Clinical Study Protocol	
Drug Substance	Saxagliptin / Dapagliflozin
Study Code	D1689C00014
Version	4.0
Date	12 January 2017
EudraCT Number	2015-002376-24

A 52-Week, Multi-Centre, Randomised, Parallel-Group, Double-Blind, Active-Controlled, Phase IV Study to Evaluate the Safety and Efficacy of Dapagliflozin or Dapagliflozin plus Saxagliptin compared with Sulphonylurea all given as Add-on Therapy to Metformin in Adult Patients with Type 2 Diabetes Who Have Inadequate Glycaemic Control on Metformin Monotherapy

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Clinical Study Protocol (CSP), ANGEL
Version 17.0
Template Form Doc ID: LDMS_001_00026737
Parent Doc ID: SOP AZDoc0018580

VERSION HISTORY

Version 4.0, 12th January 2017
Revision History (Version 2.0): This section was updated to correct the release date of Clinical Study Protocol, Version 2.0. **Protocol Synopsis** (Objectives - Other Secondary Objectives): This section was updated due to typo correction. **Protocol Synopsis** (Definitions of analysis set): This section was updated due to error correction and for further clarification of the full analysis set. **Protocol Synopsis** (Analysis of the primary variable): This section was updated to add a superiority test of the dapagliflozin plus saxagliptin added to metformin group versus the control group. **Section 2.2** (Other secondary Objective): This section was updated due to typo correction. **Section 6.3.8** (Hypoglycaemia): The section was updated for further clarification of Hypoglycaemia. **Section 8.3** (Definition of analysis sets): This section was updated due to error correction and for further clarification of the full analysis set. **Section 8.4.1.2** (Other secondary endpoints): This section was updated due to typo correction. **Section 8.5.3** (Control of type 1 error): This section was updated to add a superiority test including further specifications to this test. **Section 8.5.4** (Analysis of the primary efficacy variable): This section was updated to add a superiority test including further specifications to this test. **Section 8.5.6** (Analysis of the secondary and exploratory variables): This section was updated due to typo correction
Version 3.0, 01st November 2016 Changes to the clinical study protocol are summarized below.
Protocol Synopsis (Cover page): This section was updated due to updated adress of the International Co-ordinating Investigator.

Protocol Synopsis (Objectives - Other Secondary Objectives): This section was updated due to error correction for HbA1c range and for further clarification of hypoglycaemia.

Protocol Synopsis (Safety Objective): This section was updated for further clarification of the outcome measures (bullet point #1).

Protocol Synopsis (Definition of analysis sets): This section was updated for further clarification of required analysis sets.

Protocol Synopsis (Analysis of the key secondary variables): This section was updated for further clarification of hypoglycaemia episode.

Section 1.2 (Choice of outcome variables): This section was updated due to error correction for HbA1C range.

Section 2.2 (Other secondary Objective): This section was updated due to error correction.

Section 2.3 (Safety Objectives - Other Secondary Objectives): This section was updated for further clarification of the outcome measures (bullet point #1).

Section 4 Table 1 Study plan. Footnote A was updated to clarify scenarios Early Termination visit is expected.

Section 4.3.5 (End of Treatment period / Early Termination or Rescue visit): The section was updated to clarify and correct the process for handling of surveys.

Section 5.2.5.1 (Cardiovascular events): The section was updated for further clarification of cardiovascular events and adjudication process.

Section 6.4.1 (Adverse Events of Special Interest): The section was updated for further clarification of reporting process as this is no longer required as per FDA General Advice.

Section 6.8.2 (Cardiovascular Adjudication Committee): The section was updated for further clarification of cardiovascular events and adjudication process.

Section 8.3 (Definition of analysis sets): This section was updated for further clarification of required analysis sets.

Section 8.4.1.1 (Key secondary endpoints): This section was updated for further clarification of hypoglycaemia episode.

Section 8.4.1.2 (Other secondary endpoints): The section was updated due to error correction and for further clarification of hypoglycaemia.

Section 8.5.1 (Demographic and baseline characteristics): The section was updated for further clarification.

Section 8.5.3 (Control of type 1 error): The section was updated for further clarification of hypoglycaemia episode.

Section 8.5.6 (Analysis of the secondary and exploratory variables): The section was updated due to error correction and for further clarification of secondary and exploratory variables.

Section 8.5.8 (Safety analyses): The section was updated for further clarification.

Appendix D (Algorithm on Management of Sustained Elevated Liver Safety Abnormalities): The section was updated due to error correction.

Version 2.0, 01st February 2016

Changes to the clinical study protocol are summarized below.

Version 1.0 of clinical study protocol transferred into new template form LDMS_001_00026737.

Clinical study protocol administrative change number 1, 22nd October 2015 incorporated.

Protocol Synopsis (Study Sites and Number of Subjects planned): The section was updated to reflect the updated number of sites conducting this study.

Protocol Synopsis (Objectives - Other Secondary Objectives): This section was updated due to error correction.

Protocol Synopsis (Analysis of the primary variable): This section was updated due to error correction.

Protocol Synopsis (Analysis of the key secondary variables): This section was updated for clarification.

Section 1.3.4 (Ketoacidosis): New section was added to follow the updated Dapagliflozin Investigator's Brochure Version 12, 28th November 2015.

Section 2.2 (Secondary Objectives - Other Secondary Objectives): This section was updated due to error correction.

Section 3.1 Inclusion Criteria: This section was updated to correct C-peptide laboratory value.

Section 3.9 (Discontinuation of Investigational Product): The section was updated for further clarification of IP discontinuation process.

Section 3.9 (Discontinuation of Investigational Product – Study specific Discontinuation criteria, NN #9): Refer to clinical study protocol administrative change number 1, 22nd October 2015.

Section 3.9.3 (Procedures for Discontinuation of a Subject from Investigational Product): Refer to clinical study protocol administrative change number 1, 22nd October 2015.

Section 4. (Study Plan and Timing of Procedures – Table 1): "Register actual glimepiride dosage in IWRS" updated as not required at EOT/Rescue visit. For further changes please refer to clinical study protocol administrative change number 1, 22nd October 2015.

Section 4.1 (Screening visit): Refer to clinical study protocol administrative change number 1, 22nd October 2015.

Section 4.2.1 (Enrolment visit): Refer to clinical study protocol administrative change number 1, 22nd October 2015.

Section 4.3.3 (Dose Titration): The section was updated to precise section header and to add a time window of - 3days for glimepiride up-titration.

Section 4.3.4 (Rescue Therapy): Refer to clinical study protocol administrative change number 1, 22nd October 2015.

Section 4.3.5 (End of Treatment period / Early Termination or Rescue visit): The section was updated to clarify the process for patients who discontinue IP and agreed to follow the original visit schedule.

Section 4.4 (Follow-up visit): The section was updated to clarify the process for patients who discontinue IP and agreed to follow the original visit schedule.

Section 6.4.1 (Adverse Events of Special Interest): The section was updated to implement the requirements regarding additional safety reporting requested by the United States Food and Drug Administration (FDA).

Section 6.8.1 (Hepatic Adjudication Committee): Refer to clinical study protocol administrative change number 1, 22nd October 2015.

Section 7.3 (Labelling): Refer to clinical study protocol administrative change number 1, 22nd October 2015.

Section 7.7 (Return of Study Drug): Refer to clinical study protocol administrative change number 1, 22nd October 2015.

Section 7.8.2 (Rescue Therapy): Refer to clinical study protocol administrative change number 1, 22nd October 2015.

Section 8.1 (Statistical considerations): The section was updated to be in line with study timelines.

Section 8.4.1.1 (Key secondary endpoints): This section was updated for clarification.

Section 8.4.1.2 (Other secondary endpoints): The section was updated due to error correction.

Section 8.5.1 (Demographic and baseline characteristics): The section was updated to precise key baseline characteristics.

Section 8.5.4 (Analysis of the primary efficacy variable): This section was updated due to error correction.

Section 8.5.5 (Sensitivity Analysis): This section was updated based on health authority interactions that took place for other studies in saxa/dapa program .

Section 8.5.6 (Analysis of the secondary and exploratory variables): The section was updated for further clarification.

Section 8.5.7 (Subgroup analysis): The section was updated to precise subgroup analysis.

Appendix B: International Airline Transportation Association (IATA) 6.2 Guidance Document added.

Version 1.0, 22nd May 2015
Initial creation

AstraZeneca

PROTOCOL SYNOPSIS

A 52-Week, Multi-Centre, Randomised, Parallel-Group, Double-Blind, Active-Controlled, Phase IV Study to Evaluate the Safety and Efficacy of Dapagliflozin or Dapagliflozin plus Saxagliptin compared with Sulphonylurea all given as Add-on Therapy to Metformin in Adult Patients with Type 2 Diabetes Who Have Inadequate Glycaemic Control on Metformin Monotherapy

International Co-ordinating Investigator

Study site(s) and number of subjects planned

This will be a multicentre study conducted at approximately 200 sites mainly in Germany and the European Union (EU). Approximately 930 patients will be randomised.

Study period		Phase of development
Estimated date of first patient enrolled	3Q 2015	IV
Estimated date of last patient completed	1Q 2017	IV

Study design

Study D1689C00014 is a 52-week, multi-centre, randomised, parallel-group, double-blind, double-dummy, active-controlled Phase IV trial to study the efficacy and safety of dapagliflozin added to metformin and dapagliflozin plus saxagliptin added to metformin compared with sulphonylurea (SU [glimepiride]) added to metformin in adult patients with Type 2 diabetes mellitus (T2DM) who have inadequate glycaemic control on maximum tolerated dose (MTD) of ≥1500 mg of metformin monotherapy and with individual need for therapy escalation.

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, MTD of metformin immediate-release (IR) monotherapy (≥1500 mg/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:

- Dapagliflozin (10 mg orally once daily [QD]) as an add-on to metformin (≥1500 mg/day orally)
- Dapagliflozin (10 mg orally QD) plus saxagliptin (5 mg orally QD) as an add-on to metformin (≥1500 mg/day orally)
- Glimepiride (titrated from 1 to 6 mg orally QD) as an add-on to metformin (≥1500 mg/day orally)

Objectives

Primary Objective:	**Outcome Measure:**
To compare the absolute change from baseline in HbA1c at Week 52 between dapagliflozin plus metformin and dapagliflozin plus saxagliptin plus metformin with glimepiride plus metformin	Change in hemoglobin A1c (HbA1c) from baseline (Week 0) to Week 52

Key Secondary Objectives:	**Outcome Measures:**
To compare the proportion of patients reporting hypoglycaemia episodes during the 52-week treatment period between dapagliflozin plus metformin and dapagliflozin plus saxagliptin plus metformin with glimepiride plus metformin	Proportion of patients reporting at least one episode of hypoglycaemia (symptomatic + blood glucose ≤50 mg/dL [2.8 mmol/L]) during the double-blind treatment period
To compare the change from baseline in total body weight at Week 52 between dapagliflozin plus metformin and dapagliflozin plus saxagliptin plus metformin with glimepiride plus metformin	Change in total body weight from baseline (Week 0) to Week 52
To compare the change from baseline in fasting plasma glucose (FPG) at Week 52 between dapagliflozin plus metformin and dapagliflozin plus saxagliptin plus metformin with glimepiride plus metformin	Change in FPG from baseline (Week 0) to Week 52

Key Secondary Objectives:	**Outcome Measures:**
To compare the time to rescue among the treatment groups during the 52-week treatment period between dapagliflozin plus metformin and dapagliflozin plus saxagliptin plus metformin with glimepiride plus metformin	Time to rescue during the 52-week double-blind treatment period

Other Secondary Objectives:	
To compare the effects of dapagliflozin plus metformin and dapagliflozin plus saxagliptin plus metformin with glimepiride plus metformin at Week 52	• Proportion of patients achieving HbA1c of <7% (and <7.5%) without confirmed hypoglycaemia at Week 52 • Proportion of patients achieving HbA1c of <7% (and <7.5%) at Week 52 • Proportion of patients achieving individually agreed HbA1c targets at Week 52 • Proportion of patients achieving an HbA1c decrease of ≥1% with no weight gain at Week 52 • Time spent below HbA1C target (<7% and < 7.5%) during the 52-week double-blind treatment period • Change in body mass index (BMI) from baseline to Week 52 • Proportion of patients achieving weight reduction of ≥5% and weight gain of ≥5% from baseline to Week 52 • Proportion of patients reporting at least 1 episode of hypoglycaemia (confirmed hypoglycaemia = symptomatic + blood glucose ≤50 mg/dL, major, other hypoglycaemia) during the 52-week double-blind treatment period • Change in waist circumference from baseline to Week 52 • Change in systolic BP from baseline to Week 52

Safety Objective:	Outcome Measures:
To evaluate the safety and tolerability of dapagliflozin and dapagliflozin plus saxagliptin versus glimepiride, all as add-on therapy to metformin, during the 52-week treatment period	• Proportion of patients withdrawing from study medication due to hypoglycaemia • Adverse events (AEs)/serious AEs (SAEs) • AEs of special interest (AEOSI) • Clinical laboratory tests • Electrocardiogram (ECG) • Vital signs (pulse and blood pressure [BP]) • Hypoglycaemic events • Physical examinations, including incidence of oedema

Exploratory Objective:	Outcome Measures:
To explore the mean change from baseline in quality of life patient reported outcomes (PROs) and waist:hip ratio at Week 52 between dapagliflozin plus metformin and dapagliflozin plus saxagliptin plus metformin with glimepiride plus metformin	• Change from baseline to Week 52 in the Short Form 36-item Health Survey (SF-36), Hypoglycaemia Fear Survey (HFS-II), and Impact of Weight on Quality of Life (IWQOL)-Lite survey • Change in waist:hip ratio from baseline to Week 52

Target subject population

Approximately 930 patients with T2DM with inadequate glycaemic control receiving metformin at a MTD of ≥1500 mg/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 58 weeks, including a 1-week pre-study Screening period, a 2-week enrolment period, a 52-week double-blind treatment period, and a 3-week safety follow-up period.

Investigational product, dosage and mode of administration

Dapagliflozin and matching placebo:

Dapagliflozin 10-mg tablets or placebo matching dapagliflozin will be administered orally once daily for the 52-week double-blind treatment period.

Saxagliptin and matching placebo:

Saxagliptin 5-mg tablets or placebo matching saxagliptin will be administered orally once daily for the 52-week double-blind treatment period.

Glimepiride:

A combination of glimepiride 1, 2, and 4 mg tablets, and matching placebo will be administered orally QD for a total daily dose of 1 to 6 mg of glimepiride or matching placebo during the entire 52-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 ≥1500 mg). Metformin should be administered and stored according to product and country specific labelling.

Rescue therapy:

Patients who require rescue therapy will receive insulin at the discretion of the Investigator and in accordance with the approved product label in the applicable country.

Statistical methods

Sample size estimate:

The primary objective of this study is to examine whether, after 52 weeks of oral administration of double-blind treatment, the absolute change from baseline in glycosylated HbA1c level with dapagliflozin plus metformin and dapagliflozin plus saxagliptin added to metformin is non-inferior to glimepiride (sulphonylurea) plus metformin in patients with T2DM who have inadequate glycaemic control on MTD ≥1500 mg/day of metformin therapy.

To demonstrate non-inferiority of dapagliflozin or dapagliflozin plus saxagliptin to glimepiride for changes from baseline to Week 52 in HbA1c within a non-inferiority margin of 0.30%, assuming a standard deviation 1.0%, and at a 1-sided significance level of 0.025, 290 evaluable patients will be needed in each treatment group to provide approximately 95% power (given a true difference of zero between dapagliflozin or dapagliflozin plus saxagliptin and glimepiride). The non inferiority margin of 0.3% as well as a common standard deviation of 1.0% were selected based on information from earlier, similarly designed studies.

Assuming that 5% of patients do not have a post-baseline assessment, a total of approximately 930 patients (310 patients per treatment arm) need to be randomised.

Assuming that approximately 30% of screened patients will fail to meet entry criteria, a total of approximately 1329 patients need to be enrolled.

Statistical Considerations

Continuous variables will be presented with mean, median, 25th percentile, 75th percentile, standard deviation, minimum, maximum, and (if appropriate) the number of nonmissing observations. Categorical data will be displayed via absolute and relative frequencies for each category, including a category labeled as 'missing' when appropriate. The 'missing' category will not contribute to the denominators of relative frequencies.

Definitions of analysis sets

Classification into Randomized, Full Analysis (FA), Per Protocol (PP), and Safety analysis sets will be conducted prior to the database lock.

The primary analysis of the primary efficacy endpoint will be performed on the FA set. A supportive analysis will be carried out with the PP set. Analyses of all secondary efficacy endpoints will be performed using the FA set. All safety analyses will be based on the Safety analysis set.

The randomised set consists of all randomised patients.

The FA set will be defined as all randomised patients who receive at least one dose of study medication and who have a baseline and a post-baseline efficacy assessment value. Patients will be analysed according to the treatment assigned.

The PP analysis set 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 (SAP). Patients will be analysed according to the treatment assigned. Determinations of specific deviations will made prior to unblinding of the data.

The Safety analysis set will be defined as all randomised patients who received at least 1 dose of study medication. Patients will be analysed according to the actual treatment received.

Analysis of the primary variable

The primary objective of this study is to show non-inferiority of dapagliflozin added to metformin and dapagliflozin plus saxagliptin added to metformin versus glimepiride added to metformin in terms of the primary efficacy variable change in HbA1c from baseline to Week 52.

The following null hypothesis (H_0) will be tested against the alternative hypothesis (H_A) (α=0.025, 1-sided):

H_0: $\mu c - \mu t \leq -0.30\%$,

H_A: $\mu c - \mu t > -0.30\%$,

where μ_t denotes the mean absolute change in HbA1c from baseline to Week 52 in the group of patients treated with dapagliflozin added to metformin or dapagliflozin plus saxagliptin added to metformin (test medication) and μ_c denotes the mean absolute change in HbA1c from baseline to Week 52 in the group of patients treated with glimepiride added to metformin (control).

The absolute change from baseline to Week 52 in HbA1c will be analysed using a restricted maximum likelihood-based, Mixed-Model Repeated Measures (MMRM) model with terms for treatment group, baseline HbA1c, time (at relevant visits), and interactions baseline HbA1c-by-time and treatment group-by-time. The model will be used to derive a least-squares estimate of the mean treatment difference with corresponding 2-sided 95% confidence interval (CI). The primary assessments of efficacy will be a comparisons of each of the 2 test groups the dapagliflozin plus saxagliptin added to metformin versus the control group and the dapagliflozin added to metformin versus the control group using a 95% CI. In particular, if the observed lower limit from a 2-sided 95% (or 1-sided 97.5%) CI for the difference in adjusted means is greater than -0.30%, then the test group will be considered to be non-inferior to the control group. Note that multiplicity will be controlled using a sequential testing scheme. The dapagliflozin plus saxagliptin added to metformin group versus the control group will be tested first, followed by the dapagliflozin plus metformin group versus the control group. A superiority test of the dapagliflozin plus saxagliptin added to metformin group versus the control group will also be conducted.

Analysis of the key secondary variables

Key secondary endpoints will be analysed using the FA set and no imputation of missing values will be performed. The experiment-wise type I error will be controlled to a maximum of 5%. A hierarchical closed testing procedure will be employed.

Key secondary endpoints:

- Proportion of patients reporting at least 1 episode of confirmed hypoglycaemia during the 52-week double-blind treatment period
- Change from baseline in total body weight at Week 52
- Change from baseline in FPG at Week 52
- Time to rescue during the 52-week double-blind treatment period.

The proportion of patients experiencing at least 1 episode of confirmed hypoglycaemia will be analysed using logistic regression.

The analysis of the changes from baseline to Week 52 for total body weight and FPG will be performed using the same MMRM model as described for the primary efficacy endpoint.

Time to rescue will be analysed using a Cox proportional hazards model. Estimates of the hazard ratio and 95% CIs will be provided. Kaplan-Meier estimates will be calculated and plotted by treatment group.

Safety analyses

The assessment of safety will be based on the analyses of AEs, vital signs, physical examinations, ECGs, hypoglycaemia, and clinical laboratory evaluations. All safety analyses will be performed on the Safety set.

Interim Analysis

No interim analysis on the efficacy or safety parameters is planned for this study.

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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
ADA	American Diabetes Association
AE	adverse event
AEOSI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	aspartate aminotransferase
AZDD	AstraZeneca Drug Dictionary
β-hCG	beta human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
CMH	Cochran-Mantel-Haenszel
CrCl	creatinine clearance
CRO	contract research organization
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CSRAF	clinical supplies return authorisation form
CV	cardiovascular
DDFM	denominator degrees of freedom
DILI	drug-induced liver injury
DM	Data Management
DPP-4	Dipeptidyl peptidase-4
EC	Ethics Committee (synonymous to [IRB] and Independent Ethics Committee [IEC])
E-code	enrolment code
ECG	electrocardiogram
eCRF	electronic Case Report Form

Abbreviation or special term	Explanation
eDC	electronic data capture
eGFR	estimated glomerular filtration rate
EU	European Union
FA	full analysis
FPG	fasting plasma glucose
GAD	glutamate decarboxylase
GCP	Good Clinical Practice
GLP-1	Glucagon-like peptide-1
GMP	good manufacturing practice
GPV&E	Global Pharmacovigilance & Epidemiology
H_A	alternative hypothesis
Hb	haemoglobin
HbA1c	haemoglobin a1c
HDL	high-density lipoprotein
HDPE	high-density polyethylene
HFS-II	Hypoglycaemia Fear Survey
HL	Hy's Law
H_0	null hypothesis
HR	heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IP	investigational product
IR	immediate-release
IRB	Institutional Review Board
IWQOL	Impact of Weight on Quality of Life
IWRS	Interactive Web Response System
LDL	low-density lipoprotein
LOCF	Last-Observation-Carried-Forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MoA	mechanisms of action

Abbreviation or special term	Explanation
MODY	maturity onset diabetes of the young
MTD	maximum tolerated dose
OAD	oral antidiabetic
PHL	Potential Hy's Law
PP	Per protocol
PPG	postprandial glucose
PRO	patient reported outcome
QD	once daily
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCr	serum creatinine
SCSM	Supply Chain Study Management
SDV	study data verification
SF-36	Short Form 36-item Health Survey
SGLT2	sodium glucose cotransporter 2
SU	sulfonylurea
T2DM	Type 2 diabetes mellitus
T4	thyroxine
TB	total bilirubin
TSH	thyroid stimulating hormone
TZD	thiazolidinedione
UKPDS	United Kingdom Prospective Diabetes Study Group
ULN	upper limit of normal
US	United States
UTI	urinary tract infection
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.

Current sequential add-on OADs include sulfonylureas (SUs), such as glimepiride. Glimepiride is typically used in patients with T2DM who cannot control glucose levels with diet and exercise alone or added to other OAD drugs. Glimepiride stimulates the pancreatic beta cells to secrete insulin, which subsequently helps lower blood glucose. Some of the key limitations to glimepiride are related to its effect in increasing endogenous insulin levels, which is associated with weight gain and increased risk of 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 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 (Del Prato et al 2011, Gomis et al 2011, Owens et al 2011, Taskinen et al 2011).

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.

Given their complementary mechanisms of action, dapagliflozin, coadministered with saxagliptin, has been studied to support the development of a fixed-dose combination. A 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 each of these individual agents to metformin alone 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 body weight (Rosenstock J et al).

The aim of this present study is to test the hypothesis that dapagliflozin or dapagliflozin plus saxagliptin is non-inferior to glimepiride in patients with T2DM and inadequate glycaemic control on maximum tolerated dose (MTD) of metformin background therapy.

1.2 Rationale for study design, doses, and control groups

This is a Phase IV study performed as part of the clinical development program for saxagliptin/dapagliflozin fixed-dose combination to improve glycaemic control as an adjunct to diet, exercise, and metformin treatment.

Many medications are approved for the treatment of T2DM; however, the challenge of achieving and maintaining treatment goals within the current sequential therapy approach is linked to shortcomings of older classes of drugs. Metformin decreases hepatic glucose output and subsequently, decreases fasting glucose. Metformin is the most common initial oral antidiabetic therapy of choice for patients with T2DM and is recommended as the initial pharmacological therapy in both the US and EU because of its glycaemic efficacy, weight neutrality, low risk of hypoglycaemia, and beneficial cardiovascular (CV) profile.

Current sequential add-on second and third line OADs include SUs and thiazolidinediones (TZDs). However, these drugs are associated with increased risk for weight gain and hypoglycaemia. Since many patients with T2DM do not reach glycaemic goals with dual agent therapy, many will require an additional agent with an alternate MoA. The traditional third line therapy would be the initiation of insulin treatment.

However, further weight gain, fluid retention, and the risk of hypoglycaemia are common problems with insulin therapy and present a major concern for many patients. Furthermore, excessive weight gain may negatively interact with anti-hyperglycaemic treatment, by increasing CV risk, and reducing the ability to exercise.

Treatment with saxagliptin and dapagliflozin, both individually and added to metformin, have demonstrated a favorable safety and tolerability profile. These drugs had a low propensity for hypoglycaemia, therefore addressing a potential key concern when adding 2 glucose lowering agents simultaneously. These drugs have demonstrated weight neutrality (saxagliptin) or moderate weight reduction (dapagliflozin). Dapagliflozin has also been shown to cause a persistent reduction in HbA1c and weight after 4 years of therapy.

A second-line oral dual add-on therapy with saxagliptin coadministered with dapagliflozin could be a new option, that includes drugs with complementary mechanisms of action, opposing the effects on plasma glucagon, and endogenous glucose production, increasing renal excretion of glucose, a low risk of hypoglycaemia, and moderate weight loss, providing a more effective and patient-friendly approach to the treatment of the T2DM.

Study design, dose selection, and control groups

The current study is designed to demonstrate the efficacy and safety of dapagliflozin 10 mg and dapagliflozin 10 mg plus saxagliptin 5 mg versus glimepiride in patients with inadequate glycaemic control on a MTD ≥1500 mg/day of metformin monotherapy.

A 52-week randomised treatment period will allow for adequate information on efficacy, safety, and durability of a new OAD therapy.

Control group

This is a double-blind, active-controlled study. The comparison of dapagliflozin alone (plus metformin) or the combination of dapagliflozin plus saxagliptin (plus metformin) with glimepiride is consistent with regulatory guidance regarding the investigation of combination products (CHMP 2009). Glimepiride will be used as an active comparator because SUs are one of the most common classes of OADs started in patients inadequately controlled on metformin therapy alone (Riddle 2005).

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 (Forxiga) is approved 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 10-mg dose was chosen for this study because it has been extensively studied in Phase III trials, has demonstrated consistent clinically meaningful reductions in HbA1c, and is the approved dose for the drug label applicable for this patient population. 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. Furthermore, dapagliflozin (10 mg) reduced total body weight in patients with T2DM inadequately controlled with metformin (Bolinder et al 2012). 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 by 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 5 mg once daily (QD) in a wide range of patients with T2DM, as either monotherapy, add-on combination therapy with metformin, a TZD, a SU, insulin, or initial combination therapy with metformin. Saxagliptin 5 mg resulted in clinically meaningful reductions in HbA1c, as well as FPG, PPG, insulin, C-peptide, and glucagon levels and is the recommended dose according to the approved drug label.

Glimepiride

Glimepiride is the antidiabetic drug most commonly used as a second line of therapy for patients who do not respond to metformin. The choice of dose (starting with 1 mg/day and titrating by 1 mg every 2 weeks to a maximum dose of 6 mg/day) is per the approved product label.

Choice of outcome variables

The primary endpoint is change from baseline in HbA1c at Week 52. 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 is provided below:

- Weight and body mass index (BMI): 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).

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

- Time until the start of rescue is an indirect measure of glucose efficacy and shows the durability of efficacy.

- Proportion achieving HbA1c <7.0%: The target HbA1c for most patients with T2DM is <7.0% according to international diabetes treatment guidelines (Inzucchi et al 2012).

- Proportion achieving weight loss ≥5.0%: A weight loss of ≥5.0% in patients with T2DM has been associated with decreased insulin resistance, improved measures of glycaemia and lipemia, and reduced BP (Klein et al 2004).

- Blood pressure: The European Association for the Study of Diabetes guidelines recommend a target of systolic BP <140 mmHg in patients with diabetes (Ryden L et al 2013). Lowering blood pressure in patients with diabetes has been shown to reduce the risk of coronary heart disease events, stroke, retinopathy and nephropathy (James et al 2014).

- Waist circumference: The presence of excess fat in the abdomen out of proportion to total body fat is an independent predictor of risk factors and morbidity. Waist circumference is positively correlated with abdominal fat content (NHLBI 1998).

Choice of study population

Subjects

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

Age

The prevalence of T2DM increases with age; it is therefore important to assess antidiabetic agents in adult patients. In this study, the upper age limit (ie, 75 years) will be based on the dapagliflozin labelling guidelines.

HbA1c

The HbA1c inclusion criterion at randomisation (ie, ≥7.5% to ≤10.5%) 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, fetus, 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 (eg, 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.

C-peptide will be defined to ensure the patients with T2DM have some pancreatic reserve (as opposed to patients with Type 1 diabetics or latent auto-immune diabetes in adults who have had a significant loss of their pancreatic mass) and can potentially respond to non-insulin therapy.

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 plus metformin and dapagliflozin plus saxagliptin plus metformin compared with glimpiride, 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 placebo group will receive both placebos with metformin. All patients will be monitored throughout the study to ensure adequate glycaemic control.

1.3.1 Dapagliflozin

Dapagliflozin is approved in approximately 52 countries, including the US and countries within the EU. Prior to approval, dapagliflozin was evaluated in 5 core Phase IIb studies, 16 core Phase III studies, and 3 regional Phase III studies. These studies established that dapagliflozin is effective in reducing HbA1c in a broad range of patients, regardless of disease progression/duration or concomitant use of antidiabetic therapies. Dapagliflozin consistently demonstrated statistically and clinically significant mean reductions in HbA1c versus placebo among the 3 doses typically studied (2.5, 5, and 10 mg). Overall, the dose of 10 mg provided better efficacy than the 2 lower doses. Effects on secondary glycaemic efficacy parameters, including FPG and PPG, support the primary HbA1c efficacy findings. Dapagliflozin also resulted in a modest reduction in total body weight relative to placebo or comparator, largely attributable to a decrease in body fat mass, as well as reductions in systolic BP. Data from an active-controlled study for up to 4 years indicates that the beneficial effects on glycaemic and non-glycaemic parameters were maintained.

Overall, dapagliflozin has been well tolerated in clinical studies. For detailed information surrounding the risks associated with saxagliptin and dapagliflozin, please refer to the respective IBs.

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.

1.3.2 Saxagliptin

Prior to approval, saxagliptin was evaluated in 6 pivotal Phase III, randomised, double-blind controlled trials. Compared to the control, treatment with saxagliptin at doses of 2.5 to 10 mg resulted in clinically relevant and statistically significant improvements in HbA1c, FPG, and 2-hour PPG. Reductions in HbA1c were seen across subgroups, categorised by age, gender, race, and baseline BMI.

Overall, the clinical safety and efficacy data accumulated to date demonstrates a positive benefit/risk profile for saxagliptin. The majority of AEs reported in clinical studies have been of mild intensity and few have required treatment discontinuation. 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).

1.3.3 Glimepiride

Glimepiride will be given according to its approved label. Data from clinical trials indicate that the overall incidence of AEs associated with glimepiride is generally lower compared with other SUs, including a lower risk of hypoglycaemia and weight gain (Rosskamp R et al). Increased incidence of hypoglycaemia events has been previously noted with glimepiride therapy.

1.3.4 Ketoacidosis

There have been postmarketing 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 (eg, 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.

1.3.5 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.

1.3.6 Potential benefits to patients

Based on prior clinical trials experience and postmarketing 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 and dapagliflozin 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, the doses of saxagliptin (5 mg) and dapagliflozin (10 mg) are the most widely used clinical doses. 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.

1.3.7 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

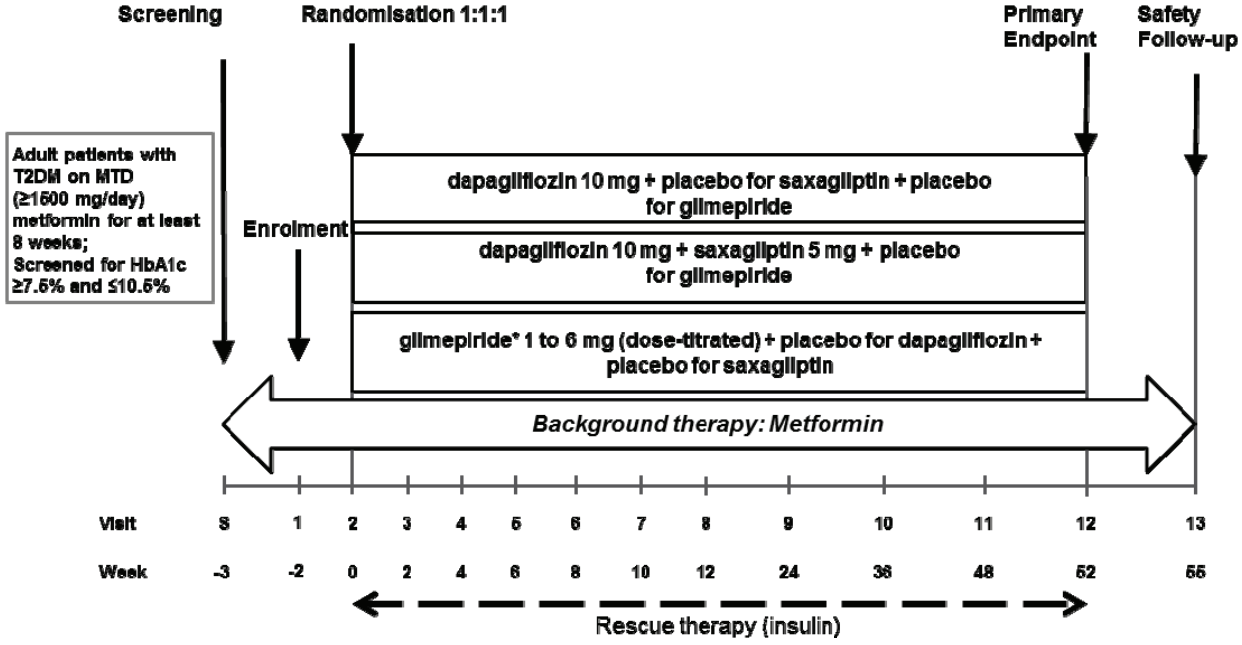
Figure 1 presents the overall design of the study.

Study D1689C00014 is a 52-week, multi-centre, randomised, parallel-group, double-blind, double-dummy, active-controlled Phase IV study to study the efficacy and safety of dapagliflozin added to metformin and dapagliflozin plus saxagliptin added to metformin compared with sulphonylurea (glimepiride) added to metformin in adult patients with T2DM who have inadequate glycaemic control (HbA1c ≥7.5% and ≤10.5%) on maximum tolerated dose of ≥1500 mg of metformin monotherapy and with individual need for therapy escalation.

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 (≥1500 mg/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:

- Dapagliflozin + saxagliptin placebo + glimepiride placebo + metformin
- Dapagliflozin + saxagliptin + glimepiride placebo+ metformin
- Glimepiride + dapagliflozin placebo + saxagliptin placebo + metformin

Figure 1 Study Design



*Note: Glimepiride treatment will begin at 1 mg/day then be titrated (upwards or downwards) in 1 mg increments at subsequent visits, if needed. In the event that a subject develop recurrent hypoglycaemic episodes with the 1 mg dose, down-titration to 0 mg is allowed during the study.
Abbreviations:

2. STUDY OBJECTIVES

Research Hypothesis:

Treatment with dapagliflozin added to metformin and dapagliflozin plus saxagliptin added to metformin will be non-inferior to glimepiride (a sulphonylurea) added to metformin, within a margin of 0.3%, for change from baseline to Week 52 in glycosylated HbA1c.

2.1 Primary objective

Primary Objective:	**Outcome Measure:**
To compare the absolute change from baseline in HbA1c at Week 52 between dapagliflozin plus metformin and dapagliflozin plus saxagliptin plus metformin with glimepiride plus metformin	Change in HbA1c from baseline (Week 0) to Week 52

2.2 Secondary objectives

Key Secondary Objectives:	**Outcome Measures:**
To compare the proportion of patients reporting hypoglycaemia episodes during the 52-week treatment period between dapagliflozin plus metformin and dapagliflozin plus saxagliptin plus metformin with glimepiride plus metformin	Proportion of patients reporting at least 1 episode of hypoglycaemia (symptomatic + blood glucose ≤50 mg/dL [2.8 mmol/L]) during the double-blind treatment period
To compare the change from baseline in total body weight at Week 52 between dapagliflozin plus metformin and dapagliflozin plus saxagliptin plus metformin with glimepiride plus metformin	Change in total body weight from baseline (Week 0) to Week 52
To compare the change from baseline in FPG at Week 52 between dapagliflozin plus metformin and dapagliflozin plus saxagliptin plus metformin with glimepiride plus metformin	Change in FPG from baseline (Week 0) to Week 52
To compare the time to rescue among the treatment groups during the 52-week treatment period between dapagliflozin plus metformin and dapagliflozin plus saxagliptin plus metformin with glimepiride plus metformin	Time to rescue during the 52-week double-blind treatment period

Other Secondary Objectives:	
To compare the effects of dapagliflozin plus metformin and dapagliflozin plus saxagliptin plus metformin with glimepiride plus metformin at Week 52	• Proportion of patients achieving HbA1c of < 7% (and <7.5%) without confirmed hypoglycaemia at Week 52 • Proportion of patients achieving HbA1c of <7% (and <7.5%) at Week 52 • Proportion of patients achieving individually agreed HbA1c targets at Week 52 • Proportion of patients achieving an HbA1c decrease of ≥1% with no weight gain at Week 52 • Time spent below HbA1C target (<7% and <7.5%) during the 52-week double-blind treatment period • Change in body mass index (BMI) from baseline to Week 52 • Proportion of patients achieving weight reduction of ≥5% and weight gain of ≥5% from baseline to Week 52 • Proportion of patients reporting at least 1 episode of hypoglycaemia (confirmed hypoglycaemia = symptomatic + blood glucose ≤50 mg/dL, major, other hypoglycaemia) during the 52-week double-blind treatment period • Change in waist circumference from baseline to Week 52 • Change in systolic BP from baseline to Week 52

2.3 Safety objectives

Safety Objective:	**Outcome Measures:**
To evaluate the safety and tolerability of dapagliflozin and dapagliflozin plus saxagliptin versus glimepiride, all as add-on therapy to metformin, during the 52-week treatment period	• Proportion of patients withdrawing from study medication due to hypoglycaemia • AEs/SAEs • AEs of special interest (AEOSI) • Clinical laboratory tests • Electrocardiogram (ECG) • Vital signs (pulse and blood pressure [BP]) • Hypoglycaemic events • Physical examinations, including incidence of oedema

2.4 Exploratory objectives

Exploratory Objective:	Outcome Measures:
To explore the mean change from baseline in quality of life patient reported outcomes (PROs) and waist:hip ratio at Week 52 between dapagliflozin plus metformin and dapagliflozin plus saxagliptin plus metformin with glimepiride plus metformin	• Change from baseline to Week 52 in the Short Form 36-item Health Survey (SF-36), Hypoglycaemia Fear Survey (HFS-II), and Impact of Weight on Quality of Life (IWQOL)-Lite survey • Change in waist:hip ratio from baseline to Week 52

3. SUBJECT 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. Patients must be receiving metformin (≥1500 mg/day) for treatment of T2DM in accordance with the product label for their country. Eligible patients will be enrolled and examined for all inclusion and exclusion criteria.

3.1 Inclusion criteria

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

1. Provision of informed consent prior to any study-specific procedures.

2. Is able to read, understand, and sign the Informed Consent Forms (ICFs) and, if applicable, an Authorisation to Use and Disclose Protected Health Information form (consistent with Health Insurance Portability and Accountability Act of 1996 legislation), communicate with the Investigator, and understand and comply with protocol requirements, including the use of diary and glucose meter measurements.

3. Is male or female and ≥18 and <75 years old at time of informed consent.

4. Has a documented diagnosis of T2DM.

5. Has a HbA1c of ≥7.5% and ≤10.5% based on central laboratory results from Visit 1, with individual need for therapy escalation.

6. Currently treated with a stable MTD (≥1500 mg/day) of metformin therapy for at least 8 weeks prior to Enrolment visit.

7. Has a BMI of ≤45 kg/m^2 at Enrolment visit.

8. Has a C-peptide laboratory value of ≥1.0 ng/mL (0.33 nmol/L; 331 pmol/L) based on central laboratory results from Visit 1.

9. For females only: Women not of childbearing potential, or if they are women of childbearing potential (WOCBP), they must comply with the following:

   - Are not pregnant or breastfeeding.
   - Have a negative urine pregnancy test result (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin, beta subunit [βhCG]) at Visit 1 (Enrolment) and prior to randomization.
   - Using or willing to adopt a highly effective method of birth control (see below) to avoid pregnancy throughout the study and for at least 4 weeks after the last dosing of study medication

Definitions:

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

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

Highly effective 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; vasectomised sexual partner; 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 (eg, 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:

Endocrine and Metabolic Disorders

1. Clinically diagnosed with Type I diabetes, known diagnosis of maturity onset diabetes of the young (MODY), or secondary diabetes mellitus or known presence of glutamate decarboxylase 65 (GAD65) antibodies.

2. History of diabetic ketoacidosis, hyperosmolar nonketotic coma, or corticosteroid-induced Type 2 diabetes.

3. Symptoms of poorly controlled diabetes including, but not limited to, marked polyuria, polydipsia, and/or greater than 10% weight loss during the 3 months prior to Enrolment.

4. FPG >270 mg/dL (>15 mmol/L) – assessed based on central laboratory results from Visits 1.

5. History of diabetes insipidus.

6. Patients with clinically significant thyroid disease or uncontrolled thyroid disease needing initiation or adjustment of thyroid treatment per Investigator's judgement. Abnormal thyroid stimulating hormone (TSH) value at Enrolment will be further evaluated by free thyroxine (T4). Patients with abnormal free T4 values will be excluded.

Medical History and Concurrent Diseases

7. History of bariatric surgery or lap-band surgery, or either procedure is planned during the time period of the study. History of liposuction is allowed.

8. History of any unstable endocrine, psychiatric, rapidly progressing or unstable renal disease, or rheumatic disorder, as judged by the Investigator.

9. Patients who, in the judgment of the Investigator, may be at risk for dehydration or volume depletion that may affect the patient's safety and/or the interpretation of efficacy or safety data.

10. Has evidence of current abuse of drugs or alcohol or a history of abuse within the past 52 weeks that, in the Investigator's opinion, would cause the individual to be noncompliant.

Cardiovascular Conditions

11. Clinically significant cardiovascular disease or procedure within 3 months prior to Enrolment (ie, MI, cardiac surgery, coronary artery bypass surgery, coronary stent placement, coronary angioplasty, unstable angina, stroke, transient ischaemic attack, or unstable or previously undiagnosed arrhythmia) or expected to require coronary revascularization procedure during the course of the study.

12. Severe uncontrolled hypertension defined as systolic BP ≥180 mmHg and/or diastolic BP ≥110 mmHg at any visit up to and including Randomization (Visit 2).

13. Presence or history of severe congestive heart failure (New York Heart Association Class III and IV [CCNYHA 1994]), unstable or acute congestive heart failure, and/or known left ventricular ejection fraction of ≤40%.

Note: eligible patients with congestive heart failure, especially those who are on diuretic therapy (note that use of loop diuretics is not allowed), should have careful monitoring of their volume status throughout the study.

Kidney Conditions

14. Creatinine clearance (CrCl) of <60 mL/min based on central laboratory results from Visit 1.

15. Familial renal glucosuria. This condition is diagnosed as glucosuria (>1.0 mmol/L urine) in the presence of normoglycaemia in patients without the diagnosis of diabetes mellitus.

Hepatic Conditions

16. Significant hepatic disease, including, but not limited to, severe hepatic insufficiency and/or significant abnormal liver function defined as aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) of >3x upper limit of normal (ULN) based on central laboratory results from Visit 1.

17. Serum total bilirubin (TB) of >2 mg/dL (34.2 μmol/L [patients with documented Gilbert's syndrome will be allowed to enrol]) based on central laboratory results from Visit 1.

18. History of, or currently have, acute or chronic pancreatitis or have triglyceride concentrations ≥500 mg/dL based on central laboratory results from Visit 1.

19. History of severe hepatobiliary disease or hepatotoxicity with any medication.

20. Positive serologic evidence of current infectious liver disease, including patients positive for Hepatitis B viral antibody IgM, Hepatitis B surface antigen, and Hepatitis C virus antibody.

Haematological/Oncological Conditions

21. History of malignancy within 5 years of Visit 1 (Enrolment), with the exception of treated in situ basal cell or squamous cell carcinoma of the skin.

22. Haemoglobin <10 g/dL (<100 g/L) or 6.2 mmol/L for men; haemoglobin <9.0 g/dL (<90 g/L) or 5.9 mmol/L for women.

23. History of chronic haemolytic anaemia or haemoglobinopathies (for example, sickle cell anaemia, thalassemia, sideroblastic anaemia). Mild haemolysis due to artificial heart valves or due to sickle cell trait is not an exclusion criterion except when haemoglobin levels are too low (as defined in haemoglobin criteria above).

24. Donation or transfusion of blood, plasma, or platelets within the past 12 weeks prior to Enrolment, or planning to donate blood during the study.

Prohibited Medications

25. Concomitant treatment with loop diuretics at Visit 2 (Randomisation/baseline.)

26. Administration of any antihyperglycaemic therapy, other than metformin, during the 8 weeks prior to Visit 1 (Enrolment).

27. Administration of any other IP or participation in any interventional clinical studies 30 days prior to Visit 1 (Enrolment).

28. Treatment with systemic glucocorticoids equivalent to oral prednisolone ≥10 mg (betamethasone ≥1.2 mg, dexamethasone ≥1.5 mg, hydrocortisone ≥40 mg) per day for >7 days within 30 days prior to enrolment.

29. Prescription or over-the-counter weight loss medications within 3 months prior to Visit 1 (Enrolment).

Other

30. Has a clinically significant medical condition that could potentially affect study participation and compliance with the treatment and study procedures, or which may pose a significant risk to the patient and/or personal well-being, as judged by the Investigator.

31. Has clinically significant abnormality identified on physical examination, ECG, or laboratory tests (clinical chemistry, haematology, and urinalysis) as judged by the Investigator at Visit 1 (Enrolment) would compromise the patient's safety or successful participation in the clinical study.

32. Has known contraindications, allergies, or hypersensitivities to any study drug or excipient as outlined in the IBs or local package inserts for metformin, SU, saxagliptin, and dapagliflozin.

33. Ongoing weight loss more than 5% over the last 3 months prior to Visit 1 (Enrolment).

34. Known immunocompromised status, including patients who underwent organ transplantation.

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

36. Previous screening, enrolment or randomisation in the present study.

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Subject enrolment and randomization

Investigators may 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 into the study, the Investigators will:

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

2. Assign potential patient a unique enrolment code (E-code), beginning with 'E#'.

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

4. Assign an eligible patient unique randomisation code.

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

The E-code will be used to identify the patient throughout study participation.

3.4 Procedures for handling incorrectly enrolled or randomized subjects

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 should not be randomised or initiated on treatment, and should be withdrawn from the study.

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

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. Assignment to treatment groups will be determined by a computer-generated random sequence.

The patients will be randomised in a 1:1:1 ratio to the following treatment groups:

- Dapagliflozin 10 mg + placebo for saxagliptin + placebo for glimepiride;
- Dapagliflozin 10 mg + saxagliptin 5 mg + placebo for glimepiride;
- Glimepiride (starting at 1 mg dose and titrated up to 6 mg, if needed) + placebo for dapagliflozin + placebo for saxagliptin (see Section 4.3.3 for details on glimepiride dose levels).

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/capsules and the respective placebo tablets/capsules will be identical in size, color, smell, and taste as described in Table 4. The bottles with IPs will be labelled with unique identification numbers allocated from the 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 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) or pharmacists from the Interactive Web Response System (IWRS). Routines for this will be described in the IWRS user manual that will be provided to each centre.

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 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 IP 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:

- Fast overnight for 8 to 12 hours prior to each study site visit, ie, no food or beverage except water. Allowed medications can be taken with water only.
- 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.
- 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.
- Refrain from alcohol intake and intense exercise 24 hours prior to each visit and recommend not to use tobacco/nicotine within 12 hours prior to each visit.
- Do not donate blood for the duration of the study and for 3 months following the last study visit.
- Comply with prescribed dosing regimen to preserve study integrity and ensure patient safety.
- Discuss any new prescriptions and over-the-counter or herbal/nutritional therapies with the Investigator, as concomitant use could result in alterations to their glycaemic control and may place them at risk for significant hypoglycaemic episodes.
- Make every attempt to adhere to the diet and exercise counseling and to the protocol visit schedule.
- 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

Patients who discontinue IP will be recommended to continue on the study and follow the original visit schedule without taking IP.

Patients may be discontinued from IPs in the following situations:

General discontinuation criteria:

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. 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 3.4).

3. The Investigator decides the patient should discontinue study medication for reasons other than AE.

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

5. Incorrectly enrolled patients (see Section 3.11).

Study-specific discontinuation criteria:

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

    (a) 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).

    (b) 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.

    (c) 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.

    (d) 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.

7. Creatinine clearance <60 mL/min (by Cockgraft-gault) confirmed by a repeated central lab measurement within 1 week.

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

    - 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

9. One or more major hypoglycaemic event or recurring minor events and the possibility of down-titration and contributing factors (eg, excessive physical activity) has been evaluated (as defined in Section 3.9.1).

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

3.9.1 Procedures for discontinuation of a subject from investigational product

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:

- 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 (eg, sweating, shakiness, increased heart rate, confusion, dizziness, light-headedness, or hunger) in the absence of environmental factors known to contribute to hypoglycaemia (ie, excess physical activity, concurrent illness, or missed or delayed meal)

  – and/or

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

  – Recurrent episodes of hypoglycaemia (see Section 6.3.8 for definitions) that did not resolve after appropriate glimepiride down-titration.

- 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.

3.9.2 Down-titration of blinded study drug and/or background antihyperglycaemic agent during the study

Blinded glimepiride/placebo dose can be down-titrated at any time during the study to a dose as low as medically necessary, including a dose of 0 mg/day. The treatment may thereafter be up-titrated again if no hypoglycaemia occured. Down-titration of other blinded study drug and/or background antihyperglycaemic agent will not be allowed at any time during the study.

3.9.3 Procedures for discontinuation of a subject from investigational product

At any time, patients are free to discontinue IP or withdraw from the study (ie, 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 12 (Week 52/End of Treatment) assessments immediately following discontinuation of study medication (see Section 4.3.5). The following data will be collected and entered onto the clinical database:

- Concomitant medication
- AEs

In the case of a decision to discontinue treatment, the Investigator will follow the patient until the event has resolved or stabilised.

For patients who discontinue IP between visit 3 & visit 8 and agree to follow the original visit schedule a Follow up visit is not required since those patients will continue in accordance with the study plan and then visits take place each second week.

For patients who discontinue IP after Visit 8 and agree to follow the original visit schedule a Follow up visit should be performed as advised by the study plan – approximately 3 weeks after the Early Discontinuation visit. The next visits and the following ones have to be planned in accrodance to the original visit schedule.

If a patient is withdrawn from study, see Section 3.10.

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.

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. Adverse event: Patient experiences an AE that, in the Investigator's opinion, necessitates withdrawal from the study.
4. Investigator decision: Investigator feels it is in the patient's best interest to terminate participation for reasons other than an AE.
5. Protocol violation: Patient is noncompliant with protocol procedures, becomes pregnant, violates study entry criteria, or starts an exclusionary concomitant medication.
6. Lost to Follow-Up: Patient fails to return for study visits and cannot be reached with reasonable, repeated attempts.
7. Study terminated by Sponsor: The Sponsor discontinues the study protocol.
8. Administrative reasons: The EU or other regulatory authority discontinues the study protocol or the clinical study site discontinues participation.

Every effort will be made to ensure that the subject 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, patients' 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 and Sponsor should be contacted.

3.10.1 Screen failures

Screening failures are patients who do not fulfill 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' (ie, 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 and no second attempts to screen the same patient will be allowed.

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 (eg, 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 subjects 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:

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

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

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

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 presents the schedule of assessments for this study

Table 1 Study Plan

				52-week Double-blind Treatment Period										
	Screening	**Enrolment**	**R/ Baseline**										**EOT/ Rescue[a]**	**Safety Follow-up**
Visit	**S[b]**	**1**	**2[c]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Weeks	-3	-2	0	2	4	6	8	10	12	24	36	48	52	55
Visit window (days)[d]	**±3**	**±3**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**	**±7**	**±7**
Informed consent	X[e]	X												
Assign E-code		X												
Demography and medical history		X												
Inclusion/ exclusion criteria		X	X											
Randomisation			X											
Brief physical examination				X	X	X	X	X	X		X	X		X
Complete physical examination		X	X							X			X	
Vital signs (BP, pulse)		X	X	X	X	X	X	X	X	X	X	X	X	X
Weight		X	X	X	X	X	X	X	X	X	X	X	X	X
Height		X												
BMI		X	X										X	
Waist and hip circumference			X										X	
12-lead ECG		X	X										X	
Concomitant medications[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

			52-week Double-blind Treatment Period												
	Screening	**Enrolment**	**R/ Baseline**											**EOT/ Rescue[a]**	**Safety Follow-up**
Visit	**S[b]**	**1**	**2[c]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Weeks	-3	-2	0	2	4	6	8	10	12	24	36	48	52	55
Visit window (days)[d]	**±3**	**±3**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**	**±7**	**±7**
Clinical chemistry[g]		X	X						X	X	X	X	X	X
Haematology			X										X	X
HbA1c	X	X	X	X	X	X	X	X	X	X	X	X	X	
Haemoglobin		X												
Creatinine (to calculate CrCl and eGFR)		X	X	X	X	X	X	X	X	X	X	X	X	X
FPG (local laboratory)			X	X	X	X	X	X	X	X	X	X	X	
FPG (central laboratory)		X	X	X	X	X	X	X	X	X	X	X	X	X
Lipids[h]			X										X	X
Triglycerides		X												
C-peptide		X												
Hepatitis screening panel[i]		X												
TSH		X												
Urinalysis		X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (urine, WOCBP only)		X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic events		X	X	X	X	X	X	X	X	X	X	X	X	X

			52-week Double-blind Treatment Period											
	Screening	**Enrolment**	**R/ Baseline**										**EOT/ Rescue[a]**	**Safety Follow-up**
Visit	**S[b]**	**1**	**2[c]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Weeks	-3	-2	0	2	4	6	8	10	12	24	36	48	52	55
Visit window (days)[d]	**±3**	**±3**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**	**±7**	**±7**
Discuss individual targets for glucose control (FPG and HbA1c)			X											
AEs/SAEs		X	X	X	X	X	X	X	X	X	X	X	X	X
Diet and lifestyle advice		X	X	X	X	X	X	X	X	X	X	X	X	
Dispense glucometer and/or supplies; provide instructions		X	X	X	X	X	X	X	X	X	X	X		
Dispense patient diary		X	X	X	X	X	X	X	X	X	X	X		
Dispense study medication			X	X	X	X	X	X	X	X	X	X		
Register actual glimepiride dosage in IWRS				X	X	X	X	X	X	X	X	X		
Patient diary review for glucometer values/ hypoglycaemic events			X	X	X	X	X	X	X	X	X	X	X	
Perform SF-36 survey			X							X			X	
Perform Hypoglycaemia Fear Survey-Worry Scale			X							X			X	
Perform IWQOL-Lite			X							X			X	
Collect unused study medication/supplies													X	X

	Screening	Enrolment		52-week Double-blind Treatment Period									EOT/ Rescue[a]	Safety Follow-up
Visit	**S[b]**	**1**	**2[c]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Weeks	-3	-2	0	2	4	6	8	10	12	24	36	48	52	55
Visit window (days)[d]	**±3**	**±3**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**	**±7**	**±7**
Dispense rescue medication (if necessary)					X	X	X	X	X	X	X	X	X	

Abbreviations: AE adverse event, Base baseline, BP blood pressure, BMI body mass index, CrCl creatinine clearance, E-code enrolment code, ECG electrocardiogram, eGFR estimated glomerular filtration rate, EOT end of treatment, FPG fasting plasma glucose, HbA1c haemoglobin A1c, HDL high-density lipoprotein, IWQOL Impact of Weight on Quality of Life, IWRS Interactive Web Response System, LDL low-density lipoprotein, R randomisation, SAE serious adverse event, SF short form, TSH thyroid stimulating hormone, WOCBP women of child-bearing potential.

[a] Early Termination procedures are to be completed for all patients who terminate the study, discontinue from IP or are rescued before Visit 12 (Week 52) of the Treatment Period.

[b] An optional Screening visit (Visit S) may occur within 1 week prior to Enrolment (Visit 1) to screen for eligibility based on a non-fasting sample of HbA1c in patients that do not have a recent HbA1c value (within 2 months).

[c] Visit 2 (Randomisation/Baseline) should be performed within 14 days after Enrolment visit, when laboratory results from Visit 1 are available.

[d] Once a patient is randomised at Visit 2, all visits should be scheduled relative to Visit 2.

[e] An abbreviated informed consent form will be signed at Screening visit.

[f] Review of concomitant medications includes over the counter drugs and herbal/nutritional therapies

[g] Specifications of clinical chemistry laboratory parameters are detailed in Section 5.2.1.3. Visits 1 and 8 to 11 have the same parameters; Visits 2, 12, and 13 have the same parameters; and no clinical chemistry is performed at Visits 3 through 7. CrCl and eGFR will be calculated at all visits.

[h] Serum lipid panel will include LDL-cholesterol, HDL-cholesterol, triglycerides, and total cholesterol.

[i] Hepatitis panel includes hepatitis B viral antibody IgM, Hepatitis B surface antigen, and hepatitis C virus antibody.

4.1 Screening visit (Visit S, Week -3)

Failure to meet the HbA1c inclusion criterion is the main reason for screening failure in diabetes treatment studies. Therefore, in this study, sites will be allowed to 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). Patients without a recent (within 2 months) local laboratory HbA1c result that allows to assess whether the patient may qualify for this study should attend the Screening visit to verify their HbA1c.

In order to be considered for screening, patients must:

- Be ≥18 and <75 years old at time of informed consent.
- Have a documented diagnosis of T2DM.
- Currently treated with a stable MTD (≥1500 mg/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:

- Abbreviated informed consent to the pre-screening procedures will be obtained (see Section 10.4)
- A blood sample will be collected for measurement of HbA1c by a central laboratory. Fasting is not required.
- Verification of current metformin therapy

Patients with HbA1c result of ≥7.0% and ≤11.0% at Screening will be scheduled for an enrolment visit within 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.

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 Investigator. This code will identify screening laboratory results together with date of birth and gender.

Patients are not allowed to be rescreened.

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 each study visit, patients are required to have fasted overnight for 8 to 12 hours (no food or 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).

In case it is not usual practice for the site to ask all patients to come to regular visits having fasted, the patients will first sign informed consent then perform the other enrolment assessments, but will need to return at least 1 day later to collect enrolment laboratory assessments while in a fasted state.

4.2.1 Enrolment Visit (Visit 1, Week -2)

Patients on a stable, MTD of metformin IR monotherapy ≥1500 mg/day for the last 8 weeks with an HbA1c ≥7.5 and ≤10.5% and with an individual need for therapy escalation 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 (Visit S; if performed). Prior to this visit, patients are to have fasted overnight (8 to 12 hours). At Enrolment, informed consent for Protocol D1689C00014 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:

- Informed consent will be obtained.
- E-code will be assigned from IWRS.
- The patient's demography and complete medical history will be recorded.
- Inclusion and exclusion criteria will be verified.
- A complete physical exam will be conducted (see Section 5.2.2).
- Vital signs (sitting systolic and diastolic BP and pulse) will be measured (see Section 5.2.4).
- Body weight and height will be measured (see Section 5.1.3 and 5.1.4).
- BMI will be calculated.
- 12-lead ECG will be performed.

- All prior medications (prescription medications within 3 months) and concomitant medications (including over the counter and herbal/nutritional supplements) will be reviewed.
- Blood samples will be collected for the following laboratory assessments:
  - Clinical chemistry (see Section 5.2.1.3)
  - HbA1c
  - Haemoglobin
  - Serum creatinine (calculated creatinine clearance [Cockcroft-Gault formula] and eGFR)
  - FPG (samples for central laboratory testing, see Section 5.2.1)
  - C-peptide
  - Hepatitis screening (hepatitis B surface antigen, antibody to hepatitis B core antigen IgM, and hepatitis C virus antibody)
  - Thyroid function (TSH)
  - Triglycerides
- Urine will be collected for urinalysis.
- Urinary pregnancy test for beta human chorionic gonatropin (βhCG) for female patients (WOCBP only)
- Hypoglycaemic events history will be recorded.
- SAEs will be reviewed.
- Diet and life-style advice will be provided.
- Glucose meter and/or supplies and instructions will be provided.
- Patient diary and instructions will be provided.

Individuals will be screen failed if results of any laboratory test 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:

- Inclusion/exclusion and randomisation criteria will be verified.
- A complete physical examination will be conducted (refer to Section 5.2.2).
- Vital signs (sitting systolic and diastolic BP and pulse) will be assessed.
- Body weight will be measured.
- BMI will be calculated.
- Waist and hip circumference will be measured.
- 12-lead ECG will be performed.
- Concomitant medications (including over the counter and herbal/nutritional supplements) will be reviewed.
- Blood samples will be collected **prior to administration of study medication** for the following assessments:
  - Clinical chemistry (see Section 5.2.1.3)
  - Haematology
  - HbA1c
  - Serum creatinine (calculated creatinine clearance [Cockcroft-Gault formula] and eGFR)
  - FPG (by local and central laboratories)
  - Lipids (low-density lipoprotein [LDL]-cholesterol, high-density lipoprotein [HDL]-cholesterol, triglycerides, total cholesterol)
- Urine will be collected for urinalysis

- Urinary pregnancy test (βhCG) for female patients (WOCBP only) will be performed.
- AEs and SAEs will be reviewed.
- Hypoglycaemic events will be reviewed.
- Investigator will discuss and agree with the patient on the individual goals for glucose control (based on FPG and HbA1c).
- Diet and life-style advice will be provided.
- Patients will be randomly assigned to 1 of 3 treatment groups (while continuing on metformin therapy):
  - Dapagliflozin 10 mg + saxagliptin 5 mg + placebo for glimepiride;
  - Dapagliflozin 10 mg + placebo for saxagliptin + placebo for glimepiride;
  - Glimepiride (Level 1 dose; 1 mg/day) + placebo for dapagliflozin + placebo for saxagliptin (see Section 4.3.3 for details on glimepiride dose levels).
- Glucose meter and/or supplies and instructions will be provided.
- Patient diary and instructions will be provided.
- Study medication will be dispensed. Study site personnel will monitor administration of study medication and morning dose of metformin with food.
- Patient diary will be reviewed for hypoglycaemic events/check glucometer values.

Prior to performing any assessments at this visit, the following surveys will be completed:

- SF-36 questionairre will be performed (see Section 5.3.2.1)
- Hypoglycaemia Fear Survey (Worry Scale) will be performed (see Section 5.3.2.2).
- IWQOL-Lite survey will be performed (see Section 5.3.2.3).

4.3.2 Treatment Period visits (Visits 3 to 11, Weeks 2, 4, 6, 8, 10, 12, 24, 36, and 48)

After the randomisation visit (Visit 2), patients will complete study visits at 2- to 12-week intervals according to Study Plan (Table 1) until the end of the randomised treatment period (Visit 12, Week 52). Prior to these visits, patients are required 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 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:

- A brief physical examination will be conducted, except at Visit 9, where a complete exam will be performed (refer to Section 5.2.2).
- Vital signs (sitting systolic and diastolic BP and pulse) will be assessed.
- Body weight will be measured.
- Concomitant medications (including over the counter and herbal/nutritional supplements) will be reviewed.
- Blood samples will be collected **prior to administration of study medication** for the following assessments:
  - Clinical chemistry (Visits 8 to 11; see Section 5.2.1.3)
  - HbA1c
  - Serum creatinine (for calculated creatinine clearance [Cockcroft-Gault formula] and eGFR)
  - FPG (samples for local on site evaluation and for testing by central laboratories at all visits)
- Urine will be collected for urinalysis (Visits 3 to 11)
- Urinary pregnancy test (βhCG) for female patients (WOCBP only) will be performed.
- Hypoglycaemic events will be reviewed.
- AEs and SAEs will be reviewed.

- Diet and life-style advice will be provided.
- Glucose meter and/or supplies and instructions will be provided.
- Patient diary will be provided.
- Study medication will be dispensed (see Table 5)
- Study medication compliance will be reviewed by drug accountability.
- Actual glimepiride dosage will be registered in IWRS.
- Patient diary will be reviewed for hypoglycaemic events/check glucometer values.
- Rescue medication will be dispensed (as necessary, see Table 2).

Prior to performing any assessments at the specified visit, the following surveys will be completed:

- SF-36 questionairre will be performed (Visit 9 only).
- Hypoglycaemia Fear Survey (Worry Scale) will be performed (Visit 9 only).
- IWQOL-Lite survey will be performed (Visit 9 only).

Study site personnel will instruct patients to take IP and metformin (with food) after study visit complete.

4.3.3 Dose Titration

During theTreatment Period, the blinded glimepiride/placebo dose will be slowly titrated in a stepwise fashion depending on glycaemic control at every visit. For the duration of the study, FPG will be measured at the study centre using a glucose analyser provided by AstraZeneca. The Investigator's decision on dose titration (either upwards or downwards) will take the plasma glucose measurements (measured at home in the days prior to the visit), and the Investigator's measurements at the study visits, as well as the occurrence of hypoglycaemia into account. The glimepiride/placebo dose should be titrated to achieve the individual target FPG of the patient (a target of approximately 110 mg/dL [6.1 mmol/L] is recommended). Up-titration should not be done in case of a recent hypoglycaemia episode.

The starting dose for glimepiride/placebo is 1 mg QD, which can be further increased by increments of 1 mg at 2-week intervals (- 3 days) to a maximum of 6 mg/day (maximum recommended dose as per the Summary of Product Characteristics and thus the maximum dose to be used in this study). The titration dose levels will be 1, 2, 3, 4, 5, and 6 mg QD.

In patients for whom titration is not medically indicated at a specific week, reassessment for titration will occur at the following visit.

The glimepiride/placebo dose can be down-titrated at any time during the study to mitigate recurrent hypoglycaemic events. If necessary, glimepiride/placebo will be allowed to be down-titrated to 0 mg (ie, 2 placebo capsules). The treatment can thereafter be up-titrated again during the treatment period.

4.3.4 Rescue Therapy

During the entire Treatment Period, patients may be eligible for treatment with open-label rescue medication (insulin) in addition to their blinded treatment regimen in order to treat ongoing hyperglycaemia. For patients who have not reached their MTD of glimepiride/placebo, up-titration of glimepiride/placebo should be attempted first before rescue is initiated.

Investigators may increase glimepiride/placebo dose or should initiate rescue insulin treatment based on progressively stricter glycaemic criteria according to Table 2. Assessment of glycaemic parameters (ie, based on FPG and HbA1c results from central laboratory) will be done at each visit to determine if criteria for rescue medication are met during the randomised treatment period.

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

Visit Period	Central Laboratory glycaemic parameters
Week 0 to 16 (after Visit 2 and including Visit 8)	FPG >240 mg/dL (13.3 mmol/L)
Week 16 to 24 (after Visit 8 and including day of Visit 9)	FPG >200 mg/dL (11.1 mmol/L)
Week 24 to 52 (after Visit 9 and including Visit 12)	HbA1c >8.0%

Abbreviations: FPG fasting plasma glucose; HbA1c haemoglobin A1c.

Patients with a laboratory value meeting the rescue criteria at a pre-specified visit will be scheduled for a follow-up visit (within 3 to 5 days) to obtain a second laboratory value and review the patient's glucose meter readings. If the repeat laboratory value still meets the rescue criterion, the patient should be rescued with insulin. Patients will continue receiving blinded study medication while receiving rescue therapy. Patients who meet rescue criteria in the double-blind treatment period must complete the Rescue visit which includes assessments indicated at Visit 12, prior to initiation of rescue therapy.

Rescued patients will be given open-label insulin in accordance with the approved product label in the applicable country at the discretion of the Investigator, in addition to their double-blinded study medication. Rescued patients will then continue in the double-blind treatment period according to their original visit schedule. Rescue therapy will be prescribed by the Investigator.

4.3.5 End of Treatment Period Visit/Early Termination or Rescue (Visit 12, Week 52)

Visit 12 (End of Treatment Visit) should occur 4 weeks after Visit 11 or if the patient discontinued early from IP or is rescued. Prior to this visit, patients are required 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 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.

The following procedures will be conducted:

- A complete physical exam will be conducted.
- Vital signs (sitting systolic and diastolic BP and pulse) will be assessed.
- Body weight will be measured.
- BMI will be calculated.
- Waist and hip circumference will be measured.
- 12-lead ECG will be performed.
- Concomitant medications (including over the counter and herbal/nutritional supplements) will be reviewed.
- Blood samples will be collected **prior to administration of study medication** for the following assessments:
  - Clinical chemistry (see Section 5.2.1.3)
  - Haematology
  - HbA1c
  - Creatinine (calculated creatinine clearance [Cockcroft-Gault formula] and eGFR)
  - FPG (samples collected for analysis by local on site laboratory and central laboratory)
  - Lipids (low-density lipoprotein [LDL]-cholesterol, high-density lipoprotein [HDL]-cholesterol, triglycerides, total cholesterol)
- Urine will be collected for urinalysis.

- Urinary pregnancy test (βhCG) for female patients (WOCBP only) will be performed.
- Hypoglycaemic events will be reviewed.
- AEs and SAEs will be reviewed.
- Diet and life-style advice will be provided.
- Study medication compliance will be reviewed.
- Actual glimepiride dosage will be registered in IWRS.
- Patient diary will be reviewed for hypoglycaemic events/check glucometer values and collected.
- Patient diary will be collected (not applicable for rescue visit, for end of treatment only).
- Unused study medication/supplies will be collected (not applicable for rescue visit).
- Glucose meter and/or supplies and instructions will be collected.

For patients who discontinue IP and agree to follow the original visit schedule, patient diary, study supplies and glucose meter will be not collected. Next visit(s) will be scheduled according to the original visit schedule.

Prior to performing any assessments at the specified visit, the following surveys will be completed:

- SF-36 questionnaire will be performed for: End of treatment visit/Early termination visit and Rescue visit .
- Hypoglycaemia Fear Survey (Worry Scale) will be performed for: End of treatment visit/Early termination visit and Rescue visit.
- IWQOL-Lite survey will be performed for: End of treatment visit/Early termination visit and Rescue visit.

For those patients who performed either IP discontinuation visit (Visit 12, End of treatment) or Rescue visit, there is no need to complete the surveys at any other study visit until the end of study.

4.4 Follow-up visit (Visit 13, Week 55)

Visit 13 (Safety Follow-up Visit) should occur approximately 3 weeks after Visit 12. Prior to this visit, patients are required 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.

The following procedures will be conducted:

- A brief physical exam will be conducted (refer to Section 5.2.2).
- Vital signs (sitting systolic and diastolic BP and pulse) will be assessed.
- Body weight will be measured.
- Concomitant medications (including over the counter and herbal/nutritional supplements) will be reviewed.
- Blood samples will be collected for the following assessments:
  - Clinical chemistry (see Section 5.2.1.3)
  - Haematology
  - Creatinine (calculated creatinine clearance [Cockcroft-Gault formula] and eGFR)
  - FPG (central laboratory only)
  - Lipids (low-density lipoprotein [LDL]-cholesterol, high-density lipoprotein [HDL]-cholesterol, triglycerides, total cholesterol)
- Urine will be collected for urinalysis.
- Urinary pregnancy test (βhCG) for female patients (WOCBP only) will be performed.
- Hypoglycaemic events will be reviewed.
- AEs and SAEs will be reviewed.
- Unused study medication/supplies will be collected.

For patients who discontinue IP between visit 3 & visit 8 and agree to follow the original visit schedule, Follow up visit is not required since those patients will continue in accordance with the study plan and then visits take place each second week.

For patients who discontinue IP after visit 8 and agree to follow the original visit schedule, Follow up visit should be performed as advised by the study plan – approximately 3 weeks after the Early Discontinuation visit. The next visits and the following ones have to be planned in accordance to the original visit schedule.

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 Safety 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 unless the values meet the defined rescue criteria. In addition, if rescue medication is initiated, the central laboratory HbA1c value will be reported to the Investigator to ensure proper follow-up of the rescued patient.

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.

Fasting plasma glucose will also be measured by local on-site laboratory within 5 minutes after vein puncture in venous EDTA blood according to a standardised protocol, using a patient-near electronic device.

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 (eg, 95.3 kg). 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.

5.1.5 Waist and hip circumference

For waist and hip circumference measurement, the study site personnel must ensure that:

- The patient stands and the examiner places a measuring tape in a horizontal plane midway between the lowest rib and the iliac crest for waist circumference and at the maximum circumference of the buttocks for hip circumference.
- The measuring tape is snug, but does not compress the skin, is parallel to the floor, and is not twisted.
- The measurement is taken at the end of a normal respiratory expiration.
- The measurement is recorded in centimeters to the first decimal point.
- Waist and hip circumference will be measured according to the schedules presented in the Study Plan (Table 1).

Waist-hip ratio is a calculated ratio between waist circumference and hip circumference (waist circumference / hip circumference, measured in centimetres) and will be computed by AstraZeneca.

5.2 Safety assessments

The Investigator will evaluate all 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 samples will be processed by a central laboratory and results will be reported back to the clinic within 72 hours.

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 centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

5.2.1.1 Volume of blood

The total blood drawn from each patient over the course of the study will not exceed 450 mL.

5.2.1.2 Haematology

Haematology assessments at Visits 2, 12, and 13 will include the following: red blood cell count, leukocyte count, haemoglobin (Hb), haematocrit, and platelets (see Table 3).

5.2.1.3 Clinical Chemistry

Chemistry assessments (see Table 3) will include the following:

- Visits 1 (Enrolment) and 8 to 11: creatinine, TB, AST, and ALT.
- Visits 2 (Randomisation), 12, and 13: creatinine, TB, AST, ALT, alkaline phosphatase (ALP), uric acid, potassium, calcium, sodium, chloride, bicarbonate, magnesium, and phosphorus (or other routine chemistry panels as approved by the Sponsor).

  Visits 3 to 7: No clinical chemistry will be performed. A separate blood sample for measurement of serum creatinine will be collected to calculate CrCl [Cockcroft Gault formula] and eGFR [MDRD].

Table 3 Laboratory Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Red blood cell count	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total (TB)
B-Haemoglobin (Hb)	S/P-Alkaline phosphatase (ALP)
B-Haematocrit	S/P-Aspartate transaminase (AST)
B-Platelet count	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

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

5.2.1.4 Urinalysis

Urinalysis assessments will be performed according to Study Plan (Table 1) and will include the following: haemoglobin, erythrocytes, blood, protein, albumin, glucose, and creatinine (or other routine urinalysis as approved by the Sponsor).

5.2.1.5 Other clinical laboratory evaluations

Blood samples will be collected for the measurement of TSH as presented in the Study Plan (Table 1). Patients with abnormal TSH values will be further evaluated by free T4. Patients with abnormal free T4 will be excluded (see Section 3.2).

Other measures will include:

- C-peptide
- Lipids (LDL-cholesterol, HDL-cholesterol, triglycerides, total cholesterol)
- Creatinine (for calculated creatinine clearance [Cockcroft-Gault formula] and eGFR)

- Hepatitis screening (hepatitis B surface antigen, antibody to hepatitis B core antigen IgM, and hepatitis C virus antibody)

5.2.1.6 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 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.

5.2.2 Physical examination

A complete physical examination will be performed according to the schedule presented in the Study Plan (Table 1). The complete physical examination includes an assessment of the following: general appearance including skin inspection (including injection site), respiratory, cardiovascular, lymph nodes, thyroid, musculoskeletal/extremities, lungs, abdomen, and reflexes. Baseline physical examination data are collected at Week 0 and new findings at the following physical examinations are recorded as change from baseline.

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 6.1 for reporting AEs.

5.2.3 ECG

A 12-lead ECG will be performed according to the schedule presented in the Study Plan (Table 1).

Standard 12-lead ECGs will be performed after approximately 5 minutes of quiet rest with the patient in a supine position. If the ECG must be performed with the patient in another position (sitting, standing, etc), the Investigator should record the alternate position. The Investigator should date and sign the ECG tracing and record the clinical significance of any abnormal result on the tracing. ECGs will be interpreted by a qualified physician (the Investigator or qualified designee) at the clinical study site.

5.2.4 Vital signs

Vital sign measurements in this study will include sitting systolic and diastolic BP and pulse. Vital signs should be measured at every visit 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.

5.2.5 Other safety assessments

5.2.5.1 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 (refer to Section 6.2).

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

5.2.5.2 Liver function test abnormalities

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

5.3 Other assessments

5.3.1 Hypoglycaemia

Patients will receive a hypoglycaemia/blood glucose diary when a glucometer is dispensed. Patients will be asked to measure their fasting blood glucose 2 to 3 days prior to each site visit during the treatment period and document results in their patient diary. Patients will be asked to also check their blood glucose when:

- The subject experiences signs or symptoms of hypoglycaemia.
- 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.

Patients will be instructed to contact the study team any time they experience a 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 subject experiences either of the following:

- Signs and symptoms of hypoglycaemia (regardless of blood glucose value by finger stick)
- Blood glucose value by finger stick ≤70 mg/dL (3.9 mmol/L) (regardless of symptoms).

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

- Date and time of hypoglycaemic event
- Symptoms
- Blood glucose value by finger stick and time of finger stick
- Whether the subject experienced incoherence, unconsciousness, or required assistance of another person to recover
- 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 subject and reviewed by site personnel at every subsequent visit. Completed diary pages will be added to the subject's source record, and data from the diary will be entered in the appropriate eCRF. Patients will also be requested to document any AEs and any concomitant medications they have taken since the last visit, and to contact the site with any questions about AEs and/or concomitant medications. The investigator should ensure these are transcribed onto the source documents during AE review.

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 6.3.8.

5.3.2 Patient reported outcomes

All patients will complete the SF-36 Health Survey, HFS-II-Worry Scale, and the IWQOL-Lite survey according to the schedule presented in the Study Plan (Table 1) prior to performing any other assessments at that visit.

The instruments/questions will be self-administered using paper and pencil questionnaires. It is important to administer the questionnaire and questions according to recommendation for standardised administration. The patient should be informed about how important his/her participation is. The patients should complete the questionnaire/questions before any other study related procedures take place and before any communication with the study personnel.

The questionnaire/questions should be completed in a quiet place without influence from study personnel or accompanied family or friend. The staff at the clinic should never help the patient to choose an answer and must be neutral in their response to the patient's questions. The staff at the clinic is not allowed to interpret or rephrase the questions for the patient.

After the patient has completed the questionnaire and questions, the study personnel will review the questionnaire/questions for completeness only.

5.3.2.1 SF-36 Health Survey

The Short Form 36-item Health Survey addresses 8 health concepts including: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. The survey also includes a single item that provides an indication of perceived change in health.

Scoring the SF-36 Health Survey consists of 8 scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0 to 100 scale on the assumption that each question carries equal weight. The lower the score the more disability. The higher the score the more favourable health state (ie, a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability).

5.3.2.2 Hypoglycaemia Fear Survey - Worry Subscale

The HFS-II is a reliable and valid measure of the fear of hypoglycaemia in adults with T2DM that measures the behavioural and affective dimensions of fear of hypoglycaemia, using modern test-theory methods, including item-response theory (Appendix E). Items in the HFSII-Worry scale describes specific concerns that patients may have about their hypoglycaemic episodes (eg, being alone, episodes occurring during sleep, or having an accident).

5.3.2.3 IWQOL-Lite

The IWQOL-Lite survey is a 31-item, self-reported assessment of quality of life in overweight/obese individuals (Appendix E). The measure consists of scores on 5 dimensions: physical function (11 items), self-esteem (7 items), sexual life (4 items), public distress (5 items), and work (4 items). In addition, there is a global score (sum of scale scores). Participants are asked to rate items with respect to the past week on this instrument (from never true to always true). Scores on the IWQOL-Lite (domains and global score) range from 0 to 100. Higher scores indicate poorer quality of life. The IWQOL-Lite has demonstrated excellent psychometric properties in overweight persons seeking treatment, in a community setting and in persons with and without diabetes (Kolotkin et al 2003). IWQOL-Lite is included for exploratory purposes and the questions will be assessed at baseline, after 24 weeks, and after 52 weeks of treatment.

Translations of the questions into local languages have or will be performed according to a linguistic validation process.

5.4 Pharmacokinetics (not applicable)

5.5 Pharmacodynamics (not applicable)

5.6 Pharmacogenetics (not applicable)

5.7 Biomarker analysis (not applicable)

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The 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 AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea and chest pain), signs (eg, tachycardia and enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). 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

An SAE is an AE occurring during any study phase (ie, treatment or follow-up) that fulfills 1 or more of the following criteria:

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

Any event of cancer, drug dependency/abuse, laboratory abnormalities fulfilling the Hy's law definition (ALT/AST >3x ULN and total bilirubin >2x ULN) or overdose (defined as the accidental or intentional ingestion of any dose of the IP that is considered both excessive and medically important), should be reported as an SAE using the most relevant SAE criteria, as judged by the Investigator.

For further guidance on the definition of an SAE, see Appendix B, 'Additional Safety Information'.

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, Enrolment, Randomisation, and throughout the treatment period and including the follow-up period (Visit 13).

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:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity or intensity or changes in intensity
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- AE caused subject's withdrawal from study (yes or no)
- Outcome.

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

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

6.3.3.1 Intensity rating scale

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

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not 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 B 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, ECG, 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 (eg, 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.

Hypoglycaemic episodes should only be reported on the AE eCRF page if the event fulfils protocol criteria for a SAE (see Section 6.2). In this case, a SAE must be reported in addition to the hypoglycaemia eCRF pages for hypoglycaemia. A separate section in the eCRF will be used to document all reported episodes of hypoglycaemia (see Section 6.3.8).

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 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3x ULN together with total bilirubin ≥2x ULN may need to be reported as SAEs. Please refer to Appendix C and D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.3.8 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 (see Section 5.3.1 for detailed instructions).

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.

Hypoglycaemia events will be summarised descriptively. Summaries will be provided overall for all events of hypoglycaemia as well as by the following subcategories:

Major hypoglycaemic events, defined as symptomatic events requiring external assistance due to severe impairment in consciousness or behaviour, with a capillary or plasma glucose value <54 mg/dL (<3.0 mmol/L), and prompt recovery after glucose or glucagon administration.

Hypoglycaemia: Typical symptoms of hypoglycaemia accompanied by blood glucose ≤70 mg/dL (3.9 mmol/L).

Other episodes of hypoglycaemia: Symptoms of hypoglycaemia without a blood glucose reading or symptoms of hypoglycaemia accompanied by blood glucose level >70 mg/dL (3.9 mmol/L).

Confirmed hypoglycaemia: Typical symptoms of hypoglycaemia accompanied by blood glucose ≤50 mg/dL (2.8 mmol/L).

Asymptomatic hypoglycaemia: An event not accompanied by typical hypoglycaemia symptoms but with measured plasma glucose ≤70 mg/dL (≤3.9 mmol/L).

6.4 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 3 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs 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 1 calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

If the WBDC system is not available, then the Investigator or other study site personnel reports 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, confirmed adjudicated hospitallizations for cardiac failure events, cardiac failure, renal impairment/renal failure, volume depletion (hypotension, dehydration, and hypovolemia), and liver injury, including confirmed adjudicated hepatic events.

6.5 Overdose

Overdose is defined as the accidental or intentional ingestion of any dose of IP that is considered both excessive and medically important. For the purpose of this study, an overdose is defined as a dose of study medication in excess of that specified in the CSP (ie, more than 1 tablet per day of either study drug).

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

- 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.

- 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. The patient should be withdrawn from study and continue treatment of diabetes according to the standard of care.

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 ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the 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 Hepatic 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, including, but not limited to:

- Hepatic events timely related to death (within 30 days before death)
- AST and/or ALT >3x ULN and TB >2x ULN (within 14 days of the AST and/or ALT elevation; see Appendix D
- AST and/or ALT >10x ULN

A separate Adjudication Manual will define and describe the procedure for the handling, reporting and classification of these cases.

6.8.2 Cardiovascular Adjudication Committee

Adjudication for hospitalization for heart failure will be performed according to the respective charter 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 4 Investigational Products for Study D1689C00014

Blinded Investigational product	Dosage, route, form and strength	Manufacturer
Dapagliflozin	10 mg, orally Green, plain, diamond-shaped, film-coated tablet	AstraZeneca
Placebo for dapagliflozin	Does not contain active ingredient, orally Green, plain, diamond-shaped, film-coated tablet	AstraZeneca
Saxagliptin	5 mg, orally Plain, yellow, biconvex, round, film-coated tablet	AstraZeneca

Blinded Investigational product	Dosage, route, form and strength	Manufacturer
Placebo for saxagliptin	Does not contain active ingredient, orally Plain, yellow, biconvex, round, film-coated tablet	AstraZeneca
Glimepiride (comparator)	1, 2, or 4 mg, orally Opaque gray capsule	AstraZeneca
Placebo for glimepiride	Does not contain active ingredient, orally. Opaque gray capsule	AstraZeneca

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

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 are described in Table 4.

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

Dapagliflozin, saxagliptin, glimepiride 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 (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 52 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 centre should notify the Investigator immediately in order to receive a replacement kit via the 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 10 mg tablets, saxagliptin 5 mg tablets, glimepiride 1 to 6 mg capsules (see Section 4.3.3), and matching placebo tablets. Study medication will be dispensed according to the schedule presented in Table 5.

Every day during the treatment period, patients will take 4 tablet/capsules: 1 from the dapagliflozin bottle, 1 from the saxagliptin/placebo bottle, 1 from each of the glimepiride/placebo bottles (Bottle A and Bottle B; see Table 6).

The first doses of study medication will be taken at the study site. Patients will subsequently self administer saxagliptin, dapagliflozin, glimepiride, and matching placebos QD orally for the 52-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.

Table 5 Schedule of Study Medication Dispensation

	Enrolment	**Blinded Study Medication during Randomised Treatment Period**										
Visit #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Study Week	**W-2**	**W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W24**	**W36**	**W48**	**W52**
Dapagliflozin or placebo (tablets)	-	X	-	-	-	-	-	X	X	X	X	-
Saxagliptin or placebo (tablets)	-	X	-	-	-	-	-	X	X	X	X	-
Glimepiride or placebo (capsules)[a]	-	X	X	X	X	X	X	X	X	X	X	-

Note: A dash denotes no dispensation of the drug and X denotes that drug will be dispensed at the specified visit.

[a] Glimepiride will be dispensed in 2 bottles, see Table 6.

Abbreviations: W week.

Table 6 Titrated Dose Levels and Contents of Blinded Glimepiride or Placebo Kit

Dose levels	**Total Dosage**	**Bottle A**	**Bottle B**
0	**0 mg**	Placebo	Placebo
1	**1 mg**	1 mg	Placebo
2	**2 mg**	2 mg	Placebo
3	**3 mg**	1 mg	2 mg
4	**4 mg**	2 mg	2 mg
5	**5 mg**	1 mg	4 mg

Dose levels	Total Dosage	Bottle A	Bottle B
6	**6 mg**	2 mg	4 mg
7	**Placebo**	Placebo	Placebo

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill 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 of children"
11. The name of the Investigator, where applicable (to be added on the label when IP is dispensed)
12. Visit date

7.4 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.

7.5 Compliance

The patient will be asked about compliance at each study visit. When study medication is returned, compliance will be assessed based upon subject's interview and a count of the tablets returned. Compliance should be between ≥80% and ≤120% of that prescribed. The Investigator (or designee) will record the amounts of study medication dispensed and returned at each visit, 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. If the subject is not ≥80% 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 administration of all study medications (including IPs) should be recorded in the appropriate sections of the eCRF.

7.6 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 (those supplied by AstraZeneca or sourced by the Investigator) 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:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- 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.

- 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.

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

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

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

7.7 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.

7.8 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 the 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 7.8.2) for any duration as clinically

Restricted Medication/Class of drug:	Usage
	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 cconsecutive 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 cconsecutive 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 ≥10 mg (betamethasone ≥1.2 mg, dexamethasone ≥1.5 mg, hydrocortisone ≥40 mg) per day	Newly initiation of treatment with any systemic corticosteroid therapy that will involve ≥5 days of therapy (inhaled and topical are allowed). The Medical Monitor 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.

7.8.1 Metformin

Patients will remain on their pre-study stable, maximum tolerated metformin doses ≥1500 mg/day, during the 52-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 in pre-packaged kits by the Sponsor as it is the usual care prior to study participation.

7.8.2 Rescue therapy

Patients may be eligible for rescue therapy (see Section 4.3.4) with open-label rescue medication (Insulin) in order to treat ongoing hyperglycaemia. Patients should continue receiving blinded study medication while receiving rescue therapy. If rescue therapy fails, further therapy will be given at the discretion of the Investigator.

Rescue therapy will be prescribed by the Investigator and not provided by the Sponsor, however could be supplied/prescribed according to local requirements.

7.8.3 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.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

All personnel involved with the analysis of the study will remain blinded until database lock and protocol violators identified at the end of the 52-week randomised treatment period.

Redacted

Due to the large number of centres and the expected low number of patients per centre, data from all sites will be pooled together and centre effects will not be investigated.

All collected data will be listed. A comprehensive Statistical Analysis Plan (SAP) and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data.

8.2 Sample size estimate

The primary objective of this study is to examine whether, after 52 weeks of oral administration of double-blind treatment, the absolute change from baseline in HbA1c levels with dapagliflozin plus metformin and dapagliflozin plus saxagliptin added to metformin is non-inferior to glimepiride plus metformin in patients with T2DM who have inadequate glycaemic control on ≥1500 mg/day metformin therapy.

To demonstrate non-inferiority of dapagliflozin and dapagliflozin plus saxagliptin to glimepiride for changes from baseline to Week 52 in HbA1c within a non-inferiority margin of 0.30%, assuming a standard deviation 1.0%, and at a 1-sided significance level of 0.025, 290 evaluable patients will be needed in each treatment group to provide approximately 95% power (given a true difference of zero between dapagliflozin or dapagliflozin plus saxagliptin and glimepiride). The non -inferiority margin of 0.3% as well as a common standard deviation of 1.0% were selected based on information from earlier, similarly designed studies.

Assuming that 5% of patients do not have a post-baseline assessment, a total of approximately 930 patients (310 patients per treatment arm) need to be randomised.

Assuming that 30% of screened patients will fail to meet screening criteria, a total of 1329 patients need to be screened.

8.3 Definitions of analysis sets

Classification into Full Analysis (FA), Per Protocol (PP), and Safety sets will be conducted prior to the database lock.

The primary efficacy analysis will be performed on the FA set. A supportive analysis will be carried out with the PP analysis set. Analyses of all secondary efficacy endpoints will be performed using the FA analysis set. All safety analyses will be based on the Safety set.

Randomised set

The randomised set will be defined as all randomised patients.

Full analysis set

The FA set will be defined as all randomised patients who receive at least one dose of study medication and who have a baseline and a post-baseline efficacy assessment value. Patients will be analysed according to the treatment assigned.

Per protocol analysis set

The PP analysis set will be defined as all FA patients without an important protocol deviation that might affect the primary efficacy analyses. The criteria for important protocol deviations will be defined in the statistical analysis plan. Patients will be analysed according to the treatment assigned.

A complete list of protocol violations will be provided in the SAP.

Safety analysis set

The safety analysis set will be defined as all randomised patients who received at least 1 dose of study medication. Patients will be analysed according to the actual treatment received.

8.4 Outcome measures for analyses

8.4.1.1 Key secondary endpoints

- Proportion of patients reporting at least 1 episode of confirmed hypoglycaemia during the double-blind treatment period.
- Change in total body weight from baseline at Week 52.
- Change in FPG from baseline at Week 52.
- Time to rescue during the 52-week double-blind treatment period.

8.4.1.2 Other secondary endpoints

- Proportion of patients achieving HbA1c of <7% (and <7.5%) without confirmed hypoglycaemia at Week 52.
- Proportion of patients achieving HbA1c of <7% (and <7.5%) at Week 52.
- Proportion of patients achieving individually agreed HbA1c targets at Week 52.
- Proportion of patients achieving an HbA1c decrease of ≥1% with no weight gain at Week 52.
- Time spent below HbA1C target (<7% and <7.5%) from baseline until Week 52.
- Change in BMI from baseline to Week 52.
- Proportion of patients achieving weight reduction of ≥5% and weight gain of ≥5% from baseline to Week 52.
- Proportion of patients reporting at least 1 episode of any hypoglycaemia during the treatment period.
- Change in waist circumference from baseline to Week 52.
- Change in systolic BP from baseline to Week 52

8.4.2 Exploratory endpoints

- Change from baseline to Week 52 in SF-36, Worry Scale of the Hypoglycaemia Fear Survey, and IWQOL-Lite survey.
- Change in waist:hip circumference ratio from baseline to Week 52.

8.5 Methods for statistical analyses

Continuous variables will be presented with mean, median, 25th percentile, 75th percentile, standard deviation, minimum, maximum, and (if appropriate) the number of nonmissing observations. Categorical data will be displayed via absolute and relative frequencies for each category, including a category labeled as 'missing' when appropriate. The 'missing' category will not contribute to the denominators of relative frequencies.

8.5.1 Demographic and baseline characteristics

Demographic and baseline characteristics will be summarised using frequency distributions and descriptive statistics using the randomized set, for each treatment group as well as for all patients combined. Key baseline characteristics that will be summarised include: age, gender, race, ethnicity, country, body weight, BMI, eGFR, duration of T2DM, baseline FPG, and baseline HbA1c. Baseline is defined as the last measurement prior to the first dose of double-blind study medication or as the last non-missing value of the visit 1 or visit 2 assessment for those subjects without first dose start date. No statistical tests will be performed to compare treatment groups at baseline.

8.5.2 Efficacy analyses

All efficacy analyses will be performed using the FA set. A sensitivity analysis will also be conducted using the PP set.

All analyses will be done using values prior to rescue of treatment. Values collected after this time will be excluded from analyses. Sensitivity analyses will be conducted for the primary endpoint using all available data. For the endpoint of the proportion of patients achieving therapeutic glycaemic response at Week 52, all available data will be used but patients rescued prior to Week 52 will be treated as non-responders.

8.5.3 Control of type 1 error

The experiment-wise type I error will be controlled to a maximum of 5%. A hierarchical closed testing procedure will be employed such that key secondary endpoints will be considered for statistical significance (in terms of superiority) only if non-inferiority of the primary endpoint is concluded and that a key secondary endpoint will be considered for statistical significance only if test ordered before it is found to be statistically significant. At each step, dapagliflozin plus saxagliptin added to metformin versus glimepiride added to metformin will be tested first followed by the test for dapagliflozin added to metformin versus glimepiride added to metformin except for the superiority tests of the primary endpoint and the endpoint of total BW. The test of superiority for HbA1c will include only the comparison of dapagliflozin plus saxagliptin added to metformin vs glimepiride added to metformin. For total BW, dapagliflozin added to metformin versus glimepiride will be tested first followed by dapagliflozin plus saxagliptin added to metformin versus glimepiride added to metformin.

The following testing order will be followed for the overall type I error control:

1. Change from baseline in HbA1c at Week 52 (test for non-inferiority)

2. Proportion of patients reporting at least 1 episode of confirmed hypoglycaemia at Week 52 (test for superiority)

3. Change in total body weight from baseline to Week 52 (test for superiority)

4. Change from baseline in HbA1c at Week 52 (test for superiority of dapagliflozin plus saxagliptin added to metformin to control only)

5. Change in FPG from baseline to Week 52 (test for superiority)

6. Time to rescue at Week 52 (test for superiority)

The statistical comparisons will be done using a comparison-wise type I error of 5% (2-sided).

For all other secondary variables and exploratory variables, nominal p-values will be reported without significance testing.

8.5.4 Analysis of the primary efficacy variable

The primary objective of this study is to show non-inferiority of dapagliflozin added to metformin and dapagliflozin plus saxagliptin added to metformin versus glimepiride added to metformin in terms of the primary efficacy variable change in HbA1c from baseline to Week 52.

The following null hypothesis (H_0) will be tested against the alternative hypothesis (H_A) (α=0.025, 1-sided):

H_0: $\mu_c - \mu_t \leq -0.30\%$,

H_A: $\mu_c - \mu_t > -0.30\%$,

where μ_t denotes the mean absolute change in HbA1c from baseline to Week 52 in the group of patients treated with dapagliflozin added to metformin or dapagliflozin plus saxagliptin added to metformin (test medication) and μ_c denotes the mean absolute change in HbA1c from baseline to Week 52 in the group of patients treated with glimepiride added to metformin (control).

The absolute change from baseline to Week 52 in HbA1c will be analysed using a restricted maximum likelihood-based (REML), Mixed-Model Repeated Measures (MMRM) model with terms for treatment group, baseline HbA1c, time (at relevant visits), and interactions baseline HbA1c-by-time and treatment group-by-time. The model will be used to derive a least-squares estimate of the mean treatment difference with corresponding 2-sided 95% confidence interval (CI). The primary assessments of efficacy will be a comparisons of each of the 2 test groups the dapagliflozin plus saxagliptin added to metformin versus the control group and the dapagliflozin added to metformin versus the control group using a 95% CI.

In particular, if the observed lower limit from a 2-sided 95% (or 1-sided 97.5%) CI for the difference in adjusted means is greater than -0.30%, then the test group will be considered to be non-inferior to the control group. Note, that multiplicity will be controlled using a sequential testing scheme as described above. The dapagliflozin plus saxagliptin added to metformin group will be tested versus the control group first, followed by the dapagliflozin plus metformin group versus the control group.

A superiority test of the dapagliflozin plus saxagliptin added to metformin group versus the control group will also be conducted using the same modelling approach as for the primary non-inferiority analysis.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom (DDFM). An unstructured variance will be used to model the within-patient errors.

8.5.5 Sensitivity analysis (if applicable)

Sensitivity analyses will be performed to assess the impact of assumptions on the results of the analyses by using other statistical methods.

Following sensitivity analyses will be performed:

- The primary analysis will be repeated with patients from the Per-Protocol analysis set
- The primary analysis will be repeated including all values according to the ITT principle (regardless of rescue or treatment or discontinuation)
- ANCOVA analysis using values prior to rescue at week 52. If Week 52 value is not available the LOCF value will be used

8.5.6 Analysis of the secondary and exploratory variables

All secondary endpoints will be analysed using the FA set. In order to protect the overall type I error rate, the interpretation of the statistical significance of treatment comparisons for key secondary efficacy endpoints will be done using a procedure as outlined in Section 8.5.3.

The analysis of the changes from baseline to Week 52 for FPG, total body weight and and systolic Blood Pressure (SBP) will be performed using the same MMRM model as described for the primary efficacy endpoint. Point estimates and 95% CI will be calculated for the adjusted mean changes from baseline within each treatment group as well as for each comparison versus control in adjusted mean changes together with the p-values corresponding to testing the hypotheses of no difference between dapagliflozin added to metformin and dapagliflozin plus saxagliptin added to metformin compared to glimepiride added to metformin.

The time spent below HbA1C target (<7% and <7.5%) from baseline until Week 52 as well as the change from baseline at Week 52 in BMI and waist circumference will be analysed using an analysis of covariance (ANCOVA) model that will include terms for treatment groups and the baseline respective covariate.

The ANCOVA model will be used to derive a least squares estimate of the contrasts of each test combination versus the control with 95% CI and a corresponding 2-sided p-value. Furthermore, a 2-sided 95% CI for the mean change within each treatment group will be calculated.

Time to rescue will be analysed using a Cox proportional hazards model. Estimates of the hazard ratio and 95% CI will be provided. Kaplan-Meier estimates will be calculated and

plotted by treatment group. For the analysis during 52 weeks, all patients will be censored at the final visit if rescue has not occurred by then.

The proportion of patients achieving a therapeutic glycaemic response at Week 52 and reporting hypoglycaemia during the double-blind treatment period will be summarised by treatment group and compared between treatment groups using logistic regression with baseline HbA1c as a covariate.

The proportion of patients achieving a weight reduction/gain at Week 52 will be summarised by treatment group and compared between treatment groups using logistic regression with baseline weight as a covariate.

The proportion of patients achieving composite endpoints will be summarised by treatment group and comparisons between treatment groups (contrasts of each test combination versus the control) will be done using a Chi-Square test.

All exploratory endpoints will be analysed only in a descriptive fashion (no inferential procedure will be applied).

8.5.7 Subgroup analysis

Subgroup analyses for age, gender, race, eGFR and baseline HbA1c for continuous endpoints will be analysed as was done for the original analysis but for the applicable subset of patients. Interaction tests will be performed for time to event and continuous endpoints using the original model with treatment interaction terms added.

8.5.8 Safety analyses

The assessment of safety will be based on the analyses of AEs, vital signs, physical examinations, ECGs, hypoglycaemia, and clinical laboratory evaluations. All safety analyses will be performed on the Safety Set.

The number and percent of patients with at least 1 AE will be summarised for each treatment group, including summaries of AEs, SAEs, AEs leading to discontinuation of study medication, and AEOSI. Summaries will include the number of patients with events by specified system organ classes and preferred terms.

Additionally, the incidence and frequency of AEs will be summarised for each treatment group for both frequent events (occurring in at least 5% of patients) and for selected AEOSI.

Summary statistics will be presented at each assessment visit for the continuous laboratory parameters. Descriptive statistics of changes from baseline by study visits will also be presented.

A frequency table of results of categorical laboratory parameters will be produced. Furthermore, laboratory abnormalities will be analysed by shift tables where each patient will be counted only once with the worst grade in the summary tables. The number and percent of

patients with laboratory values meeting marked abnormality criteria will be summarised for each treatment group.

All laboratory data will be listed with abnormal values flagged.

Vital signs will be listed and summarised over time by treatment group. Changes from baseline will also be summarised. Notable values and changes will be tabulated.

The normality/abnormality of the ECG tracing (as determined by the investigator) at baseline versus week 52 of the double-blind treatment period will be summarised.

The number of patients with hypoglycaemic events and the percentage of patients withdrawing from the study medication due to hypoglycaemia will be presented descriptively by treatment group.

8.6 Interim analysis

No interim analysis on the efficacy or safety parameters is planned for this study.

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 CRO and study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed

- Perform source data verification including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)

- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

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

9.2.1 Source data

Refer to the CSA for location of source data.

9.2.2 Study agreements

The Investigator at each/the centre 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 or representative and the Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the 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 3rd Quarter of 2015. The study is expected to complete 1st Quarter 2017.

The study may be terminated at individual centres 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 AstraZeneca or representative, according to the Data Management Plan. AEs and medical/surgical history will be classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary

(AZDD). Classification coding will be performed by the Medical Coding Team at AstraZeneca or representative.

Data entered in the electronic data capture (eDC) system will be immediately saved to a central database and changes tracked to provide an audit trail. When the Principal Investigator has signed the eCRF electronically as per eCRF instructions, then the patient's data will be locked.

Electronic case report forms

The eCRF and the protocol are both confidential. The eCRF will be created by AstraZeneca or representative and programmed into the eDC system. All study centres will need internet access to access the eCRFs and will only have access to data for patients at their own study centres. Data Management (DM) and other coordinator teams will have access to data at all study centres. All eCRFs are to be completed by an authorised member of the study centre staff and reviewed and signed by the Investigator. All entries, corrections, and alterations are to be made by the responsible Investigator or an authorised member of the study centre staff. All eCRFs are to be completed in a manner that ensures accurate interpretation of data. It is each Investigator's responsibility to ensure that all discontinued orders or changes in the study or other medications entered on the patient's eCRF correspond to the entries on the patient's medical records.

The eCRFs for any patient leaving the study should be completed at the time study medication is terminated or a patient discontinues study participation for whatever reason. The eCRFs must accurately reflect data contained in the patient's records (eg, source).

Dataflow

After the data are entered into the eCRF by study centre, auto-queries that are generated by the eDC system should be addressed by the study centre. Data queries will be raised for inconsistent, impossible, or missing data.

At the monitoring visit, the Study Monitor must perform the study data verification (SDV) of the required fields on completed forms, and if there are no open queries, freeze the form. Data management will run manual consistency checks outside of the eDC system and will raise manual queries for study centres to address; if the form is frozen, DM will unfreeze it to allow study centres to amend data. The same process is to be followed by any other groups creating manual queries in the eDC system (eg, for SAE reconciliation). Once all data are entered, SDV complete on required fields, manual queries and electronic data reconciliation complete, and all queries closed, then the casebook can be signed. Once the casebook is signed, DM will then lock the casebook so that no amendments can be made.

Database lock

Once all patient casebooks are locked, the final data transfer can be sent to statistics. A database lock checklist will also be completed by DM and the programmer to confirm all

applicable quality control checks were performed. When all data have been coded, validated, and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked

Coding

All AEs and Medical Histories recorded in the eCRF will be classified according to the terminology of the latest version of the MedDRA. Medications will be classified according to the AZDD. The coding will occur outside of the eDC system and will be merged with the clinical datasets sent to statistics.

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

The data will be validated as defined in the DM 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 DM Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

Serious Adverse Event (SAE) Reconciliation

AstraZeneca or representative will perform SAE reconciliation between the clinical study database and the safety data entry site clinical patient safety database.

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 International Conference on Harmonisation (ICH)/GCP, applicable regulatory requirements and the AstraZeneca global standard: Human Biological Samples.

10.2 Subject data protection

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

10.3 Ethics and regulatory review

An Ethics Committee (EC) 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, and to the study site staff.

The opinion of the EC should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The EC 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 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, and Investigators with safety updates/reports according to local requirements.

Each Principal Investigator is responsible for providing the EC/ Institutional Review Board (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 Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File

- Ensure a copy of the signed ICF is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an EC.

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 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 see Section 10.3.

If a protocol amendment requires a change to a centre's ICF, AstraZeneca and the centre's EC 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.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an EC may perform audits or inspections at the centre, 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, GCP, guidelines of the ICH, and

any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

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Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation

Development of drug dependency or drug abuse

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

Labelling and shipment of biohazard samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

TABLE OF CONTENTS PAGE

1. INTRODUCTION

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on the managing liver abnormalities can be found in Section 5.2.5.2 of the protocol.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TB) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3x ULN **together with** TB ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TB, but there is no specified timeframe within which the elevations in transaminases and TB must occur.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TB ≥ 2xULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the Hy's law lab kit should be used.
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TB elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TB elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Appendix D Algorithm on Management of Sustained Elevated Liver Safety Abnormalities

ALGORITHM ON MANAGEMENT OF SUSTAINED ELEVATED LIVER SAFETY ABNORMALITIES

The monitoring for liver safety will be performed using the serum levels of AST, ALT, and TB (see Figure 2 Sustained elevated liver safety abnormalities flow chart**Error! Reference source not found.** - algorithm flow chart).

Patients with a central laboratory ALT and/or AST >3X ULN will be scheduled for a follow-up visit within 3 days following receipt of the initial laboratory results, to obtain repeat central laboratory ALT, AST, TB and Alkaline Phosphatase (ALK-P). In the event that the repeat laboratory assessments cannot be obtained within 3 days, the Investigator is encouraged to discuss possible alternatives with the Sponsor. Patients should remain on study medication until confirmatory results are obtained, unless otherwise contraindicated.

- **If the repeat ALT and AST are ≤3X ULN,** patient should continue double-blind treatment according to their original visit schedule unless otherwise contraindicated.

- **If the repeat ALT and/or AST are >3X ULN but ≤8X ULN and TB ≤2X ULN,** the patient's medical history, including details of risk factors for liver diseases, should be evaluated for potential underlying aetiologies. In addition, specialized blood sampling will be performed to evaluate liver function as well as identify potential causes of laboratory elevation(s). The Investigator should continue to monitor the patient's liver tests every 3 days following receipt of the prior laboratory results until the ALT and AST are ≤2X ULN or until ALT and AST are at or below baseline levels. The frequency of retesting can decrease to once a week or less if abnormalities stabilize and the patient is asymptomatic. Patients should remain on study medication unless confirmatory results indicate that a criterion for discontinuation has been met or continuing study medication would be otherwise contraindicated.

Patients must be discontinued from the study if an initial and repeat confirmatory laboratory tests meet any of the following criteria:

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

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

- ALT and/or AST are >8 x ULN

In each of these situations, study medication will be discontinued, the Sponsor notified and the End of Treatment Visit performed within 3 days of the confirmed laboratory results (see Section 4.3.5). At the End of Treatment Visit, medical history including details of risk factors for liver diseases (if not previously assessed) will be requested and additional blood sampling performed (**Specialized Liver Panel** and **Liver Discontinuation Panel**, see detailed below). Patient should also be scheduled for a Follow-up Visit 3 weeks after discontinuation of investigational product. A referral consultation to a hepatologist or gastroenterologist (specializing in liver abnormalities) should be obtained.

Any additional tests and/or examinations should be carried out at the discretion of the Investigator. Any further investigations and laboratory results for patients with abnormal laboratory values at the Follow-up Visit should be made available to the Sponsor upon request.

Additional information, including but not limited to completion of supplemental eCRFs may be requested for certain adverse events and/or laboratory abnormalities which are reported/identified as part of the hepatic safety surveillance.

Following the End of Treatment Visit, the Investigator should continue to monitor the subject's liver tests every 3 days following receipt of the prior laboratory results until the ALT and AST are ≤2 x ULN or until ALT and AST are at or below baseline levels. The frequency of retesting can decrease to once a week or less if abnormalities stabilize and the subject is asymptomatic.

Guidance on Assessment of Hepatic Laboratory Abnormalities

The following is presented to assist in the evaluation and management of hepatic laboratory values. It is not intended to supplant Investigators' clinical judgment.

Patients who experience ALT and/or AST values >3 x ULN confirmed with a repeated test will have the following performed within 3 days of the confirmed laboratory results:

- AE assessment
- Physical Examination for jaundice and other signs of liver diseases
- Review of relevant risk factors and current history focusing on possible causes of the increased ALT and/or AST and/or TB, including:
  - Use of suspect concomitant medication [including over-the-counter (ie, acetaminophen/paracetamol), herbal and vitamin preparations]
  - Recent alcohol consumption or recreational drug/narcotic use
  - Recent unaccustomed physical exertion
  - Occupational or environmental exposure to hepatotoxins

  - Other conditions which may cause liver diseases or which may cause abnormal test results

- Specialized Liver Laboratory Panel (see below)

Specialized Liver Panel

For patients who are being monitored frequently as a result of confirmed AST and/or ALT >3X ULN, additional central laboratory tests will be performed within 3 days of receipt of confirmatory results. These laboratory tests will study the possible causes of the increased ALT and/or AST and/or TB, and may include, but are not limited to, the following tests:

- Hepatitis A IgM
- Hepatitis BsAg
- Hepatitis B Core Ab IgM
- Hepatitis C virus RNA
- Hepatitis C Ab
- Hepatitis E IgM
- Epstein-Barr Virus (EBV) IgM Ab
- Lactate Dehydrogenase (LDH)
- Gamma-glutamyl-transpeptidase (GGT)
- Carbohydrate deficient transferrin (CDT)
- Prothrombin time (PT/INR)
- Iron Panel - iron, ferritin, total iron binding capacity (TIBC)
- Immunology Panel including Antinuclear Antibody (ANA), Anti-Smooth Muscle Antibody (SMA) and Anti-Liver/Kidney Microsomal Antibody (Anti-LKM)
- Anti-tissue Transglutaminase Antibody

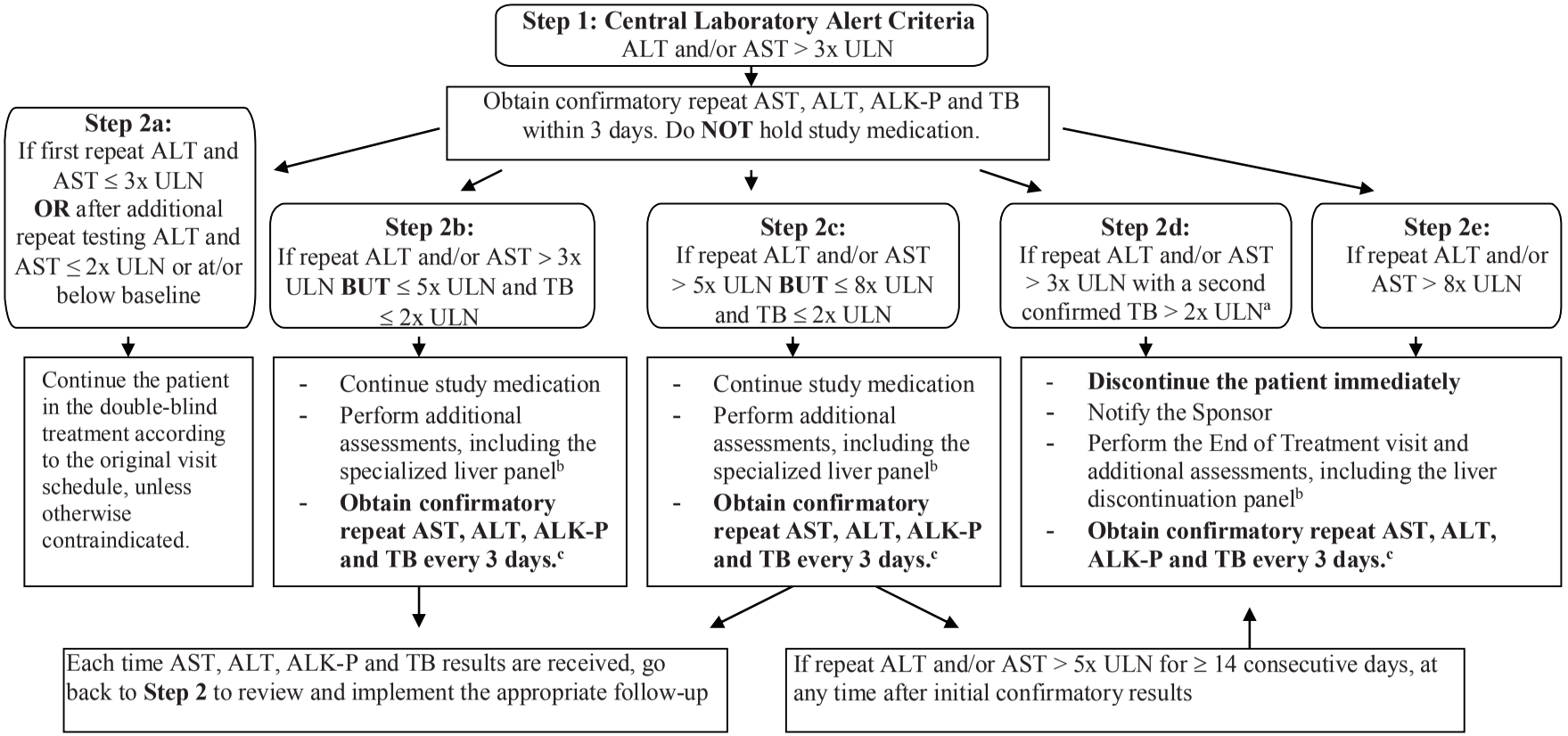
Liver Discontinuation Panel

For patients who are discontinued from the study as a result of sustained elevated liver safety abnormalities, additional central laboratory tests will be performed at the time of End of Treatment Visit. Similar to the Specialized Liver Panel, these laboratory tests will study the possible causes of the increased ALT and/or AST and/or TB, and may include, but are not limited to, the following tests:

- Cytomegalovirus (CMV) IgM Ab
- Herpes Simplex Virus (HSV) 1 and 2
- Ceruloplasmin
- Toxoplasmosis
- Alpha-1 antitrypsin

For specific details regarding the Specialized Liver Panel or the Liver Discontinuation Panel laboratory tests, refer to the Central Laboratory Manual for this study.

Figure 2 Sustained elevated liver safety abnormalities flow chart



[a] In patients with repeat ALT or AST > 3x ULN but ≤ 8x ULN, only patients with TB ≤ 2x ULN at Step 1 should be followed according to Step 2b. Patients with an initial TB and confirmatory repeat TB > 2x ULN should be followed according to Step 2d.

[b] Please see text above in the Appendix for details on additional assessments to be performed (AE assessment, PE, review of current medical history including focused review of current medical history including focused review of risk factors for liver diseases and collection of blood samples [specialized liver panel or liver discontinuation panel]).

[c] Confirmatory repeat AST, ALT, ALK-P and TB should be obtained every 3 days following receipt of prior laboratory results, until the ALT and AST are ≤ 2x ULN or until ALT and AST are at or below baseline levels. The frequency of retesting can decrease to once a week or less if abnormalities stabilize and the patient is asymptomatic.

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Appendix E Patient Reported Outcomes

SF-36 HEALTH SURVEY

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐1	☐2	☐3	☐4	☐5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐1	☐2	☐3
b	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐1	☐2	☐3
c	Lifting or carrying groceries	☐1	☐2	☐3
d	Climbing <u>several</u> flights of stairs	☐1	☐2	☐3
e	Climbing <u>one</u> flight of stairs	☐1	☐2	☐3

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f Bending, kneeling, or stooping ..... ☐1 ..... ☐2 ..... ☐3

g Walking more than a mile ..... ☐1 ..... ☐2 ..... ☐3

h Walking several hundred yards ..... ☐1 ..... ☐2 ..... ☐3

i Walking one hundred yards ..... ☐1 ..... ☐2 ..... ☐3

j Bathing or dressing yourself ..... ☐1 ..... ☐2 ..... ☐3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	▼	▼	▼	▼	▼
a Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

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5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very Severe
☐1	☐2	☐3	☐4	☐5	☐6

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8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
b Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h Have you been happy?	☐1	☐2	☐3	☐4	☐5
i Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐1	☐2	☐3	☐4	☐5
b I am as healthy as anybody I know	☐1	☐2	☐3	☐4	☐5
c I expect my health to get worse	☐1	☐2	☐3	☐4	☐5
d My health is excellent	☐1	☐2	☐3	☐4	☐5

THANK YOU FOR COMPLETING THESE QUESTIONS!

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HYPOGLYCAEMIA FEAR SURVEY – WORRY SUBSCALE

Adult Low Blood Sugar Survey, University of Virginia

II. Worry: Below is a list of concerns people with diabetes sometimes have about low blood sugar. Please read each item carefully (do not skip any). Circle one of the numbers to the right that best describes how often in the last 6 months you WORRIED about each item because of low blood sugar.

Because my blood sugar could go low, I worried about...

	Never	Rarely	Sometimes	Often	Almost Always
16. Not recognizing/realizing I was having low blood sugar.	0	1	2	3	4
17. Not having food, fruit, or juice available.	0	1	2	3	4
18. Passing out in public.	0	1	2	3	4
19. Embarrassing myself or my friends in a social situation.	0	1	2	3	4
20. Having a hypoglycemic episode while alone.	0	1	2	3	4
21. Appearing stupid or drunk.	0	1	2	3	4
22. Losing control.	0	1	2	3	4
23. No one being around to help me during a hypoglycemic episode.	0	1	2	3	4
24. Having a hypoglycemic episode while driving.	0	1	2	3	4
25. Making a mistake or having an accident.	0	1	2	3	4
26. Getting a bad evaluation or being criticized.	0	1	2	3	4
27. Difficulty thinking clearly when responsible for others.	0	1	2	3	4
28. Feeling lightheaded or dizzy.	0	1	2	3	4
29. Accidently injuring myself or others.	0	1	2	3	4
30. Permanent injury or damage to my health or body.	0	1	2	3	4
31. Low blood sugar interfering with important things I was doing.	0	1	2	3	4
32. Becoming hypoglycemic during sleep.	0	1	2	3	4
33. Getting emotionally upset and difficult to deal with.	0	1	2	3	4

IMPACT OF WEIGHT ON QUALITY OF LIFE QUESTIONNAIRE – LITE VERSION (IWQOL-LITE)

Please answer the following statements by circling the number that best applies to you in the past week. Be as open as possible. There are no right or wrong answers.

Physical Function		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I have trouble picking up objects.	5	4	3	2	1
2.	Because of my weight I have trouble tying my shoes.	5	4	3	2	1
3.	Because of my weight I have difficulty getting up from chairs.	5	4	3	2	1
4.	Because of my weight I have trouble using stairs.	5	4	3	2	1
5.	Because of my weight I have difficulty putting on or taking off my clothing.	5	4	3	2	1
6.	Because of my weight I have trouble with mobility.	5	4	3	2	1
7.	Because of my weight I have trouble crossing my legs.	5	4	3	2	1
8.	I feel short of breath with only mild exertion.	5	4	3	2	1
9.	I am troubled by painful or stiff joints.	5	4	3	2	1
10.	My ankles and lower legs are swollen at the end of the day.	5	4	3	2	1
11.	I am worried about my health.	5	4	3	2	1
Self-esteem		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I am self-conscious.	5	4	3	2	1
2.	Because of my weight my self-esteem is not what it could be.	5	4	3	2	1
3.	Because of my weight I feel unsure of myself.	5	4	3	2	1
4.	Because of my weight I don't like myself.	5	4	3	2	1
5.	Because of my weight I am afraid of being rejected.	5	4	3	2	1
6.	Because of my weight I avoid looking in mirrors or seeing myself in photographs.	5	4	3	2	1
7.	Because of my weight I am embarrassed to be seen in public places.	5	4	3	2	1

Redacted

IWQOL-Lite – English (US).

Sexual Life		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I do not enjoy sexual activity.	5	4	3	2	1
2.	Because of my weight I have little or no sexual desire.	5	4	3	2	1
3.	Because of my weight I have difficulty with sexual performance.	5	4	3	2	1
4.	Because of my weight I avoid sexual encounters whenever possible.	5	4	3	2	1

Public Distress		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I experience ridicule, teasing, or unwanted attention.	5	4	3	2	1
2.	Because of my weight I worry about fitting into seats in public places (e.g. theaters, restaurants, cars, or airplanes).	5	4	3	2	1
3.	Because of my weight I worry about fitting through aisles or turnstiles.	5	4	3	2	1
4.	Because of my weight I worry about finding chairs that are strong enough to hold my weight.	5	4	3	2	1
5.	Because of my weight I experience discrimination by others.	5	4	3	2	1
Work (Note: For homemakers and retirees, answer with respect		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I have trouble getting things accomplished or meeting my responsibilities.	5	4	3	2	1
2.	Because of my weight I am less productive than I could be.	5	4	3	2	1
3.	Because of my weight I don't receive appropriate raises, promotions or recognition at work.	5	4	3	2	1
4.	Because of my weight I am afraid to go on job interviews.	5	4	3	2	1

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IWQOL-Lite – English (US).

Document Name:	d1689c00014-csp-v-4
Document Title:	D1689C00014 Clinical Study Protocol version 4
Document ID:	Doc ID-003101183
Version Label:	4.0 Approved CURRENT LATEST

Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)	**Signed By**	**Meaning of Signature**
19-Jan-2017 12:02 GMT+0000	Redacted	Quality Control Approval
19-Jan-2017 12:13 GMT+0000	Redacted	Clinical Operations Approval
19-Jan-2017 12:33 GMT+0000	Redacted	Medical Monitor Approval
19-Jan-2017 15:22 GMT+0000	Redacted	Biostatistics Approval
24-Jan-2017 14:59 GMT+0000	Redacted	Clinical Approval

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