of choice for initiating oral antidiabetic (OAD) therapy, while other classes of antidiabetic agents are typically added sequentially as second and third line agents. An ideal add-on to metformin would provide strong HbA1c reduction through complementary mechanisms of action (MoA), with weight loss, and no hypoglycaemia.

Other classes of OADs include inhibitors of the human renal sodium glucose co-transporter 2 (SGLT2), the major transporter responsible for glucose reabsorption in the kidney. Dapagliflozin is a potent, highly selective, and orally active SGLT2 inhibitor and its MoA results in the direct and insulin-independent elimination of glucose by the kidney. Dapagliflozin is approved in the United States (US) and the European Union (EU [trade names: Farxiga™ and Forxiga™, respectively]) as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM. Clinical studies with dapagliflozin demonstrated the safety and efficacy of dapagliflozin in a wide range of patients with T2DM. Treatment with dapagliflozin led to significant and clinically relevant reductions in HbA1c, fasting plasma glucose (FPG), and postprandial glucose (PPG) levels, and was associated with weight loss.

Inhibitors of dipeptidyl peptidase -4 (DPP-4), the enzyme responsible for the inactivation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide, are another class of OADs. Saxagliptin is a highly potent, selective, reversible, and competitive DPP-4 inhibitor. By inhibiting DPP-4, saxagliptin potentiates active endogenous GLP-1 concentrations, augmenting the physiological mechanism of insulin secretion and suppressing glucagon release, thereby reducing PPG and FPG levels in patients with T2DM. Saxagliptin is approved by the US and EU for the treatment of T2DM and in Phase III trials, has effectively reduced HbA1c in patients with inadequately controlled T2DM on a stable dose of metformin, SUs, or thiazolidinedione, and has favorable safety and tolerability profiles (A. R. Chacra et al 2009, Jaime A. Davidson 2014, Priscilla L Hollander et al 2011, Ralph A. Defronzo et al 2009).

Dapagliflozin and saxagliptin have demonstrated, both individually and added to metformin, a favorable safety and tolerability profile. These OADs have demonstrated a low propensity for hypoglycaemia, therefore addressing a potential key concern when adding 2 glucose lowering agents simultaneously. Both drugs have either demonstrated weight neutrality (saxagliptin) or

moderate weight reduction (dapagliflozin). Dapagliflozin has also demonstrated persistent effects on HbA1c over 4 years of therapy.

Phase III study (CV181169) demonstrated that early combination treatment with dapagliflozin and saxagliptin, added together with metformin as triple therapy, elicited superior reduction in HbA1c as compared to the addition of either saxagliptin OR dapagliflozin to metformin in patients with inadequately controlled T2DM. Despite larger decreases in HbA1c, this was not associated with an increase in hypoglycaemic event rates, which were overall low and similar across the different therapies tested. While saxagliptin plus metformin has a neutral effect on weight, combination therapy including dapagliflozin plus metformin or dapagliflozin combined with saxagliptin plus metformin therapy resulted in a significant reduction of bodyweight (Rosenstock J et al 2015).

The recommended starting dose of dapagliflozin is 5mg in a few countries. The dose can be increased to 10mg in patients tolerating dapagliflozin 5mg who require additional glycaemic control. The aim of this study is thus to provide relevant clinical data regarding the efficacy and short term safety of saxagliptin 5mg co-administered with dapagliflozin 5mg after 24 weeks.

This is a double-blind, randomised, active-controlled, multi-center, 24 week, parallel-group study to evaluate safety and efficacy of saxagliptin 5mg co-administered with dapagliflozin 5mg, compared with either saxagliptin 5mg or dapagliflozin 5mg all given as add-on therapy to metformin in patients who are inadequately controlled on metformin alone. After randomisation the patients will visit the clinic after 6, 12, and 24 weeks. Efficacy as well as safety assessments will be taken before randomisation and at each visit at the clinic.

1.2 Rationale for study design, doses and control groups

This is a Phase III study, performed as part of the clinical development program for saxagliptin plus dapagliflozin fixed dose combination (FDC) therapy to improve glycaemic control as an adjunct to diet and exercise and metformin when treatment with both saxagliptin and dapagliflozin is appropriate.

Study design, dose selection, and control groups

The current study is designed to evaluate safety and efficacy of therapy with saxagliptin 5mg co-administered with dapagliflozin 5mg, compared to therapy with saxaglipgtin 5mg or dapagliflozin 5mg in patients who are inadequately controlled on ≥1500mg/day of metformin monotherapy.

A 24-week randomised, double-blinded treatment period will allow for adequate information on efficacy and safety of the studied doses.

Active control group

This is a double-blind, active-controlled study. All three study arms, saxagliptin 5mg plus dapagliflozin 5mg, saxagliptin 5mg plus placebo and dapagliflozin 5mg plus placebo, contain

at least one approved, oral anti-diabetic medication added to the background of metformin. Therefore all patients are anticipated to benefit from better glycaemic control during the study.

Background therapy

Metformin is a biguanide; its major effect is to decrease hepatic glucose output and lower fasting glucose. It is recommended as the initial pharmacological therapy in both the US and the EU because of its glycaemic efficacy, weight neutrality, low risk of hypoglycaemia, good tolerability, and relatively low cost (Inzucchi et al 2012).

Dapagliflozin

Dapagliflozin (Farxiga™) is approved in many countries worldwide, including the US, Canada, and countries in the EU, as an adjunct to diet and exercise to improve glycaemic control in patients with T2DM for whom metformin use is considered inappropriate due to intolerance, and in combination with other glucose-lowering medicinal products when these, in combination with diet and exercise do not provide adequate glycaemic control. The 5mg dose was chosen for this study because it is the starting dose in the US, Canada and Switzerland, has demonstrated clinically meaningful reductions in HbA1c, and is used at that dose in the combination under evaluation in this study. Treatment with dapagliflozin, with its unique mechanism of action, induces a persistent loss of excess glucose with associated calories in the urine, resulting in a consistent and maintained reduction of total body weight, in addition to improved glycaemic control. Dapagliflozin also has a mild diuretic effect, which in combination with weight loss, has the potential to reduce blood pressure.

Saxagliptin

Saxagliptin (Onglyza™) is approved in many countries worldwide, including the US, Canada and countries in the EU as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM. The results from the 8 Phase II and III clinical studies with saxagliptin support the oral dose of 5mg once daily (QD) in a wide range of patients with T2DM, as either monotherapy, add on combination therapy with metformin, a Thiazolidinediones(TZD), a Sulphonylurea (SU), insulin, or initial combination therapy with metformin. Saxagliptin 5mg resulted in clinically meaningful reductions in HbA1c, as well as Fasting Plasma Glucose (FPG), Post Prandial Glucose (PPG), insulin, C-peptide, and glucagon levels and is the recommended dose according to the approved drug label.

Combination of saxagliptin and dapagliflozin

The combination of saxagliptin 5mg and dapagliflozin 10mg has been studied in 3 phase III trials. The main study CV181-169, was a double blind randomised trial has compared dual add on saxagliptin 5mg/ dapagliflozin 10mg FDC to both of the components and found the FDC to be safe and superior to each of the components. The treatment was given on the background of metformin and lasted for 24 weeks.

Two other studies were sequential add on of saxagliptin 5mg to a background of dapagliflozin 10mg and metformin (study CV181-168) and add on dapagliflozin 10mg to a background of

saxagliptin 5mg and metformin (study MB102-129). Both studies found the co-administration of saxagliptin 5mg and dapagliflozin 10mg to be well tolerated and efficacious.

Choice of outcome variables

The primary endpoint is change from baseline in HbA1c at Week 24. HbA1c is the clinical and regulatory parameter used to estimate glycaemic efficacy of an OAD therapy in patients with T2DM. Because of its novel, complementary mechanism of action, dapagliflozin may have additive or synergistic HbA1c-lowering effects when given in combination with other anti-hyperglycaemic agents. Additionally, as beneficial effects on FPG and weight have been observed in other dapagliflozin studies, these variables have been chosen as key secondary objectives.

The rationale for selection of the secondary variables and exploratory variables is provided below:

1. Proportion of patients achieving HbA1c <7.0%: The target HbA1c for most patients with T2DM is <7.0% according to international diabetes treatment guidelines.

2. FPG is a well-established measure of short-term glycaemic efficacy (CHMP 2012).

3. Weight: More than 85% of patients with T2DM are overweight or obese (CDC 2004) Weight loss is a fundamental goal for the majority of patients with T2DM as it has been shown to improve comorbid conditions such as hypertension, dyslipidemia, heart disease, osteoarthritis, and sleep apnea (NHLBI 1998).

4. The start of rescue is an indirect measure of glucose efficacy and shows the durability of efficacy.

Choice of study population

Patients

Patients with T2DM with inadequate glycaemic control while being treated with at least 1500mg/day, of metformin therapy.

HbA1c

The HbA1c inclusion criterion at randomisation (i.e., ≥7.5% to ≤10.0%) was selected to include patients with poor glycaemic control, a population that would potentially achieve the greatest benefit from simultaneous addition of 2 antidiabetic agents.

Pregnancy or breastfeeding

Neither dapagliflozin nor saxagliptin have been tested in pregnant women and the risks to embryo, foetus, and infant are unknown. For this reason, women who are pregnant or breastfeeding are excluded and women of childbearing age are instructed to take precautions to avoid becoming pregnant during the study.

Other

The purpose of the majority of the inclusion and exclusion criteria is to limit confounding factors that may complicate the interpretation of the study results (e.g., corticosteroid-induced T2DM or haemoglobinopathies that would interfere with the HbA1c analyses) or to exclude patients whose safety could be compromised by participation in the study.

1.3 Benefit/risk and ethical assessment

Details regarding potential risks associated with administration of dapagliflozin and saxagliptin are provided in the Investigator's Brochure (IB) for each medication.

The study will provide efficacy and safety information for dapagliflozin 5mg plus saxagliptin 5mg added to metformin compared to dapagliflozin 5mg added to metformin or saxagliptin 5mg added to metformin, in patients with T2DM who are on metformin therapy. Patients in the dapagliflozin plus placebo group will receive saxagliptin-matching placebo with metformin; and patients in the saxagliptin group will receive dapagliflozin matching placebo with metformin. All patients will be monitored throughout the study to ensure adequate glycaemic control.

Dapagliflozin and Saxagliptin

Prior to approval, dapagliflozin was evaluated in 5 core Phase IIb studies, 16 core Phase III studies, and 3 regional Phase III studies.

Prior to approval, saxagliptin was evaluated in 6 pivotal Phase III, randomised, double-blind controlled trials at doses of 2.5 to 10mg. When added to standard of care in patients with T2DM at high cardiovascular (CV) risk, saxagliptin neither reduced nor increased the risk of the primary composite endpoint of CV death, myocardial infarction (MI), or ischemic stroke (Scirica et al 2013).

Considering the comprehensive previous clinical experience with saxagliptin and dapagliflozin, the study's design features (including the inclusion, exclusion, and discontinuation criteria), and the planned safety procedures, participation in this study presents a minimal and thus acceptable risk to the individual patients who will be included.

Protection against risks

This study has been designed with appropriate measures in place to monitor and minimise any of the potential health risks to participating patients. To ensure the safety of all patients participating in this study, AstraZeneca is conducting a real-time review of all safety information from all ongoing clinical dapagliflozin and saxagliptin studies as they become available. Safety signal detection will include the integration of all available sources of safety information, including clinical study data, adverse event (AE) reports, preclinical data, epidemiological studies, and literature reports, to identify and characterise unrecognised safety risks or changes in those which are currently expected Adverse Drug Reactions. Any information that may affect the benefit-risk profile of dapagliflozin or saxagliptin will be immediately communicated to relevant Health Authorities and appropriate actions will be

taken regarding the clinical program as needed. Thus real-time, active safety surveillance will be conducted during the entire duration of this study. In addition, all dapagliflozin and saxagliptin studies are subject to a carefully designed patient risk management plan that includes the temporary and if necessary permanent discontinuation of investigational product (IP) in individual patients in whom a potential health risk or a laboratory abnormality of clinical concern has been identified.

Ketoacidosis

There have been post-marketing reports of ketoacidosis, including diabetic ketoacidosis, in patients with type 1 and type 2 diabetes mellitus taking dapagliflozin and other SGLT2 inhibitors, although a causal relationship has not been established. Dapagliflozin is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with dapagliflozin who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise, and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL). If ketoacidosis is suspected, discontinuation or temporary interruption of dapagliflozin should be considered and the patient should be promptly evaluated.

Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (e.g, type 1 diabetes, history of pancreatitis, or pancreatic surgery), insulin dose reduction, reduced caloric intake, or increased insulin requirements due to infections, illness or surgery and alcohol abuse. Dapagliflozin should be used with caution in these patients.

Potential benefits to Patients

Based on prior clinical trials experience and post-marketing information, both saxagliptin and dapagliflozin have a favorable benefit-risk ratio as monotherapy and add-on combination therapy. Integrated analyses of the safety data from 3 Phase III clinical studies demonstrated that the combined use of saxagliptin 5mg and dapagliflozin 10mg administered as either a dual or a sequential add-on to metformin was well tolerated in patients who were inadequately controlled on metformin alone. The combined use of saxagliptin and dapagliflozin was associated with a low risk of hypoglycaemia. Overall, the safety profile of administering the 2 agents together was consistent with prior clinical trials which evaluated the safety of these agents as monotherapy or as add-on therapy. In these 3 prior Phase III clinical studies, treatment with saxagliptin and dapagliflozin showed clinically relevant decreases in HbA1c, leading to a large proportion of patients achieving the therapeutic goal of HbA1c <7%, and modest reduction in body weight in patients with T2DM. In the present study, a lower than commonly used dose of dapagliflozin (5mg) is used in combination with the standard dose of saxagliptin (5mg) so the risks of adverse events (AEs) are further reduced. In addition, saxagliptin is expected to be weight neutral and dapagliflozin to reduce weight moderately, while both have shown a low risk for hypoglycaemia in combination with metformin. Patients are also expected to receive some benefit in the form of increased medical care/attention when participating in study procedures, which includes multiple clinic visits and physical

examinations over the duration of the study. Patients will also receive counselling on dietary and life-style modifications.

Informed consent and alternatives to participation

All prospective participants will be informed of the possible risks and benefits associated with this study, and their consent will be received prior to performing any study-related activity. When a prospective participant elects to not participate in the study or to withdraw from the study, other medications are available to treat their diabetes, and the patient will not be disadvantaged in any way.

1.4 Study Design

Figure 1 presents the overall design of the study.

Study D1683C00005 is a 24-week, multi-center, randomised, parallel-group, double-blind, active-controlled Phase III study to evaluate safety and efficacy of therapy with saxagliptin 5mg co-administered with dapagliflozin 5mg added to metformin, compared to therapy with saxaglipgtin 5mg or dapagliflozin 5mg added to metformin in adult patients with T2DM who have inadequate glycaemic control (HbA1c ≥7.5% to ≤10.0%) on maximum tolerated dose of ≥1500mg/day of metformin monotherapy.

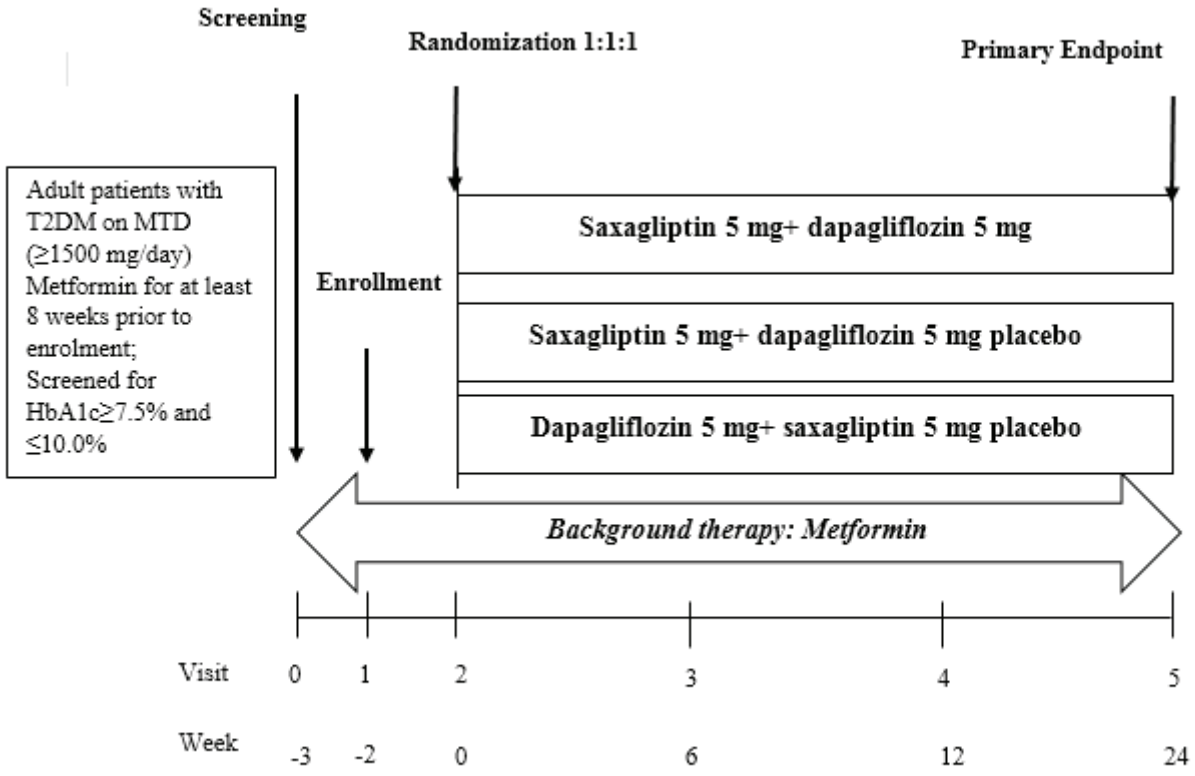
In this study, sites will be allowed to perform a pre-study screening assessment (at Week -3) prior to enrolment visit to screen for HbA1c criteria. All potentially eligible patients will be enrolled, provide informed consent, undergo screening for all applicable inclusion/exclusion criteria, and submit laboratory samples at Enrolment (Visit 1, 2 weeks prior to randomisation). Patients should be treated with a stable, maximum tolerated dose of metformin monotherapy (≥1500mg/day) for at least 8 weeks prior to enrolment, and remain on the same type and dose of metformin therapy for the duration of the study as the background therapy for all treatment arms as indicated below:

1. Dapagliflozin 5mg + saxagliptin 5mg + metformin

2. Dapagliflozin 5mg + saxagliptin placebo + metformin

3. Saxagliptin 5mg + dapagliflozin placebo + metformin

Figure 1 Study Design



2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To demonstrate the superiority of the change from baseline HbA1c achieved with the co-administered saxagliptin 5mg and dapagliflozin 5mg to either agent individually after 24 weeks	Change from baseline HbA1c to week 24

2.2 Secondary objectives

Secondary Objective:	Outcome Measure :
To demonstrate the effect of the co-administered saxagliptin 5mg and dapagliflozin 5mg to either agent individually on proportion of patients achieving therapeutic glycaemic response with after 24 weeks	Proportion of patients achieving HbA1c <7.0% at 24 weeks
To demonstrate the effect of the co-administered saxagliptin 5mg and dapagliflozin 5mg to either agent individually on fasting plasma glucose after 24 weeks	Change in fasting plasma glucose at 24 weeks
To demonstrate the effect of the co-administered saxagliptin 5mg and dapagliflozin 5mg to saxagliptin 5mg on total body weight after 24 weeks	Change in total body weight at 24 weeks

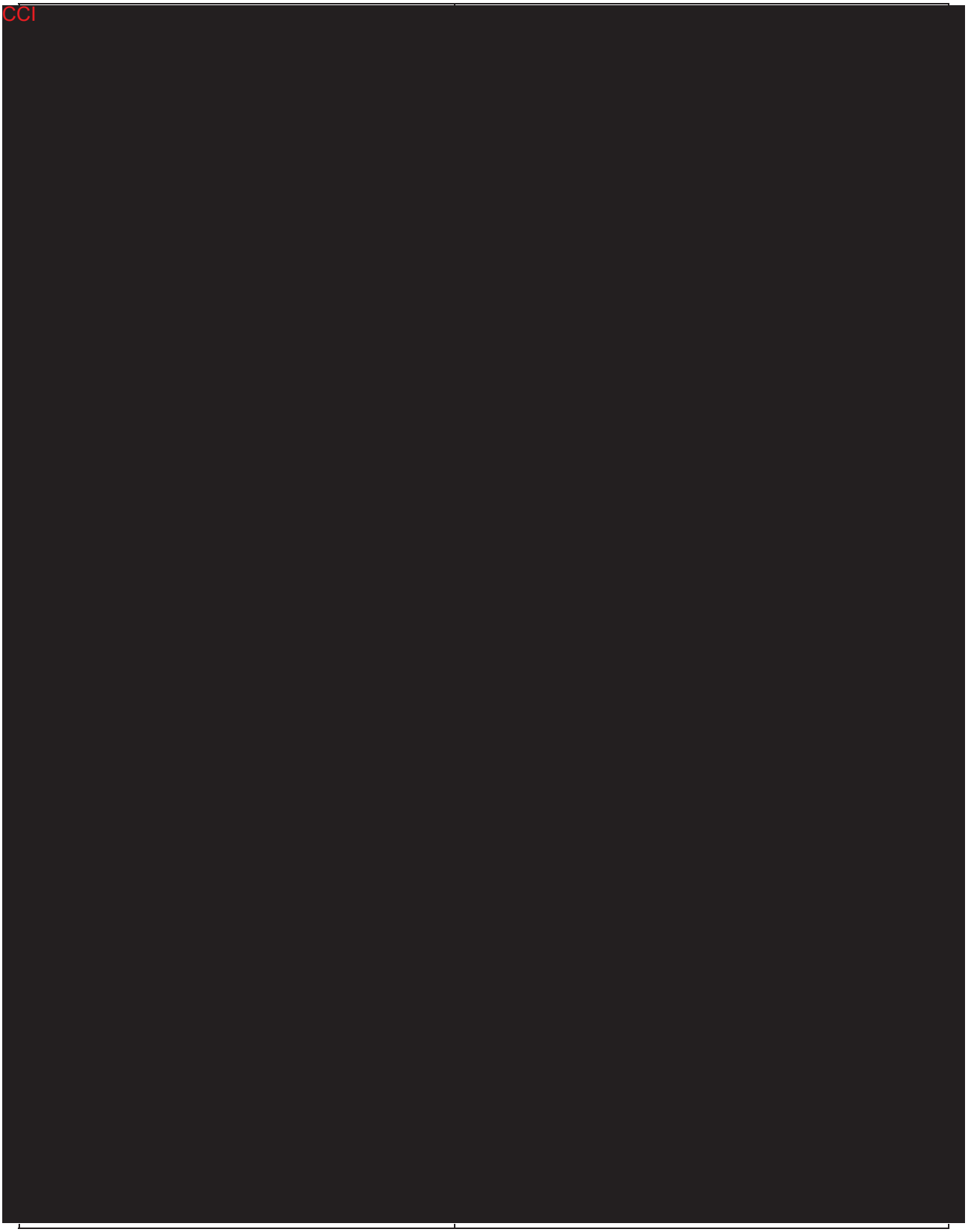
2.3 Safety objectives

Safety Objective:	Outcome Measure :
To evaluate the safety and tolerability of the co-administered saxagliptin 5mg and dapagliflozin 5mg to either agent individually after 24 weeks	AEs/SAEs Vital signs Collection of clinical chemistry/hematology parameters

2.4 Exploratory objectives

Exploratory Objective:	Outcome Measure :
CCI [redacted]	

CCI



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3. PATIENT SELECTION, ENROLMENT, RANDOMISATION, 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. **Signed written informed consent:** Patients must be willing and able to give signed and dated written informed consent.

2. **Target population:**

(a) Patients with T2DM with inadequate glycaemic control, defined as a central laboratory HbA1c ≥7.5% to ≤10.0% obtained at the screening visit.

(b) Fasting Plasma Glucose (FPG) ≤ 270mg/dl (15.0mmol/L) at the enrolment visit.

Note: At Week -2 (Visit 1), a qualification check will be performed and patients will be excluded, if their FPG is >270mg/dl. A re-test will be permitted within 7 days if the initial result was >270mg/dl but <300mg/dl (16.7mmol/L). Patients will be excluded if the mean value of the Week -2 result and the re-test result is >270mg/dl.

(c) Stable metformin therapy for at least 8 weeks prior to enrolment at a dose of ≥1500mg per day.

(d) BMI ≤45.0kg/m^2 at Enrolment visit.

3. **Age and reproductive status:**

(a) Men and women, aged ≥18 years old at time of screening visit.

(b) For Females Only: Women of childbearing potential (WOCBP) must be using an acceptable method of contraception to avoid pregnancy throughout the study and

for at least 4 weeks after the last dose of study medication in such a manner that the risk of pregnancy is minimized.

- WOCBP must have a negative urine pregnancy test (minimum sensitivity 25IU/L or equivalent units of HCG) within 24 hours prior to the start of investigational product.

- Women are not pregnant or breastfeeding.

Definitions

Women NOT of childbearing potential: Women who are permanently or surgically sterilized or postmenopausal. Permanent sterilization includes hysterectomy, and/or bilateral oophorectomy, and/or bilateral salpingectomy.

Postmenopausal women: Women are considered postmenopausal if they have amenorrhea for ≥12 consecutive months after the last menstrual period and marks the end of menstrual cycles.

Acceptable method of birth control: defined as one that results in a failure rate of <1% per year, when used consistently and correctly. The following are considered acceptable methods of contraception: total sexual abstinence; vasectomized sexual partner; male condom with spermicidal gel, tubal occlusion (ligation); intrauterine device; levonorgestrel intrauterine system (eg, Mirena®); etonogestrel implants (eg, Implanon®, Norplan®); normal and low dose combined oral contraceptive pills; norelgestromin/ethinyl estradiol transdermal system; intravaginal device (e.g., ethinyl estradiol and etonogestrel); and desogestrel (Cerazette®).

3.2 Exclusion criteria

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

1. **Target disease exceptions:**

(a) History of diabetes insipidus.

(b) Symptoms of poorly controlled diabetes that would preclude participation in this trial including but not limited to marked polyuria and polydipsia with greater than 10% weight loss during the 3 months prior to Enrolment (Visit 1), or other signs and symptoms.

(c) Type 1 diabetes or Latent Autoimmune Diabetes of Adults (LADA).

(d) History of diabetic ketoacidosis or hyperosmolar nonketotic coma.

2. **Medical history and concurrent diseases:**

(a) History of bariatric surgery or lap-band procedure within 12 months prior to Enrolment.

(b) 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.

(c) Patient who, in the judgment of the Investigator, may be a risk for dehydration or volume depletion that may affect the interpretation of efficacy or safety data.

(d) Patient is currently abusing alcohol or other drugs or has done so within the last 6 months.

3. **Acute vascular event:**

(a) Uncontrolled hypertension defined as systolic blood pressure (SBP) ≥160mmHg and/or diastolic blood pressure (DBP) ≥100mmHg.

Note: Patients with SBP≥160mmHg and < 180mmHg or a DBP ≥100mmHg and < 110mmHg will be able to enter the Enrolment (Visit 1), provided their hypertension treatment is adjusted as deemed appropriate by the investigator. These patients cannot be randomised if their blood pressure remains SBP ≥ 160mmHg or DBP ≥ 100mmHg measured at randomisation (Visit 2).

(b) Cardiovascular Disease within 3 months prior to Enrolment visit [ie myocardial infarction, cardiac surgery or revascularization (CABG/PCI), unstable angina, stroke or transient ischemic attack (TIA).

(c) Congestive heart failure as New York Association (NYHA) class III-IV (see Appendix C), unstable or acute congestive heart failure.

Note: eligible patients with congestive heart failure, especially those who are on diuretic therapy, should have careful monitoring of their volumes status throughout the study.

4. **Renal diseases:**

(a) Moderate or severe impairment of renal function [defined as eGFR <60mL/min/1.73m^2 (estimated by MDRD) or serum creatinine ≥1.5mg/dL in males or ≥1.4mg/dL in females].

(b) Conditions of congenital renal glucosuria, history of unstable or rapidly progressing renal disease.

5. **Hepatic diseases:**

(a) Significant hepatic disease, including, but not limited to, chronic active hepatitis and/or severe hepatic insufficiency and/or significant abnormal liver function, including patients with ALT and/or AST ≥3x ULN and/or Total Bilirubin ≥2.0x ULN.

(b) History of severe hepatobiliary disease or hepatotoxicity with any medication.

(c) Positive serologic evidence of current infectious liver disease, including patients who are known to be positive for Hepatitis viral antibody IgM, Hepatitis B surface antigen, and Hepatitis C virus antibody.

6. **Pancreatic disease:**

(a) History of pancreatitis.

7. **Hematological/Oncological disease/conditions:**

(a) History of haemoglobinopathy, with the exception of sickle cell trait (SA) or thalassemia; or chronic or recurrent hemolysis.

(b) Malignancy within 5 years of the Enrolment (Visit 1) with the exception of treated basal cell or treated squamous cell carcinoma.

(c) Known immunocompromised status, including but not limited to, individuals who have undergone organ transplantation or who are positive for the human immunodeficiency virus.

(d) Donation of blood or blood products to a blood bank, blood transfusion, or participation in a clinical study requiring withdrawal of >400mL of blood during the 6 months prior to the Enrolment (Visit 1).

8. **Prohibited treatment and therapies:**

(a) Administration of any antihyperglycaemic therapy, other than metformin, for more than 14 days (consecutive or not) during the 8 weeks prior to enrolment.

(b) Any use of DPP-4 inhibitor or SGLT-2 inhibitor within 8 weeks prior to enrolment.

(c) Current treatment with potent cytochrome P450 3A4/5 inhibitors (in countries where dose adjustment would be required by the saxagliptin label)

(d) Prescription and over-the-counter weight loss medications within 3 months prior to Enrolment (Visit 1)

(e) Current or frequent use of therapeutic doses of systemic glucocorticoids is an exclusion criterion. Treatment with any stable replacement therapy at the time of enrolment is permitted (See Section 7.9).

Note: Topical or inhaled corticosteroids are allowed.

(f) Administration of any other investigational drug or participation in any interventional clinical studies within 30 days prior to Enrolment (Visit 1).

9. **Physical and laboratory test findings:**

(a) Haemoglobin ≤11.0g/dL (110g/L) for men; haemoglobin ≤10.0g/dL (100g/L) for women

(b) Male patients with a confirmed benign cause of microscopic hematuria can be randomised with a documented negative microscopic urinalysis.

NOTE: Female patients with hematuria can be randomised, but should be investigated according to local standards and best clinical practices (See *Appendix E****).***

(c) Other central laboratory test findings:

- Abnormal free T4 values. Abnormal thyroid stimulating hormone (TSH) value at Enrolment (Visit 1) will be further evaluated by free T4. Patients with abnormal free T4 values will be excluded.

10. **Allergies and adverse drug reaction:**

(a) Patients who have contraindications, including but not limited to a history of serious hypersensitivity reaction to saxagliptin, dapagliflozin as outlined in the saxagliptin and dapagliflozin Investigator Brochure, the local saxagliptin and dapagliflozin package insert, or the local metformin package insert.

11. **Sex and reproductive status:**

(a) Women who are pregnant or breast-feeding.

12. **Other exclusion criteria:**

(a) Prisoners or patients who are involuntarily incarcerated.

(b) Patients who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

(c) Patients on a commercial weight loss program with ongoing weight loss, or on an intensive exercise program.

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

(e) Patient is a participating investigator, study coordinator, employee of an investigator or immediate family member of any of the aforementioned.

(f) Previous enrolment or randomisation in the present study.

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrolment and randomisation

Investigators will screen potential patients prior to enrolment based on information from medical history and a blood sample for measurement of HbA1c. The Investigator must obtain patient's consent to this screening procedure through an abbreviated informed consent (see Section 10.4.1). Investigator(s) should keep a record of patients who entered pre-study screening and keep it as the patient screening log.

For patients that are enrolled (Visit 1) into the study, the Investigators will:

1. Obtain signed informed consent from the potential patient before any study-specific procedures are performed.

2. Assign (using the Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS) potential patient a unique enrolment number, beginning with 'E + 4-digit site number + 3 digit patient number starting with 001. For example, the first patient at site 9999 would be assigned the patient number: E9999001. This number will be used for identification throughout the study.

3. Determine patient eligibility in accordance with inclusion/exclusion criteria.

4. Assign an eligible patient unique randomisation code, by accessing IVRS or IWRS, see Section 3.5. Patient is considered randomised in the study after this assignment.

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

3.4 Procedures for handling incorrectly enrolled or randomised 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 randomised or initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the following steps need to be taken:

1. The Investigator or Study Monitor should inform the AstraZeneca study physician immediately, ensuring patient safety must always be the number one priority.

2. Study Treatment must be discontinued in all cases where continued treatment is deemed to pose a safety risk to the patient. A discussion should occur between the AstraZeneca study physician and the investigator, a decision may be reached that whether to continue or discontinue the patient from study treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3. In those cases where continuation of study therapy is judged not to present a concern related to safety and disease management, the rationale for continuing study therapy must be clearly documented. The patient should continue follow up in accordance with defined study procedures.

3.5 Methods for assigning treatment groups

At Visit 2 (Baseline/Week 0), enrolled patients who meet all study requirements based on inclusion and exclusion criteria will be randomised strictly sequentially within each center as patients are eligible for randomisation. The randomisation codes will be computer generated using the AZ Randomisation system (AZRand) and loaded into the IVRS/IWRS database. The patients will be randomised in a 1:1:1 ratio to the following treatment groups:

1. Dapagliflozin 5mg + placebo for saxagliptin

2. Dapagliflozin 5mg + saxagliptin 5mg

3. Saxagliptin 5mg + placebo for dapagliflozin

If a randomisation number is allocated incorrectly, no attempt should be made to remedy the error once study material has been dispensed. The patient will continue with the allocated number and study material. AstraZeneca or representative should be notified as soon as the error is discovered. Subsequent patients will continue using the first unallocated randomisation number in the original numbering sequence.

3.6 Methods for ensuring blinding

Blinding is ensured by using a double-blind, double-dummy technique. Patients, the Investigator, study site personnel, and Sponsor personnel involved with data review and analysis will be blinded throughout the study until database lock. The active tablets and the respective placebo tablets will be identical in size, colour, smell, and taste as described in Table 5. The bottles with IPs will be labelled with unique identification numbers allocated from the IVRS/IWRS.

No member of the study team at AstraZeneca, at study sites, or any clinical research organization (CRO) handling data will have access to the randomisation scheme during the conduct of the study, with the exception of the AstraZeneca personnel generating the randomisation scheme as well as AstraZeneca's Supply Chain Study Management (SCSM), AstraZeneca Global Pharmacovigilance (GPV), and the CRO providing the IVRS/IWRS and carrying out the packaging and labelling of IPs.

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the Investigator(s) 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 randomisation. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient and 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.

3.8 Restrictions

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

1. Fast overnight for 8 to 12 hours prior to each study site visit, i.e., no food or beverage except water. Allowed medications can be taken with water only.

2. Continue metformin therapy at current dosage and at approximately the same time each day, except that the morning dose of metformin should be delayed on the morning of study site visits.

3. Delay administering the IPs (as applicable) and metformin on the morning of the clinic visit and bring study medication and metformin to each study site visit.

4. 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.

5. Do not donate blood for the duration of the study and for 3 months following the last study visit.

6. Comply with prescribed dosing regimen to preserve study integrity and ensure patient safety.

7. Discuss any new prescriptions and over-the-counter or herbal/nutritional therapies with the Investigator, as concomitant use could result in alterations to their glycaemic control and may place them at risk for significant hypoglycaemic episodes.

8. Make every attempt to adhere to the diet and exercise counseling and to the protocol visit schedule.

9. 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.

3.9 Discontinuation of investigational product

3.9.1 General discontinuation criteria:

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

1. Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.

2. Patient experiences an AE or SAE that, in the Investigator's opinion, necessitates discontinuation from study medication.

3. The Investigator feels it is in the patient's best interest to discontinue study medication for reasons other than AE. If this decision is made because of an SAE or a clinically significant abnormal laboratory value, appropriate measures are to be taken. The Sponsor or its designee is to be alerted immediately (see Section 6.4).

4. Severe non-compliance with the study protocol as judged by the Investigator and/or AstraZeneca

5. Incorrectly enrolled patients (see Section 3.4)

6. Lack of Therapeutic response

3.9.2 Study-specific discontinuation criteria:

1. Initial and repeat laboratory tests meet any of the following criteria (see Appendix D):

   – ALT and/or AST are >3x ULN and TB >2x ULN

   – ALT and/or AST are >5x ULN for ≥14 consecutive days, at any time after initial confirmatory results

   – ALT and/or AST are >8x ULN

2. Pregnancy confirmed by a positive pregnancy test or otherwise verified

3. Hypoglycaemia episodes as defined in Section 3.9.3

4. Use of (need for) any anti-hyperglycaemic medication other than IP or background metformin or rescue therapy allowed by protocol. Insulin use is permitted in the following situations:

   – For up to 14 days in total during the study and up to 7 continuous days if patients are unable to take oral medications (for example during a gastrointestinal illness)

   – For up to 14 days in total during the study and up to 7 continuous days if there is a documented illness or infection that requires additional therapy for maintaining glycaemic control

   – For up to 14 days in total during the study and up to 7 continuous days if patients have to temporarily stop IP and/or metformin due to recommendations made in this clinical study protocol

   – For up to 7 days during hospitalisation. When the reason for hospitalisation is the management of the patient's glycaemic control, treatment with insulin is considered a rescue and is allowed for as long as clinically necessary.

5. eGFR <60mL/min/1.73m^2 (by MDRD) confirmed by a repeated central lab measurement within 1 week.

   Note: Withhold the study medication until results for the retest of eGFR are available ONLY for randomisation visit (For all other visits, there is no need to interrupt the study medication)

3.9.3 Discontinuation guidelines for protocol-defined severe hypoglycaemia episodes or recurrent non-severe hypoglycaemia episodes

Patients will be recommended to continue on the study and not discontinue from treatment based on single episodes of hypoglycaemia or symptoms of hypoglycaemia unless clinically indicated. The assessment of a single finger stick or central laboratory glucose value should not be the sole assessment used to determine patient discontinuation for hypoglycaemia.

Clinical indications for discontinuation because of hypoglycaemia should include the following:

(a) Multiple occasions of episodes outlined below that, in the opinion of the Investigator, indicate that continued treatment with study therapy is not in the best interest of the patient. This includes, but is not limited to:

   – Symptoms suggestive of hypoglycaemia (e.g., sweating, shakiness, increased heart rate, confusion, dizziness, light-headedness, or hunger) in the absence of environmental factors known to contribute to hypoglycaemia (i.e., excess physical activity, concurrent illness, or missed or delayed meal)

and/or

– Documented finger stick glucose values <54mg/dL (<3.0mmol/L)

(b) A patient may also be discontinued from the study because of severe hypoglycaemia, as determined by the Investigator.

If finger stick glucose values are discordant from glycaemic control assessed by the laboratory or with clinical symptoms, the patient's glucose meter should be tested and the instructions for use reviewed with the patient.

3.9.4 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue IP or withdraw from the study (i.e., IP and assessments – see Section 3.10), without prejudice to further treatment. A patient who decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. If possible, the patient will be seen and assessed by an Investigator. Any AEs will be followed up (see Section 6.3.5); patient diaries and all study drugs should be returned by the patient.

Patients who discontinue from the study medication will have an Early Termination Visit equivalent to the Visit 5 (Week 24/End of Treatment) assessments immediately following discontinuation of study medication (see Section 4.5).

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

All patients who discontinue study drug should remain in the study and follow the original visit schedule. Patients unable or unwilling to return for scheduled visits will have the opportunity to receive follow-up via telephone calls placed by the site mainly to review safety and concomitant medications. The only exception to this procedure is when a patient withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

3.10 Criteria for withdrawal

Every reasonable effort should be made to conduct all protocol-required procedures to complete the study. Patients may be removed from the study for the following reasons:

1. Screen failures: see Section 3.10.1.

2. Withdrawal by patient: see Section 3.10.2.

3. Lost to Follow-Up: Patient fails to return for study visits and cannot be reached with reasonable, repeated attempts.

To prevent patients being lost to follow-up, their contact details, including next of kin contacts should be collected initially and updated regularly by the site staff or representative. The Investigator should educate the patient on the importance of contact with the Investigator throughout the study. Every effort will be made to ensure that the patient continues to return to the clinic for study visits and to avoid "lost to follow-up" during the conduct of the study. The study staff should make diligent attempts to contact patients who fail to return for study visits by using institutional databases, patient's health professionals, and any other means that comply with country and local laws and regulations. After the first missed visit, patients who are considered temporarily lost to follow-up will have 2 documented telephone contact attempts and 1 certified letter in an effort to contact patients.

Any withdrawal must be fully documented in the patient's source records and recorded in the electronic Case Report Form (eCRF). The documentation must include the reason for the withdrawal and details of any sequelae (followed until symptoms resolve or improve, as appropriate).

If a patient is withdrawn from the study, they must complete the procedures outlined in Section 3.10.2.

3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These patients should have the reason for study withdrawal recorded as 'Eligibility Criteria not fulfilled' (i.e., patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomised patients). Patients can only be enrolled 1 time into this study.

3.10.2 Withdrawal of the informed consent

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

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The Investigator will follow-up AEs outside of the clinical study. All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (e.g., withdrawal due to an AE or lack of efficacy should not be recorded in the "voluntary withdrawal" category).

If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn patients will not be replaced.

3.11 Discontinuation of the study

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

1. Meet individual stopping criteria or are otherwise considered significant.

2. Are assessed as causally related to IP.

3. Are not considered to be consistent with continuation of the study.

In addition to above, study may be stopped if:

1. Study terminated by Sponsor: The Sponsor discontinues the study protocol.

2. Administrative reasons: The EU or other regulatory authority discontinues the study protocol or the clinical study site discontinues participation.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation must be recorded in the eCRF. All reasons for discontinuation of study 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 1 Study Plan

Evaluation	**Screening**[a] Non-fasting	**Enrolment** Fasting	**Treatment Period** Fasting			**End of Treatment / Early Termination/ Rescue** Fasting	**Notes**
Visit	**0**	**1**[c]	**2**[d]	**3**	**4**	**5**	
Week	**-3**	**-2**	**0**	**6**	**12**	**24**	
Relative to Randomisation (days) [e]	**-21**	**-14**	**R**	**42**	**84**	**168**	
Visit window (days)		**+3**	**±3**	**±7**	**±7**	**±7**	
Informed consent	X[b]	X					Section 10.4
Assign E-code		X					Section 3.3
Demography and medical history		X					
Inclusion/exclusion criteria		X	X				Section 3.1 Section 3.2
Randomisation			X				Section 3.5 Section 4.3.1
Complete physical examination		X				X	Section 5.2.2
Brief Physical examination [f]			X	X	X		Section 5.2.2
Vital signs (Blood Pressure, Heart Rate)		X	X	X	X	X	Section 5.2.3
Height		X					Section 5.1.4
Weight		X	X	X	X	X	Section 5.1.3
BMI		X				X	
Review Concomitant medications[g]	X	X	X	X	X	X	
Diet and Exercise Counseling		X	X	X	X	X	Section 5.3.2
Safety Assessment							
Assess Adverse Events/Serious Adverse Events		X	X	X	X	X	Section 6
Patient diary review for glucometer values and/or			X	X	X	X	Section 5.3.1

Table 1 Study Plan

Evaluation	**Screening**[a] Non-fasting	**Enrolment** Fasting	**Treatment Period** Fasting			**End of Treatment / Early Termination/ Rescue** Fasting	**Notes**
Visit	**0**	**1**[c]	**2**[d]	**3**	**4**	**5**	
Week	**-3**	**-2**	**0**	**6**	**12**	**24**	
Relative to Randomisation (days) [e]	**-21**	**-14**	**R**	**42**	**84**	**168**	
Visit window (days)		**+3**	**±3**	**±7**	**±7**	**±7**	
hypoglycaemic events							
Central Laboratory							
eGFR (MDRD)		X	X	X	X	X	Section 5.2.1. eGFR will be calculated by central laboratory
HbA1c[j]	X		X	X	X	X	Section 5.2.1
FPG		X	X	X	X	X	Section 5.2.1
Urinalysis		X	X	X	X	X	Section 5.2.1
Pregnancy test (urine, WOCBP only)[h]		X	X				Section 5.2.1
Clinical Chemistry		X	X	X	X	X	Section 5.2.1
Hematology		X	X		X	X	Section 5.2.1
CCI							
Hematuria Dipstick Urinalysis		X					Positive dipstick result requires repeat test with microscopy (Refer to Appendix E)
Hematuria Microscopic Urinalysis*		X					* Urinalysis with microscopy will be repeated until its negative (Refer

Table 1 Study Plan

Evaluation	**Screening**[a] Non-fasting	**Enrolment** Fasting	**Treatment Period** Fasting			**End of Treatment / Early Termination/ Rescue** Fasting	**Notes**
Visit	**0**	**1**[c]	**2**[d]	**3**	**4**	**5**	
Week	**-3**	**-2**	**0**	**6**	**12**	**24**	
Relative to Randomisation (days) [e]	**-21**	**-14**	**R**	**42**	**84**	**168**	
Visit window (days)		**+3**	**±3**	**±7**	**±7**	**±7**	
							to Appendix E)
Hepatitis Screening Panel, TSH		X					Section 5.2.1
Other							
Dispense patient diary		X	X	X	X		Section 5.3.1
Dispense glucometer and/or supplies/instructions		X	X	X	X		Section 5.3.1
Dispense study medication			X		X		Section 7
Return study medication[k]					X	X	Section 4.5
Study Medication Compliance Review				X	X	X	Section 7.6
Dispense open label rescue medication (if necessary)				X	X		Section 4.4

Abbreviations: AE adverse event, BP blood pressure, BMI body mass index, E-code enrolment code, eGFR estimated glomerular filtration rate, FPG fasting plasma glucose, HbA1c haemoglobin A1c, R randomisation, SAE serious adverse event, WOCBP women of child-bearing potential, EOT end of treatment.

a Screening visit (Visit 0) will occur 1 week prior to Enrolment (Visit 1) to screen for eligibility based on a non-fasting sample of HbA1c (assessed at central lab). See Section 4.1 for details.

b An abbreviated informed consent form will be signed at Screening visit.

c Enrolment visit will occur 7 days (+3 days) after patient provides signed abbreviated screening Informed Consent form. However patient can be enrolled as soon as laboratory screening results for HbA1c are available and it is determined that the value meets the inclusion/exclusion criteria.

d Visit 2 (Randomisation/Baseline) should be performed 14 days (±3 days) after Enrolment visit, when laboratory results from Visit 1 are available.

e Once a patient is randomised at Visit 2, all subsequent visits should be scheduled relative to Visit 2.

f Brief physical examination could be performed at visit 2,3 and 4 at Investigators discretion

g Review of concomitant medications includes over the counter drugs and herbal/nutritional therapies.

h Urine HCG pregnancy test for WOCBP (performed at site by dipsticks provided by central laboratory) at Visit 1 and 2. In case of suspected pregnancy, home pregnancy testing should be performed after randomization

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i CCI [redacted]

j Re-testing of HbA1c at central laboratory is permitted once within one month of the initial screening visit if central laboratory result of HbA1c is >7.0% and <7.5% or >10% and <10.5%.

k For rescued patients, rescue medication should also be returned at Visit 4 and 5.

4.1 Screening Visit

Procedures will be performed according to the Study Plan Table 1.

Failure to meet the HbA1c inclusion criterion is the main reason for screening failure in diabetes treatment studies. Therefore, in this study, sites need to mandatorily perform a pre-study screening assessment (at Week -3) within 1 week prior to enrolment visit, which will comprise of a collection of 1 non-fasting blood sample to determine HbA1c at the central laboratory. Investigators will screen only patients who are potentially eligible for the study based on their medical conditions and existing therapies, and only those who are expected to meet all entry criteria at Enrolment (Visit 1).

In order to be considered for screening, patients must:

1. Be ≥18 years old at time of informed consent.

2. Have a documented diagnosis of T2DM.

3. Currently treated with a stable MTD (≥1500mg/day) of metformin therapy and not have received any other antihyperglycaemic therapy within 8 weeks from the expected date of Enrolment (Visit 1).

At this Screening visit, the following will be performed:

1. Abbreviated informed consent to the pre- study screening procedures will be obtained (see Section 10.4.1).

2. A blood sample will be collected for measurement of HbA1c by a central laboratory. Fasting is not required.

3. Verification of current metformin therapy

Patients with HbA1c result of ≥7.5% to ≤10.0% assessed based on central laboratory results from screening visit will be scheduled for an enrolment visit in approximately 7 days. Patients should be fasting at the next visit (Enrolment, Visit 1) and a full ICF will be obtained before any assessments at that visit are initiated.

Note: Re-testing of HbA1c is permitted once within one month of the initial screening visit if central laboratory result of HbA1c is >7.0% and <7.5% or >10% and <10.5%.

All patients who are screened should be listed on a patient screening log. A screening code will be created for all screened patients by the site personnel. Patients with re-tested HbA1c at screening will have the same screening code. This code will identify screening laboratory results including retest results together with date of birth and gender.

4.2 Enrolment Period

Procedures will be performed according to the Study Plan (Table 1). Patients will be instructed to arrive in the morning for each scheduled visit. Prior to this visit, patients are to have fasted overnight for 8 to 12 hours (no food, no beverage, except water). Patients are advised to 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. Patients should delay administering their morning dose of metformin on the morning of the enrolment visit (Visit 1).

4.2.1 Enrolment visit (Visit 1, Week -2)

Patients on a stable, MTD of metformin monotherapy ≥1500mg/day for the last 8 weeks prior to enrolment with an HbA1c ≥7.5% to ≤10.0% will be eligible to enter the study. The patient should maintain the prescribed stable dose of metformin for the duration of the study.

Visit 1 (Enrolment) should take place approximately 1 week after Screening visit. At Visit 1, informed consent for Protocol D1683C00005 will be obtained prior to performing any protocol-required procedures. 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 and will be considered screen failures.

Enrolment (Visit 1) procedures should be scheduled for at least 1 day later than the day of informed consent signature if the patient is not in a fasting state on the consent date.

The following will be performed during this visit:

1. Informed consent will be obtained.
2. E-code will be assigned from IVRS/IWRS.
3. The patient's demography and complete medical history will be recorded.
4. Inclusion and exclusion criteria will be verified.
5. A complete physical examination will be conducted (see Section 5.2.2).
6. Vital signs (sitting systolic and diastolic BP and Heart Rate) will be measured (see Section 5.2.3).
7. Body weight and height will be measured (see Section 5.1.3 and 5.1.4).
8. BMI will be calculated.
9. All prior medications (prescription medications within 3 months) and concomitant medications (including over the counter and herbal/nutritional supplements) will be reviewed.

10. Blood samples will be collected for the following laboratory assessments:

    - Clinical chemistry and Hematology (see Section 5.2.1)
    - eGFR (MDRD) (see Section 5.2.1)
    - FPG (samples for central laboratory testing, see Section 5.2.1)
    - Hepatitis screening (hepatitis B surface antigen, antibody to hepatitis B core antigen IgM, and hepatitis C virus antibody)
    - Thyroid Function (TSH)

11. Urine will be collected for following (see Section 5.2.1)

    - Urinalysis
    - Urinary pregnancy test for beta human chorionic gonadotropin (βhCG) for female patients (WOCBP only)
    - Hematuria Dipstick and/or Microscopic Urinalysis

12. AEs/SAEs will be reviewed.

13. Diet and Exercise counseling will be provided.

14. Glucose meter and supplies and instructions will be provided.

15. Patient diary and instructions will be provided.

Individuals will be screen failed if results of any laboratory tests are abnormal and clinically significant as judged by the Investigator or medical monitor.

4.3 Treatment period

4.3.1 Randomisation and baseline visit (Visit 2, Week 0)

Visit 2 (Randomisation/Baseline) should take place approximately 2 weeks after Visit 1. Prior to this visit, patients are to have fasted overnight (8 to 12 hours). Patients are advised to 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. Patients should delay administering their morning dose of metformin on the morning of the study site visit.

The following will be performed during this visit:

1. Inclusion/exclusion and randomisation criteria will be verified.

2. Patients will be randomly assigned to 1 of 3 treatment groups (while continuing on metformin therapy) by IVRS/IWRS:

   – Dapagliflozin 5mg + saxagliptin 5mg

   – Dapagliflozin 5mg + placebo for saxagliptin

   – Saxagliptin 5mg + placebo for dapagliflozin

3. A brief physical examination may be conducted at Investigators discretion (see Section 5.2.2).

4. Vital signs (sitting systolic and diastolic BP and Heart Rate) will be measured (see Section 5.2.3).

5. Body weight will be measured Section 5.1.3.

6. Concomitant medications (including over the counter and herbal/nutritional supplements) will be reviewed.

7. Blood samples will be collected prior to administration of study medication for the following assessments:

   – Clinical chemistry and Hematology (see Section 5.2.1)

   – HbA1c

   – eGFR (MDRD)

   – FPG (samples for central laboratory testing, see Section 5.2.1)

CCI

8. Urine will be collected for following (see Section 5.2.1)

   – Urinalysis

   – Urinary pregnancy test for beta human chorionic gonadotropin (βhCG) for female patients (WOCBP only)

9. AEs and SAEs will be reviewed.

10. Diet and Exercise counseling will be provided.

11. Glucose meter and/or supplies and instructions will be provided.

12. Patient diary and instructions will be provided.

13. Patient diary will be reviewed for glucometer values and/or hypoglycaemic events history.

14. Study medication will be dispensed. Study site personnel will monitor administration of study medication and morning dose of metformin with food.

4.3.2 Treatment period visits (Visits 3 and 4; Weeks 6 and 12)

Prior to these visits, patients are required to have fasted overnight (8 to12 hours). Patients are advised to 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. Patients should delay administering their morning dose of metformin and study medication on the morning of the study site visits. Patients should bring their metformin and study medication with them to the study site and will self-administer study medication as directed by study-site personnel.

The following will be performed during these visits:

1. A brief physical examination may be conducted at Investigators discretion (see Section 5.2.2).

2. Vital signs (sitting systolic and diastolic BP and Heart Rate) will be measured (see Section 5.2.3).

3. Body weight will be measured Section 5.1.3.

4. Concomitant medications (including over the counter and herbal/nutritional supplements) will be reviewed.

5. Blood samples will be collected prior to administration of study medication for the following assessments:

   – Clinical chemistry (see Section 5.2.1)

   – Hematology except Visit 3 (see Section 5.2.1)

   – HbA1c

   – eGFR (MDRD)

   – FPG (samples for central laboratory testing, see Section 5.2.1

6. Urine will be collected for urinalysis.

7. AEs and SAEs will be reviewed.

8. Patient diary will be reviewed for glucometer values and/or hypoglycaemic events history

9. Diet and Exercise counseling will be provided.

10. Glucose meter and/or supplies and instructions will be provided.

11. Patient diary and instructions will be provided.

12. Study medication will be dispensed and returned (except Visit 3). Study site personnel will monitor administration of study medication and morning dose of metformin with food.

13. Study medication compliance will be reviewed

14. Rescue medication will be dispensed (as necessary, see Table 1)

4.4 Rescue therapy

During the double-blind treatment period of the trial, patients may be eligible for treatment with open-label rescue medication (see Table 6) to replace their blinded treatment regimen in order to treat ongoing hyperglycaemia. The sub-sections and table listed below define the lack of glycaemic control criteria for initiation of rescue medication.

Pre-specified glycaemic criteria (see Table 2), based upon repeat confirmatory central laboratory FPG have been established during the double-blind treatment period, starting at

Table 2 Criteria for Initiation of Rescue Therapy During the Randomised Treatment Period

Visit Period	Central Laboratory glycaemic parameters
At Week 6	FPG >270mg/dL (15.0mmol/L)
From Week 6 to Week 12 (Excluding Week 12)	FPG > 240mg/dL (13.3mmol/L)
Week 12 to Week 24	FPG > 200mg/dL (11.1mmol/L)

Week 6, to determine eligibility for open-label rescue medication.

Abbreviations: FPG Fasting plasma glucose

Patients with a central laboratory FPG value meeting the lack of glycaemic control criterion at a pre-specified visit will be scheduled for a follow-up visit (within 3 to 5 days) to obtain a second central laboratory FPG value and review the patients glucose meter readings. **If the repeat central laboratory FPG value still meets the criterion, the patient must be rescued.**

Patients who meet rescue criteria in the double-blind treatment period must first complete the Rescue Visit procedures before receiving open-label rescue medication to ensure that important trial endpoint measurements are collected.

Following completion of the Rescue Visit, rescued patients will be given open-label anti-diabetic rescue medication (Saxagliptin 5mg and Dapagliflozin 10 mg as a first line or Insulin as a second line at Investigators discretion) and will discontinue study medication. Rescued patients will then continue in the double-blind treatment period according to their original visit schedule.

Note: Rescue medication (Saxagliptin 5mg and Dapagliflozin 10mg) will be provided by Sponsor in this study. Insulin will not be provided by Sponsor since it is part of patients standard of care.

4.5 End of treatment period visit/ Early Termination or Rescue (Visit 5, Week 24)

Visit 5 (End of Treatment Visit) should occur 12 weeks after Visit 4 or if the patient discontinued early from IP or is rescued. Prior to this visit, patients are required to have fasted overnight (8 to12 hours). Patients are advised to 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. Patients should delay administering the morning dose of metformin and study medication on the morning of the visit and bring metformin and study medication to the study site visit.

All patients who are rescued or who discontinue study drug should remain in the study and follow the visit schedule.

The following procedures will be conducted:

1. A complete physical examination may be conducted at Investigators discretion (see Section 5.2.2).

2. Vital signs (sitting systolic and diastolic BP and Heart Rate) will be measured (see Section 5.2.3).

3. Body weight will be measured Section 5.1.3.

4. BMI will be calculated.

5. Concomitant medications (including over the counter and herbal/nutritional supplements) will be reviewed.

6. Blood samples will be collected prior to administration of study medication for the following assessments:

   - Clinical chemistry (see Section 5.2.1)
   - Hematology (see Section 5.2.1)
   - HbA1c

- eGFR (MDRD)
- FPG (samples for central laboratory testing, see Section 5.2.1)

CCI [redacted]

7. Urine will be collected for urinalysis.
8. AEs and SAEs will be reviewed.
9. Patient diary will be reviewed for glucometer values and/or hypoglycaemic events history.
10. Diet and Exercise counseling will be provided.
11. Study medication compliance will be reviewed.
12. Patient diary will be collected (not applicable for rescue visit, for end of treatment only).
13. Study medication will be returned (not applicable for rescue visit).
14. Glucose meter and/or supplies and instructions will be collected.

5. STUDY ASSESSMENTS

A 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 eCRFs as specified in the Clinical Study Protocol (CSP) 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 (CSA).

The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

5.1 Efficacy assessments

Study outcome measures are summarised in Section 8.4

5.1.1 HbA1c

Blood samples for measurement of HbA1c will be collected according to the schedule presented in the Study Plan (Table 1). The instructions for collection, processing, packaging, and shipping of the samples will be detailed in the laboratory manual.

The results from baseline and onwards will not be reported to the Investigator.

5.1.2 Fasting plasma glucose

Blood samples for measurement of FPG will be collected according to the schedule presented in the Study Plan (Table 1). The instructions for collection, processing, packaging and shipping of the samples to central laboratory will be detailed in the laboratory manual.

The results from baseline and onwards will not be reported to the Investigator unless the values meet the defined rescue criteria. In addition, if rescue medication is initiated, the central laboratory FPG value will be reported to the Investigator to ensure proper follow-up of the rescued patient.

5.1.3 Body weight

Body weight will be measured according to the schedule presented in the Study Plan (Table 1). The study site staff should use a digital precision scale if possible, and record the weight in kilograms to the first decimal point (e.g., 95.3kg). The same scale should be used and the patient should wear a standard hospital-type gown or equivalent light clothing and no shoes for the body weight measurement at each visit.

5.1.4 Body height

Body height will be measured according to the schedule presented in the Study Plan (Table 1). The study site staff should record the height in centimetres. The patient should remove their footwear and head gear and stand with feet together, heels against the back board, and knees straight.

5.2 Safety assessments

The Investigator will evaluate all Screening, Enrolment 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 1), 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, haematology, and urinalysis will be taken at the times indicated in the Study Plan (Table 1).

The date and time of sampling will be recorded on the laboratory requisition form. The instructions for collection, processing, packaging, and shipping of the samples will be detailed in the laboratory manual.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator.

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 6.3.5

Volume of blood

The total blood drawn from each patient over the course of the study will be approximately 100ml.

Table 3 Volume of blood to be withdrawn from each patient

	Sample Volume (ml)						Total Volume (ml)
VISIT	S	V1	V2	V3	V4	V5	
Label	Screen	Enrol	Randomisation				
Week	-3	-2	0	6	12	24	
Haematology		2	2		2	2	8 (approx.)
Chemistry[a]		5	2.5	2.5	2.5	2.5	15 (approx.)
FPG		2	2	2	2	2	10 (approx.)
HbA1c	2		2	2	2	2	10 (approx.)
CCI							
Hepatitis Panel		3.5					3.5 (approx.)
Total	2	22.5	8.5	6.5	8.5	18.5	67 to 100[b]

a. Includes TSH and Free T4
b. Includes a margin for additional visits such as rescue or unscheduled visits.

Protocol-Specific central laboratory assessments

- HbA1c
- FPG

Chemistry and haematology assessments (see Table 4) will include the following

Table 4 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Red blood cell count Red Blood Count indices: _Mean Cell Haemoglobin (MCH) _Mean Cell Volume (MCV) _Mean Cell Haemoglobin Concentration (MCHC) **_White blood cell Count and Differential** _Platelet count	S/P-Creatinine. Glomerular Filtration Rate will be calculated by the Central Laboratory using the re-expressed abbreviated (four-variable) Modification in Diet and Renal Disease (MDRD) formula and results will be reported to the sites and the Sponsor. (*Levey AS, Coresh J,Greene T, et al. Expressing the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate with Standardized Serum Creatinine Values. Clinical Chemistry 2007; 53:766-72*). S/P-Bilirubin, total (TB)
B-Haemoglobin (Hb)	S/P-Alkaline phosphatase (ALP)
B-Haematocrit	S/P-Aspartate transaminase (AST) S/P-Alanine transaminase (ALT) S/P-Uric acid S/P-Potassium S/P-Calcium, total S/P-Sodium S/P-Chloride S/P-Bicarbonate S/P-Magnesium S/P-Phosphorus S/P- Total Protein S/P Creatine Kinase (CK). *Reflex Testing: Troponin I will be ordered if CK >400IU/L).*

Abbreviations: AST aspartate transaminase, ALP alkaline phosphatase, ALT alanine transaminase, B blood, Hb haemoglobin, P plasma, S serum, TB total bilirubin.

NB. In case a patient shows an AST or ALT >3xULN or total Bilirubin > 2xULN please refer to Appendix D 'Algorithm on Management of Sustained Elevated Liver Safety Abnormalities', for further instructions.

Urinalysis

Urinalysis assessments will be performed according to Study Plan (Table 1) and will include the following: blood, protein, albumin, glucose, urine ketones, creatinine and calculated urinary albumin:creatine ratio.

In addition to the above assessments, if dipstick urinalysis at Visit 1 is positive, urinalysis with microscopy will be repeated until its negative.

1. Hematuria

Pregnancy testing

All female patients, unless postmenopausal (amenorrhea for 12 months after the last menstrual period and marks the end of menstrual cycles) or has been surgically sterilised, will provide urine samples for pregnancy tests (dipsticks provide by central laboratory and analysed at local lab) according to the schedule presented in the Study Plan (Table 1). The first dose of study medication or any other in-clinic dose of study medication will not be administered until a negative result is obtained.

Enrolment specific safety panel

1. Thyroid Stimulating Hormone (TSH)

   – Reflex Testing: Abnormal TSH value at enrolment will be further evaluated by free T4.

2. Hepatitis Panel:

   – Hepatitis C virus antibody

      ▪ Reflex Testing: HCV Ab Low Positive results require confirmation.

   – Hepatitis B surface antigen

   – Antibody to Hepatitis B core antigen IgM

5.2.2 Physical examination

A complete physical examination will be performed according to the schedule presented in the Study Plan (Table 1). A complete physical examination includes an assessment of the following: general appearance including skin inspection (including injection site), head, eyes, ears, nose, throat, neck,cardiovascular, lymph nodes, thyroid, musculoskeletal/extremities, lungs, abdomen, neurological and reflexes. Baseline physical examination data are collected

at Visit 1 and new findings at the following physical examinations are recorded as change from baseline.

A brief physical examination should include cardiovascular, lungs, abdomen and extremities; and any organ systems pertinent to the patient's signs, symptoms or adverse events.

A physical examination, either complete or brief could be performed at any of the other visits at the Investigator's discretion.

Clinically significant abnormalities in physical examination findings at Study Termination must be followed up by the Investigator and evaluated with additional tests if necessary, until the underlying cause is diagnosed or resolution occurs. As appropriate, the diagnosis and resolution date physical examination abnormalities must be reported as AEs.

Refer to Section 6.4 for reporting AEs.

5.2.3 Vital signs

Vital sign measurements in this study will include sitting systolic and diastolic BP and heart rate (HR). Vital signs should be measured from Visit 1 after the patient rests for approximately 5 minutes and with the patient in a sitting position.

Blood pressure measurement with a properly calibrated and validated instrument should be used. Patients should be seated quietly for at least 5 minutes in a chair rather than on an examination table, with feet on the floor and arm supported at heart level. An appropriate sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure accuracy. At least 3 measurements should be made at least 30 seconds apart. The average of 3 readings is to be entered in the eCRF. This will be documented in the source documents at the investigative site. The same arm should be used for all BP measurements during the study.

Vital sign measurements must be performed in the seated position.

5.2.4 Other safety assessments

5.2.4.1 Cardiovascular events

Deaths (including cause of death [CV related vs. non-CV]) and CV events (including MI, stroke, acute coronary syndrome, ventricular fibrillation/tachycardia, and congestive heart failure requiring hospitalisation) considered to be SAEs should be reported to the safety data entry site within 24 hours.

Adjudication for heart failure will be performed according to the respective charter.

5.2.4.2 Liver function test abnormalities

Please see Appendix D, 'Algorithm on Management of Sustained Elevated Liver Safety Abnormalities'', for further guidance.

5.3 Other assessments

5.3.1 Self-monitored blood glucose and hypoglycaemic events

Patients will receive a hypoglycaemia/blood glucose diary. Glucose meter will be supplied to each study site. Patients will receive a glucose meter, supplies and instructions on their use. The Sponsor recommends instructing the patients to self-monitor their blood glucose at least one time per day and document results in their patient diary. Patients should bring their glucose meter with them to each study visit to ensure that it is functioning properly. Patients will be asked to also check their blood glucose when:

1. The patient experiences signs or symptoms of hypoglycaemia.

2. At additional time points at the Investigator's discretion which may include change of dose of standard of care medications or any other relevant signs or symptoms.

3. Patients will be instructed to contact the Investigator any time they experience a frequent or severe hypoglycaemic event. Patients will also be instructed to document any hypoglycaemia events that have occurred since their last visit. Hypoglycaemic events must be recorded in the diary anytime a patient experiences either of the following:

4. Signs and symptoms of hypoglycaemia (regardless of blood glucose value by finger stick).

5. Blood glucose value by finger stick ≤70mg/dL (3.9mmol/L) (regardless of symptoms).

For these hypoglycaemic events, patients must record the following information in the diary:

1. Date and time of hypoglycaemic event.

2. Whether symptoms, were present and list of symptoms.

3. Blood glucose value by finger stick and time of finger stick.

4. Whether the patient experienced incoherence, unconsciousness, or required assistance of another person to recover.

5. Treatments administered.

Patients should be instructed to document exact date and time of last dose of study medication prior to each event. The diary will be returned by the patient and reviewed by site personnel at every subsequent visit. Completed diary pages will be added to the patient's source record, and data from the diary will be entered in the appropriate eCRF page for hypoglycaemic episodes.

Hypoglycaemia eCRF pages will be used to document all reported episodes of hypoglycaemia. **The Investigator or designee is responsible for questioning the patient about all symptoms reported on the hypoglycaemia log and for determining if they meet the clinical definition of hypoglycaemia.** Signs and symptoms of hypoglycaemia, hypoglycaemia episode or discontinuation due to hypoglycaemia should not be reported on AE eCRF page, unless the event fulfills protocol criteria for a Serious Adverse Event (see section 6.2), in which case an SAE form must be completed in addition to hypoglycaemia eCRF page for hypoglycaemia. Hypoglycaemia events will be summarised descriptively. Summaries will be provided overall for all events of hypoglycaemia as well as the subcategories as defined in Section 6.3.7.

5.3.2 Diet and exercise counseling

Starting at the Enrolment Visit (Visit 1), patients will be instructed on a diet and exercise program in accordance with the ADA or similar local guidelines to be followed for the study duration.

A Registered Dietitian, Registered Nurse, Physician, Certified Diabetes Educator, Nutritionist, or other qualified member of the study team who has appropriate documented training will provide this counseling.

In addition, as part of the diet and exercise program, the Investigator or designee should ensure that each patient receives an adequate daily intake of minerals and vitamins, in accordance with the National Academy of Sciences or similar local guidelines.

5.4 Pharmacokinetics (Not Applicable)

5.5 Pharmacodynamics (Not Applicable)

5.6 Pharmacogenetics (Not Applicable)

CCI

[redacted]

CCI

[redacted]

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 (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., 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.

6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., enrolment and), that fulfils one or more of the following criteria:

1. Results in death
2. Is immediately life-threatening
3. Requires in-patient hospitalisation or prolongation of existing hospitalisation
4. Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
5. Is a congenital abnormality or birth defect
6. Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix A, ‘Additional Safety Information’ to the Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

AEs will be collected from time of signature of informed consent, during the Enrolment, Randomisation, and throughout the treatment period and until End of treatment (Visit 5)/early termination.

SAEs will be recorded from the time of informed consent.

All AEs/SAEs will be recorded on source documents and the eCRFs.

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 eCRF. 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;

1. AE (verbatim)
2. The date when the AE started and stopped
3. Maximum intensity
4. Whether the AE is serious or not
5. Investigator causality rating against the IP (yes or no)
6. Action taken with regard to IP
7. AE caused patient's withdrawal from study (yes or no)
8. Outcome

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

1. Date AE met criteria for SAE
2. Date Investigator became aware of SAE
3. AE is serious due to
4. Date of hospitalisation

5. Date of discharge

6. Probable cause of death

7. Date of death

8. Autopsy performed

9. Causality assessment in relation to Study procedure(s)

10. Description of AE

11. Whether treatment of AE was required

6.3.3.1 Intensity rating scale

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

1. Mild (awareness of sign or symptom, but easily tolerated)

2. Moderate (discomfort sufficient to cause interference with normal activities)

3. 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 an 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 an SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

The Investigator will assess causal relationship between IP and each AE, 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. 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 eCRF. 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 summarised in the Clinical Study Report (CSR). Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory values or 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 (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as an AE.

Hyperglycaemia due to insufficient clinical response is not necessarily considered an AE/SAE, unless the Investigator does not consider it expected for that patient, based on an increased frequency or severity in relation to the patient's usual clinical course.

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.

6.3.7 Hypoglycaemia

Patients will be asked to test their blood glucose if they experience symptoms suggestive of hypoglycaemia and to record specific symptoms and glucose values in the patient diary.

Study site personnel must obtain accurate information for the patient's file and for the hypoglycaemia page of the eCRF. If the hypoglycaemic episode intensity is classified as severe, the Investigator is required to contact the Sponsor.

Hypoglycemia episodes will be classified in the Clinical Study Report according to the ADA Criteria. The ADA Workgroup on Hypoglycemia classifies hypoglycemia as follows (Elizabeth R. Seaquist et al 2013)

Severe hypoglycaemia: An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Documented symptomatic hypoglycaemia: An event during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration less than or equal to 70mg/dL (3.9mmol/L).

Asymptomatic hypoglycaemia: An event not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration less than or equal to 70mg/dL (3.9mmol/L). Since the glycaemic threshold for activation of glucagon and epinephrine secretion as glucose levels decline is normally 65 to 70mg/dL (3.6 to 3.9mmol/L) and since antecedent plasma glucose concentrations of less than or equal to 70mg/dL (3.9mmol/L) reduce sympathoadrenal responses to subsequent hypoglycaemia, this criterion sets the lower limit for the variation in plasma glucose in nondiabetic, nonpregnant individuals as the conservative lower limit for individuals with diabetes.

Probable symptomatic hypoglycaemia: An event during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination, but was presumably caused by a plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L). Since many people with diabetes choose to treat symptoms with oral carbohydrate without a test of plasma glucose, it is important to recognize these events as probable hypoglycaemia. Such self-reported episodes that are not confirmed by a contemporaneous low plasma glucose determination may not be suitable outcome measures for clinical studies that are aimed at evaluating therapy, but they may be reported.

Relative hypoglycaemia: An event during which the person with diabetes reports any of the typical symptoms of hypoglycaemia, and interprets the symptoms as indicative of hypoglycaemia, but with a measured plasma glucose concentration greater than 70mg/dL (3.9mmol/L). This classification reflects the fact that patients with chronically poor glycaemic control can experience symptoms of hypoglycaemia at plasma glucose levels greater than 70mg/dL (3.9mmol/L) as plasma glucose concentrations decline toward that level. Though causing distress and interfering with the patient's sense of well-being, and potentially limiting the achievement of optimal glycaemic control, such episodes probably pose no direct harm and, therefore, may not be a suitable outcome measure for clinical studies that are aimed at evaluating therapy, but they may be reported.

At a minimum, hypoglycaemic events should be reported in each of the first three classifications: severe hypoglycaemia, documented symptomatic hypoglycaemia, and asymptomatic hypoglycaemia

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 i.e., 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 i.e., 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 an SAE to the appropriate AstraZeneca representative by designated back-up procedures. AstraZeneca will provide appropriate local contact information for safety reporting to the Investigator during site initiation.

The AstraZeneca representative will advise investigators/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 for the active comparator product (including any AstraZeneca comparator).

6.4.1 Adverse events of special interest

Event categories of special interest for this study may include, but are not limited to, hypoglycaemia, hypersensitivity reactions, severe cutaneous adverse reactions, all infections, decreased lymphocyte count, pancreatitis, all malignancies, cardiac failure (including confirmed adjudicated cardiac failure events), renal impairment/renal failure, volume depletion (hypotension, dehydration, and hypovolemia), and liver injury(including confirmed adjudicated hepatic events).

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 (i.e., more than 1 tablet per day of either study drug) as reported by patient.

If an overdose is suspected, monitoring of vital functions as well as treatment as appropriate should be performed:

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

2. An overdose without associated symptoms is only reported on the Overdose eCRF 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 an SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

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 all study medication should be discontinued immediately. Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP 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 1 day i.e., 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 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.

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

Dose reductions are not permitted in this study.

6.8 Study governance and oversight

6.8.1 Hepatic Adjudication Committee

An independent Adjudication Committee, blinded to the treatment of the patients, will determine the probability that drug-induced liver injury (DILI) is the cause of liver-related abnormalities.

Criteria for adjudication of hepatic events are defined as follows:

1. AST and/or ALT >3x ULN and TB >2x ULN (within 14 days of the AST and/or ALT elevation); see Appendix D

2. AST and/or ALT >10x ULN

3. Hepatic events timely related to death (within 30 days before death)

A separate HAC adjudication charter further defines and describes the procedure for the handling, reporting and classification of these events.

6.8.2 Cardiovascular Adjudication Committee

Adjudication for heart failure will be performed using pre-specified criteria by an adjudication committee composed of independent cardiologists blinded to study treatment. The adjudication committee operations and criteria will be described in a separate charter.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Table 5 Investigational Products for Study D1683C00005

Investigational product	Dosage, route, form and strength	Manufacturer
Dapagliflozin	5mg, orally, Green, plain, diamond-shaped, film-coated tablet	CCI
Placebo for dapagliflozin	Does not contain active ingredient, orally, Green, plain, diamond-shaped, film-coated tablet	
Saxagliptin	5mg, orally, plain, Yellow, biconvex, round, film-coated tablet	
Placebo for saxagliptin	Does not contain active ingredient, orally, plain, Yellow, biconvex, round, film-coated tablet	

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).

It is the responsibility of the Investigator to ensure that IP is only dispensed to study patients. The IP must be dispensed only from official study sites by authorised personnel according to local regulations.

In this protocol, the identity of the IPs is described in Table 5.

The formulation number and batch number will be recorded in the electronic Trial Master File and identified in the CSR.

Dapagliflozin, saxagliptin, and their matching placebo tablets will be packed in bottles and provided as individual patient kits at Visit 2. The tablets may contain lactose, which may cause discomfort in lactose-intolerant individuals. For additional information refer to the prescribing information for saxagliptin and dapagliflozin.

Non IP medications: Rescue medication (Saxagliptin 5mg and dapagliflozin 10mg) will be provided by the sponsor. However, insulin and metformin will not be provided by the Sponsor, since it is part of patient's standard of care.

7.2 Dose and treatment regimens

The study consists of an Enrolment visit (Visit 1), a Randomisation visit (Visit 2), followed by a 24-week randomised, double-blind, double-dummy treatment period.

AstraZeneca or a designated representative will provide all IPs. In the event the patient loses her/his study medication, the study center should notify the Investigator immediately in order to receive a replacement kit via the IVRS/IWRS.

At Visit 2, patients will be randomly assigned to 1 of the 3 treatment arms and randomised study medication will be dispensed in kits as dapagliflozin 5mg tablets, saxagliptin 5mg tablets, and matching placebo tablets. Study medication will be dispensed according to the schedule presented in Table 1.

During the treatment period, patients will take 2 tablets everyday: 1 from the dapagliflozin/placebo bottle, 1 from the saxagliptin/placebo bottle.

The first doses of study medication will be taken at the study site. Patients will subsequently self-administer saxagliptin, dapagliflozin, and matching placebos QD orally for the 24-week treatment period.

On days of scheduled study visits, patients should bring their study medication with them to the study site and will take that daily dose as directed by study site personnel.

If any dose is missed, it should be taken as soon as noticed, unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time.

7.3 Identity of Open Label Rescue Medications

Table 6 Open label Rescue Medication for Study D1683C00005

Rescue Medication	Dosage, route, form and strength	Manufacturer
Dapagliflozin	10mg, orally, Green, plain, diamond-shaped, film-coated tablet	CCI
Saxagliptin	5mg, orally, plain, Yellow, biconvex, round, film-coated tablet	

7.4 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 at least the following information

1. Name of Sponsor
2. Pharmaceutical dosage form, route of administration, and quantity of dosage units
3. Code number to identify the contents and packaging operation
4. Study code
5. Enrolment code (to be added on the label when IP is dispensed)
6. Directions for use
7. "For clinical trial use only"
8. Storage conditions
9. Period of use, eg, expiration date
10. "Keep out of the reach and sight of children"
11. The name of the Investigator, where applicable (to be added on the label when IP is dispensed)
12. Visit number (to be added on the label when IP is dispensed)

7.5 Storage

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

7.6 Compliance

The patient will be asked about compliance at each study visit starting from visit 2 onwards. When study medication is returned, compliance will be assessed based upon patients interview and a count of the tablets returned. Compliance should be between ≥80% and ≤120% of that prescribed. If the patient is not compliant with recording study drug doses during the study, then the period of non-compliance should be noted as a protocol deviation and the sponsor should be notified. Patients judged to be non-compliant may continue in the study, but should be counselled on the importance of taking their study medication and applicable ancillary medications as prescribed. The Investigator (or designee) will record the amounts of study

medication dispensed and returned at each visit as described in Table 1, as well as document reasons for non-compliance in the source document. The dates of all study medication dosing, including interruptions, missed doses or overdose, must be recorded on the eCRF.

The administration of all study medications (including IPs) should be recorded in the appropriate sections of the eCRF.

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the eCRF.

7.7 Accountability

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

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

Study site personnel will account for all study medications received at the site, unused study medications and for appropriate destruction. Certificates of delivery, destruction, and return should be signed.

For this study, study drugs CCI such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

1. On-site disposal practices must not expose humans to risks from the drug.

2. On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.

3. Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures (SOPs) and a copy provided to AstraZeneca upon request.

4. Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal (ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor) must be documented.

5. Accountability and disposal records are complete, up-to-date, and available for the Study Monitor to review throughout the clinical trial period.

6. If conditions for destruction cannot be met, the responsible Study Monitor will make arrangements for return of study drug.

7. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

7.8 Return of study drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by AstraZeneca must be returned to AstraZeneca or designee. The return of study drug will be arranged by the responsible Study Monitor.

Arrangements for the return of study drug will be made by the responsible Study Monitor.

7.9 Concomitant and other treatments

Patients must follow the medication restrictions outlined in the inclusion and exclusion criteria (Sections 3.1 and 3.2, respectively) during the study. Dosages of concomitant medications should be maintained constant during the study, unless instructed otherwise by the Investigator or a treating physician in accordance to the standard of care. Use of restricted medication must be reported to the Sponsor. Any change in regimen for any concomitant medication must then be documented in source documents and entered into the eCRF. Concomitant herbal or nutritional therapies must also be entered into the eCRF.

The table below lists prohibited medications during the study and the applicable time frames.

Restricted Medication/Class of drug:	**Usage:**
Sulfonylureas, pioglitazone, rosiglitazone, GLP-1 receptor agonists, any DPP-4 and SGLT2 inhibitors other than IP	Prohibited during the study
Insulin therapy (with the exception of insulin therapy during a hospitalisation or use in gestational diabetes)	Use of insulin during the study is only acceptable if given as a rescue treatment as allowed per the protocol (Section 4.4) for any duration as clinically necessary, or for a temporary use in the following situations: -For up to 14 days in total and up to 7 consecutive days if patient is unable to take oral medications -For up to 14 days in total and up to 7 consecutive days if there is a documented illness or infection that requires additional therapy to maintain glycaemic control.

	-For up to 14 days in total and up to 7 consecutive days if patients have to temporarily stop study medication or metformin due to recommendations made in this protocol -For up to 7 days during hospitalization. When the reason for hospitalisation is the management of the patient's glycaemic control, treatment with insulin is considered a rescue and is allowed for as long as clinically necessary
Other investigational drugs or participation in any interventional clinical study	Prohibited during the study
Treatment with systemic glucocorticoids equivalent to oral prednisolone ≥10mg (betamethasone ≥1.2mg, dexamethasone ≥1.5mg, hydrocortisone ≥40mg) per day	Treatment with any stable replacement corticosteroid therapy at the time of screening is permitted. Newly initiation of treatment with any systemic corticosteroid therapy that will involve ≥5 days of therapy (inhaled and topical are allowed). The Medical Monitor (AZ study physician) should be consulted prior to beginning therapy with corticosteroids for patients who require systemic corticosteroid treatment.
Prescription or over-the-counter weight loss medications	Prohibited during the study

7.9.1 Metformin

Patients will remain on their pre-study stable, maximum tolerated metformin doses ≥1500mg/day, during the 24-week double-blind treatment period of the study. Metformin should be administered and stored according to product and country-specific labelling.

Metformin will not be provided by the Sponsor as it is the usual care prior to study participation.

7.9.2 Open label Rescue Medications

Patients may be eligible for rescue therapy (see Section 4.4) with open-label rescue medication (Saxagliptin 5mg and Dapagliflozin 10mg as a first line therapy) in order to treat ongoing hyperglycaemia. Patients should stop receiving blinded study medication while receiving rescue therapy. If rescue therapy fails, sufficient therapy will be given at the discretion of the Investigator.

Rescue medication (Saxagliptin 5mg and dapagliflozin 10mg) will be provided by the sponsor. However, insulin will not be provided by the Sponsor, since it is part of patient's standard of care.

7.9.3 Other concomitant treatment

Other medication other 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 eCRF.

7.10 Post Study Access to Study Treatment (Not Applicable)

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

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

2. Analyses will be performed by AstraZeneca or its representatives.

3. Refer to Statistical Analysis Plan (SAP) for details.

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.

A comprehensive SAP will be initiated prior to first patient randomised and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data.

8.2 Sample size estimate

The mean change from baseline in HbA1c at Week 24 will be assessed comparing the saxagliptin plus dapagliflozin treatment group versus the saxagliptin treatment group and versus the dapagliflozin treatment group.

Power calculations for longitudinal repeated measures analyses depend on many factors, including the pattern of drop out over time and correlations among the various time points included in the model. The choice of these parameters will affect any estimates of power and their true values may not be known. Based on comparisons of results of longitudinal repeated measures analyses and analysis of covariance using last observation carried forward (ANCOVA with LOCF) from previous diabetes trials, the estimated standard errors of the treatment differences were similar between analyses. Therefore, power calculations are based on ANCOVA with LOCF, with the expectation that this will provide a good estimate of the power for the primary analysis using a longitudinal repeated measures model.

A sample size of 300 patients per group will provide at least 90% power to simultaneously detect a difference in mean change from baseline to week 24 in HbA1c of -0.30 (%) for both primary endpoint comparisons of saxagliptin / dapagliflozin vs its components at the 2-sided

alpha = 0.05 level. This assumes a common standard deviation of 1.0% and a 3% non-evaluability rate.

8.3 Definitions of analysis sets

The Enrolled patients Data Set will consist of all patients who sign informed consent. This data set will be used to summarize the patient disposition data.

8.3.1 Efficacy analysis set

Full analysis set

The full analysis (FA) set will be defined as all randomised patients who take at least one dose of the study medication and have a baseline value for HbA1c.

Per protocol

The per protocol (PP) population will be defined as all FA patients without an important protocol deviation that might affect the primary analyses. The criteria for important protocol deviations will be defined in the statistical analysis plan.

8.3.2 Safety analysis set

The safety analysis set will be defined as all randomised patients who received at least one dose of study medication. This data set will be used to summarize safety data (AE, Vital signs and Laboratory parameters), and patient demography and their baseline data as well.

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

8.3.3 PK analysis set (Not Applicable)

8.3.4 PRO analysis set (Not Applicable)

8.4 Outcome measures for analyses

Primary endpoint

1. Mean change from baseline in HbA1c at Week 24

Secondary endpoints

1. Percent of patients achieving a therapeutic glycaemic response, defined as a HbA1c <7.0% at Week 24

2. Mean change in Fasting plasma glucose (FPG) at 24 weeks

3. Mean change in total body weight at 24 weeks

Exploratory endpoint(s)

1. Mean change from baseline in HbA1c at Week 12

2. Proportion of patients achieving therapeutic glycaemic response, defined as HbA1c <7.0%, after 12 weeks

3. Percent of patients who require glycaemic rescue or discontinue study treatment for lack of efficacy (12 and 24 weeks)

4. Mean change in Fasting plasma glucose (FPG) at 12 weeks

5. Mean change in total body weight at 12 weeks

6. Mean change from baseline in systolic blood pressure (12 and 24 weeks)

7. Mean change from baseline HbA1c after 12 weeks in patients whose baseline HbA1c was >8%

8. Mean change from baseline HbA1c after 12 weeks in patients whose baseline HbA1c was ≤8%

9. Mean change in HbA1c from baseline in patients with baseline >8% at 24 weeks

10. Mean change in HbA1c from baseline in patients with baseline ≤8% at 24 weeks

11. Proportion of patients achieving HbA1c <7.0% and a weight loss of 2 kg after 24 weeks

CCI [redacted]

8.5 Methods for statistical analyses

Efficacy analyses will be run for the FA population and for the PP population if more than 10% of patients from the FA population are excluded from the PP population for important protocol deviations.

All analyses related glycaemic variables (for example, HbA1c) will be done using values regardless of rescue/intensification of treatment or discontinuation of the study treatment. Sensitivity analyses will be conducted for the primary endpoint excluding the data after rescue or more than 8 days after discontinuation of the study treatment.

The primary endpoint will be tested for saxagliptin plus dapagliflozin versus saxagliptin and dapagliflozin arms simultaneously at the alpha = 0.05 level (two sided). The secondary endpoints then will be tested sequentially as follows:

1. saxagliptin plus dapagliflozin versus saxagliptin on percent of patients achieving a therapeutic glycaemic response, defined as a HbA1< 7.0% at Week 24

2. saxagliptin plus dapagliflozin versus dapagliflozin on percent of patients achieving a therapeutic glycaemic response, defined as a HbA1< 7.0% at Week 24

3. saxagliptin plus dapagliflozin versus saxagliptin on mean change from baseline in fasting plasma glucose at Week 24

4. saxagliptin plus dapagliflozin versus dapagliflozin on mean change from baseline in fasting plasma glucose at Week 24

5. saxagliptin plus dapagliflozin versus saxagliptin on mean change from baseline in total body weight at Week 24

Each comparison will be tested at the alpha = 0.05 (two-sided) level.

8.5.1 Analysis of the primary variable (s)

The primary efficacy analysis will be performed using a longitudinal repeated measures analysis (using a MIXED model) for the change from baseline at Week 24, with terms for treatment group, baseline value, time (each relevant visit), the interaction of treatment and time, and the interaction of baseline value and time in the model. This model assumes that data are missing at random (MAR). 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.

8.5.2 Analysis of the secondary variable(s)

The analysis of the change from baseline for FPG and total body weight at week 24 will be performed using the same longitudinal repeated measures model as for the primary efficacy endpoint.

The proportion of patients achieving a therapeutic glycaemic response (defined as HbA1c <7.0%) at Week 24 will be summarized by treatment group and compared between treatment groups. A 95% confidence interval for the difference in response rate or odd ratio between treatment groups will be calculated with adjustment for baseline HbA1c by a logistic regression.

8.5.3 Subgroup analysis (if applicable)

The subgroup analysis will be performed on the primary efficacy endpoint (mean change from baseline in HbA1C) in subgroups defined by the following variables:

1. Baseline HbA1c

2. Gender

3. Age

4. Region

Subgroup analyses will be analysed as was done for the primary analysis model with subgroup by treatment interaction term. Within each subgroup, 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. A nominal interaction p-value will be provided for the purpose of the completeness of the data analysis.

8.5.4 Interim analysis (Not Applicable)

8.5.5 Sensitivity analysis (if applicable)

Sensitivity analyses for HbA1c will be performed using analyses that do not assume the data are missing at random and incorporate patients randomised and treated but with only baseline data for HbA1c. Details will be stated in the SAP. In addition, the repeated measures analyses will be performed by excluding values after rescue, and more than 8 days after study treatment discontinuation and based upon all patients completing the double-blind treatment period.

8.5.6 Exploratory analysis (if applicable)

Analyses for exploratory efficacy endpoints will use the same methodology for binary and continuous endpoints as described above.

Safety analyses will be performed using the Safety analysis set, including data after rescue. 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, and AEs of special interest. Summaries will include the number of patients with events by specified system organ classes and preferred terms. The summary of AEs will be performed both overall and by subgroup. 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 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 and by shift tables. 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 will be performed excluding data after rescue in the double-blind treatment period. The primary analysis of events of hypoglycaemia will be performed excluding data after rescue, and more than 4 days after study treatment discontinuation.

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 CSP and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system utilised.

The 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 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:

1. Provide information and support to the Investigator(s)

2. Confirm that facilities remain acceptable

3. Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed

4. Perform source data verification (a comparison of the data in the eCRFs 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 (e.g., clinic charts)

5. 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.

6. Ensure site is compliant with study procedures to avoid "lost to follow-up" as listed in Section 3.10.

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 (CSA) for location of source data.

9.2.2 Patients study agreements

The Principal Investigator at each center should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP 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 CSA shall prevail.

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

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the 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 first patient is expected to be enrolled 1st Quarter of 2016. The study is expected to complete 3rd Quarter 2017.

The study may be terminated at individual centers if the study procedures are not being performed according to Good Clinical Practice (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 or dapagliflozin.

9.4 Data management by AstraZeneca or delegate

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

Data entered in the WBDC system or data captured electronically will be immediately saved to the applicable database and changes tracked to provide an audit trail.

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

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.

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

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

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 laboratory(ies) internal or external 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 Subject 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 or Institutional Review Board (EC/IRB) should approve the final study protocol, including the final version of the ICF 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 enrolment of any patient into the study.

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

AstraZeneca or designee should approve any modifications to the ICF that are needed to meet local requirements.

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

Before enrolment of any patient into the study, the final CSP, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

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

AstraZeneca or designee will provide Regulatory Authorities, ECs/IRBs and 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 IP. AstraZeneca will provide this information to the Investigator so that he/she can meet these reporting requirements.

10.4 Informed consent

The Principal Investigator(s) at each center will:

1. Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study

2. Ensure each patient is notified that they are free to discontinue from the study at any time

3. Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided

4. Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study

5. Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File

6. Ensure a copy of the signed Informed Consent Form is given to the patient.

7. Ensure that any incentives for patient 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 EC/IRB.

10.4.1 Screening informed consent

The screening informed consent is an abbreviated document that explains the risks associated with the screening laboratory test (HbA1c) 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 screening ICF will also document the patient's consent to return to the enrolment visit in a fasting state, in case they are considered eligible for the study. For any patient that undergoes the 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 International Coordinating Investigator, the Investigator, and AstraZeneca.

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

The CSP Amendment is to be approved by the relevant EC/IRB 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 CSP to each Investigator(s). For distribution to EC/IRB see Section 10.3.

If a protocol amendment requires a change to a centers ICF, AstraZeneca and the centers EC/IRB are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each EC/IRB.

10.6 Audits and inspections

Authorised 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, analysed, and accurately reported according to the protocol, Good Clinical.

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