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Clinical Protocol CV181365

A 52-week International, Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel Group, Phase 3bTrial with a Blinded 104-week Long-term Extension Period to Evaluate the Efficacy and Safety of Saxagliptin Co-administered with Dapagliflozin in Combination with Metformin Compared to Glimepiride in Combination with Metformin in Adult Patients with Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Therapy Alone.

Revised Protocol Number: 04
Incorporates amendment 05

Medical Monitor

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden
Study being conducted by AstraZeneca AB

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 04	08-Feb-2018	Incorporates Amendment 05
Amendment 05	08-Feb-2018	The purpose of this amendment is to provide an update on language for safety (details added regarding the Diabetic Ketoacidosis Adjudication Committee and clarification that local laboratory results will also be monitored for liver function text abnormalities), adverse events (clarification provided for collection and reporting, including those leading to amputation and those with potential risk factor for amputations), confirmed hypoglycemia, magnetic resonance imaging, pregnancy (clarification that study drug will be permanently discontinued in any subjects that become pregnant during the study), blinding, investigational medicinal products, efficacy analyses, rescue therapies, and prohibited treatments; to define the end of the study; and to incorporate administrative changes.
Revised Protocol 03	27-May-2016	Incorporates Amendment 04
Amendment 04	27-May-2016	Provide updated safety information and protocol guidance regarding ketoacidosis, urosepsis and pyelonephritis. Also updated contraceptive language and sub-study clarification on evaluable data.
Revised Protocol 02	12-Aug-2015	Incorporates Amendment 03
Amendment 03	12-Aug-2015	The primary purpose of this amendment is to revise the CrCl discontinuation criteria. In addition changes were made to accommodate internal feedback and comments made by regulatory institutions.
Revised Protocol 01	11-Mar-2015	Incorporates Amendment 02
Amendment 02	11-Mar-2015	The primary purpose of this amendment is to correct information in the Inclusion and Exclusion Criteria regarding glimepiride and to align the current protocol to its sister study, CV181-363.
Original Protocol	26-Jan-2015	Not applicable

SYNOPSIS

Clinical Protocol CV181365

Protocol Title: A 52-week International, Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel Group, Phase 3bTrial with a Blinded 104-week Long-term Extension Period to Evaluate the Efficacy and Safety of Saxagliptin Co-administered with Dapagliflozin in Combination with Metformin Compared to Glimepiride in Combination with Metformin in Adult Patients with Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Therapy Alone.

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Saxagliptin 5 mg and dapagliflozin 10 mg tablets or glimepiride 1-6 mg tablets administered orally once daily for the 156-week blinded treatment period.

Study Phase: 3b

Research Hypothesis: The research hypothesis of the present study is that the co-administration of saxagliptin and dapagliflozin, in addition to metformin, results in better glycemic control, as measured by HbA1c, over a treatment period of 52 weeks, compared to the addition of glimepiride to metformin in subjects with inadequately controlled T2DM.

Objectives:

Primary objective:

To compare the mean change from baseline in HbA1c achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin at Week 52.

Secondary efficacy objectives:

Short-term:

- To compare the mean change from baseline in total body weight achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin at Week 52.
- To compare the proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, at Week 52 with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.
- To compare the mean change from baseline in systolic blood pressure (SBP) achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin at Week 52.
- To compare the time to treatment intensification (addition of insulin or other glucose-lowering agent for rescue therapy or discontinuation for lack of glycemic control) achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin during the 52 week double-blind treatment period.

Long-term:

- To compare the time to treatment intensification (addition of insulin or other glucose-lowering agent for rescue therapy or discontinuation for lack of glycemic control) achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin during the 156 week treatment period.
- To compare the proportion of subjects achieving therapeutic glycemic response, defined as HbA1c < 7.0%, at Week 156 with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.

Exploratory Objectives

Short-term:

- To assess the proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, without any hypoglycemia at Week 52 achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.
- To assess the proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, without any hypoglycemia and weight gain at Week 52 achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.
- To assess mean change from baseline in fasting plasma glucose (FPG) achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin at Week 52.
- To assess change from baseline of metabolic measures (glucagon, C-peptide, pro-insulin, insulin, iHOMA2) at Week 52 achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.
- To assess change from baseline in average glucose values and postprandial glucose values measured by 6-point self-monitored blood glucose (SMBG) profiles at Week 52 achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.
- To assess change from baseline of urinary albumin to creatinine ratio at Week 52 achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.
- To assess change from baseline of biomarkers (high-sensitivity C-reactive protein [hsCRP], N-terminal pro-brain natriuretic peptide [NT Pro-BNP]) at Week 52 of double-blind treatment achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.
- To assess changes in patient-reported treatment satisfaction, quality of life, and barriers to medication adherence achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin at Week 52.
- To assess change from baseline in glycemic variability, as defined by mean amplitude of glycemic excursions (MAGE), in a sub-group using continuous glucose monitoring (CGM) achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin at Week 52 in the subpopulation of subjects who undergo CGM.
- To assess changes from baseline to Week 52 in visceral and subcutaneous adipose tissue volume, and percent hepatic lipid content achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin in the subpopulation of subjects who undergo magnetic resonance imaging (MRI)-estimated proton density fat fraction (PDFF).

Long-term:

- To assess the mean change from baseline in HbA1c achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin at Week 156.
- To assess the time spent at or below HbA1c target (HbA1c < 7.0%) achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin during 156 weeks
- To assess the proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, without any hypoglycemia at Week 156 achieved with saxagliptin, in co-administration with dapagliflozin,

added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.

- To assess the proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, without any hypoglycemia and weight gain at Week 156 achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.
- To assess mean change from baseline in FPG achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin at Week 156.
- To assess change from baseline of metabolic measures (glucagon, C-peptide, pro-insulin, insulin, iHOMA2) at Week 156 achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.
- To assess change from baseline of urinary albumin to creatinine ratio at Week 156 achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.
- To assess change from baseline of biomarkers (high-sensitivity C-reactive protein [hsCRP], N-terminal pro-brain natriuretic peptide [NT Pro-BNP]) at Week 156 achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.
- To compare the mean change from baseline in total body weight achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin at Week 156.
- To compare the mean change from baseline in SBP achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin at Week 156.
- To assess changes in patient-reported treatment satisfaction, quality of life, and barriers to medication adherence achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin at Week 156.
- To assess changes from baseline to Week 122 in visceral and subcutaneous adipose tissue volume and percent hepatic lipid content achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin in the subpopulation of subjects who undergo MRI-PDFF.

Safety objectives

- Confirmed hypoglycemia defined as: blood glucose ≤ 70 mg/dL (3.9 mmol/L) recorded in the hypoglycemia module of the electronic Case Report Form (eCRF) for saxagliptin co-administered with dapagliflozin vs glimepiride at 52 and 156 weeks of therapy.
- To evaluate the safety and tolerability of blinded treatment achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin at 52 and 156 weeks of therapy.

Study Design: This is an international, multicenter, randomized, double-blind, active-controlled, parallel-group Phase 3b study whose primary endpoint is the change from baseline in HbA1c with saxagliptin, in combination with dapagliflozin, on top of background therapy with metformin, compared to glimepiride in combination with metformin. The primary endpoint of HbA1c will be assessed at 52 weeks; however, the trial will continue for 156 weeks as a subject- and site-blinded extension.

Subjects with documented T2DM treated with metformin monotherapy will be enrolled. Subjects will continue to receive background metformin ≥ 1500 mg/day throughout the duration of the study, unless metformin treatment is temporarily withheld due to decreased creatinine clearance (CrCl). All subjects should be treated according to regional standards of care for diabetes.

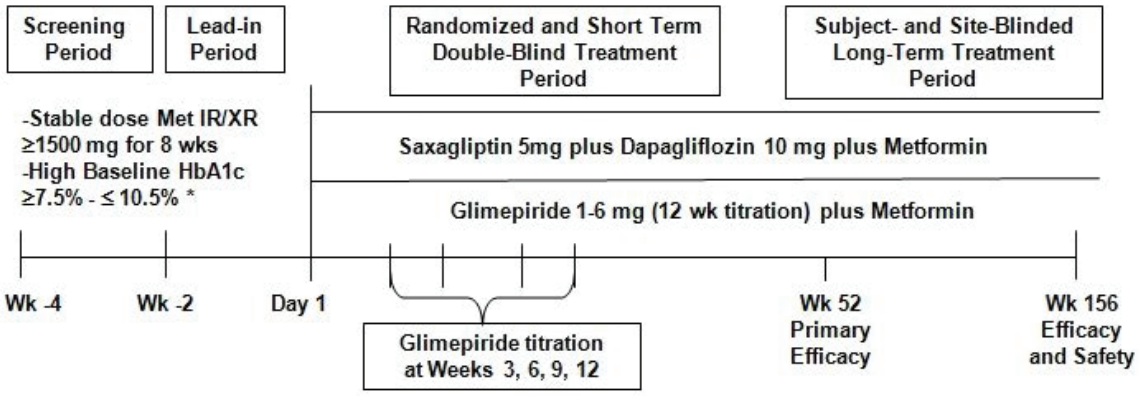
Magnetic Resonance Imaging (MRI) Sub-study: Body composition measurements by MRI can separately quantify the subcutaneous and visceral adipose tissue. Non-invasive quantification of liver lipid content by MRI-estimated proton density fat fraction (PDFF) is an emerging biomarker for assessment of the beneficial effects of weight loss and improvement in glycemic control on liver lipid metabolism.

In this protocol, a subpopulation of approximately 60 randomized subjects (~ 30 subject/treatment arm) who agree to participate (separate informed consent) will undergo MRI-PDFF measurement of subcutaneous and visceral adipose tissue, together with hepatic lipid content, at baseline and Week 52. At Week 122, the subjects will undergo an MRI-PDFF measurement of subcutaneous and visceral adipose tissue, together with liver volume and liver lipid content. Subjects who require rescue therapy or discontinue from treatment early will be asked to return for an unscheduled MRI visit within 4 weeks of initiation of rescue therapy or the Early Termination visit.

Continuous Glucose Monitoring (CGM) Sub-study: CGM is a useful technology (in addition to HbA1c) to qualitatively, as well as quantitatively, monitor the quality of glycemic control in the form of time spent in the euglycemic/hyperglycemic/hypoglycemic ranges (blood glucose ≤ 70 mg/dL (3.9 mmol/L)) and the mean amplitude of glucose excursions (MAGE). Co-administration of saxagliptin and dapagliflozin is expected to demonstrate less variability in glycemic control and more time spent in the euglycemic range compared to treatment with glimepiride.

In this protocol, a subpopulation of approximately 120 randomized subjects (~ 60 subject/treatment arm) who agree to participate (separate informed consent) will have CGM performed for periods of 7 days at baseline (between Week - 2 and Week - 1 [ie, prior to receiving study medication]) and at Week 52 of treatment.

Study Schematic:



Study Population: Subjects should be selected without bias. Each subject on stable background therapy with metformin monotherapy should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be any exceptions to this rule. All subjects who were screened and have submitted a blood sample should be listed on the subject enrollment and identification log. Investigator(s) must keep a record of subjects who entered pre-trial screening but were never enrolled.

Subjects will be enrolled globally, including representation from North America and Europe.

Study Drug: includes both Investigational Medicinal Products (IMP) and Non-investigational Medicinal Products (Non-IMP) as listed:

Study Drug for CV181365		
Medication	**Potency**	**IMP/Non-IMP**
Dapagliflozin	10 mg	IMP
Matching placebo for dapagliflozin	0 mg	IMP
Saxagliptin	5 mg	IMP
Matching placebo for saxagliptin	0 mg	IMP
Glimepiride	1-6 mg (titrated)	IMP
Matching placebo for glimepiride	0 mg	IMP

Dapagliflozin, saxagliptin, glimepiride and their matching placebo tablets/capsules will be packaged in bottles. The tablets/capsules may contain lactose, which may cause discomfort in lactose-intolerant individuals.

Dose and treatment regimens Blinded Study Medication

Saxagliptin 5 mg tablets or matching placebo tablets, administered orally once daily, will be provided for the 156-week blinded treatment period. Saxagliptin 5 mg is the maximum recommended daily dose. No up- or down-titration of saxagliptin will be allowed.

Dapagliflozin 10 mg tablets or matching placebo tablets, administered orally once daily, will be provided for the 156-week blinded treatment period. Dapagliflozin 10 mg is the maximum recommended daily dose. No up- or down-titration of dapagliflozin will be allowed.

Glimepiride 1-6 mg or matching placebo capsules, administered orally once daily, will be provided for the 156-week blinded treatment period. During the first 12 weeks, the glimepiride/placebo dose will be slowly titrated in a stepwise blinded fashion depending on glycaemic control. For the duration of the study, FPG will be measured at the study center using a glucose analyzer provided by the Sponsor. The investigator's decision on dose titration (either upwards or downwards) will take both the plasma glucose measurements (measured prior to the visit), and the investigator's measurements at the titration visits, into account. The glimepiride/placebo dose will be titrated to optimal effect (FPG $\leq$ 110 mg/dL [$<$ 6.1 mmol/L]) or the highest tolerable dose during the first 12 weeks. The starting dose for glimepiride/placebo is 1 mg per day (once daily), which can be further increased by increments of 1-2 mg at 3-week intervals to a maximum of 6 mg per day (maximum recommended dose as per the Summary of Product Characteristics and thus the maximum dose to be used in this study). The titration steps will be 2 mg, 3 mg, 4 mg, and 6 mg once daily if needed. In subjects for whom titration is not medically indicated at Week 3, re-assessment for titration will occur at Week 6, Week 9, and Week 12.

The glimepiride/placebo dose can be down-titrated during the titration period if hypoglycemic events occur. The treatment can thereafter be up-titrated once during the titration period. Subjects reaching the 6 mg dose at Week 12 will have a follow-up phone call 3 weeks later. The glimepiride dose can be down-titrated from Week 12 onwards (maintenance period) if hypoglycemic events occur.

During the randomized treatment period, diet and life-style modification will continue to be reinforced.

All randomized subjects rescued with insulin and taking randomized investigational medicinal product (IMP) should continue scheduled study visits as planned in the Time and Events Table (Section 5).

Subjects who decide to prematurely discontinue the IMP will always be asked about the reason(s) for discontinuation and the presence of any adverse events (AEs). Subjects should return and complete the procedures described for the End of Treatment (EOT) visit as soon as possible, but at the latest 7 days after discontinuation of IMP. Subjects with unresolved AEs should also be followed-up as long as medically indicated as judged by investigator.

All subjects who discontinue from treatment should also comply with protocol-specified follow up procedures. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

Subjects lost to follow-up are defined by: 1) unable to reach after three documented phone calls, fax, email or attempts to contact him/her through subject locator agencies (if allowed per national regulation); and 2) having sent one letter by registered/certified mail. All should be documented in the subject's medical records.

Concomitant and other treatments

Treatment with sulfonylureas (other than IMP), pioglitazone, rosiglitazone, glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors other than IMP, and any sodium glucose co-transporter 2 (SGLT2) inhibitors other than IMP is not permitted for the duration of the study.

Other concomitant treatment

Medication other than that described above, which is considered necessary for the subject's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the Case Report Form (CRF).

In addition, all new or changed concomitant medications that the subject is treated with when an AE (Section 6.7) occurs needs to be recorded on a specific eCRF page, regardless of the treatment duration. Note that this should also apply to concomitant medications which have been discontinued before the start of the AE, if judged as important by the investigator.

Study Assessments:

Efficacy assessments

Assessments consist of the central laboratory measurement of HbA1c and other relevant laboratory tests, collected during the study.

A core laboratory evaluates all MRI measurements centrally. No local evaluation will be performed. Results of MRI measurements will be blinded to investigators, MRI sites, subjects, and the Sponsor during the duration of the study.

MRI

Body composition will be measured with MRI using a body scan based on the Dixon method with multiple gradient-echoes and multislice acquisition centered at the L4-L5 interface. All acquisitions will be performed using clinical MRI scanners with the subjects in the supine position. The analysis will be done centrally using semi-automated software that will give visceral, subcutaneous, and total fat volume as output in liters (l).

Liver lipid content will be calculated from a separate scan covering the liver using the Dixon technique giving liver lipids as output in percent (%).

Safety assessments

Self monitored blood glucose (SMBG) and reporting of hypoglycemia

Glucose meters will be supplied to each study site. At the lead-in period, subjects will receive a glucose meter, supplies, and instruction on their use. Supplies will be provided to allow for approximately 60 blood glucose assessments per month for the duration of the study. The investigator may require more frequent readings based on local clinical practice. Subjects should bring their glucose meter with them to each study visit to ensure that it is functioning properly.

Subjects should self-monitor their blood glucose approximately two times per day and when symptoms suggestive of hypoglycemia occur. All subjects will also be asked to perform 3 days of 6-point SMBG (do not have to be consecutive) between Week -2 and Week -1 (ie, prior to the Day 1/Randomization visit), and between Week 51 and Week 52, with capillary blood glucose measurements taken prior to and after the three main meals of the day. Study subjects should contact the investigator in the event of an unusually high or low blood glucose value.

The investigator may require more frequent readings based on local clinical practice. In addition, study subjects should comply with the site's instructions with regard to self monitoring of blood glucose and should promptly report blood glucose values and/or signs and symptoms suggestive of a hypoglycemic episode to the site.

The glucose values should be reviewed by the site to identify any unusual high or low values, and to confirm that the values (from the glucose meter's memory and/or from the subject's hypoglycemia log diary) were obtained for the subject. If fingerstick glucose values are discordant from glycemic control assessed by the central laboratory or with clinical symptoms, the subject's glucose meter should be tested and the procedure for using it reviewed with the subject. Additionally, other potential factors that may account for the discrepancy between glucose meter measurements and central laboratory measurements, such as variation with alternate site testing, hypotension (decreased perfusion), variation in hematocrit, and hemolysis should be also considered.

Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in the protocol.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

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 the site as source data for laboratory variables.

Subjects with a central laboratory alaninine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 3x the upper limit of normal (ULN) will be scheduled for a follow-up visit within 3 days following the receipt of the result (see Appendix 4 for further guidance). Subjects should be discontinued from study if the initial and repeat laboratory tests meet any of the following criteria:

- ALT and/or AST are > 3x ULN and total bilirubin (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 ≥ 10x ULN

Statistical Considerations:

Sample Size Estimates: Assuming a mean change from baseline in HbA1c difference effect of 0.35% for the saxagliptin/dapagliflozin plus metformin vs glimepiride plus metformin groups, a common standard deviation of 1.1%, and using a 2-sided significance level of 0.05, and assuming a 5% non-evaluability rate, then a sample size of 220 subjects per arm will yield approximately 90% power.

# Screened	980 (50% SF)
# Enrolled	490 (10% EF)
# Randomized	440 (5% Rand Drop)

Endpoints and Analysis:

The primary endpoint for analysis is change from baseline to week 52 in HbA1c.

A repeated measures analysis (using a MIXED model) will be used to analyze the change from baseline in HbA1c at Week 52 using values prior to rescue/intensification of treatment. The model will contain terms for treatment group, baseline measurement, time (each relevant visit), the interaction of treatment and time, and the interaction of baseline value and time. Descriptive statistics as well as adjusted means and 95% confidence intervals will be calculated for the change from baseline in HbA1c, as well as for the difference between treatment groups.

The primary endpoint analysis will be repeated using all available values, including those after rescue/intensification and also using all available data and including a time varying covariate which indicates rescue status.

The comparator (glimepiride) will be tested against saxagliptin/dapagliflozin for the primary endpoint at the alpha = 0.05 level (2-sided). The secondary endpoints (described below) will then be tested sequentially. Each comparison will be tested at the alpha = 0.05 (2-sided) level.

Secondary endpoints for analysis for the short-term treatment period include:

- Mean change from baseline in total body weight at Week 52
- Proportion of subjects achieving a therapeutic glycemic response (HbA1c < 7.0 %) at Week 52.
- Mean change from baseline in systolic blood pressure (SBP) at Week 52.
- Time to treatment intensification (addition of insulin or other glucose-lowering agents for rescue therapy or discontinuation for lack of glycemic control) during the 52-week double-blind controlled treatment period.

Secondary endpoints for analysis for the long-term treatment period include:

- Time to treatment intensification (addition of insulin or other glucose-lowering agents for rescue therapy or discontinuation for lack of glycemic control) during the 156-week treatment period.
- Proportion of subjects achieving therapeutic glycemic response (HbA1c < 7.0%) at Week 156.

Analyses:

The analysis of change from baseline for total body weight and systolic blood pressure will be performed using the same longitudinal repeated measures model as for the primary efficacy endpoint.

The proportion of subjects achieving a therapeutic glycemic response (defined as HbA1c < 7.0%) will be summarized by treatment group and compared between treatment groups using logistic regression with adjustment for baseline HbA1c. 95% confidence intervals for the response rate within each treatment group, odds ratio, and 95% confidence intervals for odds ratio will be calculated.

Time to treatment intensification will be analyzed using a Cox proportional hazards model. Estimates of the hazard ratio and 95% confidence intervals will be provided. Kaplan-Meier Estimates will be calculated and plotted by treatment group.

Safety analyses will be performed for the 52-week double-blind period and combined short-term and long-term subject- and sited-blinded treatment periods, including data after rescue. Additional analyses for adverse events and laboratory marked abnormalities will be performed excluding data after rescue for the short-term double-blind treatment period. The primary analyses of events of hypoglycemia will be performed excluding data after rescue.

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1 INTRODUCTION AND STUDY RATIONALE

Type 2 diabetes mellitus (T2DM) is a chronic disease characterized by hyperglycemia and an increased risk of microvascular and macrovascular complications. Given the progressive nature of T2DM, it is challenging to achieve and maintain glycemic targets. Typically the treatment paradigm consists of a step-wise addition of different classes of antihyperglycemic drugs, as most patients eventually require two or more agents to achieve or maintain glycemic targets. Among the medications approved for the treatment of T2DM, metformin is the recommended drug of choice for initiating oral therapy, while other classes of antidiabetic agents are typically added sequentially as second and third line agents. Despite the availability of multiple classes of medications, many patients are still inadequately controlled. An ideal add-on to metformin would provide strong HbA1c reduction through complementary mechanisms of action (MoA), with weight loss, and no hypoglycemia.

Saxagliptin (BMS-477118) is a highly potent, selective, reversible, and competitive dipeptidyl peptidase 4 (DPP4) inhibitor. DPP4 is the enzyme responsible for the inactivation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). By inhibiting the enzyme DPP4, saxagliptin potentiates active endogenous GLP-1 concentrations, augmenting the physiological mechanism of insulin secretion and suppressing glucagon release, thereby reducing postprandial and fasting glucose levels in patients with T2DM.

The results from the eight clinical studies in the saxagliptin Phase 2b and 3 programs in over 4600 patients, combined with the results from clinical pharmacology studies, support the oral dose of saxagliptin 5 mg once daily in a wide range of patients with T2DM, as either monotherapy, add-on combination therapy with metformin, a thiazolidinedione (TZD), a sulfonylurea (SU), insulin, or initial combination therapy with metformin. The results from the Phase 3 studies confirmed clinically meaningful benefits of saxagliptin 5 mg on glycosylated hemoglobin (HbA1c), as well as fasting plasma glucose (FPG), postprandial glucose (PPG), insulin, C-peptide, and glucagon levels. In an extensive Phase 2b/3 program, most reported adverse events (AEs) were non-serious and did not require discontinuation of treatment. The safety profile was comparable to placebo and generally consistent when saxagliptin was given as monotherapy, as add on combination treatment to metformin, to insulin (with or without background metformin), and as initial therapy in combination with metformin. Treatment with saxagliptin led to rates of hypoglycemia that were generally similar compared to placebo, except in combination with insulin or a sulfonylurea.

Dapagliflozin is a stable, competitive, reversible, highly selective, and orally active inhibitor of human renal sodium glucose co-transporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption in the kidney. Dapagliflozin's mechanism of action results in the direct and insulin-independent elimination of glucose by the kidney.

The dapagliflozin clinical development program was designed to demonstrate the safety and efficacy of dapagliflozin in a wide range of subjects with T2DM. The program included both placebo-controlled and active comparator studies in drug naïve patients at an early stage of

disease and subjects who require additional therapy after failure to reach adequate glycemic control with their current regimen. To date, the program has consisted of a total of 28 clinical pharmacology studies, 5 core Phase 2b studies, 16 core Phase 3 studies, and 3 regional Phase 3 studies. One Phase 2b study (MB102009) and one Phase 3 study (D1690C00006) specifically focused on the safety and efficacy of dapagliflozin when added on to insulin in subjects with T2DM.

Dapagliflozin's pharmacodynamic effect of glucosuria is detected almost immediately (within 1 hour post-dose), is maintained through 104 weeks of treatment, and results in reductions in FPG, PPG, and HbA1c. Clinically meaningful reductions in HbA1c were consistently observed with dapagliflozin 10 mg. Treatment with dapagliflozin, with its unique mechanism of action, induces a persistent loss of glucose with associated calories in the urine, resulting in a consistent and maintained reduction of total body weight, in addition to improved glycemic control. In a 24-week study, dapagliflozin 10 mg reduced total body weight, predominantly by reducing fat mass, visceral adipose tissue, and subcutaneous adipose tissue in subjects with T2DM inadequately controlled with metformin.[1] Dapagliflozin also has a mild diuretic effect, which in combination with weight loss, has the potential to reduce blood pressure. Across 11 clinical studies, treatment with dapagliflozin 10 mg decreased the placebo-corrected systolic blood pressure by an average of 1.3 to 5.3 mmHg from baseline at 24 weeks in all of the monotherapy and placebo-controlled add-on combination therapy studies (DAPA CCDS).

Given their complementary mechanisms of action, saxagliptin, co-administered with dapagliflozin, has been studied to support the development of a fixed-dose combination (FDC). A Phase 3 study (CV181169) demonstrated that early combination treatment with saxagliptin and dapagliflozin, 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 subjects with inadequately controlled T2DM. The current study seeks to expand on these findings and provide further support for early intensified treatment of T2DM.

1.1 Study Rationale

This is a Phase 3b study performed as part of the development program for saxagliptin/ dapagliflozin FDC (BMS-986098) to improve glycemic control as an adjunct to diet, exercise, and metformin treatment when treatment with both saxagliptin and dapagliflozin is appropriate.

The study is intended to compare effects of: 1) saxagliptin co-administered with dapagliflozin in combination with metformin; and 2) glimepiride in combination with metformin.

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 is the first-line gold standard for oral agents. Metformin is a biguanide; its major mechanism of action is to decrease hepatic glucose output, thus lowering fasting hyperglycemia. Metformin is recommended as the initial pharmacological therapy because of its glycemic efficacy, weight neutrality, low risk of hypoglycemia and

beneficial cardiovascular (CV) profile. Current sequential add-on 2nd and 3rd line oral therapy includes oral drugs such as sulfonylureas (SUs) and thiazolidinediones (TZDs). Some of their key limitations are weight gain and increased risk of hypoglycemia (SU only). Hypoglycemia is a clinically important issue in optimizing treatment and there is emerging evidence that hypoglycemia is associated with negative CV outcomes. Sulfonylureas (and insulin) are associated with a high risk for hypoglycemia and caution is recommended when using combination therapy with other agents known to cause hypoglycemia. Efforts by patients to lose weight as part of a therapeutic lifestyle program are undermined by therapies that lead to weight gain. The majority of patients with T2DM are overweight or obese, and additional weight gain often results in reduced treatment compliance. Thiazolidinediones, SUs and insulin, are all associated with a significant weight gain.

Over the past few years, it has been widely recognized that the management approach for each patient with T2DM needs to be personalized based on his or her clinical characteristics: for example, the likelihood of weight gain, comorbidities such as the risk for hypoglycemia, as well as lifestyle preferences (many patients may be reluctant to use injections).[2] Based on data from the National Health and Nutrition Examination Survey (NHANES) in 2007–2010, it is estimated that HbA1c is not appropriately controlled in about one-third of patients, even using less stringent targets.[3]

Because of the challenge to achieve glycemic control in patients with T2DM, the progressive nature of the disease, and the limitations of available oral and non-oral therapies, there is a significant medical need, not only for oral combination treatment options, but also for dual add-on therapy in patients with high baseline HbA1c. To improve glycemic control, expert groups have increasingly suggested making use of combination therapy early after diagnosis.[4,5] In a recent study, initiating therapy in patients with new onset T2DM with triple therapy (pathophysiologic-based approach) versus metformin, followed by sequential addition of sulfonylurea and basal insulin (treat-to-fail approach), demonstrated more durable HbA1c reduction over 24 months and less hypoglycemia with initial triple therapy.[6] Initial combination therapy with saxagliptin and dapagliflozin added to metformin may have similar potential for durable glucose lowering in combination with low risk of hypoglycemia.

Saxagliptin and dapagliflozin have demonstrated, both individually and in combination with metformin, a favorable safety and tolerability profile. They have demonstrated a low propensity for hypoglycemia, therefore addressing a potential key concern when adding two glucose lowering agents simultaneously. Both drugs have either demonstrated weight neutrality (saxagliptin) or moderate weight reduction (dapagliflozin). Both dapagliflozin and saxagliptin have also demonstrated persistent effects on HbA1c over 2 years of therapy.

The reduction in body weight consistently observed during treatment dapagliflozin has been shown to result in total body fat reduction. It is not known, however, whether this reduction in body fat is equally distributed among subcutaneous and visceral adipose tissue or if there is a preferential loss of adipose tissue in the visceral compartment. Body composition measurements by magnetic resonance imaging (MRI) can separately quantify the subcutaneous and the visceral

adipose tissue. Non-invasive quantification of liver lipid content by magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF) is an emerging biomarker for assessment of the beneficial effects of weight loss and improvement in glycemic control on liver lipid metabolism.

In this protocol, a subpopulation of approximately 60 randomized subjects (~ 30 subject/treatment arm) who agree to participate (separate informed consent) will undergo MRI-PDFF measurement of subcutaneous and visceral adipose tissue, together with liver lipid content at baseline and Week 52. At Week 122, the subjects will undergo an MRI-PDFF measurement of subcutaneous and visceral adipose tissue, together with liver volume and liver lipid content.

Continuous Glucose Monitoring (CGM) is a useful technology (in addition to HbA1C) to qualitatively, as well as quantitatively, monitor the quality of glycemic control in the form of time spent in the euglycemic/hyperglycemic/hypoglycemic (blood glucose ≤ 70 mg/dL; (3.9 mmol/L)) ranges and the mean amplitude of glucose excursions (MAGE). Co-administration of saxagliptin and dapagliflozin is expected to better demonstrate less variability in glycemic control and more time spent in the euglycemic range compared to treatment with glimepiride administration.

In this protocol, a subpopulation of approximately 120 randomized subjects (~ 60 subject/treatment arm) who agree to participate (separate informed consent) will have CGM performed for periods of 7 days at baseline and at Week 52 of treatment.

Thus, a second-line oral dual add-on therapy with saxagliptin, co-administered with dapagliflozin, could be a new option, as part of a triple combination that includes drugs with complementary mechanisms of action, low risk of hypoglycemia, and the potential for moderate weight loss, providing a more effective and patient-friendly approach to the treatment of T2DM.

1.2 Research Hypothesis

The research hypothesis of the present study is that the co-administration of saxagliptin and dapagliflozin, in addition to metformin, results in better glycemic control, as measured by HbA1c, over a treatment period of 52 weeks, compared to the addition of glimepiride to metformin in subjects with inadequately controlled T2DM.

1.3 Objectives(s)

1.3.1 Primary Objectives

To compare the mean change from baseline in HbA1c achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin at Week 52.

1.3.2 Secondary Objectives

Secondary efficacy objectives:

Short-term:

- To compare the mean change from baseline in total body weight achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin at Week 52.
- To compare the proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, at Week 52 with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.
- To compare the mean change from baseline in systolic blood pressure achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin at Week 52.
- To compare the time to treatment intensification (addition of insulin or other glucose-lowering agent for rescue therapy or discontinuation for lack of glycemic control) achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin during the 52 week double-blind treatment period.

Long-term:

- To compare the time to treatment intensification (addition of insulin or other glucose-lowering agents for rescue therapy or discontinuation for lack of glycemic control) achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin during the 156 week treatment period.
- To compare the proportion of subjects achieving therapeutic glycemic response, defined as HbA1c < 7.0%, at Week 156 with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin

1.3.3 Exploratory Objectives

Short-term:

- To assess the proportion of subjects achieving therapeutic glycemic response, defined as HbA1c < 7.0%, without any hypoglycemia at Week 52 achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.
- To assess the proportion of subjects achieving therapeutic glycemic response, defined as HbA1c < 7.0%, without any hypoglycemia and weight gain at Week 52 achieved with

saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.

- To assess mean change from baseline in FPG achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin at Week 52.
- To assess change from baseline of metabolic measures (glucagon, C-peptide, pro-insulin, insulin, iHOMA2) at Week 52 achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.
- To assess change from baseline in average glucose values and postprandial glucose values measured by 6-point self-monitored blood glucose (SMBG) profiles at Week 52 achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.
- To assess change from baseline of urinary albumin to creatinine ratio at Week 52 achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.
- To assess change from baseline of biomarkers (high-sensitivity C-reactive protein [hsCRP], N-terminal pro-brain natriuretic peptide [NT Pro-BNP]) at Week 52 of double-blind treatment achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.
- To assess changes in patient-reported treatment satisfaction, quality of life, and barriers to medication adherence achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin at Week 52.
- To assess change from baseline in glycemic variability, as defined by mean amplitude of glycemic excursions (MAGE), in a sub-group using CGM achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin at Week 52 in the subpopulation of subjects who undergo CGM.
- To assess changes from baseline to Week 52 in visceral and subcutaneous adipose tissue volume, and percent hepatic lipid content achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin in the subpopulation of subjects who undergo MRI-PDFF.

Long-term:

- To assess the mean change from baseline in HbA1c achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin at Week 156.

- To assess the time spent at or below HbA1c target (HbA1c < 7.0%) achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin during 156 weeks.
- To assess the proportion of patients achieving therapeutic glycemic response, defined as HbA1c < 7.0%, without any hypoglycemia at Week 156 achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.
- To assess the proportion of patients achieving therapeutic glycemic response, defined as HbA1c < 7.0%, without any hypoglycemia and weight gain at Week 156 achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.
- To assess mean change from baseline in FPG achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin at Week 156.
- To assess change from baseline of metabolic measures (glucagon, C-peptide, pro-insulin, insulin, iHOMA2) at Week 156 achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.
- To assess change from baseline of urinary albumin to creatinine ratio at Week 156 achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.
- To assess change from baseline of biomarkers (high-sensitivity C-reactive protein [hsCRP], N-terminal pro-brain natriuretic peptide [NT Pro-BNP]) at Week 156 achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin.
- To compare the mean change from baseline in total body weight achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin at Week 156.
- To compare the mean change from baseline in systolic blood pressure achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin at Week 156.
- To assess changes in patient-reported treatment satisfaction, quality of life, and barriers to medication adherence achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin at Week 156.
- To assess changes from baseline to Week 122 in visceral and subcutaneous adipose tissue volume and percent hepatic lipid content achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to

glimepiride added to current background therapy with metformin in the subpopulation of subjects who undergo MRI-PDFF.

1.3.4 Exploratory Safety Objectives

- Confirmed hypoglycemia defined as: blood glucose ≤ 70 mg/dL (3.9 mmol/L) recorded in the hypoglycemia module of the electronic Case Report Form (eCRF) for saxagliptin co-administered with dapagliflozin vs glimepiride at 52 and 156 weeks of therapy.
- To evaluate the safety and tolerability of treatment achieved with saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, compared to glimepiride added to current background therapy with metformin at 52 and 156 weeks of therapy.

1.4 Product Development Background

Dapagliflozin has been designed as a potent and selective inhibitor of the renal sodium-glucose transporter, SGLT-2. Multiple phase 2 and phase 3 studies, where dapagliflozin was used as monotherapy or in combination with other oral hypoglycemic agents or insulin in subjects with T2DM, have shown that dapagliflozin is associated with a significant reduction of HbA1c from baseline compared to placebo (0.4 - 0.56% and 0.54 - 0.68% for the 5 and 10 mg doses, respectively).

Results from Studies MB102009 and D1690C00006, where dapagliflozin was added in subjects with T2DM receiving high doses of insulin, confirmed that dapagliflozin was effective in lowering A1C when combined with insulin in this population (HbA1c reduction of 0.6% relative to placebo).

Overall, dapagliflozin as monotherapy and in combination with other antidiabetic agents (metformin, SU, TZD, insulin) was generally safe and well tolerated in subjects with T2DM. In Phase 2/3 studies, the frequency of overall adverse events (AEs) was similar to placebo. Most AEs were mild or moderate in intensity and resolved while continuing treatment. No clinically relevant changes from baseline were seen in either renal function or serum electrolytes in subjects treated with dapagliflozin. The frequency of genital infections and urinary tract infections was higher in subjects treated with dapagliflozin. Most of the genital infections and urinary tract infections were mild-to-moderate in intensity and were easily treatable.

Besides data obtained from subjects with T2DM, results from Study MB102072, where dapagliflozin was added to insulin therapy in subjects with T1DM, showed that dapagliflozin 5 mg and 10 mg may improve glycemic control during a 2-week study period. In this pilot study, adverse events, including hypoglycemia and genitourinary infections, were generally balanced across treatment groups.

Additional clinical safety and efficacy information is available in the Investigator Brochure.

1.5 Overall Risk/Benefit Assessment

Saxagliptin and dapagliflozin, as well as their metformin fixed-dose combinations, have been approved as antidiabetic agents in many countries, including the United States (US) and the European Union (EU). Clinical studies with the combination of saxagliptin and dapagliflozin are ongoing.

Considering the complementary mechanism of action, 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 will cause a minimal and acceptable risk to the individual subjects. The frequent follow-up visits and dietary consultation may result in improved glycemic control, compared with not participating in the trial.

Saxagliptin

Prior to approval, saxagliptin was evaluated in 6 core Phase 3, randomized, double-blind controlled trials. Compared to control, treatment with saxagliptin at doses of 2.5 mg 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 including age, gender, race and baseline body mass index (BMI).

Overall, saxagliptin has been well tolerated in clinical studies. The majority of AEs reported in clinical studies have been of mild intensity and few have required treatment discontinuation. The following identified risks are included in the Risk Management Plan for saxagliptin: hypersensitivity reactions, pancreatitis, and infections. The following potential risks include lymphopenia, hypoglycemia, cardiac failure leading to hospitalization, and severe cutaneous adverse reactions.

When added to standard of care in patients with T2DM at high CV risk, saxagliptin neither reduced nor increased the risk of the primary composite endpoint of CV death, myocardial infarction (MI), or ischemic stroke in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) trial.[7]

Hypersensitivity reactions

Hypersensitivity reactions are classified as an identified risk based on the analysis of clinical trial data and reports of hypersensitivity, primarily of spontaneous origin, in the post- marketing setting. These findings may represent a class effect for DPP4 inhibitors.

Pancreatitis

These events have been reported with DPP4 inhibitors, including saxagliptin. Reports of pancreatitis have been received in the post-marketing setting, primarily of spontaneous origin, although a causal association has not been established. However, no excess of pancreatitis was identified in the controlled clinical trials experience, or a significant increase from placebo in the SAVOR CV outcomes trial.

Infections

These are potentially a class effect. The specific infections generally associated with the use of saxagliptin 5 mg were upper respiratory infection, urinary tract infection, sinusitis, and gastroenteritis. These are listed as common reactions in the product labeling.

Lymphopenia

The frequency of investigator-reported AEs of lymphopenia was similar for patients who received saxagliptin and placebo. Mean lymphocyte counts remained stable and within normal limits with daily dosing up to 102 weeks in duration. Overall, a small decrease in mean absolute lymphocyte count was observed at doses of saxagliptin of 5 mg and above. This decrease in lymphocyte count does not appear to result in the selective loss of a particular population of lymphocytes, be related to a defect in proliferation, or in the increased destruction of lymphocytes. While the clinical significance of the decreases in lymphocyte count relative to placebo is not known, the reductions were not associated with clinically relevant adverse events or opportunistic infections.

Hypoglycemia

Treatment with saxagliptin led to rates of hypoglycemia that were generally similar to placebo, except in combination with a SU or insulin. This is consistent with the mechanism of action of DPP4 inhibitors, which exert their insulinotropic effects on the β-cell in a glucose-dependent manner.

Gastrointestinal-related AEs

Gastroenteritis and vomiting are the two gastrointestinal-related events that presented with higher incidences than those of the placebo/comparators and are listed as common reactions in the product labeling.

Cardiovascular outcomes

A recent large, randomized placebo-controlled CV outcomes study (SAVOR) was conducted in individuals with T2DM and either a history of CV disease or multiple risk factors for vascular disease. Saxagliptin neither increased nor decreased the frequency of a combined cardiovascular endpoint of CV death, MI, or stroke.

In summary, the clinical safety and efficacy data accumulated to date demonstrates a positive benefit / risk profile for saxagliptin.

Dapagliflozin

Dapagliflozin is approved in approximately 40 countries including the US and EU. Prior to approval, dapagliflozin was evaluated in 5 core Phase 2b studies, 16 core Phase 3 studies, and 3 regional Phase 3 studies. These studies established that dapagliflozin is effective in reducing HbA1c in a broad range of subjects, 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 three doses typically studied

(2.5, 5, and 10 mg). Overall, the dose of 10 mg provided better efficacy than the two lower doses. Effects on secondary glycemic 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 blood pressure. Placebo-controlled data for up to 2 years indicate that the beneficial effects on glycemic and non-glycemic parameters were maintained.

Overall, dapagliflozin has been well tolerated in clinical studies. Included in the Risk Management Plan for dapagliflozin are the identified risks of genital infections and urinary tract infections. Potential risks include hypoglycemia, volume depletion, clinical consequences related to an increase in hematocrit, renal impairment/failure, bone fracture, liver injury, bladder cancer, and breast cancer.

Hypersensitivity reactions

Hypersensitivity reactions are classified as an identified risk based on the analysis of clinical trial data and reports of hypersensitivity, primarily of spontaneous origin, in the post- marketing setting.

Genital tract infections

There was a slightly increased frequency of genital infections with dapagliflozin, which is likely a consequence of urinary glucose favoring the growth of microbial pathogens. These infections were more frequently reported in females and were generally not serious, were easily treated, and rarely led to discontinuation.

Urinary tract infections

There was a slightly increased frequency of urinary tract infections and cystitis, primarily in females. Most responded to standard treatments. There have also been post-marketing reports of serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization in patients receiving dapagliflozin and other SGLT2 inhibitors.

Hypoglycemia

Consistent with its insulin-independent mechanism, dapagliflozin showed a low propensity for causing hypoglycemia. However, when used in combination with agents known to cause hypoglycemia, such as SUs or insulin, an increase in the frequency of hypoglycemic events was observed.

Volume depletion, hematocrit, renal impairment/failure

Consistent with its diuretic effect, there was a trend towards a reduction in mean systolic and diastolic blood pressure in dapagliflozin-treated subjects. However, the diuretic action of dapagliflozin is relatively mild and serious adverse events related to volume depletion (including reports of dehydration, hypovolemia, or hypotension) were few (0.2%) and balanced between treatment groups across the clinical study program. In addition, no clinically meaningful changes in serum electrolytes, such as sodium and potassium, were observed. As expected, polyuria and pollakiuria were more often reported with dapagliflozin than for comparator or placebo. Small

increases in mean hematocrit were also observed, also likely related to the diuretic effect of dapagliflozin and a consequent reduction in plasma volume, but were not associated with any imbalance in thromboembolic events between dapagliflozin and comparator. A clinically insignificant early decrease in estimated glomerular filtration rate (eGFR) with subsequent return to baseline was observed with dapagliflozin therapy. There were no cases of tubulonecrosis or other nephrotoxic effects, and no evidence of progressive renal dysfunction in the clinical development program.

Bone fracture

In the overall dapagliflozin clinical program, there was no imbalance in the frequency of bone fractures with up to 4 years of treatment between dapagliflozin and placebo.

Liver injury

There was also no evidence of an association of dapagliflozin therapy with liver toxicity and no evidence of severe drug-induced liver injury. Similar proportions of subjects with elevations of liver enzymes were seen in dapagliflozin- and placebo-treated subjects across the Phase 2b and 3 studies.

Malignancies

During clinical trials, the overall proportion of subjects with malignant or unspecified tumors was similar between those treated with dapagliflozin (1.50%) and placebo/comparator (1.50%), and there were no carcinogenicity or mutagenicity signals in animal data. When considering the cases of tumors occurring in the different organ systems, the relative risk associated with dapagliflozin was above 1 for some tumors (bladder, prostate, breast) and below 1 for others (eg, blood and lymphatic, ovary, renal), not resulting in an overall increased tumor risk associated with dapagliflozin. The risk was not statistically significant for any organ system. Considering the lack of tumor findings in non-clinical studies, as well as the short latency between first drug exposure and tumor diagnosis in the clinical program, a causal relationship to dapagliflozin is considered unlikely. The imbalance of breast, bladder, and prostate tumors will be further investigated in post-authorisation studies and has been included in the Risk Management Plan for dapagliflozin.

A pre-specified CV safety meta-analysis of confirmed, adjudicated events demonstrated no CV harm with dapagliflozin treatment. There is an ongoing large, randomized, placebo-controlled cardiovascular outcomes study (DECLARE) to explore if dapagliflozin, when added to subjects' current anti-diabetes therapy, is effective in reducing CV events (MI, ischemic stroke, and CV-related death), compared with placebo.

Ketoacidosis

There have been postmarketing reports of ketoacidosis, including diabetic ketoacidosis (DKA), 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.

In summary, evaluation of the clinical safety and efficacy data accumulated so far indicates a positive benefit/risk profile for dapagliflozin.

Glimepiride

Glimepiride, a sulfonylurea, is a widely used anti-diabetic treatment. Glimepiride will be prescribed according to its approved label. Data from clinical trials indicate that the overall incidence of adverse events associated with glimepiride is generally lower compared with other SUs, including a lower risk of hypoglycemia and weight gain.[8]

Protection against risks

The present study has been designed with appropriate measures to monitor and minimize any potential health risks to participating subjects. To ensure patient safety, the Sponsor will conduct a real-time review of all safety information from all ongoing clinical saxagliptin and dapagliflozin 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 reports, pre-clinical data, epidemiological studies, and literature reports, to identify and characterize unrecognized safety risks or changes in those which are currently expected Adverse Drug Reactions (ADRs). Any information that may affect the benefit-risk profile of saxagliptin and dapagliflozin will be immediately communicated to relevant Health Authorities and appropriate actions will be taken regarding the clinical program as needed

MRI

The MRI investigations will be performed to assess subcutaneous and visceral adipose tissue volume, liver volume, and percent hepatic lipid content, using standard clinical scanners. The magnetic field created attracts ferromagnetic objects into the scanner. Subjects with a ferromagnetic implant or device, such as pacemakers, metallic splinters in the eye, and clips in the central nervous system, are contraindicated for MRI. A standardized questionnaire will be used before each MRI scan is performed to screen subjects for any contraindication to MRI. No contrast agent will be used.

CGM

CGM is used to measure subcutaneous interstitial glucose and will give profiles of mean glucose values over 24 hours using the system recorded data approximately every 5-10 minutes. There is

a low risk that inserting the CGM sensor and wearing the adhesive patch might cause bleeding, infection, or skin irritations (redness, swelling).

Potential benefits to subjects

All subjects will receive active dual antihyperglycemic therapy. The efficacy and safety of saxagliptin in combination with dapagliflozin, as well as the dual add-on of both agents in this clinical setting, has been recently established. A Phase 3 study (CV181169) demonstrated that early combination treatment with saxagliptin and dapagliflozin, 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 subjects with inadequately controlled T2DM. In the present study, the doses of saxagliptin (5 mg) and dapagliflozin (10 mg) are the maximum doses that are currently approved and used in clinical practice. In addition, saxagliptin is expected to be weight neutral and dapagliflozin is anticipated to reduce weight moderately, and both have shown a low risk for hypoglycemia in combination with metformin. Subjects 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. Subjects will also receive counseling on dietary and life-style modifications.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects in the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Prior to study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials

(eg, advertisements), and any other written information to be provided to subjects. The investigator or the Sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator or the Sponsor should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given by subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

The Sponsor (or designee) will provide the investigator with an appropriate (ie, global or local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for the subject or the subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC’s written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject’s legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed Informed Consent Form (ICF) and, in the US, the subjects' signed Health Information Portability & Accountability Act (HIPAA) Authorization.

The consent form must also include a statement that the Sponsor and regulatory authorities have direct access to subject records.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

Study CV181365 is an international, multicenter, randomized, double-blind, active-controlled, parallel-group Phase 3b study whose primary endpoint is the change from baseline in HbA1c with saxagliptin, in combination with dapagliflozin, on top of background therapy with metformin, compared to glimepiride as an adjunct to metformin monotherapy. The primary endpoint of HbA1c will be assessed at 52 weeks; however, the trial will continue for 156 weeks as a subject- and site-blinded extension.

Subjects with documented T2DM treated with metformin monotherapy will be enrolled. All subjects should be treated according to regional standards of care for diabetes.

Subjects must be receiving metformin in accordance with the product label for their country.

Approximately 440 subjects meeting all eligibility criteria at approximately 110 study sites will be randomized (1:1) to receive either saxagliptin co-administered with dapagliflozin or glimepiride.

Enrollment of subjects based on disease state, and geographic region will be monitored and may be capped to ensure adequate representation.

All potentially eligible subjects will undergo a screening visit. Each subject will sign an Informed Consent Form (ICF) prior to having any screening evaluations performed. Subjects who fulfill all eligibility requirements will enter into a 2-week screening period and a 2-week lead-in period, during which they will continue to take their background medication with at least 1500 mg metformin.

Approximately 2 weeks after entering the lead-in period, subjects will be expected to undergo a randomization visit. Subjects may withdraw prior to the randomization visit, or be withdrawn by study staff for any reason. At this visit, subjects will be re-evaluated by study staff to determine, if, after testing performed at the screening visit, after assessment of compliance, and any clinical changes that may have occurred during the run-in period, the subject remains eligible and committed to participation in the study. If for any reason, prior to or during the randomization visit, the subject is no longer eligible or interested in participating in the trial, he or she will be considered a run-in failure, will not be randomized, and will not have additional follow up.

If a subject is committed to participation, completes the lead-in period, and continues to meet eligibility criteria at the randomization visit, he or she will be randomized and will receive either saxagliptin 5 mg, co-administered with dapagliflozin 10 mg, plus metformin, or glimepiride plus metformin in a double-blind fashion. Subjects will continue to receive background metformin ≥ 1500 mg/day throughout the duration of the study, unless metformin treatment is temporarily withheld due to decreased creatinine clearance (CrCl; Section 3.5).

Subjects will return to the site every 3 weeks to enable titration of glimepiride from Week 3 up to Week 12, and then approximately every 12 to 13 weeks until the last visit (up to Week 156) for assessment of events related to the objectives of the study, tolerability and safety. Assessment of treatment compliance and provision of IMP will be done at these visits.

Dose and Treatment Regimens Blinded Study Medication

Saxagliptin 5 mg tablets or matching placebo tablets, administered orally once daily, will be provided for the 156-week blinded treatment period. Saxagliptin 5 mg is the maximum recommended daily dose. No up- or down-titration of saxagliptin will be allowed.

Dapagliflozin 10 mg tablets or matching placebo tablets, administered orally once daily, will be provided for the 156-week blinded treatment period. Dapagliflozin 10 mg is the maximum recommended daily dose. No up- or down-titration of dapagliflozin will be allowed.

Glimepiride 1-6 mg or matching placebo capsules, administered orally once daily, will be provided for the 156-week blinded treatment period. During the first 12 weeks, the glimepiride dose will be slowly titrated in a stepwise blinded fashion depending on glycemic control. For the duration of the study, FPG will be measured at the study center using a glucose analyzer provided by the Sponsor. The investigator's decision on dose titration (either upwards if no issues with hypoglycemia or downwards if recurrent hypoglycemia occurs) will take both the plasma glucose measurements (measured prior to the visit), and the investigator's measurements at the titration visits, into account. The glimepiride dose will be titrated to optimal effect (FPG ≤ 110 mg/dL [≤ 6.1 mmol/L]) or the highest tolerable dose during the first 12 weeks. The starting dose for glimepiride is 1 mg per day (once daily), which can be further increased by increments of 1-2 mg at 3-week intervals to a maximum of 6 mg per day (maximum recommended dose in the Summary of Product Characteristics[9] and thus the maximum dose to be used in this study). The titration steps will be 2 mg, 3, mg, 4 mg, and 6 mg once daily if needed. In subjects for whom titration is not medically indicated at Week 3, re-assessment for titration will occur at Week 6, Week 9, and Week 12.

The glimepiride dose can be down-titrated during the titration period if hypoglycemic events occur. The treatment can thereafter be up-titrated once during the titration period. Subjects whose IMP dose was up-titrated to the maximum level will have a follow-up phone call 3 weeks later. The glimepiride dose can be down-titrated from Week 12 onwards (maintenance period) if hypoglycemic events occur.

During the randomized treatment period, diet and life-style modification will continue to be reinforced.

All randomized subjects who are rescued and taking randomized IMP should continue to attend scheduled study visits as planned in the time and events table (Section 5).

Subjects who decide to prematurely discontinue the IMP will always be asked about the reason(s) for discontinuation and the presence of any AEs. Subjects should return and complete the procedures described for the End of Treatment (EOT) visit as soon as possible, but at the latest 7 days after discontinuation of IMP. Subjects with unresolved AEs should also be followed-up as long as medically indicated as judged by the investigator.

All subjects who discontinue from treatment should remain in the study and comply with protocol-specified follow-up procedures. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

Subjects lost to follow-up are defined by: 1) unable to reach the subject after three documented phone calls, fax, email or attempts to contact him/her through subject locator agencies (if allowed per national regulation); and 2) having sent one letter by registered/certified mail; all should be documented in the subject's medical records.

MRI-PDFF

A MRI-PDFF sub-study will be conducted at approximately 11 MRI sites in Europe. Approximately 60 (30 per arm) subjects from selected recruiting sites are expected to participate in the MRI-PDFF sub-study. Each subject participating in the MRI sub-study will be referred to a MRI site for MRI measurements. Several recruitment sites can refer subjects to one MRI site. Subjects participating in the MRI-PDFF sub-study will be required to provide informed consent. The date of these MRI assessments need not be the same as for Visit 1, but should be performed before Visit 3.

All subjects suitable for the study, including the MRI-PDFF sub-study, will be screened and recruited by the recruiting sites (sites treating subjects with T2DM). The recruiting investigator will be the main point of contact for the subject and also responsible for the documentation of study data within the eCRF. All subjects should have MRI visits scheduled to coincide with randomization, Week 52, and Week 122.

All MRIs will be sent for central evaluation to a core laboratory. No local reading will be performed. The results will be kept blinded to recruiting sites, the MRI sites, the subjects, and the Sponsor until the study is completed.

Continuous Glucose Monitoring (CGM)

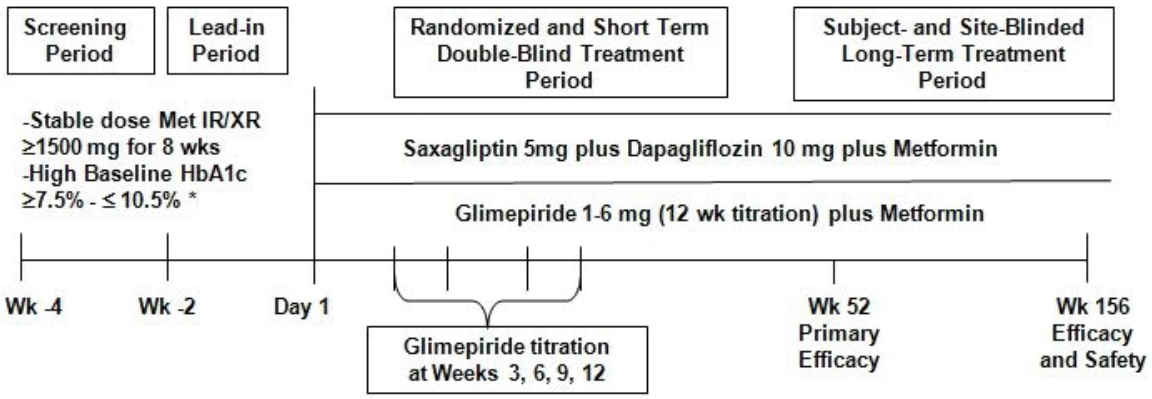
CGM measures the subject's interstitial glucose level using electrodes that measure an electric signal produced by the glucose oxidase reaction. The system records data approximately every 5 minutes, giving profiles of mean glucose values over 24 hours. The data will remain blinded to the subject during the recording and will be downloaded into a data file. A CGM sensor will be inserted subcutaneously at the site for a 7 day monitoring period prior to randomization and prior to Week 52. Insertion on alternate days is permitted in the event that the sensor needs to be

replaced. Detailed procedures (including calibration) will be described in an operations manual and site staff will be fully trained on the use of the CGM. Subjects will be instructed on use of the device according to the manufacturer's instructions.

The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Design Schematic

Study Schematic:



Study Population: Subjects should be selected without bias. Each subject on stable background therapy with metformin monotherapy should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be any exceptions to this rule. All subjects who were screened and have submitted a blood sample should be listed on the subject enrollment and identification log. Investigator(s) must keep a record of subjects who entered pre-trial screening but were never enrolled.

Subjects will be enrolled globally, including representation from North America and Europe.

3.2 Post Study Access to Study

At the end of the 156 week study period, the Sponsor will not continue to provide Sponsor-supplied study drug to subjects/investigators unless the Sponsor chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

3.3 Study Population

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Subjects (or designee) must be willing and able to give signed and dated written informed consent.

2. Target Population

a) Subjects with T2DM with inadequate glycemic control, defined as a central laboratory HbA1c ≥ 7.5% and ≤ 10.5% obtained at the screening visit.

i) Note: The proportion of subject with HbA1c 7.5 % - 8.5 % will be capped at 40%.

ii) Note: At Week -2 (Lead-In), a qualification check will be performed and subjects will be included if their FPG is ≤ 270 mg/dL. A re-test will be permitted within 7 days if the initial result was > 270mg/dL but < 300mg/dL. Subjects will be excluded if the mean value of the Week -2 (Lead-In) result and the re-test result is > 270mg/dL.

b) Subjects should be taking the same daily dose of metformin ≥ 1500 mg for at least 8 weeks prior to the enrollment visit and must not take any other antihyperglycemic therapy for more than 14 days (consecutive or not) during 12 weeks prior to screening.

c) BMI 20.0 to 45.0 kg/m^2 (inclusive) at the enrollment visit.

d) Subject Re-enrollment: This study permits the re-enrollment of a subject who has been discontinued from the study as a pre-treatment failure (ie, subject has not been randomized / has not been treated). If re-enrolled, the subject must be re-consented.

Inclusion criteria at randomization (Visit 3, based on laboratory results from Visit 2):

a) FPG ≤ 270 mg/dL (≤15 mmol/L).

For inclusion in the MRI-PDFF sub-study and/or CGM sub-study, subjects must fulfill the following criteria:

b) Provision of informed consent for the MRI-PDFF and/or CGM sub-study.

c) BMI 20.0 to 40.0 kg/m^2 (inclusive) at the enrollment visit and upper weight of 140 kg max (MRI-PDFF sub-study only).

If a subject declines to participate in the MRI-PDFF sub-study or CGM sub-study, there will be no consequences for the subject's participation in the main study. The subject will not be excluded from other aspects of the study described in this Clinical Study Protocol, as long as proper consent is obtained.

3. Age and Reproductive Status

a) Males and females, aged ≥ 18 years old at the time of the screening visit.

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drugs: saxagliptin, and dapagliflozin, and glimepiride plus 5 half-lives of study drugs: saxagliptin, dapagliflozin, and glimepiride (30 days) plus 30 days (duration of ovulatory cycle) for a total of 60 days post-treatment completion.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drugs: saxagliptin, dapagliflozin, and glimepiride plus 5 half-lives of the study drug (30 days) plus 90 days (duration of sperm turnover) for a total of 120 days post-treatment completion.

f) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% per year when used consistently and correctly.

At a minimum, subjects must agree to the use of one method of highly effective contraception as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Progestogen only hormonal contraception associated with inhibition of ovulation.
- Hormonal methods of contraception including combined oral contraceptive pills containing a combination of estrogen + progesterone, vaginal ring, injectables, implants and intrauterine devices (IUD).
- Nonhormonal IUDs
- Bilateral tubal occlusion
- Vasectomised partner with documented azoospermia 90 days after procedure
- Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.
- Intrauterine hormone-releasing system (IUS)

- Complete Abstinence*

*Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but WOCBP subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

3.3.2 Exclusion Criteria

4. Target Disease Exceptions

a) Clinical diagnosis of type I diabetes, known diagnosis of mature onset diabetes of youth (MODY), secondary diabetes mellitus, or diabetes insipidus.

b) History of diabetic ketoacidosis

5. Medical History and Concurrent Diseases

a) Any of the following cardiovascular/vascular diseases within 3 months of the enrollment visit:

i) Myocardial infarction

ii) Cardiac surgery or revascularization (coronary artery bypass surgery [CABG]/percutaneous transluminal coronary angioplasty [PTCA])

iii) Unstable angina

iv) Unstable congestive heart failure (CHF)

v) Transient ischemic attack (TIA) or significant cerebrovascular disease

vi) Unstable or previously undiagnosed arrhythmia

vii) Congestive heart failure, defined as New York Heart Association (NYHA) Class III and IV, 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, should have careful monitoring of their volume status throughout the study.

b) Renal disease:

i) History of unstable or rapidly progressing renal disease

ii) Impairment of renal function (defined as CrCl < 60 mL/min [estimated by Cockcroft-Gault] or serum creatinine [SCr] ≥ 1.5 mg/dL in males or ≥ 1.4 mg/dL in females).

iii) Hematuria (confirmed by microscopy at screening) with no explanation as judged by the investigator up to randomization. If bladder cancer is identified, subjects are not eligible to participate.

c) Hepatic diseases:

i) Severe hepatic insufficiency and/or significant abnormal liver function defined as aspartate aminotransferase (AST) > 3x upper limit of normal (ULN) and/or alanine aminotransferase (ALT) > 3x ULN.

ii) Serum total bilirubin > 2.0 mg/dL (> 34.2 μmol/L).

iii) Severe hepatic disease, including chronic active hepatitis. Positive serologic evidence of current infectious liver disease, including subjects who are positive for hepatitis B viral antibody IgM, hepatitis B surface antigen, and hepatitis C virus antibody.

d) Pancreatic disease

i) History of, or current, acute or chronic pancreatitis.

e) Hematological and oncological disease/conditions:

i) History of hemoglobinopathy, with the exception of sickle cell trait (SA) or thalassemia minor; or chronic or recurrent hemolysis.

ii) Malignancy within 5 years of the screening visit (with the exception of treated basal cell or treated squamous cell carcinoma).

iii) History of bladder cancer or history of radiation therapy to the lower abdomen or pelvis at any time.

6. Physical and Laboratory Test Findings

a) Hemoglobin ≤ 11.0 g/dL (110 g/L) for men; hemoglobin ≤ 10.0 g/dL (100 g/L) for women.

b) An abnormal TSH value at enrollment will be further evaluated for free T4. Subjects with abnormal free T4 values will be excluded. (Note: A one-time retest of TSH may be allowed, as determined by the investigator, after a minimum of 6 weeks following the adjustment of thyroid hormone replacement therapy in subjects who have had a prior diagnosis of a thyroid disorder and who are currently receiving thyroid replacement therapy. Such cases should be discussed with the Sponsor prior to re-testing. The subject must have all enrollment procedures and laboratory assessments performed as part of this re-test, and all of these must meet enrollment eligibility criteria. The subject's number will however remain the same as initially assigned.)

c) Any clinically significant abnormality identified on physical examination, ECG or laboratory tests, which in the judgment of the investigator would compromise the subjects' safety or successful participation in the clinical study.

7. Allergies and Adverse Drug Reaction

a) Subjects who have contraindications to therapy as outlined in the saxagliptin and dapagliflozin Investigator Brochures, the local saxagliptin or dapagliflozin or glimepiride or metformin package insert, including current treatment with potent cytochrome P450 3A4/5 inhibitors (in countries where dose adjustment would be required by the local saxagliptin label).

8. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated.

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

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

d) Subjects who are taking any prescription or over-the-counter (OTC) medications for weight loss within 3 months of the screening visit.

e) History of any bariatric surgical procedure, Nissen fundoplication, or other procedures that can affect endogenous GLP-1 levels prior to screening.

f) Replacement or chronic systemic corticosteroid therapy, defined as any dose of systemic corticosteroid taken for > 4 weeks within 3 months prior to the Day 1 visit

   i) NOTE: Topical or inhaled corticosteroids are allowed

g) Any unstable endocrine, psychiatric or rheumatic disorders as judged by the investigator

h) Volume depleted subjects. Subjects at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics, should carefully monitor their volume status.

i) Subject with any condition which, in the judgment of the investigator, may render the subject unable to complete the study or which may pose a significant risk to the subject or subject suspected or with confirmed poor protocol or medication compliance.

j) Subject is currently abusing alcohol or other drugs or has done so within the last 6 months prior to the screening visit.

k) Subject is a participating investigator, study coordinator, employee of an investigator or immediate family member of any of the aforementioned.

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

m) Previous randomization in the present study.

n) Administration of any other investigational drug within 30 days of the screening visit

o) Clinical conditions or clinically significant abnormalities, in any laboratory value(s) collected after screening and prior to randomization which, in the investigator's judgment, should preclude entry into the treatment period.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

A woman of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

*Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

Once enrolled, subjects may not receive any of the following for the duration of the screening (qualification period), lead-in, double-blinded short-term and subject- and site-blinded long-term treatment periods:

- Treatment with sulfonylureas other than IMP, pioglitazone, rosiglitazone, glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) other than IMP, and any sodium glucose co-transporter 2 (SGLT2) inhibitors other than IMP is not permitted for the duration of the study. If rescue therapy is required and a subject refuses treatment with insulin or is not a candidate for insulin, other diabetic agents can be considered as second-line rescue therapy (Section 3.5.2).
- Insulin therapy within one year of enrollment (with the exception of insulin therapy during a hospitalization or use in gestational diabetes), other than as a first-line rescue therapy (Section 3.5.2).
- Current treatment with potent cytochrome P450 3A4/5 inhibitors (in countries where dose adjustment would be required by the saxagliptin label).

- Administration of any other investigational drug or participation in any interventional clinical studies 30 days prior of planned screening to this study.
- Newly initiated treatment with any systemic corticosteroid therapy (including oral and injectable) that will involve ≥ 5 days of therapy is not permitted (inhaled and topical are allowed). The Sponsor Medical Monitor should be consulted prior to beginning therapy with corticosteroids for subjects who require systemic corticosteroid treatment.

3.4.2 Other Restrictions and Precautions

- Subjects must comply with their prescribed dosing regimen to preserve study integrity and ensure subject safety.
- Subjects should be cautioned that any new prescription, OTC or herbal/nutritional therapies should be discussed thoroughly with the investigator as concomitant use could result in alterations to their glycemic control and may place them at risk for significant hypoglycemic episodes.
- Subjects must make every attempt to adhere to the diet and exercise counseling and to the study flow chart/time and event schedule (see Section 5.1)
- Women of child-bearing potential 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 (see Section 6.5).

3.5 Discontinuation of Subjects following any Treatment with Study Drug

Subjects MUST discontinue IMP (and non-IMP at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment.
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.
- Termination of the study by the Sponsor.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.
  - Unblinding a subject for any reason (emergency or non-emergency).
- Severe non-compliance to protocol, as judged by the investigator and/or Sponsor.
- Safety reasons as judged by the investigator and/or Sponsor.
- Incorrect enrollment (ie, the subject does not meet the require inclusion/exclusion criteria) for the study.
- Pregnancy.
- CrCl < 60 mL/min (estimated by Cockcroft-Gault), with a repeat confirmation test result 3 to 7 days following the receipt of the initial result. Subjects with a CrCl < 60 ml/min will have background therapy metformin withheld until the confirmatory repeat CrCl is received.

  - If the repeat CrCl > 60 ml/min the subject may resume background therapy metformin.
  - If the repeat CrCl < 60 ml/min the subject must be discontinued from all study medication.
- Subjects with a central laboratory ALT and/or AST > 3xULN will be scheduled for a follow-up visit within 3 days following the receipt of the result (see Appendix 4 for further guidance). Subjects should be discontinued from study if the initial and repeat laboratory tests meet any of the following criteria:
  - ALT and/or AST are > 3x ULN and total bilirubin (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 ≥ 10x ULN.

In the case of pregnancy, the investigator must immediately notify the Sponsor Medical Monitor/designee of this event. Study drug will be permanently discontinued in any subjects that become pregnant during the study; the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Table 5.1-4. The only exception to this requirement is when a subject withdraws consent for all study procedures, including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate Case Report Form (CRF) page.

3.5.1 Procedures for handling patients incorrectly enrolled or randomized

Subjects who fail to meet the inclusion/exclusion criteria must not, under any circumstances, be enrolled or randomized. There can be no exceptions to this rule.

Subjects who are incorrectly enrolled, but are not yet randomized, should be withdrawn from the study. The procedures included in the protocol for the discontinuation of such subjects must be followed. Study medication should be permanently stopped and the subject should be further treated according to the investigators judgment and local therapy tradition.

If a subject not meeting the study criteria is randomized in error, and if the error is identified after randomization, a discussion must occur between the Sponsor Medical Monitor and the investigator regarding whether to continue or discontinue the subject from the study. If agreement is reached, the subject should complete the study unless there are safety concerns or if the subject withdraws the consent. In situations in which an agreement cannot be reached, the subject should have the randomized therapy stopped and be discontinued from the study. The procedures included in the protocol for the discontinuation of such subjects must be followed.

The Sponsor Medical Monitor is to ensure all such contacts with the investigator and such decisions are appropriately documented.

3.5.2 Rescue Guidelines for Subjects with Protocol-Defined Lack of Glycemic Control

During the course of the trial, subjects may be eligible for the addition of open-label rescue medication to their blinded treatment regimen in order to treat ongoing hyperglycemia. Insulin is recommended as the first-line rescue therapy, as subjects will already be taking dual or triple-therapy (based on their randomization assignment). If a subject refuses treatment with insulin or is not a candidate for insulin, other options for rescue therapy can be considered. However, initiation of a DPP4 inhibitor, SGLT2 inhibitor, or SU is not permitted for rescue therapy. The sub-sections and tables listed below define the lack of glycemic control criteria for initiation of rescue medication in both short-term and long-term periods of the study.

Pre-specified glycemic criteria (see Table 3.5.2-1), based upon central laboratory HbA1c, FPG, and repeat confirmatory FPG were established during the treatment period; to determine eligibility for open-label rescue medication, FPG is to be used from Week 9 to Week 52, and HbA1c after Week 52 to Week 156.

Table 3.5.2-1: Lack of Glycemic Control Criteria for Initiation of Rescue Medication

Visit Label	Central Laboratory FPG/HbA1c
Week 9	FPG > 270 mg/dL (15.0 mmol/L)
After Week 9 to Week 16 (including Week 16)	FPG > 240 mg/dL (13.3 mmol/L)
After Week 16 to Week 28 (including Week 28)	FPG > 220 mg/dL (12.2 mmol/L)
After Week 28 to Week 52 (including Week 52)	FPG > 200 mg/dL (11.1 mmol/L)
After Week 52 to Week 156	HbA1c > 7.5%

Subjects with a central laboratory FPG value meeting the lack of glycemic control criterion at a pre-specified visit will be scheduled for a follow-up visit (within 3 - 5 days) to obtain a second central laboratory FPG value and review the subject's glucose meter readings.

If the repeat central laboratory FPG value still meets the criterion, the subject must be rescued. Subjects who meet rescue criteria in the blinded treatment period must first complete the Rescue Visit procedures before receiving open-label rescue medication to ensure that important trial endpoint measurements are collected.

Following completion of the Rescue Visit, rescued subjects will be given open-label antidiabetic rescue medication (insulin is recommended) within 2 weeks of meeting the rescue criteria, which should be initiated at the lowest starting dose and titrated in accordance with the approved product label in the applicable country at the discretion of the investigator, in addition to their

blinded study medication. Rescued subjects will then continue in the blinded treatment period according to their original visit schedule.

Note: Rescue medication will NOT be provided by the Sponsor in this study. Reimbursement will be provided for insulin given as rescue medication.

Following initiation of open-label rescue antidiabetic medication, rescued subjects should be scheduled for titration visits to increase their rescue antidiabetic medication dose, as tolerated and in accordance with the approved product label for that country and by their glycemic response, and as per the investigator's judgment.

3.5.3 Discontinuation Guidelines due to Protocol-Defined Hypoglycemia Episodes

Subjects should not be discontinued from any treatment phase based on single episodes of hypoglycemia or symptoms of hypoglycemia unless clinically indicated. The assessment of a single fingerstick or central laboratory glucose value should not be the sole assessment used to determine subject discontinuation for hypoglycemia.

Clinical indications for discontinuation because of hypoglycemia may 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 subject. This includes, but is not limited to:

- Recurrent symptoms suggestive of hypoglycemia (eg, sweating, shakiness, increased heart rate, confusion, dizziness, light-headedness, or hunger) in the absence of environmental factors known to contribute to hypoglycemia (ie, excess physical activity, concurrent illness, or missed or delayed meal).
- Recurrent documented capillary or plasma blood glucose values < 54 mg/dL (< 3.0 mmol/L).
- A subject may also be discontinued from the study because of severe hypoglycemia as determined by the investigator.

Down-titration of blinded study drug and/or background antihyperglycemic agent during the study.

The glimepiride dose can be down-titrated during the titration period if hypoglycemic events occur. The treatment may thereafter be up-titrated once during the titration period. The glimepiride dose can be down titrated from Week 12 onwards (maintenance period) if hypoglycemic events occur. Down titration of other blinded study drug will not be allowed at any time during the study. The dose of metformin must be ≥ 1500 mg/day throughout the duration of the study, unless metformin treatment is temporarily withheld due to CrCl < 60 mL/min (estimated by Cockcroft-Gault; Section 3.5).

If fingerstick glucose values are discordant from glycemic control assessed by the central laboratory or with clinical symptoms, the subject's glucose meter should be tested and the

procedure for using it reviewed with the subject. Section 5.3.1.2 provides additional guidance on management and reporting of hypoglycemia.

3.5.4 Discontinuation Guidelines due to Ketoacidosis

Patients 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 blinded study drug should be considered and the patient should be promptly evaluated.

Details regarding the recording and adjudication of DKA events are provided in Section 7.3.

3.6 Post-Study Drug Study Follow up

In this study, safety is a key endpoint of the study. Post-study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required, and in line with Section 5, until death or the conclusion of the study.

Therefore, all subjects who discontinue IMP in the 52 week double-blinded short-term treatment period or in the long-term treatment period should be asked to continue study participation for each scheduled visit for the remaining length of the study and complete all procedures as outlined in Section 5 [Table 5.1-4] study flowchart, with the exception of study drug management. If continued study participation according to the protocol schedule is not possible, the investigator should contact the Sponsor to discuss alternatives (eg, return to the clinic 4 weeks after discontinuation of study drug to perform the Week 56 post-treatment follow-up procedures as outlined in Section 5 [Table 5.1-4] study flowchart or be contacted by telephone 4 weeks after discontinuation of study drug to evaluate the following safety assessments: AEs and hypoglycemia events. Please note that after the discontinuation of study drug, the management of the subject's diabetes will be under the care and direction of the investigator.)

The only exception to any of these follow-up methods are when a subject withdraws consent for all study procedures, including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate eCRF page. In

the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined as the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails, as well as lack of response by the subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If an investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

3.7 End of Study

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

4 STUDY DRUG

Study drug includes both investigational medicinal product (IMP) and non-IMP and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)

Table 4-1: Study Drugs for CV181365: Product Description: Short-term Double-Blinded Treatment Period and Long-term Subject- and Site-Blinded Treatment Period

Product Description / Class and Dosage Form	Potency	IMP/ Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Saxagliptin Film Coated Tablet (as the free base)	5 mg	IMP	Blinded Label	Plain, yellow, biconvex, round, film coated tablet HDPE Bottle	All study drugs should be kept in a secure place under appropriate storage conditions. The IMP label on the bottle specifies the appropriate storage
Placebo for Saxagliptin Film Coated Tablets	0 mg	IMP	Blinded Label	Plain, yellow, biconvex, round, film coated tablet HDPE Bottle	All study drugs should be kept in a secure place under appropriate storage conditions. The IMP label on the bottle specifies the appropriate storage
Dapagliflozin Film Coated Tablet	10 mg	IMP	Blinded Label	Green, plain, diamond shaped, film coated tablet HDPE Bottle	All study drugs should be kept in a secure place under appropriate storage conditions. The IMP label on the bottle specifies the appropriate storage
Placebo for Dapagliflozin Film Coated Tablets	0 mg	IMP	Blinded Label	Green, plain, diamond shaped, film coated tablet HDPE Bottle	All study drugs should be kept in a secure place under appropriate storage conditions. The IMP label on the bottle specifies the appropriate storage
Glimepiride Capsule	1 mg 2 mg 4 mg	IMP	Blinded Label	Opaque gray Capsule HDPE Bottle	All study drugs should be kept in a secure place under appropriate storage conditions. The IMP label on the bottle specifies the appropriate storage
Placebo for Glimepiride Capsule	0 mg	IMP	Blinded Label	Opaque gray Capsule HDPE Bottle	All study drugs should be kept in a secure place under appropriate storage conditions. The IMP label on the bottle specifies the appropriate storage

4.1 Investigational Product

An investigational product, also known as IMP in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

All study drugs should be kept in a secure place under appropriate storage conditions. The IMP label on the bottle specifies the appropriate storage. It is the responsibility of the investigator to ensure that IMP is only dispensed to study subjects. The IMP must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, IMP(s) is/are: (also described in Table 4-1) are saxagliptin 5 mg, dapagliflozin 10 mg, glimepiride 1 mg, glimepiride 2 mg, glimepiride 4 mg, and matching placebos. Rescue medication insulin (will be reimbursed) and metformin will not be provided by the Sponsor, since it is part of patient's standard of care.

- Blinded saxagliptin 5 mg and dapagliflozin 10 mg administered orally for the 52 week double - blinded short-term treatment period, and the 104-week subject- and site-blinded long-term treatment period of the study
- Blinded glimepiride 1 mg, 2 mg, 3 mg, 4 mg, or 6 mg administered orally for the 52-week double blinded short-term treatment period, and the 104-week subject- and site-blinded long-term treatment period of the study

4.2 Non-investigational Product

Other medications used as support or rescue medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-IMPs.

In this protocol, non-IMP(s) are: insulin (or other rescue therapies) and metformin; the Sponsor will not be providing these medications.

4.3 Storage and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the Sponsor. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and the product storage manager should contact the Sponsor immediately.

Study drug not supplied by the Sponsor will be stored in accordance with the package insert.

IMP documentation (whether supplied by the Sponsor or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

4.4 Method of Assigning Subject Identification

CCI

[redacted]

Subjects entering the 52-week double-blinded short-term treatment period

Following completion of the lead-in period, subjects who meet the criteria will be randomly assigned by the IVRS at the Day 1 Randomization visit, to one of the following two (2) double blind treatment arms in a 1:1 ratio:

- Blinded saxagliptin 5 mg and dapagliflozin 10 mg
- Titrated to blinded glimepiride 1 mg, 2 mg, 3 mg, 4 mg, or 6 mg

Randomization schedules for both subject treatment and containers will be generated and kept by the Sponsor.

Subjects entering the 104-week long-term subject- and site-blinded treatment period

Following completion of the 52-week double-blinded treatment period, subjects eligible for the long-term subject- and site-blinded treatment period will be continued in their same randomization assignment based on their original randomization grouping. Subjects that were assigned to be on the blinded saxagliptin 5 mg and dapagliflozin 10 mg arm will continue to receive the blinded saxagliptin 5 mg and dapagliflozin 10 mg. Subjects that were assigned to be on the blinded glimepiride 1 mg, 2 mg, 3 mg, 4 mg, or 6 mg arm will continue to receive blinded glimepiride. At all study visits when study drug is dispensed, each subject will be assigned multiple container numbers by the IVRS. Container numbers will be assigned non-sequentially and will correspond to the numbers printed on the containers and bottles containing study drug, and will be recorded on the appropriate eCRF. The IVRS will be available 24 hours per day, 7 days a week.

4.5 Selection and Timing of Dose for Each Subject

Saxagliptin 5 mg tablets or matching placebo tablets, will be administered orally once daily for the 156-week treatment period (52 week double-blinded and 104 week subject- and site-blinded treatment periods). Saxagliptin 5 mg is the maximum recommended daily dose. No up- or down-titration of saxagliptin will be allowed.

Dapagliflozin 10 mg tablets or matching placebo tablets, will be administered orally once daily for the 156-week treatment period (52 week double-blinded and 104 week subject- and

site-blinded treatment periods). Dapagliflozin 10 mg is the maximum recommended daily dose. No up- or down-titration of dapagliflozin will be allowed.

Glimepiride 1 mg, 2 mg, and 4 mg tablets and matching placebo capsules, will be administered orally once daily for the 156 week treatment period (52 week double-blinded and 104 week subject- and site-blinded treatment periods). The starting dose for glimepiride is 1 mg per day (once daily), which can be further increased by increments of 1-2 mg at 3-week intervals to a maximum of 6 mg per day in this study. The titration steps will be 2 mg, 3, mg, 4 mg, and 6 mg once daily if needed. In patients for whom titration is not medically indicated at Week 3, re-assessment for titration will occur at Week 6, Week 9, and Week 12. The glimepiride dose can be down-titrated during the titration period if hypoglycemic events occur. The treatment can thereafter be up-titrated once during the titration period. The patients, whose IMP dose was up-titrated to the maximum level, will have a follow-up phone call 3 weeks later. The glimepiride dose can be down-titrated from Week 12 onwards (maintenance period) if hypoglycemic events occur.

4.6 Blinding/Unblinding

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject in which knowledge of the treatment assignment is critical to the subject's management, the blind for that subject may be broken by the investigator. The subject’s safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual subject's treatment, the investigator should determine that the unblinded information is necessary, ie, that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not related to the IMP, the problem may be properly managed by assuming that the subject is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Sponsor Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The investigator should only call in for emergency unblinding AFTER the decision to discontinue the subject has been made.

For this study, the method of unblinding for emergency purposes is IVRS.

For information on how to unblind in case of an emergency, consult the IVRS manual.

In cases of accidental unblinding, contact the Sponsor Medical Monitor and ensure every attempt is made to preserve the blind.

Any request to unblind a subject for non-emergency purposes should be discussed with the Sponsor Medical Monitor.

4.7 Treatment Compliance

Each time study medication is dispensed, compliance will be reinforced. 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 significant protocol deviation and the Sponsor should be notified. The subject should be re-educated regarding recording these values.

4.8 Destruction of Study Drug

For this study, study drugs (those supplied by the Sponsor 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 the Sponsor (or designee) 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.

4.9 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 the Sponsor must be returned to the Sponsor or designee. The return of study drug will be arranged by the responsible Study Monitor.

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.

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

4.10 Retained Samples for Bioavailability / Bioequivalence

Not applicable:

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline Flow chart for Protocol CV181365 - Qualification (Period A Week - 4) and Lead-in (Period B Week - 2)

Procedure	Screening Wk - 4	Lead-In Wk - 2[a]	Lead-In Wk - 1[b]	Notes
Eligibility Assessments				The Week-2 visit cannot be performed until all laboratory results from the screening period have been received and reviewed to confirm eligibility. Once eligibility is confirmed, Wk-2 can be performed within 2 weeks of Wk-4
Informed consent	X			
Informed consent MRI sub-study		X		Only needed for subject participating in the MRI sub-study
Informed consent CGM sub-study		X		Only needed for subject participating in the CGM sub-study
Inclusion/exclusion criteria	X	X		
Medical history	X			
Safety Assessments				
Complete physical examination	X			Section 5.3.5 (in protocol)
Brief physical examination		X		Section 5.3.5 (in protocol)
Vital signs (seated blood pressure and heart rate)	X	X		Section 5.3.6 (in protocol)
Body weight	X	X		Section 5.8.2 (in protocol)
Height	X			Section 5.8.3 (in protocol)
Body mass index (BMI)	X			Section 5.8.3 (in protocol)
Waist circumference		X		Section 5.8.4 (in protocol)
Review concomitant medications / procedures	X	X		

Table 5.1-1: Screening Procedural Outline Flow chart for Protocol CV181365 - Qualification (Period A Week - 4) and Lead-in (Period B Week - 2)

Procedure	Screening Wk - 4	Lead-In Wk - 2[a]	Lead-In Wk - 1[b]	Notes
*Contact IVR system	X	X		* Call to register subject and study termination (if applicable)
Provide diet and exercise counseling		X		Section 5.8.1 (in protocol)
Provide glucose meter and supplies / instructions		X		
Provide logs / instructions		X		
Assessment of signs and symptoms of hypoglycemia episodes		X		
Serious AE assessment	X	X		
AE assessment		X		
Central Laboratory Tests				
Pregnancy test (urine) WOCBP only	X	X		
Dipstick urinalysis	X	X*		*Positive dipstick at Wk -2 will require repeat test with microscopy prior to randomization Section 5.3.2 (in protocol) Appendix 3 (in protocol)
Microscopic urinalysis	X	X*		*Microscopic urinalysis only performed at Wk -2 if dipstick test is positive Section 5.3.2 (in protocol) Appendix 3 (in protocol)
Spot urine for glucose, albumin and creatinine quantification and determination of glucose: creatinine and albumin:creatinine ratios	X			
HbA1c	X			
Fasting C-peptide	X			
FPG	X	X*		* FPG must be ≤ 270 mg/dL to be eligible (see inclusion/ exclusion criteria section for more details)

Table 5.1-1: Screening Procedural Outline Flow chart for Protocol CV181365 - Qualification (Period A Week - 4) and Lead-in (Period B Week - 2)

Procedure	Screening Wk - 4	Lead-In Wk - 2[a]	Lead-In Wk - 1[b]	Notes
Estimated CrCl (Cockcroft-Gault) and serum creatinine (SCr)	X			
Hepatitis screen panel and TSH	X			
Clinical chemistry, haematology, urinalysis (standard safety laboratory panel)	X	X		
Subjects identified for randomization to CGM substudy.		X		
Insert CGM.		X		Section 5.8.7 (in protocol) CGM device to be worn for 7 consecutive days between the Week-2 and Week -1 visits.
CGM data collection, data upload and review.			X*	Section 5.8.7 (in protocol) *Only subjects in the CGM substudy would be required to attend the Week - 1 visit at the site.
Remove CGM device.			X	Section 5.8.7 (in protocol)
6-point SMBG profiles (for all subjects)		X		Section 5.8.7.2 (in protocol)
MRI-PDFF		X		Subjects will be identified for randomization to MRI during this visit. MRI-consented subjects will then have an ad-hoc visit at the imaging site within the 2 weeks PRIOR to the Day 1 (Randomization) visit (eg, Wk - 2 or Wk - 1) as described in Section 5.8.6.

[a] Lead-in (Week - 1) visit should be scheduled at least 7 days but not longer than 10 days after Week - 2 visit to accommodate for CGM data collection. If issues arise with the CGM device insertion or data upload, contact the Sponsor Medical Monitor to discuss alternative visit dates.

[b] Week - 1 visit is specific to CGM subjects only if required.

Table 5.1-2: Short-term Procedural Outline CV181-365 (52-week) Double-blinded Treatment (Period C, Day 1 to Week 52)

Procedure	Rand Day 1[a,b]	Wk 3[b]	Wk 6[b]	Wk 9[b]	Wk 12[b]	Wk 16[b]	Wk 28[b]	Wk 40[b]	Wk 51[c]	Wk 52 Rescue / D/C[b]	Notes
Eligibility Assessments											
Review randomization criteria	X										
Safety Assessments											
Complete physical examination	X						X			X	Section 5.3.5 (in protocol)
Brief physical examination		X	X	X	X	X		X			Section 5.3.5 (in protocol)
Vital signs (seated blood pressure and heart rate)	X	X	X	X	X	X	X	X		X	Section 5.3.6 (in protocol)
Body weight	X	X	X	X	X	X	X	X		X	Section 5.8.2 (in protocol)
Body mass index (BMI)	X						X			X	Section 5.8.3 (in protocol)
Waist circumference	X						X			X	Section 5.8.4 (in protocol)
12-lead ECG	X									X	
Review concomitant medications / procedures	X	X	X	X	X	X	X	X		X	
Provide diet and exercise counseling	X	X	X	X	X	X	X	X		X	Section 5.8.1 (in protocol)
Provide glucose meter supplies / instructions	X	X	X	X	X	X	X	X		X	
Provide logs/ instructions	X	X	X	X	X	X	X	X		X	
Review study logs	X	X	X	X	X	X	X	X		X	
Assess AEs and hypoglycemia episodes	X	X	X	X	X	X	X	X		X	Section 5.3.1.2 (in protocol)

Table 5.1-2: Short-term Procedural Outline CV181-365 (52-week) Double-blinded Treatment (Period C, Day 1 to Week 52)

Procedure	Rand Day 1[a,b]	Wk 3[b]	Wk 6[b]	Wk 9[b]	Wk 12[b]	Wk 16[b]	Wk 28[b]	Wk 40[b]	Wk 51[c]	Wk 52 Rescue / D/C[b]	Notes
Central Laboratory											
Pregnancy test (urine) WOCBP only	X	X	X	X	X	X	X	X		X	Home pregnancy test kits sent home with WOCBP subjects to perform pregnancy test between visits and record result in log book
Clinical chemistry, haematology, urinalysis (standard safety laboratory panel)	X		X		X		X			X	
Microscopic urinalysis					X					X	Section 5.3.2 (in protocol) Appendix 3 (in protocol)
Spot urine for glucose, albumin and creatinine quantification and determination of glucose: creatinine and albumin:creatinine ratios	X						X			X	
HbA1c	X				X	X	X	X		X	
FPG	X	X	X	X	X	X	X	X		X	
Estimated CrCl (Cockcroft-Gault) and serum creatinine (SCr)	X	X	X	X	X	X	X	X		X	
Fasting Serum Lipids (Total-C, LDL-C, HDL-C, TG)	X									X	
Fasting serum insulin and proinsulin for proinsulin/insulin ratio, C-peptide, and glucagon	X									X	
hsCRP, NT-proBNP	X									X	

Table 5.1-2: Short-term Procedural Outline CV181-365 (52-week) Double-blinded Treatment (Period C, Day 1 to Week 52)

Procedure	Rand Day 1[a,b]	Wk 3[b]	Wk 6[b]	Wk 9[b]	Wk 12[b]	Wk 16[b]	Wk 28[b]	Wk 40[b]	Wk 51[c]	Wk 52 Rescue / D/C[b]	Notes
Additional Assessments											
Patient reported outcomes questionnaires	X				X		X			X	Section 5.8.8 (in protocol)
MRI-PDFF	X*								X**	X**	* Subjects will be identified for randomization to MRI during this visit. MRI-consented subjects will then have an ad-hoc visit at the imaging site within the 2 weeks PRIOR to the Day 1 (Randomization) visit (eg, between Week -2 and up to, but not including, Day 1). Section 5.8.6 (in protocol) **Subjects assigned to the MRI-PDFF sub-study will have an ad-hoc visit at the imaging site within ± 2 weeks of the Wk 52 visit (eg, between Week 50 up to Week 54) as described in Section 5.8.6. Subjects who require rescue therapy or discontinue from study treatment early will be asked to return to the imaging site for an unscheduled MRI visit (if possible) within 4 weeks of initiating rescue medication or the Early Termination visit as described in Section 5.8.6

Table 5.1-2: Short-term Procedural Outline CV181-365 (52-week) Double-blinded Treatment (Period C, Day 1 to Week 52)

Procedure	Rand Day 1[a,b]	Wk 3[b]	Wk 6[b]	Wk 9[b]	Wk 12[b]	Wk 16[b]	Wk 28[b]	Wk 40[b]	Wk 51[c]	Wk 52 Rescue / D/C[b]	Notes
Insert CGM									X*		*Only subjects in the CGM substudy will be required to attend the Week 51 visit for insertion of the CGM.
CGM data collection, data upload, and review										X	CGM data collection not needed if CGM insertion was not completed
Remove CGM device										X	
6-point SMBG profiles (all subjects)	X								X		Section 5.8.7.2 (in protocol)
Assess FPG for rescue				X	X	X	X	X		X	
Study Drug											
Dispense blinded saxagliptin, blinded dapagliflozin or blinded placebo	X		X		X	X	X	X		X	
Dispense blinded glimepiride or blinded placebo and titrate during titration period (Weeks 3-12)	X	X	X	X	X	X	X	X		X	
Review study medication compliance		X	X	X	X	X	X	X		X	
Register down-titration of glimepiride during maintenance period (if applicable in IVRS)		X	X	X	X	X	X	X		X	
*Contact IVR system	X	X	X	X	X	X	X	X		X	

[a] If issues arise with the CGM device insertion or data upload, contact the Sponsor Medical Monitor to discuss alternative visit dates. If CGM device is inserted (or reinserted) at the Week -1 visit, then CGM data collection, data upload, review of data, and removal of device will occur at the Day 1 visit.

[b] Visits may be scheduled ± 5 days to allow flexibility of scheduling.

[c] Week 51 visit is specific to CGM and MRI subjects only if required.

Table 5.1-3: Long-term Procedural Outline for Protocol CV181365 (104-week) Subject- and Site-Blinded Treatment (Period D Week 52 to Week 156)

Procedure	Wk 65[a]	Wk 78[a]	Wk 91[a]	Wk 104[a]	Wk 117[a]	Wk 122[b]	Wk 130[a]	Wk 143[a]	Wk 156 Rescue / D/C[a]	Notes
Safety Assessments										
Complete physical examination					X				X	Section 5.3.5 (in protocol)
Brief physical examination	X	X	X	X			X	X		Section 5.3.5 (in protocol)
Vital signs (seated blood pressure and heart rate)	X	X	X	X	X		X	X	X	Section 5.3.6 (in protocol)
Body weight	X	X	X	X	X		X	X	X	Section 5.8.2 (in protocol)
Body mass index (BMI)	X	X	X	X	X		X	X	X	Section 5.8.3 (in protocol)
Waist circumference	X				X				X	Section 5.8.4 (in protocol)
12-lead ECG				X					X	
Review concomitant medications / procedures	X	X	X	X	X		X	X	X	
Provide diet and exercise counseling	X	X	X	X	X		X	X	X	Section 5.8.1 (in protocol)
Provide glucose meter supplies / instructions	X	X	X	X	X		X	X		
Provide logs / instructions	X	X	X	X	X		X	X		
Review study logs	X	X	X	X	X		X	X	X	
Assess AEs and hypoglycemia episodes	X	X	X	X	X		X	X	X	Section 5.3.1.2 (in protocol)

Table 5.1-3: Long-term Procedural Outline for Protocol CV181365 (104-week) Subject- and Site-Blinded Treatment (Period D Week 52 to Week 156)

Procedure	Wk 65[a]	Wk 78[a]	Wk 91[a]	Wk 104[a]	Wk 117[a]	Wk 122[b]	Wk 130[a]	Wk 143[a]	Wk 156 Rescue / D/C[a]	Notes
Central Laboratory										
Pregnancy test (urine) WOCBP only	X	X	X	X	X		X	X	X	Home pregnancy test kits sent home with WOCBP subjects to perform pregnancy test between visits and record result in log book.
Clinical chemistry, haematology, urinalysis (standard safety laboratory panel)		X		X			X		X	
Microscopic urinalysis		X			X				X	Section 5.3.2 (in protocol) Appendix 3 (in protocol)
Spot urine for glucose, albumin and creatinine quantification and determination of glucose: creatinine and albumin:creatinine ratios					X				X	
HbA1c	X	X	X	X	X		X	X	X	
FPG	X	X	X	X	X		X	X	X	
Estimated CrCl (Cockcroft-Gault) and serum creatinine (SCr)	X	X	X	X	X		X	X	X	
Fasting serum lipids (Total-C, LDL-C, HDL-C, TG)									X	

Table 5.1-3: Long-term Procedural Outline for Protocol CV181365 (104-week) Subject- and Site-Blinded Treatment (Period D Week 52 to Week 156)

Procedure	Wk 65[a]	Wk 78[a]	Wk 91[a]	Wk 104[a]	Wk 117[a]	Wk 122[b]	Wk 130[a]	Wk 143[a]	Wk 156 Rescue / D/C[a]	Notes
Fasting C-peptide					X				X	
hsCRP, NT-proBNP									X	
Fasting serum insulin and proinsulin for proinsulin/insulin ratio, and glucagon									X	
Additional Assessments										
Patient-reported outcomes questionnaires				X					X	Section 5.8.8 (in protocol)
MRI-PDFF						X				Subjects assigned to the MRI-PDFF sub-study will have an ad-hoc visit at the imaging site within ± 4 weeks of the Week 122 visit (eg, between Week 118 up to Week 126) as described in Section 5.8.6. Subjects who require rescue therapy or discontinue from study treatment early will be asked to return to the imaging site for an unscheduled MRI visit (if possible) within 4 weeks of initiating rescue medication or the Early Termination visit as described in Section 5.8.6.
Assess HbA1c for rescue	X	X	X	X	X		X	X		

Table 5.1-3: Long-term Procedural Outline for Protocol CV181365 (104-week) Subject- and Site-Blinded Treatment (Period D Week 52 to Week 156)

Procedure	Wk 65[a]	Wk 78[a]	Wk 91[a]	Wk 104[a]	Wk 117[a]	Wk 122[b]	Wk 130[a]	Wk 143[a]	Wk 156 Rescue / D/C[a]	Notes
Study Drug										
Dispense blinded study medication	X	X	X	X	X		X	X		
Review study medication compliance	X	X	X	X	X		X	X	X	
Register down-titration of glimepiride during maintenance period (if applicable in IVRS	X	X	X	X	X		X	X		
*Contact IVR system	X	X	X	X	X		X	X	X	

[a] Visits may be scheduled ± 5 days to allow flexibility of scheduling.

[b] Visits may be scheduled ± 4 weeks to allow flexibility of scheduling.

Table 5.1-4: Early Discontinued (D/C)/End of Treatment (EOT) Follow-up Non-Treatment Phase (Period X)

Procedure	Non-treatment Follow-up (X) Office Visit[a,b]	Non-treatment Follow-up (X) Phone Assessment[b,c]	Notes
Safety Assessments			
Targeted physical examination	X		Section 5.3.5 (in protocol)
Vital signs	X		Section 5.3.6 (in protocol)
Body weight and waist circumference	X		Section 5.8.2 (in protocol)
Review concomitant medications	X	X	
AE assessment	X *	X *	*Assessment of serious infections; and opportunistic infections, upper respiratory infections, urinary tract infections regardless of seriousness criteria
Standard safety laboratory panel (Blood)	X		
HbA1c	X		

[a] In office assessments to occur at time points corresponding to originally scheduled Week 28, Week 52, 104, and 156 visits

[b] Visits may be scheduled ± 5 days to allow flexibility of scheduling.

[c] Phone assessments only to occur at time points corresponding to originally scheduled that is not identified above as an in office visit

5.1.1 Retesting During Screening or Lead-in Period

Retesting of laboratory parameters and/or other assessments during the screening or lead-in period will not be permitted (this does not include parameters that require a confirmatory result).

5.2 Study Materials

The Sponsor will supply the sites with the following materials:

- Blood glucose meters. One (1) meter will be provided to each study subject at enrollment and one (1) meter will be provided to each investigative site.
- Glucose test strips
- Lancets
- Glucose control solutions
- CGM devices and software to download data
- Subject education and site support materials (eg, CGM instruction manuals)
- eCRFs [Serious Adverse Events Forms, Pregnancy Surveillance Forms, Events of Special Interest]
- Subject alert cards
- Study drug inventory control forms
- Site file
- DKA Adjudication Manual for Sites
- Subject diary:
  - Full diary review by site staff is required for this study
  - Use of subject diaries are mandatory for the study and will be maintained by each study subject for documentation of SMBG results, study medication dosing, hypoglycemia episodes, meal times (applicable during periods of 6-point SMBG and CGM), and if applicable, WOCBP urine pregnancy results.
    - 6-point SMBG profiles: Subjects will be instructed to perform and record in their diaries the results for their 6-point SMBG profiles. The 6-points consist of the following; 3 glucose measurements obtained preprandially (within 15 minutes prior to meal) and 3 glucose measurements obtained postprandially (1.5 - 2 hours after the meal) for the 3 main meals of the day. All subjects should perform 6-point SMBG on any 3 days (do not have to be on consecutive days) during the following periods:
      - Prior to the Day 1 visit (between Weeks -2 and -1)
      - Prior to the Week 52 visit (between Week 51 and Week 52). Electronic CRF pages will be provided to the sites so they can record the data obtained from the diaries into the study database
    - Subjects are to record their meal times in their diary on the days that they perform 6-point SMBG.

- The dates and number of tablets of study medication taken by the subject are to be recorded in the study diary. Electronic CRF pages will be provided to the sites so they can record the data obtained from the diaries into the study database.
- Subjects are to record any hypoglycemic symptoms they may experience and SMBG values if they perform capillary glucose testing when they have symptoms in their diaries. All events recorded in subject diary to be reviewed by site staff according to Section 5.3.1

Any other materials as locally required or agreed.

The central laboratory will provide all laboratory-related materials, including home pregnancy testing kits for WOCBP to the study sites.

5.3 Safety Assessments

Safety assessments will include adverse event reporting, as well as marked abnormalities in clinical laboratory tests. Please refer to Appendix 2 for details on central laboratory assessments.

The procedures described in the sections that follow will also be completed to ensure subjects' safety.

5.3.1 Self-Monitored Blood Glucose (SMBG) and Guidance on Management and Reporting of Hypoglycemia Episodes

5.3.1.1 Self-Monitoring of Blood Glucose (SMBG)

Glucose meters will be supplied to each study site. At the entry into the lead-in period (Week -2 visit), subjects will receive a glucose meter, supplies and instruction on their use. Supplies will be provided to allow for approximately 60 blood glucose assessments per month for the duration of the study. The investigator may require more frequent readings based on local clinical practice. Subjects should bring their glucose meter with them to each study visit to ensure that it is functioning properly. Subjects may keep the glucose meter at the end of the study, but the Sponsor will not continue to provide glucose meter supplies.

Subjects should self-monitor their blood glucose approximately 2 times per day and when symptoms suggestive of hypoglycemia occur. Subjects should contact the investigator in the event of an unusually high or low blood glucose value. In addition, study subjects should comply with the site's instructions with regard to self-monitoring of blood glucose and should report to the site blood glucose values and/or signs and symptoms suggestive of a hypoglycemic episode.

The memory of the glucose meter should be reviewed to compare readings with the subject's hypoglycemia episode log, as applicable. The glucose values should be reviewed by the site to identify any unusual high or low values, and to confirm that the values (from the glucose meter's memory and/or from the subject's hypoglycemia log) were obtained for the subject. If fingerstick glucose values are discordant from glycemic control assessed by the central laboratory or with clinical symptoms, the subject's glucose meter should be tested and the procedure for using it reviewed with the subject. The glucose values should be reviewed by the site to identify any

unusual high or low values, and to confirm that the values (from the glucose meter's memory and/or from the subject's hypoglycemia log diary) were obtained for the subject. If capillary blood glucose values are discordant from glycemic control assessed by the central laboratory or with clinical symptoms, the subject's glucose meter should be tested and the procedure for using it reviewed with the subject. Additional reasons for discrepancy should also be considered. Variables that can affect capillary blood glucose results include hypotension (decreased perfusion), alternate site testing (eg, forearm, palm, thigh versus finger tip), and drugs (eg, acetaminophen). Variables that can affect central laboratory measurement include variation in hematocrit, hemolysis, and laboratory error (whole blood glucose concentration measured instead of plasma glucose concentration).

5.3.1.2 Guidance on Management and Reporting of Hypoglycemia Episodes

Mild hypoglycemia may occur in subjects who are treated for type 2 diabetes, particularly when treated with an insulin secretagogue (eg, SU) or insulin. Subjects and their family members should be informed of the dangers associated with low blood sugar and properly instructed on the recognition and management/treatment of hypoglycemia.

Subjects should record any hypoglycemic symptoms in their log books. They should be encouraged to measure, when possible, their blood glucose values when they have symptoms of hypoglycemia. Subjects should carry easily ingestible forms of carbohydrate with them at all times in order to treat an event of hypoglycemia should it occur.

During clinical trials, subjects frequently report symptoms of hypoglycemia when asked, even when treated with placebo or medications not otherwise associated with hypoglycemia. As hypoglycemia is an important event associated with diabetes therapy, all episodes which could be consistent with the clinical definition of hypoglycemia as assessed by the investigator should be documented and reported on the appropriate eCRF page.

The following definitions of hypoglycemia will be used:

- **Severe hypoglycemia.** An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
- **Documented symptomatic hypoglycemia:** An event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤ 70 mg/dl (3.9 mmol/l).
- **Asymptomatic hypoglycemia:** An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤ 70 mg/dl (3.9 mmol/l).
- **Probable symptomatic hypoglycemia:** An event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination (but that was presumably caused by a plasma glucose concentration ≤ 70 mg/dl [3.9 mmol/l]). Since many people with diabetes choose to treat symptoms with oral carbohydrate without a test of plasma glucose, it is

important to recognize these events as "probable" hypoglycemia. Such self-reported episodes that are not confirmed by a contemporaneous low plasma glucose determination may not be suitable outcome measures for clinical studies that are aimed at evaluating therapy, but they should be reported.

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

Hypoglycemia eCRF pages will be used to document all reported episodes of hypoglycemia. The investigator is responsible for questioning the subject about all symptoms reported on the hypoglycemia log and for determining if they meet the clinical definition of hypoglycemia. Only symptoms and/or blood glucose values deemed by the investigator to meet the definition of hypoglycemia should be reported on the hypoglycemia eCRF pages. Signs and symptoms of hypoglycemia, hypoglycemic episodes, or discontinuation due to hypoglycemia should not be reported on the adverse event (AE) eCRF page, unless the event fulfills protocol criteria for a Serious Adverse Event (SAE) (see Section 6.1.1), in which case an SAE form must be completed in addition to the hypoglycemia eCRF pages for hypoglycemia.

5.3.2 Guidance on Assessment of Urinary Infections & Hematuria

5.3.2.1 Guidance on Assessment of Urinary Tract Infections

The following is presented to assist in the classification and management of urinary tract infections (UTI). It is not intended to supplant investigators' clinical judgment. It is at the discretion of an investigator to determine whether and when to send an initial urine culture.

Urosepsis and Pyelonephritis

There have been post-marketing reports of serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization in patients receiving dapagliflozin and other SGLT2 inhibitors. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly.

Study drug should be withheld in subjects with clinical evidence of upper tract UTI (eg, pyeloneprhitis) or presumed urosepsis until the course of treatment of the infection has been completed and clinical recovery has occurred.

Asymptomatic bacteriuria

Asymptomatic bacteriuria is defined as the presence of $\geq 10^5$ colony forming units/mL of bacteria, in a properly collected voided urine specimen, without signs or symptoms typically attributed to urinary tract infection. Asymptomatic bacteriuria is prevalent among diabetic women, and is associated with pyuria in 70% of cases. Neither guidelines from the Infectious Disease Society of American (IDSA) and the US Preventive Services Task Force[10,11] recommend screening for, or treatment of, asymptomatic bacteriuria in non-pregnant diabetic patients. In this study, the central laboratory will report urinary dipstick test results for hemoglobin but will not routinely report the results of urinary dipstick tests for leukocyte esterase as a screening test for pyuria in surveillance urine examinations.

It is recommended that a culture be obtained within 7 days of clinical recovery for all treated UTIs. Whether or not additional therapy is prescribed because of culture results should be determined by investigator judgment, after consultation with the Sponsor Medical Monitor.

It is the investigator's responsibility to report, as applicable based on the investigator's judgment and the subject's medical history, related adverse events as defined in Section 6. Additional information, including but not limited to completion of supplemental eCRFs or questionnaires may be requested for certain adverse events and/or laboratory abnormalities which are reported/identified during the course of the study.

5.3.2.2 Guidance on Assessment of Hematuria

All events of hematuria (microscopic and/or macroscopic) during the study should be worked up for a possible cause. If no immediate or benign cause is identified as judged by the investigator (eg, menstruation, kidney stone, urinary tract infection [UTI], where hematuria is subsequently resolved after successful treatment), subjects should undergo further evaluation by the investigator or another qualified professional. The evaluation may include, but is not limited to, tests such as urine cytology, NMP-22, or abdominal CT scans. The choice of tests should be per local standard of care/professional society guidance. The subject should continue to receive IMP treatment during these investigations (unless otherwise contraindicated). All confirmed events of bladder cancer should lead to the discontinuation of IMP (See Appendix 3).

It is the investigator's responsibility to report, as applicable based on the investigator's judgment and the subject's medical history, related adverse events as defined in Section 6. Additional information, including but not limited to, completion of supplemental eCRFs or questionnaires may be requested for certain adverse events and/or laboratory abnormalities which are reported/identified during the course of the study.

5.3.3 Guidance on Assessment of Cardiovascular Events

A Cardiovascular Adjudication Committee that is blinded to the treatment of the subjects will independently adjudicate all events of heart failure requiring hospitalization.

5.3.4 Guidance on Assessment of Hepatic Laboratory Abnormalities

An independent Hepatic Adjudication Committee, blinded to the treatment of the subjects, will determine the probability that drug-induced liver injury (DILI) is the cause of liver-related abnormalities, included, but not limited to:

- Hepatic disorders leading to death
- Liver laboratory abnormalities, such as elevated AST and/or ALT with or without total bilirubin elevations

The following is presented to assist in the evaluation and management of hepatic laboratory values. It is not intended to supplant the investigator's clinical judgment. Subjects who experience ALT and/or AST values > 3x 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 total bilirubin, 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 Appendix 2)

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

For subjects who are discontinued from study medication as a result of sustained elevated liver safety abnormalities, as described in Section 3.5, additional blood sampling must be done within 3 days of the confirmed laboratory results (see Appendix 4), in conjunction with an Early Treatment Discontinuation (End-of-Treatment) visit, in addition to the procedures noted above. 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 subjects with abnormal laboratory values at the follow-up visit should be made available to the Sponsor upon request.**

5.3.5 Physical Examination

- A brief physical examination should include cardiovascular, lungs, abdomen, and extremities, and any organ systems pertinent to the subject's signs, symptoms, or adverse events
- A complete physical examination should include general appearance, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdomen, lymph nodes, extremities, neurological, skin, and musculoskeletal.
- The individual performing the physical examinations must be licensed by state law (or applicable local law) to perform this procedure.

5.3.6 Blood Pressure and Heart Rate

Blood pressure (BP) and heart rate (HR) measurements must be taken consistently throughout the study. Only the right or the left arm should be used when measuring these parameters. The arm that has been used should be documented, along with the observer's initials; the same arm should be used for each position and at each visit. The subject should be allowed at least 5 minutes of rest before measurement. Blood pressure should be measured with the subject's arm resting on a table, and with subject's back support and feet flat on the floor.

Blood pressure and HR will be determined from three replicate measurements obtained at least 1 minute apart. The average BP and HR will be determined from these three replicate measurements and reported in the eCRF.

All measurements should occur at least 8 hours after the last ingestion of caffeine, alcohol, or nicotine.

It is critical that the BP and HR measurements be obtained prior to the administration of blinded study medication.

5.3.7 Guidance on Volume Depletion

Dapagliflozin has a modest diuretic effect. The risk of volume depletion is enhanced when two diuretics are used in combination and in subjects that otherwise are at risk for volume depletion. Therefore, caution should be exercised when administering dapagliflozin to subjects at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics. These subjects should be carefully monitored for volume status, electrolytes, and renal function.

5.3.8 Supplemental Visits

5.3.8.1 Rescue or Early Treatment Discontinuation Visit

Subjects rescued during or discontinued from the short-term double-blind treatment period

Any subject who qualifies for rescue or discontinues from the short-term double-blind treatment period must have all Rescue/Early Treatment Discontinuation (ETD) visit procedures performed at the time of study discontinuation or rescue. The IVRS must be called to record the subject status (ie, rescue, or discontinuation status). All subjects who are rescued or who discontinue study drug should remain in the study and follow the visit schedule.

- For subjects qualifying for rescue PRIOR to Week 52, Rescue/ETD procedures will be performed and the subject will then continue in the treatment period according to the regular visit schedule. The Rescue/ETD supplemental eCRF will need to be completed to collect rescue-related endpoint data. A Week 52/Rescue/ETD visit laboratory kit will need to be used to collect the Rescue Visit blood and urine samples.
- Subjects who discontinue study medication during the short-term double-blind treatment period should have all ETD procedures performed (Rescue/ETD visit). The Rescue/ETD eCRF will also need to be completed and a Week 52/Rescue/ETD visit laboratory kit will need to be used to collect the ETD Visit blood and urine samples. Subjects will then continue in the study according to the regular visit schedule, including the long-term subject- and site-blinded treatment period.

Subjects rescued during or discontinued from the long-term subject- and site-blinded treatment period

Any subject who qualifies for rescue or discontinues from the long-term subject- and site-blinded treatment period must have all Rescue/Early Treatment Discontinuation (ETD) visit procedures performed at the time of study discontinuation or rescue. The IVRS must be called to record the subject status (ie, rescue, or discontinuation status). All subjects who are rescued or who discontinue study drug should remain in the study and follow the long-term visit schedule.

- For subjects qualifying for rescue AFTER Week 52, Rescue/ETD procedures will be performed and the subject will then continue in the treatment period according to the regular long-term visit schedule. The Rescue/ETD supplemental eCRF will need to be completed to collect rescue-related endpoint data. A Week 156/Rescue/ETD visit laboratory kit will need to be used to collect the Rescue Visit blood and urine samples.
- Subjects who discontinue study medication during the long-term subject- and site-blinded treatment period should have all ETD procedures performed (Rescue/ETD visit). The Rescue/ETD eCRF will also need to be completed and a Week 156/Rescue/ETD visit laboratory kit will need to be used to collect ETD Visit blood and urine samples. Subjects will then continue in study according to the regular long-term visit schedule.

5.3.8.2 Other Supplemental (Unscheduled) Visits

At any time during the trial, the investigator may at his/her discretion arrange for a subject to have an unscheduled (supplemental) assessment(s), especially in the case of AEs that require follow-up. If a subject is seen for an unscheduled assessment, the appropriate Supplemental Pages of the eCRF must be completed.

5.4 Efficacy Assessments

Assessments consist of the central laboratory measurement of HbA1c and other relevant laboratory tests, collected during the study.

5.5 Pharmacokinetic Assessments

Not applicable.

5.6 Biomarker Assessments

Biomarkers, such as but not limited to, hsCRP and NT-proBNP will be assessed at Week 52 and Week 156.

5.7 Outcomes Research Assessments

Not applicable

5.8 Other Assessments

5.8.1 Diet and Exercise Counseling

Starting at entry into the lead-in period, subjects will be instructed on a diet and an exercise program in accordance with the American Diabetes Association (ADA) or similar local guidelines to be followed for the study duration.

A registered dietitian, registered nurse, physician, Certified Diabetes Educator (CDE), nutritionist, or other qualified member of the study team who has appropriate documented training, will provide this counseling.

5.8.2 Weight

Body weight will be measured according to the schedule presented in the study flow chart/time and event schedule (see Section 5.1) and will be recorded in the eCRF. The study-site staff should use a digital precision scale if possible, and record the weight in kilograms or pounds to the first decimal point (eg, 69.3 kg). The subject should wear a standard hospital-type gown or equivalent light indoor clothing, have shoes removed, and bladder empty for the body weight measurement at each visit. Subjects should be weighed on the same scale at all visits.

5.8.3 Height and Body Mass Index (BMI)

- Measurement of height should be performed with the subject's shoes removed. The subject's knees should be straightened, head held erect and eyes forward

- BMI is used as an index of obesity and is a method of defining normal body weight and excess body fat. It correlates in a population with percent body fat.
- BMI is determined by weight (kg) divided by height (m) squared.

Method of BMI Calculation:

- Use actual height and weight
- To calculate BMI:
- Convert pounds (lbs) to kilograms (kg = lb / 2.2)
- Convert inches (in) to centimeters (cm = in x 2.54)
- BMI = (weight in kg) / (height in cm/100)^2
- Round to one decimal place (if 0.05 or greater, round up)

5.8.4 Waist Circumference

The waist circumference measurements will be performed at various time points during the course of the study (refer to Table 5.1-1, Table 5.1-2, Table 5.1-3, and Table 5.1-4). Waist circumference will be measured by placing a measuring tape midway between the lower rib and iliac crest. The measuring tape should pass over the umbilicus.

The waist measurement reported on the eCRF should represent the average of at least 2 measurements. The average measurement should agree with 1 cm. If not, additional measurement(s) should be taken.

5.8.5 Survey of Subject Vital Status

Subjects who prematurely discontinue from the study may be contacted after discontinuation from the study to collect vital status and safety information.

Sub-studies:

5.8.6 Magnetic Resonance Imaging (MRI)

The reduction in body weight consistently observed during treatment with dapagliflozin has been shown to result in total body fat reduction. It is not known, however, whether this reduction in body fat is equally distributed among subcutaneous and visceral adipose tissue or if there is a preferential loss of adipose tissue in the visceral compartment. Body composition measurements by MRI can separately quantify the subcutaneous and the visceral adipose tissue. Non-invasive quantification of liver lipid content by MRI is an emerging biomarker for assessment of the beneficial effects of weight loss and improvement in glycemic control on liver lipid metabolism.

Body composition will be measured with MRI using a body scan based on the Dixon method with multiple gradient-echoes and multislice acquisition centered at the L4-L5 interface. All acquisitions will be performed using clinical MRI scanners with the subjects in the supine

position. The analysis will be done centrally using semi-automated software that will give visceral, subcutaneous, and total fat volume as output in liters (l)

Liver lipid content will be calculated from a separate scan covering the liver using a Dixon technique giving liver lipids as output in percent (%).

The MRI investigations will be performed for assessing subcutaneous and visceral adipose tissue volume, liver volume, and percent hepatic lipid content, using standard clinical scanners. The magnetic field created attracts ferromagnetic objects into the scanner. Subjects with a ferromagnetic implant or device, such as pacemakers, metallic splinters in the eye, and clips in the central nervous system, are contraindicated for MRI. A standardized questionnaire will be used before each MRI scan is performed to screen subjects for any contraindication for MRI. No contrast agent will be used.

The MRI-PDFF sub-study will be conducted at approximately 11 MRI sites in Europe. Approximately 60 (30 per arm) subjects from selected recruiting sites are expected to participate in the MRI-PDFF sub-study. Each subject participating in the MRI-PDFF sub-study will be referred to a MRI site for MRI measurements. Several recruitment sites can refer subjects to one MRI site. Subjects participating in the MRI sub-study will be required to provide informed consent.

All MRI consented subjects should have MRI visits scheduled at the imaging site in close proximity to the Day 1 (Randomization), Week 52 and Week 122 visits at the clinical sites. The MRI assessments do not need to occur on the same day as these visits. An ad-hoc visit at the imaging site will be scheduled within 2 weeks prior to the Day 1 (Randomization) visit (eg, between Week -2 and up to, but not including, Day 1). Ad-hoc visits at the imaging site will be scheduled within ± 2 weeks of the Week 52 visit (eg, between Week 50 up to Week 54) and within ± 4 weeks of the Week 122 visit (eg, between Week 118 up to Week 126). Additionally, subjects who require rescue therapy or discontinue from study treatment early will be asked to return for an unscheduled MRI visit (if possible) within 4 weeks of initiating rescue medication or the Early Termination visit.

All MRIs will be sent for central evaluation to a core laboratory. No local reading will be performed. During the double-blinded short-term treatment period (Day 1 to Week 52), the MRI results will be blinded to recruiting sites, investigators, the MRI sites, the subjects, and the Sponsor. After Week 52, the MRI results will not be blinded for the Sponsor, but will remain blinded to the recruiting sites, investigators, the MRI sites, and the subjects. Subjects who are found to have unevaluable data at baseline will be removed from the MRI sub-study population but will remain active in the base study through trial completion. Additional subjects will be added to obtain the protocol required subpopulation.

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the investigator as per standard medical/clinical judgment.

The Sponsor will not provide MRI results to subjects or investigators at the conclusion of the study, unless specifically requested by the subject.

5.8.7 Continuous Glucose Monitoring (CGM)

CGM measures the subject's interstitial glucose level using a sensor which utilizes a small electrode that measures an electrical signal produced by the glucose oxidase reaction. The system records data approximately every 5 minutes, giving profiles of mean glucose values over 24 hours. The data will remain blinded to the subject and the investigator during the recording. A CGM sensor will be inserted subcutaneously on the subject between Week - 2 and Week - 1, (and removed prior to the first dose on Day 1), and between Week 51 and Week 52, (and removed prior to the dose at the Week 52 visit) to allow monitoring for a 7-day time period. During each day that the CGM sensor is worn, subjects will document their three main meal times and any snacks, along with their blood glucose meter readings in the 'Blood Glucose and Meal Time Diary'. Also, subjects will be required to perform a 4-point SMBG profile on days that they are not performing the 6-point SMBG profile. This 4-point SMBG should be performed at the approximate times: before breakfast, before lunch, before dinner and before bedtime. The CGM data will be uploaded, along with the blood glucose meter data and the 'Blood Glucose and Meal Time Diary' to the Phase V® Health Outcomes Information System. Detailed procedures will be described in an operations manual and site staff will be fully trained.

CGM is a useful technology (in addition to HbA1c) to qualitatively, as well as quantitatively, monitor the quality of glycemic control in the form of time spend in euglycemic/hyperglycemic/hypoglycemic (blood glucose ≤ 70 mg/dL (3.9 mmol/L)) range and mean amplitude of glucose excursions (MAGE). Co-administration of saxagliptin and dapagliflozin, on top of background metformin therapy, is expected to better demonstrate benefits in glycemic control compared to treatment with glimepiride, on top of background metformin therapy.

In this protocol, a subpopulation of approximately 120 randomized subjects (~ 60 subject/treatment arm) who agree to participate (separate informed consent) will have CGM performed for periods of 7 days at baseline and at Week 52. Subjects who are found to have unevaluable data at baseline will be removed from the CGM sub-study population but will remain active in the base study through trial completion. Additional subjects will be added to obtain the protocol required subpopulation.

5.8.7.1 Fasting Plasma Glucose

Blood samples will be drawn for measurement of FPG concentration according to the schedule presented in study flow chart/time and event schedule (see Section 5.1).

5.8.7.2 6-point SMBG profiles

Subjects will be instructed to perform 6-point SMBG profiles on any 3 days during the period between Week - 2 and Week - 1 (eg, prior to the Day 1 [Randomization]) and within a week of the Week 52 visit, according to the schedules presented in study flow chart/time and event

schedule (see Section 5.1). Each separate 6-point SMBG profile encompasses one day within one week before the scheduled visits, with three glucose measurements obtained preprandially (within 15 minutes prior to meal) and three glucose measurements obtained postprandially (1.5 - 2 hours after the meal) for the three main meals of the day. Subjects will be provided with a diary to record these SMBG measurements and mealtimes, and eCRFs will available for the investigator sites to capture these results.

5.8.8 Patient-reported outcomes (PRO)

The Phase V® Health Outcomes Information System Diabetes Module will be used for the PRO assessments.[12] The self-administered PRO questionnaires consist of validated generic and diabetes-specific modules of treatment satisfaction, quality of life, and barriers to medication adherence. These measures have been found to be responsive to the effects of therapeutic interventions and the impact of side effects of medication, symptoms of diabetes, change in HbA1c, diabetes-related treatment satisfaction, diabetes-related weight changes, and glycemic variability.

See User Guide for instructions and response options for the Phase V® Health Outcomes Information System Diabetes Module. This questionnaire will be administered at the Day 1, Week 12, Week 28, Week 52, Week 104, and Week 156 visits, as well as at the Early Discontinuation Visit (if applicable).

Translations of the Phase V® Health Outcomes Information System Diabetes Module into local languages have or will be performed according to a linguistic validation process.

5.9 Results of Central Assessments

Blood and urine samples will be obtained at specified time points for laboratory evaluations (see Appendix 2). The central laboratory for this study will perform the analysis of all scheduled laboratory tests and will provide reference ranges for these tests. The central laboratory will provide specific instructions for collection, processing, packaging, and shipping of all samples.

During the Short Term double-blind treatment period (in non-rescued subjects), the HbA1c values will be blinded to the Investigator, subject, and to the Sponsor. These values will be provided to the Investigator after the study has been completed or after completion of the rescue visit in subjects who require the initiation of rescue medication. During the subject and site blinded long-term treatment period, after the Week 52 visit, the HbA1c values will not be blinded.

Spot urine samples were taken for glucose, albumin, creatinine, and determination of glucose:creatinine and albumin:creatinine ratios. Results for glucose and the glucose:creatinine ratio will be blinded to the Investigator and Sponsor throughout the study, (short-term treatment period and long-term treatment period). These values will be provided to the Investigator after the study has been completed. The albumin, creatinine, and albumin:creatinine ratio results will not be blinded during the study.

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

> Related: There is a reasonable causal relationship between study drug administration and the AE.
>
> Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

6.1 Serious Adverse Events

A S***erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug-induced liver injury (DILI) is also considered an important medical event. (See Section 6.7 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug-induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death) is an endpoint and should be reported as an SAE. (For example, if death occurred due to anaphylaxis, anaphylaxis must be reported as an SAE.) See Section 6.1.1 for reporting details.

NOTE:

The following hospitalizations are not considered SAEs in this clinical study:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessments requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing.

The investigator should report any SAE that occurs after these time periods that is believed to be related to study drug or a protocol-specified procedure.

An SAE Report Form should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs (whether related or not related to study drug) and pregnancies must be reported to the Sponsor (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: PPD

SAE Facsimile Number:

Note: All numbers redirect to the same recipient – so chose the most convenient number.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event that the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): Contact should be made to the Sponsor or its designee. Refer to provided Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the Sponsor (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

The reporting of Serious Adverse Events (SAEs) to the Sponsor for this trial will be monitored by CRO on behalf of the Sponsor. The responsibilities for safety reporting to regulatory authorities, IRB/EC and investigators are based on the local regulatory requirements for each country.

Safety reporting to local regulatory authorities

The Sponsor Marketing Company (MC) or designee will perform all expedited and periodic Safety reporting to the regulatory authority as required locally. The Sponsor is responsible for the production of all expedited and periodic reports for regulatory reporting (i.e. Investigator Safety Letters, CIOMS forms for Suspected Unexpected Serious Adverse Reactions (SUSARs),

E2B, MedWatch, Development Safety Update Reports (DSURs) and Periodic SUSAR line listings (PSLLs)).

Safety reporting to investigational review boards/ethics committees and investigators

In most countries, there are local requirements to report safety information to concerned Investigational Review Boards (IRB)/Ethics Committees (EC) and investigators.

The Sponsor is responsible for the production of all safety update reports (expedited and periodic) to inform IRBs/ECs and investigators (i.e. Investigator Safety Letters, CIOMS for SUSARs, DSURs and Periodic SUSAR line listings (PSLLs)).

In the 31 countries within the EEA as well as some countries adjacent to EEA, the principles for safety reporting to ECs and investigators are governed by Article 17 of the European Union (EU) Clinical Trials Directive 2001/20/EC and Guideline NTR/CT/ 3 Revision 2 (2006), but there are country specific variations.

In order to ensure expedited reporting timelines are met, the Sponsor's Clinical Operations or designee will handle all expedited reporting of individual SUSARs to ECs and, where required to investigators.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Non-serious Adverse Event Collection and Reporting

Non-serious AE information should be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects, until the end of the follow up period.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified non-serious AEs must be recorded and described on the non-serious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for non-serious AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Adverse Events (AEs) Leading to Amputation and Potential Risk Factor AEs for Amputations Affecting Lower Limbs ("Preceding Events")

To ensure that data on amputations are systematically collected, amputations and underlying conditions relevant to amputation will be recorded on a specific eCRF page.

If any of these relevant events have occurred, relevant information must be provided (this will be collected on a dedicated eCRF page).

6.4 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the non-serious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy
- Any microscopic hematuria with NO common cause identified, if a malignancy is otherwise suspected or positive hematuria (by microscopy) is found at the unscheduled repeat visit (See section 5.3.2 & Appendix 3)

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.5 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives (30 days) after product administration, the investigator must immediately notify the Sponsor Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to Sponsor Designee within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

Study drug will be permanently discontinued in any subjects that become pregnant during the study; the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the Sponsor (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to the Sponsor (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcomes and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the Sponsor. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.6 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs (see Section 6.1.1 for reporting details).

6.7 Potential Drug Induced Liver Injury (DILI)

Specific criteria for identifying potential DILI have not been identified for this protocol. Standard medical practice in identifying and monitoring hepatic issues should be followed.

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILI, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

9. Aminotransferase (ALT or AST) elevation > 3x upper limit of normal (ULN)

AND

10. Total bilirubin > 2x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

11. No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.8 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

6.8.1 AEs of Special Interest

Event categories of special interest for this study may include, but are not limited to, skin, decreased lymphocyte count, decreased thrombocyte count, infection, opportunistic infection, pancreatitis, hepatic abnormalities, fracture, hypersensitivity, renal failure and renal impairment, genital infections, urinary tract infections, bladder neoplasm, and breast neoplasm.

For the purposes of regulatory reporting, the following events must be reported in 24 hours regardless of whether the events are classified as serious or non-serious:

Liver function test (LFT) abnormalities accompanied by jaundice or hyperbilirubinemia

This category of events includes all AEs where hepatocellular damage (with elevation of ALT or AST > 3x ULN) is combined with hepatic dysfunction (with elevation of total bilirubin

> 2x ULN) or jaundice. With respect to LFT abnormalities, both central and local laboratory results and adverse events will be monitored.

Opportunistic infections

This category of events includes infections of interest that are consistent with AIDS-defining diagnoses and are specific for immunosuppression, including unusual infections caused by bacteria, mycobacteria, fungi, viruses and protozoa. Herpes zoster is of interest only if the case is multidermatomal, neurological (eg, transverse myelitis, encephalitis, aseptic meningitis, or other neurologic complications) or systemic.

Severe Hypersensitivity

This category of events includes all cases of severe hypersensitivity including: angioedema, anaphylaxis, and Stevens-Johnson Syndrome.

When one of these events meets the criteria for a serious adverse event, report the event using SAE reporting procedures (Section 6.1.1). When one of these events does not meet the criteria for a serious adverse event, report the event within 24 hours as a non-serious event.

For each non-serious event in these three categories, notify the Sponsor Medical Monitor within 24 hours to discuss the next steps in reporting.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

7.1 Cardiovascular Adjudication Committee

An independent Cardiovascular Adjudication Committee, blinded to the treatment of the subjects, will adjudicate all potential events of heart failure requiring hospitalization (see Section 5.3.3 for more details).

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

7.2 Hepatic Adjudication Committee

An independent Hepatic Adjudication Committee, blinded to the treatment of the subjects, will determine the probability that drug-induced liver injury (DILI) is the cause of liver-related abnormalities, including but not limited to, hepatic disorders leading to discontinuation from death, and liver laboratory abnormalities such as elevated AST and/or ALT with or without total bilirubin elevations (see Section 5.3.4 for more details).

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

7.3 Diabetic Ketoacidosis Adjudication Committee

The DKA Adjudication Committee will assess available information on each potential DKA event and will classify the event in accordance with the definitions in the DKA Adjudication

Charter T2DM. All potential events of DKA will be recorded in the electronic case report form (eCRF) and submitted to an independent DKA Adjudication Committee.

The DKA Adjudication Committee will be kept blinded to the study drug treatment received by each subject with a potential DKA event in the clinical study. A separate DKA Adjudication Manual will define and describe the procedures for the collection of DKA information, handling, adjudication criteria and reporting of these events/cases.

8 .STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The mean change in baseline in HbA1c at Week 52 will be assessed by comparing saxagliptin, in co-administration with dapagliflozin, added to current background therapy with metformin, versus the active comparator treatment group (glimepiride added to current background therapy with metformin).

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

Assuming a mean change from baseline in HbA1c difference effect of 0.35% for saxagliptin in co-administration with dapagliflozin plus metformin vs glimepiride plus metformin, a common standard deviation of 1.1%, and using a 2-sided significance level of 0.05 for the comparison, and assuming a 5% non-evaluability rate, then a sample size of 220 patients per arm will yield 90% power for the comparison of saxagliptin in co-administration with dapagliflozin plus metformin against glimepiride plus metformin.

8.2 Populations for Analyses

- The **Enrolled Subjects Data Set** will consist of all subjects who sign informed consent.
- The **Randomized Subjects Data Set** will consist of all randomized subjects who receive at least one dose of study medication during the treatment period. This is also known as the Intent-to-Treat (ITT) population. This will be the primary efficacy data set. Data in this data set will be analyzed based on randomized treatment group.
- The **Evaluable Subjects Data Set** will be a subset of the Randomized Subjects, with all data points collected after relevant protocol deviations are excluded from the data set. Relevant protocol deviations are defined as deviations that could potentially affect the interpretability of the study results. This is also known as the per-protocol population. This data set will be used for sensitivity analyses of the primary efficacy endpoint if > 10% of subjects in any treatment group have relevant protocol deviations.

- The **Treated Subjects Data Set** will consist of all subjects who receive at least one dose of study medication during the treatment group. This will be the primary safety data set. Data in this data set will be analyzed based on randomized treatment, except in cases where a subject received a different treatment for the entire course of his/her participation in the treatment period. In this case, safety data for such a subject will be analyzed based on the first treatment the subject actually received.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

Mean change from baseline in HbA1c at Week 52.

8.3.2 Secondary Endpoint(s)

The secondary efficacy endpoints for the short-term treatment period include:

- Mean change from baseline in total body weight at Week 52.
- Proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, at Week 52.
- Mean change from baseline in systolic blood pressure (SBP) at Week 52.
- Time to treatment intensification (addition of insulin or other glucose-lowering agent for rescue therapy or discontinuation for lack of glycemic control) during the 52-week double-blind treatment period.

The secondary efficacy endpoints for the long-term treatment period include:

- Time to treatment intensification (addition of insulin or other glucose-lowering agent for rescue therapy or discontinuation for lack of glycemic control) during the 156-week treatment period.
- Proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, at Week 156.

8.3.3 Exploratory Endpoint(s)

The exploratory endpoints for the short-term treatment period include:

- Proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, without any hypoglycemia at Week 52.
- Proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, without any hypoglycemia and weight gain at Week 52.
- Mean change from baseline in FPG at Week 52.
- Mean change from baseline of metabolic measures (glucagon, C-peptide, pro-insulin, insulin, iHOMA2) at Week 52.

- Mean change from baseline in average glucose values and postprandial glucose values measured by 6-point SMBG profiles at Week 52.
- Mean change from baseline in urinary albumin to creatinine ratio at Week 52.
- Mean change from baseline in biomarkers (hsCRP and NT Pro-BNP) at Week 52.
- Mean change from baseline in patient-reported treatment satisfaction, quality of life, and barriers to medication adherence at Week 52.
- In a sub-study: Mean change from baseline in glucose variability, as defined by mean amplitude of glycemic excursions (MAGE), using CGM at Week 52.
- In a sub-study: Mean change from baseline in visceral and subcutaneous adipose tissue volume, and percent hepatic lipid content as assessed by MRI at Week 52 in the subpopulation of subjects who undergo MRI-PDFF.

The exploratory endpoints for the long-term treatment period include:

- Mean change from baseline in HbA1c at Week 156.
- Mean time spent at or below HbA1c target (HbA1c < 7.0%) during 156 weeks.
- Proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, without any hypoglycemia at Week 156.
- Proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, without any hypoglycemia and weight gain at Week 156.
- Mean change from baseline in FPG at Week 156.
- Mean change from baseline of metabolic measures (glucagon, C-peptide, pro-insulin, insulin, iHOMA2) at Week 156.
- Mean change from baseline in urinary albumin to creatinine ratio at Week 156.
- Mean change from baseline in biomarkers (hsCRP and NT Pro-BNP) at Week 156.
- Mean change from baseline in total body weight at Week 156.
- Mean change from baseline in systolic blood pressure (SBP) at Week 156.
- Mean change from baseline in patient-reported treatment satisfaction, quality of life, and barriers to medication adherence at Week 156.
- Mean change from baseline in visceral and subcutaneous adipose tissue volume and percent hepatic lipid content as assessed by MRI at Week 122 in the subpopulation of subjects who undergo MRI-PDFF.

8.4 Analyses

Analysis of data from the double-blind treatment period will be performed after all subjects have completed or discontinued from this period. In addition, all relevant queries must be answered and the database must be locked and unblinded for the double-blind treatment period prior to the analysis.

Analysis of data from the combined short-term and long-term treatment periods will be performed after all subjects have completed or discontinued from the study. In addition, all relevant queries must be answered and the database must be locked for the combined short-term and long-term treatment periods prior to the analysis.

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized using frequency distributions and descriptive statistics using the Randomized Subjects data set, for each treatment group as well as for all subjects combined. Key baseline characteristics that will be summarized include: age, gender, race, ethnicity, geographic region, body weight, body mass index (BMI), duration of T2DM, baseline HbA1c, and baseline FPG. The baseline value of a parameter is defined as the last assessment on or prior to the date of the first dose of the double-blind study medication. No statistical tests will be performed to compare treatment groups at baseline.

8.4.2 Efficacy Analyses

All efficacy analyses will be performed using the Randomized Subjects data set. In addition, the primary efficacy analysis will be performed using the Evaluable Subjects data set if > 10% of subjects in any treatment group have relevant protocol deviations.

All analyses will be done using values prior to rescue/intensification 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 and also using all available data and including a time varying covariate which indicates rescue status. Sensitivity analyses will also be conducted for endpoints of total body weights at Week 52 and Week 156. For the endpoint of the proportion of patients achieving a therapeutic glycemic response at Week 52/Week 156, all available data will be used, but subjects rescued prior to Week 52/Week 156 will be treated as non-responders.

The comparator (glimepiride plus metformin) will be tested against saxagliptin, in co-administration with dapagliflozin plus metformin, for the primary efficacy endpoint at the alpha = 0.05 level (two-sided). The secondary efficacy endpoints will then be tested sequentially, each comparison tested at the alpha = 0.05 level (two-sided). The following testing hierarchy (shown in order of the step-wise testing sequence) for treatment comparisons will be used:

- Mean change from baseline in HbA1c at Week 52 (primary endpoint).
- Mean change from baseline in total body weight at Week 52.
- Percent of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, at Week 52.
- Mean change from baseline in systolic blood pressure (SBP) at Week 52.
- Time to treatment intensification (addition of insulin or other glucose-lowering agent for rescue therapy or discontinuation for lack of glycemic control) during the 52-week double-blind treatment period.

- Time to treatment intensification (addition of insulin or other glucose-lowering agent for rescue therapy or discontinuation for lack of glycemic control) during the 156-week treatment period.
- Proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, at Week 156.

8.4.2.1 Primary Efficacy Analysis

The primary efficacy analysis of HbA1c at Week 52 will be performed using a longitudinal repeated measures model with terms for treatment group, baseline value, time, the interaction of treatment and time, and the interaction of baseline value and time in the model, including observations prior to rescue. Point estimates and 95% confidence intervals will be calculated for the adjusted mean changes within each treatment group, as well as for the differences in adjusted mean changes between treatment groups.

Sensitivity analyses for HbA1c will include additional repeated measures analyses and analysis of covariance (ANCOVA) analyses. The repeated measures analyses will include two separate analyses, including values after rescue, and including and excluding a time-dependent covariate for rescue. Two separate ANCOVA analyses of the change from baseline at Week 52 will be performed, with terms for treatment group and baseline value in the model. One analysis will be based on measurements at Week 52 (if prior to rescue, if applicable) or the last post-baseline measurement prior to Week 52 and prior to rescue (if applicable), if no Week 52 assessment is available (eg, last observation carried forward [LOCF]). The second sensitivity analysis using ANCOVA will be based on all subjects completing the double-blind treatment period without requiring glycemic rescue therapy.

8.4.2.2 Secondary Efficacy Analyses

In order to protect the overall type I error rate, the interpretation of the statistical significance of treatment comparisons for each secondary efficacy endpoint will be done using a step-wise procedure as outlined in Section 8.4.2.

The analysis of change from baseline for total body weight and systolic blood pressure will be performed using the same longitudinal repeated measures model as for the primary efficacy endpoint.

The proportion of subjects achieving a therapeutic glycemic response (defined as HbA1c < 7.0%) at Week 52 and Week 156 will be summarized by treatment group and compared between treatment groups using logistic regression with adjustment for baseline HbA1c. The 95% confidence intervals for the response rate within each treatment group, odds ratio, and 95% confidence intervals for odds ratio will be calculated. Subjects who are rescued, discontinued or have missed measurements at Week t (t = 52 and 156, respectively) will be considered not achieving glycemic response.

Time to treatment intensification will be analyzed using a Cox proportional hazards model. Estimates of the hazard ratio and 95% confidence intervals will be provided. Kaplan-Meier estimates will be calculated and plotted by treatment group. For the analysis during 52 / 156 weeks, all subjects will be censored at 52 / 156 weeks if treatment intensification has not occurred by then. Subjects rescued at Week 52 / 156 will be counted as having an event for the analysis.

8.4.2.3 Other Efficacy Analyses

Analyses for other efficacy objectives will use the same methodology for continuous endpoints as described above. For composite response endpoints (glycemic control without hypoglycemia or weight gain), the proportion of subjects achieving targets will be summarized by treatment group without adjustment for baseline. All exploratory endpoints will not be statistically tested.

8.4.3 Safety Analyses

The number and percent of subjects with at least one adverse event will be summarized for each treatment group, including summaries of AEs, SAEs, AEs leading to discontinuation of study medication, and AEs of special interest. Summaries will include the number of subjects with events by specified System Organ Class (SOC) and Preferred Terms (PTs).

Additionally, the incidence of AEs and frequency of recurring AEs will be summarized for each treatment group for both frequent events (occurring in at least 5% of subjects) and for selected AEs of special interest.

Values and changes from baseline at each scheduled time point for clinical laboratory parameters, body weight, and vital signs, including seated BP and HR, will be summarized by treatment group using descriptive statistics. The normality/abnormality of ECG tracings, as determined by the investigator, will be summarized by shift tables overall and by ECG tracing at baseline. The number and percent of subjects with laboratory values meeting marked abnormality criteria will be summarized for each treatment group. Other safety assessments including serum creatinine and CrCl by the Cockcroft-Gault equation and eGFR by the Modification of Diet in Renal Disease (MDRD) equation will be summarized by treatment group using descriptive statistics of values and changes from baseline at each scheduled time point.

Safety analyses for the 52-week double-blind treatment period and combined short-term and long-term treatment periods will be performed using the Treated Subjects data set, including data after rescue. Additional analyses for adverse events and laboratory marked abnormalities will be performed excluding data after rescue. The primary analyses of events of hypoglycemia will be performed excluding data after rescue.

8.4.4 Pharmacokinetic Analyses

Not applicable

8.4.5 Biomarker Analyses

The exploratory biomarker measurements of hsCRP and NT-proBNP will be summarized with descriptive statistics by treatment.

8.4.6 Outcomes Research Analyses

8.4.6.1 Patient-reported outcomes (PRO)

Mean change from baseline in patient-reported treatment satisfaction, quality of life, and barriers to medication adherence will be analyzed using longitudinal repeated measures model with terms for treatment group, baseline value, time, the interaction of treatment and time, and the interaction of baseline value and time. Point estimates and 95% confidence intervals will be calculated for the adjusted mean changes within each treatment group as well as for the differences in adjusted mean changes between treatment groups.

8.4.7 Subgroup analysis

Subgroup analyses for age, gender, race, female age, region, and baseline HbA1c category for continuous endpoints will be analyzed 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.

8.4.8 Other Analyses

Not applicable

8.5 Interim Analyses

Not applicable

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by the Sponsor. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- The Sponsor

- Regulatory Authority(ies), if required by local regulations
- Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to the Sponsor

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

Sponsor representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Sponsor representatives must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents: CGM data, fingerstick blood glucose values recorded in the diary and meter data (SMBGs), and the diary data as noted in Section 5.3.1.

In addition, the study may be evaluated by the Sponsor's internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. Audit reports will be kept confidential.

The investigator must notify the Sponsor promptly of any inspections scheduled by Regulatory Authorities, and promptly forward copies of inspection reports to the Sponsor.

9.1.2.1 Source Documentation

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records [EMRs/EHRs], adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a

copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.1.3 Investigational Site Training

The Sponsor will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the Sponsor, whichever is longer. The investigator must contact the Sponsor prior to destroying any records associated with the study.

The Sponsor will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to the Sponsor.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include IMP and the following non-IMP(s). Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to the Sponsor
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for IMP dispensing/accountability, as per the Delegation of Authority Form

The Sponsor will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor's electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by the Sponsor.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the Sponsor's electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet the Sponsor's training requirements and must only access the Sponsor's electronic data capture tool using the unique user account provided by the Sponsor. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- National Coordinating Investigator
- Subject recruitment (eg, among the top quartile of enrollers)
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to the Sponsor. Any publications or abstracts arising from this study require approval by the Sponsor prior to publication or presentation and must adhere to the Sponsor's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the Sponsor at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. The Sponsor shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. WOCBP subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but WOCBP subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. **Expanded definition** Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but WOCBP subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

11 LIST OF ABBREVIATIONS

Term	Definition
ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AM or am	Morning (ante meridian)
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
A-V	atrioventricular
AstraZeneca AB	AZ
BMI	body mass index
BP	blood pressure
C	Celsius
Ca++	calcium
CABG	Coronary Artery Bypass Graft
Cavg	average concentration
CBC	complete blood count
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CI	confidence interval
C1-	chloride
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CRC	Clinical Research Center
CrCl	creatinine clearance
CRF	Case Report Form, paper or electronic
CTA	Clinical Trial Agreement

Term	Definition
CSP	Clinical Safety Program
CV	cardiovascular
D/C	discontinue
DKA	diabetic ketoacidosis
dL	deciliter
DPP4	dipeptidyl peptidase 4 (inhibitor)
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eg	exempli gratia (for example)
EOT	End of Treatment Visit
ESR	Expedited Safety Report
EU	European Union
FPG	Fasting Plasma Glucose
FDA	Food and Drug Administration
FFA	Free fatty acids
FSH	follicle stimulating hormone
g	gram
GI	Gastrointestinal
GCP	Good Clinical Practice
eGFR	Estimated glomerular filtration rate
GGT	gamma-glutamyl transferase
GIP	Gastric inhibitory polypeptide
GLP-1	Glucagon-like peptide-1
hr or h	hour
HbA1c	glycosylated hemoglobin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	Human Chorionic Gonadotropin
HCV	hepatitis C virus
HDL-C	High-density lipoprotein cholesterol

Term	Definition
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigation Brochure
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
ITT	Intent to Treat
IU	International Unit
IV	intravenous
IVRS	Interactive Voice Response System
K	slope of the terminal phase of the log concentration-time curve
K+	potassium
kg	kilogram
L	liter
LDH	lactate dehydrogenase
LDL-C	Low density lipoprotein cholesterol
LLC	Liver lipid content (%)
LOCF	Last observation carried forward
M or m	Meter
MAGE	mean amplitude of glucose excursions
max	Maximum
MCH	Mean cell hemoglobin
MCHC	Mean cell hemoglobin concentration
MCV	Mean cell volume
MDRD	Modification in Diet and Renal Disease
mg	milligram

Term	Definition
Mg++	magnesium
min	minute
mL	milliliter
mm Hg	millimeters of mercury
mmol	Millimole
MoA	mechanisms of action
MRI	Magnetic Resonance Imaging
MODY	Maturity Onset Diabetes of Young
µg	microgram
N	number of subjects or observations
Na+	sodium
N/A	not applicable
ng	nanogram
NMP 22	Nuclear Matrix Protein 22
NYHA	New York Heart Association
PD	pharmacodynamics
PDFF	proton density fat fraction
PK	pharmacokinetics
PM or pm	Afternoon (or post meridian)
PO	per os (by mouth route of administration)
PPG	postprandial glucose
PT	prothrombin time
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTT	partial thromboplastin time
QC	quality control
QD, qd	quaque die, once daily
RBC	red blood cell
SA	Sickle cell trait
SAE	serious adverse event
SAT	Subcutaneous adipose tissue (l)

Term	Definition
SBP	Systolic Blood Pressure
SCr	Serum Creatinine
SD	standard deviation
SGLT1	sodium glucose co-transporter 1
SGLT2	sodium glucose co-transporter 2
SI	Systéme International d'Unités
SMBG	Self -monitoring of blood glucose
SOP	Standard Operating Procedures
sp.	species
Subj	subject
SU	sulfonylurea
t	temperature
T	time
T2DM	Type 2 diabetes mellitus
TAT	Total adipose tissue (l)
TB	Total bilirubin
TG	Triglycerides
TIA	Transient Ischemic Attack
Tmax, TMAX	time of maximum observed concentration
Total-C	Total cholesterol
TR_Cmax	Cmax treatment ratio
TSH	Thyroid Stimulating Hormone
TSQM	Treatment Satisfaction Questionnaire for Medication
TZD	Thiazolidinedione
U	Units
U/A	Urinalysis
UACR	Urine albumin creatinine ratio
ULN	Upper limit normal
µmol	Micromole
UR	urinary recovery
US	United States
VAT	Visceral adipose tissue (l)
WBC	white blood cell

Term	Definition
WK or Wk	Week
WOCBP	women of childbearing potential

12 REFERENCES

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STUDY ACKNOWLEDGMENT/DISCLOSURE

I understand that this protocol contains information that is confidential and proprietary to AstraZeneca AB (AZ). Any supplemental information that may be added to this document is also confidential and proprietary to AZ and must be kept in confidence in the same manner as the contents of this protocol.

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein and will make a reasonable effort to complete the study within the time designated.

I will provide copies of the protocol and access to all information furnished by AZ to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I will provide protocol information to my Institutional Review Board(s) [IRB(s)] or Independent Ethics Committee(s) [IEC(s].

I agree that the contents of the protocol may not be disclosed to any other person or entity or used for any other purpose without the prior written consent of AZ. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to AZ of any such disclosure.

I agree that the study data derived from this protocol may only be used and disclosed in furtherance of the protocol, for the medical treatment of a study subject or for publication of study results in accordance with the terms of the CTAg or as otherwise permitted by the terms of the CTAg.

I agree not to collect or use samples (e.g., tissue, blood, serum, urine) or collect data (other than for diagnostic or treatment purposes) from the study subjects while enrolled in the study, except as expressly permitted by the protocol or the terms of the CTAg.

I understand that I may terminate or suspend enrollment of the study at any time if it becomes necessary to protect the best interests of the study subjects. Unless otherwise provided in the CTAg, the study may be terminated at any time by AZ, with or without cause.

Original Protocol ☐ Revised protocol ☒ Amendment ☐

Protocol Number: CV181365 Site Number: _

Date of Protocol:

IND Number: 63,634 EUDRACT Number: 2014-003721-18

Investigator _____ Date _____
(signature)

_____
(printed name)

As Study Director / Medical Monitor and an authorized representative of AZ, I accept responsibility for the initiation, management and/or financing of this Protocol.

Medical Monitor PPD [redacted] Date 8 Feb 2018
(If required by a

Protocol Number: CV181365
Site Number: All
IND Number 63,634
EUDRACT Number 201-003721-18
Date: 28-Jan-2015

Protocol CV181365: A 52-week International, Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel Group, Phase 3b Trial with a Blinded 104-week Long-term Extension Period to Evaluate the Efficacy and Safety of Saxagliptin Co-administered with Dapagliflozin in combination with Metformin Compared to Glimepiride in Combination with Metformin in Adult Patients with Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Therapy Alone.

Pharmacogenetics Blood Sample Amendment Number 01 - Site Specific Site All

Medical Monitor

24-hr Emergency Telephone Number:

Sponsor: AstraZeneca Research and Development
Study being conducted by Bristol-Myers Squibb on behalf of AstraZeneca

Bristol-Myers Squibb Research and Development
Avenue de Finlande 4
B-1420 Braine-l'Alleud, Belgium
Route 206 & Province Line Road
Lawrenceville, NJ 08543

TABLE OF CONTENTS

1 AMENDMENT RATIONALE

The information gained from Pharmacogenetic research studies is expected to result in safer and more effective therapies and to lead to the discovery of new diagnostics, prognostics and molecular targets and pathways. To learn more about the association between a subject's genetic makeup and drug response, subjects will be asked to voluntarily give a blood sample so that scientists can perform exploratory pharmacogenetic research.

This research will be limited to information recorded on the case report form or generated from the main clinical trial and results from the associated pharmacogenetic blood sample. Subjects will not be contacted in the future by the sponsor to provide any further information.

Pharmacogenetics can be defined as the study of how variations in genes influence drug response. Genetic factors are considered to play an important role in the observed inter-individual differences in the metabolism, toxicity, and pharmacological response of drugs. The ability to determine which genes and their variants are associated with toxicity and efficacy for a specific drug will improve drug therapy and subsequently be beneficial to patients.

2 OBJECTIVES

The objective of this Amendment is to permit the collection and storage of blood samples for use in future exploratory pharmacogenetic research. Bristol-Myers Squibb is conducting this study on behalf of AstraZeneca. AstraZeneca is the sponsor for the CV181365 study and they will be responsible for the pharmacogenetic portion of this study including the logistically aspects related to this amendment.

AstraZeneca will use DNA obtained from the blood sample and health information collected from the main clinical trial, CV181365, to study the association between genetic variation and drug response. AstraZeneca may also use the DNA to study the causes and further progression of Type 2 Diabetes and other Metabolic Diseases. Samples from this study may also be used in conjunction with pharmacogenetic research results from other clinical studies to accomplish this objective.

3 STUDY SITES

Pharmacogenetic sample collection will be performed at sites that permit pharmacogenetic studies to be conducted in compliance with all applicable laws, rules, and regulations.

4 SUBJECT SELECTION CRITERIA

To participate in this Pharmacogenetic Sample Amendment, subjects must provide a signed Pharmacogenetic Blood DNA informed consent and must have consented to participate in the main clinical trial CV181365.

Inclusion criteria

For inclusion in this Pharmacogenetic Sample Amendment:

- Subjects must fulfill all of the inclusion criteria described in the main body of the Clinical Study Protocol and must have consented to participate in the main clinical trial CV181365
- Provide informed consent for the genetic sampling and analyses

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous bone marrow transplant
- Whole blood transfusion within 120 days of genetic sample collection

5 PROCEDURES

Subjects who have consented to participate in this study and who have voluntarily given written informed consent for pharmacogenetic sample collection will have a one-time blood sample collected at Day 1. If the pharmacogenetic blood sample is not collected at visit Day 1, it may be collected at any other subsequent scheduled sample collection. For each subject, approximately 10mL of blood (less than 2 teaspoons) will be collected. The sample will be stored at AstraZeneca Sample Bank for pharmacogenetic research.

No pre-determined number of study subjects is required, as participation for pharmacogenetic analysis is strictly voluntary. Subjects will be asked to read, understand, and sign an informed consent form designed for the purpose of collecting a one time sample for pharmacogenetic research. **Subjects will be informed that they will not be excluded from the main clinical trial CV181365 if they do not wish to participate in the Pharmacogenetics Sample Amendment.**

6 PHARMACOGENETIC STATISTICAL ANALYSIS

Joint exploratory data analysis may be performed in the future to investigate if genetic variants (genotypes) are associated with clinical outcomes (phenotypes) such as, but not limited to, drug response, efficacy, safety, toxicity, and overall survival. The following potential analyses may be performed as appropriate:

- Examine demographic factors such as race/ethnicity, age and gender to determine appropriate stratification or adjustment for the analysis.
- Summarize allele and genotype frequencies from the sample with 95% confidence intervals.
- Explore the relationship among genetic variation, expression of genes and proteins and clinical outcomes using methods such as, but not limited to, chi-squared tests, linear models, generalized linear models, non-parametric models, survival models or clustering algorithms.

7 CODING AND STORAGE OF DNA SAMPLES

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

The samples and data for genetic analysis in this study will be de-identified. The sample and data will not be labeled with a personal identifier. The study number and patient number will be linked to a second unique identifier.

Once DNA is extracted from the de-identified blood sample it is given another unique identifier. The DNA number will be used to identify the sample and corresponding data at the designated contract laboratory. No personal details identifying the individual donor will be available to any AstraZeneca or external provider working with the DNA. A link between the blood sample and the DNA extracted from the sample will be maintained in a confidential link file maintained by AstraZeneca DNA Biobank or contracted storage facility.

All genetic samples will be stored under secure conditions with restricted access at AstraZeneca. The blood or data derived from the samples may be made available to groups or organizations working with AstraZeneca on this study or as part of the development drug project. However, the samples and any results will remain the property of AstraZeneca at all times. AstraZeneca will not give blood, DNA samples or data derived from the samples to any other parties, except as required by law. All samples and DNA will be destroyed maximum of 15 years from the date of last subject last visit after or according to local legislation. Samples may be destroyed prior to this timeframe if the patient has withdrawn consent

8 SUBJECT DATA PROTECTION

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

9 DATA MANAGEMENT

Any genotype data generated in this study will be in the secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyze the samples.

The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

10 SUBJECT RIGHTS

Study subjects can withdraw their consent to participate in the Pharmacogenetic Sample Amendment even after the sample has been shipped to the AstraZeneca Sample Bank. As long as the Investigator or Investigator's designee retains the clinical trial records, a study subject will be able to contact his/her Investigator or the Investigator's designee and ask for his/her sample to be withdrawn from the Sample Bank and destroyed.

As the collection of the biological samples is an optional part of the study, the subject may continue in the main study even if they choose not to participate in this amendment.

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of the donated samples is timely communicated to AZ or its representative
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented in subject's source documents
- Ensures that the subject and AZ are informed about the sample disposal

In the instance that the samples have been sent from the study site:

- On receipt of the notification of withdrawal of consent, (Appendix 1), AZ or its representative ensure the relevant samples are located and sample disposal/destruction is requested and appropriately documented
- A copy of the completed disposal/destruction documentation is returned to the study site

11 RECORD RETENTION

The Investigator must retain essential documents for the maximum period required by applicable regulations and guidelines[1] or Institutional procedures, or for the period specified by the sponsor, whichever is longer. The Investigator must contact Astra Zeneca or its representative prior to destroying any records associated with the study.

Astra Zeneca will notify the Investigator when the trial records are no longer needed.

If the Investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another Investigator, IRB). Notice of such a transfer will be given in writing to Astra Zeneca.

12 WITHDRAWAL OF SUBJECTS FROM PHARMACOGENETIC RESEARCH

Subjects have, at any time, the option to withdraw consent for participation from:

1) Only the Pharmacogenetic Sample Amendment independent of the main clinical trial (CV181365);

OR

2) Only the main clinical trial (CV181365) independent of the Pharmacogenetic Sample Amendment;

OR

3) Both the main clinical trial (CV181365) and Pharmacogenetic Sample Amendment.

Subjects who wish to withdraw their consent from the Pharmacogenetic Sample Amendment (ie, have their sample in the Sample Bank destroyed) should contact the Investigator. The Investigator will submit a Sample Withdrawal Form to the AstraZeneca Sample Bank (see Appendix 1).

It is possible that subjects may decide to withdraw consent from the main clinical trial (CV181365) but continue with their consent for the Pharmacogenetic Sample Amendment. In such cases the Investigator should inform subjects that their sample would remain stored at the AstraZeneca Sample Bank and may be used for pharmacogenetic research.

If a subject requests to withdraw consent for the Pharmacogenetic Sample Amendment after the time the Investigator is legally required to maintain the records linking the subject's sample and coded health information to their identity, and the records have been destroyed, the sample will become anonymous and unable to be withdrawn.

13 DESTRUCTION OF BLOOD SAMPLE AND RELATED MATERIAL

In the case of subjects who have withdrawn their consent for participation in the Pharmacogenetic Sample Amendment the Investigator will send a Sample Withdrawal Form to the AstraZeneca Sample Bank. Upon receipt of the Sample Withdrawal Form, AstraZeneca Sample Bank, will destroy any remaining blood sample and any material obtained from the sample in accordance with AstraZeneca procedure for Sample Destruction. A copy of the sample withdrawal form is provided in Appendix 1. After all samples have been destroyed AstraZeneca Sample Bank will provide the Investigator with verification of the sample destruction. In the case of samples that have been partially analyzed, the remaining sample will be destroyed but AstraZeneca shall be entitled to retain and use any research results obtained prior to the withdrawal of consent.

14 FLOW CHART/TIME AND EVENTS SCHEDULE

Time and Events Schedule:

Procedure	Visit Day Day 1
Pharmacogenetic Sample Informed Consent	X[a]
Pharmacogenetic Sample Collection	X[b]

[a] Informed consent for pharmacogenetic testing may be obtained at any time during the trial PRIOR to the collection of the pharmacogenetic sample.

[b] If the pharmacogenetic sample is not collected at visit Day Day 1, it may be collected at any other subsequent scheduled sample collection.

15 PHARMACOGENETIC SAMPLE COLLECTION AND PROCESSING

The whole blood pharmacogenetic sample will be shipped at frozen temperature to the designated central laboratory Quintiles Central Laboratory. The samples will be stored frozen and transferred to the designated extraction lab and then to AstraZeneca Sample Bank for storage and future analysis. Details for collection, processing, storing and shipping these samples will be provided in a separate procedure manual.

16 INFORMED CONSENT

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representative are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from every subject or, in those situations where consent cannot be given by subjects, their legally acceptable representative, prior to study participation.

The rights, safety, well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

The following section contains Bristol-Myers Squibb procedures on obtaining informed consent from subjects or their legally acceptable representative prior to participating in a clinical trial. Procedures are described for all subjects including those who are unable to give informed consent. The relevant procedures must be used whenever they are applicable.

A separate informed consent will be obtained from study subjects who voluntarily agree to participate in the Pharmacogenetic Sample Amendment. The informed consent form for pharmacogenetic sample collection reflecting this Amendment will be submitted for review and approval to the IRB/Ethics Committee charged with this responsibility.

16.1 Informed Consent Procedures

Preparation of the consent form is the responsibility of the Investigator and must include all elements required by ICH, GCP and applicable regulatory requirements, and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent

form must also include a statement that Bristol-Myers Squibb and regulatory authorities have direct access to subject records. Prior to the beginning of the study, the Investigator must have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects.

The Investigator must provide the subject or legally acceptable representative with a copy of the informed consent form and written information about the study in the language in which the subject is most proficient. The language must be non-technical and easily understood. The Investigator should allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study, then informed consent must be signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion. The subject or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study subjects prior to subject's participation in the trial

17 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

This amendment, the informed consent form for pharmacogenetic sample collection and any advertisement for subject recruitment will be submitted for review and approval to the IRB/Ethics Committee charged with this responsibility. The investigator must have on file written and dated approval/favorable for this amendment from the IRB/Ethics Committee before this sample is collected.

18 REFERENCES

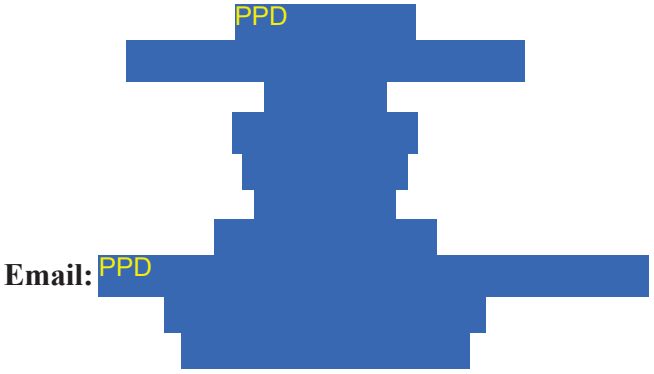
1. Code of Federal Regulations, CFR 312.57, and International Conference on Harmonisation, ICH Guidelines.

APPENDIX 1 SAMPLE WITHDRAWAL PROCEDURES

AstraZeneca
Research & Development

FAX TRANSMITTAL SHEET

FAX THIS COMPLETED PAGE TO:



WITHDRAWAL OF PERMISSION FOR USE OF SPECIMENS IN FUTURE PHARMACOGENETIC RESEARCH

This section is to be completed by either the Investigator or the coordinator at the institution.

The study subject indicated below (Only identify the study subject using the study subject number; **DO NOT** provide any other identifying information such as the study subject's name or social security number) initially provided informed consent for his/her samples to be used for pharmacogenetic research by AstraZeneca. After discussion with a study staff member at our institution, he/she has now indicated that he/she wants to withdraw consent for future pharmacogenetic research by AstraZeneca and have his/her sample destroyed.

PROTOCOL NUMBER: _____ **SITE NUMBER:** _____

STUDY SUBJECT NUMBER: _____

INVESTIGATOR NAME: _____ **INVESTIGATOR FAX:** _____

INVESTIGATOR SIGNATURE: _____

DATE OF REQUEST: _____

This section is to be completed by the AstraZeneca Sample Bank and faxed back to the Investigator.

CONFIRMATION OF SAMPLE DESTRUCTION

The pharmacogenetic sample and related material derived from the sample obtained from the study subject indicated above has been destroyed. Please notify the study subject that this has occurred.

VERIFIED BY: _____ **DATE:** _____

PRINT NAME: _____

AMENDMENT ACKNOWLEDGEMENT

I have read this Amendment and agree that it contains all necessary details for carrying out the changes described. I understand that it must be reviewed by the Institutional Review Board/Ethics Committee overseeing the conduct of the study and approved or given favorable opinion before implementation unless to eliminate an immediate hazard to subjects.

If this Amendment substantially alters the study design or increases potential risk to subjects, the consent form will be revised and submitted to the Institutional Review Board/Independent Ethics Committee for approval/positive opinion. I will use the new consent form for any new subjects prior to enrollment, and for subjects currently enrolled in the study if they are affected by the Amendment.

_____ _____

Investigator's printed name and signature *Date*

PPD _____ 02-April-2015

Medical Monitor/Study Director *Date*
(If required by applicable regulations and guidelines.)

Protocol Number: CV181365
Site Specific: All
Amendment Number: 01

Protocol Number: CV181365
IND Number: 63,634
EUDRACT Number 2014-003721-18
Date: 11-Mar-2015

Protocol CV181365: A 52-week International, Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel Group, Phase 3bTrial with a Blinded 104-week Long -term Extension Period to Evaluate the Efficacy and Safety of Saxagliptin Co-administered with Dapagliflozin in combination with Metformin Compared to Glimepiride in Combination with Metformin in Adult Patients with Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Therapy Alone.

Amendment Number 02
Site Number: All

Medical Monitor

24-hr Emergency Telephone Number:

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden
Study being conducted by Bristol-Myers Squibb on behalf of AstraZeneca AB

Bristol-Myers Squibb Research and Development
Metabolics Clinical Research and Development
Avenue de Finlande 4
B-1420 Braine-l'Alleud, Belgium
Route 206 & Province Line Road
Lawrenceville, NJ 08543

Amendment Rationale:

The primary purpose of this amendment is to correct information in the Inclusion and Exclusion Criteria pertaining to the active comparator (glimepiride) and to align the current protocol to its sister study, CV181-363. As enrollment has not yet started, these changes will be applicable to future enrolled subjects and will not impact the overall study conduct or proposed data analyses.

- In the Inclusion Criteria described in Section 3.3.1 sitagliptin was erroneously listed as the active comparator. Glimepiride is now correctly identified as the active comparator.
- In the Exclusion Criteria described in Section 3.3.2, it is now specified that subjects who have contraindications to therapy as described in the glimepiride package insert should be excluded.
- In the Exclusion Criteria described in Section 3.3.2; the word "enrollment" was removed as an exclusion because the study does permit the re-enrollment of a subject who has been discontinued from the study as a pre-treatment failure (eg, was not randomized). The criterion now excludes only previous randomization in the present study.
- In the Exclusion Criteria described in Section 3.3.2; the number of days that a subject may not have taken any other investigational agent prior to screening has been changed from 90 to 30 days to be consistent with CV181-363 and other studies in the saxagliptin/dapagliflozin clinical development program.
- Two efficacy objectives seek to compare the time to treatment intensification (defined as the addition of insulin for rescue therapy or discontinuation for lack of glycemic control) between the saxagliptin/dapagliflozin and glimepiride arms. Although insulin is recommended as the initial choice for rescue therapy (since these subjects are already taking dual or triple therapy), the protocol permits other options to be considered. The definition for treatment intensification was broadened to include the addition of insulin or other glucose-lowering agents for rescue therapy or discontinuation for lack of glycemic control.
- Hypersensitivity has been identified as a potential risk for dapagliflozin (and is already specified as a potential risk for saxagliptin). In the Overall Risk/Benefit Section (Section 1.5), we have added hypersensitivity as a potential risk for dapagliflozin.

Changes to Protocol

1) Synopsis, Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Products, added: glimepiride 1-6 mg.
2) Synopsis, Secondary efficacy objectives, Short-term, 4th bullet, added: or other glucose-lowering agent.
3) Synopsis, Secondary efficacy objectives, Long-term, 1st bullet: added: or other glucose-lowering agent.
4) Synopsis Exploratory Objectives, Short-term, 9th bullet revised: to assess CGM.
5) Synopsis, Exploratory Objectives, Long-term, 2nd bullet, removed: for saxagliptin/ dapagliflozin.
6) Synopsis, Exploratory Objectives, Long-term, 6th bullet, revised: double-blind treatment.

7) Synopsis, Safety objectives, 1st bullet, added: for saxagliptin co-administered with dapagliflozin.
8) Synopsis, Study Schematic: removed: plus placebo.
9) Synopsis, Study Population: removed Asia
10) Synopsis, Study Drug: added: glimepiride
11) Synopsis, Dose and Treatment Regimens, added; Glimepiride 1-6mg or matching placebo capsules, administered orally once daily, will be provided for the 156-week blinded treatment period.
12) Synopsis, Concomitant and other treatments, added: other than IP.
13) Synopsis Sample Size Estimates: revised #Screened and #Enrolled
14) Synopsis, Secondary endpoints for analysis for the short-term treatment period include, added: or other glucose-lowering agents.
15) Synopsis, Secondary endpoints for analysis for the long-term treatment period include, added: or other glucose-lowering agents.
16) Section 1.3.2., Secondary objectives, Secondary efficacy objectives, Short-term, 4th bullet, add: or other glucose-lowering agents.
17) Section 1.3.2., Secondary objectives, Secondary efficacy objectives, Long-term, 1st bullet, add: or other glucose-lowering agents.
18) Section 1.3.3, Exploratory Objectives, Long-term, 2nd bullet, removed: for saxagliptin/dapagliflozin.
19) Section 1.3.3, Exploratory Objectives, Long term, 6th bullet revised: double-blind treatment.
20) Section 1.3.4, Exploratory Safety Objectives, 1st bullet, added: for saxagliptin co-administered with dapagliflozin.
21) Section 1.5, Overall Risk/Benefit Assessment, Dapagliflozin, added section: Hypersensitivity reactions paragraph.
22) Section 3.1 Study Design added; Glimepiride 1-6mg or matching placebo capsules, administered orally once daily, will be provided for the 156-week blinded treatment period
23) Figure 3.1-1 Study Design Schematic: removed: plus placebo
24) Section 3.3.1 Inclusion Criteria; Number 1, added: or designee
25) Section 3.3.1 Inclusion Criteria; Number 3, Age and Reproductive Status; removed letter (d) and (e) statements.
26) Section 3.3.1 Inclusion Criteria; Number 3, Age and Reproductive Status; revised letter (f) and (g) statements.
27) Section 3.3.2 Exclusion Criteria; Number 4 Allergies and Adverse Drug Reaction; Letter a, add: glimepiride
28) Section 3.3.2 Exclusion Criteria; Number 5, Other Exclusion Criteria; Letter m: remove enrollment.
29) Section 3.3.2 Exclusion Criteria; Number 5 Other Exclusion Criteria; Letter n: changed administration of any other investigational agent from within 90 days of the screening visit to 30 days
30) Section 3.3.2 Exclusion Criteria; Number 5, Other Exclusion Criteria; Letter o" remove no

31) Section 3.4.1 Prohibited and/or Restricted Treatments; 1stth bullet added; other than IP
32) Section 3.4.1 Prohibited and/or Restricted Treatments; 4th bullet changed administration of any other investigational agent from within 90 days of the screening visit to 30 days
33) Table 3.5.2-1, Lack of Glycemic Control Criteria for Initiation of Rescue Medication, provided additional clarification to recue time points.
34) Section 3.5.3 Discontinuation Guidelines due to Protocol-Defined Hypoglycemia Episodes, removed term placebo
35) Section 4.5 Selection and Timing of Dose for Each Subject; replaced the paragraph
36) Section 4.10 Retained Samples for Bioavailability/Bioequivalence removed associated subsequent text, added; Not applicable
37) Table 5.1-1 Flow Chart/Time and Event Schedule, Eligibility, added 'sub-study' text to Informed consent for MRI and CGM
38) Table 5.1-1 Flow Chart/Time and Event Schedule, Safety Assessment, amended scheduling of 'Complete physical examination' and 'Brief physical examination'; Screening week -4 and Lead-in week -2 respectively
39) Table 5.1-1 Flow Chart/Time and Event Schedule, Central Laboratory Tests, removed procedure, Blood & Urine Standard Safety Laboratory Panel
40) Table 5.1-1 Flow Chart/Time and Event Schedule, Central Laboratory Tests, Clinical Chemistry, hematology, urinalysis (new wording added)
41) Table 5.1-2 Flow Chart/Time and Event Schedule, Safety Assessment, reworded text 'Provide glucose meter supplies / instructions'
42) Table 5.1-2 Flow Chart/Time and Event Schedule, Central Laboratory, removed Blood & Urine Standard Safety Laboratory Panel; added Clinical chemistry, haematology, urinalysis (standard safety laboratory panel)
43) Table 5.1-2 Flow Chart/Time and Event Schedule, Safety Assessment, removed procedure 'Height'.
44) Table 5.1-2 Flow Chart/Time and Event Schedule, Central Laboratory, removed procedure, B* Clinical chemistry haematology, urinalysis
45) Table 5.1-2 Flow Chart/Time and Event Schedule, Central Laboratory, MRI-PDFF, notes, provided added clarification
46) Table 5.1-2 Flow Chart/Time and Event Schedule, Study Drug, added text 'or blinded placebo' to study drug dispensations
47) Table 5.1-2 Flow Chart/Time and Event Schedule, Study Drug, removed text 'placebo' from: Register down-titration of glimepiride/placebo during maintenance period (if applicable in IVRS).
48) Table 5.1-3 Flow Chart/Time and Event Schedule, Safety Assessment, removed procedure 'Height'.
49) Table 5.1-3 Flow Chart/Time and Event Schedule, Safety Assessment, reworded 'Provide glucose meter supplies / instructions'
50) Table 5.1-3 Flow Chart/Time and Event Schedule, Central Laboratory, removed Blood & Urine Standard Safety Laboratory Panel; added Clinical chemistry, haematology, urinalysis (standard safety laboratory panel)

51) Table 5.1-3 Flow Chart/Time and Event Schedule, Central Laboratory, removed procedure, B* Clinical chemistry haematology, urinalysis
52) Table 5.1-3 Flow Chart/Time and Event Schedule, Additional Assessment, MRI-PDFF, notes, provided added clarification
53) Table 5.1-3 Flow Chart/Time and Event Schedule, Additional Assessment, amended to 'Assess HbA1c for rescue'.
54) Table 5.1-3 Flow Chart/Time and Event Schedule, Additional Assessment, removed procedure, Contact IVR system
55) Table 5.1-3 Flow Chart/Time and Event Schedule, Study Drug, added schedule time-point wk 156
56) Table 5.1-3 Flow Chart/Time and Event Schedule, Study Drug, removed text 'placebo' from: Register down-titration of glimepiride/placebo during maintenance period (if applicable in IVRS).
57) Table 5.1-4 Flow Chart/Time and Event Schedule, Safety Assessment, amended terminology to Body weight and waist circumference.
58) Section 5.3.3 Guidance on Assessment of Cardiovascular Events; add Cardiovascular Adjudication Committee and delete Clinical Event Committee (CEC)
59) Section 5.3.7 Guidance on Volume Depletion, added dapagliflozin.
60) Section 5.8.7 Continuous Glucose Monitoring (CGM); second paragraph added term; on top of background metformin therapy
61) Section 5.9 Results of Central Assessments; update the language to clarify visits
62) Section 6.1.1 Revised segment to identify AstraZeneca (or designee) as point of contact for SAE reporting.
63) Section 7.1 Cardiovascular Adjudication Committee; 2nd paragraph; replace manual with charter.
64) Section 8.3.2, Secondary Endpoint(s), short-term treatment & long-term treatment, added: or other glucose-lowering agent
65) Section 8.3.3 Exploratory Endpoint(s); add 5th bullet; Mean change from baseline in average glucose values and postprandial glucose values measured by 6-point SMBG profiles at Week 52
66) Section 8.3.3 Exploratory Endpoint(s); modify 9th bullet; add as defined by mean amplitude of glycemic excursions (MAGE)
67) Section 8.4.2, Efficacy Analyses(s), 5th & 6 th bullet, added: or other glucose-lowering agent
68) Section 11 List of abbreviations, removed BID, BUN, CYP, HCO3, K3EDTA, TID and WHO; added NMP 22 and SI
69) Appendix 4; step 2; replace total bilirubin (TB) ≤ 1.5X upper limit of normal (ULN) with TB ≤ 2X ULN in guidance for monitoring liver function
70) Appendix 5, Guidance on Contraception, removed: Any Single Method is Acceptable.
71) Addition of other minor clarifications and correction of typographical errors

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.

AMENDMENT ACKNOWLEDGMENT

I have read this Amendment and agree that it contains all necessary details for carrying out the changes described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion by all necessary Health Authorities before implementation unless to eliminate an immediate hazard to subjects.

If this Amendment substantially alters the study design or increases potential risk to subjects, the consent form will be revised and submitted to the Institutional Review Board/Independent Ethics Committee for approval/positive opinion. I will use the new consent form for any new subjects prior to enrollment, and for subjects currently enrolled in the study if they are affected by the Amendment.

_____ _____

Investigator's printed name and signature *Date*

PPD _____ 02-April-2015

Medical Monitor/Study Director *Date*
(If required by applicable regulations and guidelines.)

Protocol Number: CV181365
Site Number:
Amendment Number: 02

Protocol Number: CV181365
IND Number: 63,634
EUDRACT Number 2014-003721-18
Date: 12-Aug-2015

Protocol CV181365: A 52-week International, Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel Group, Phase 3b Trial with a Blinded 104-week Long-term Extension Period to Evaluate the Efficacy and Safety of Saxagliptin Co-administered with Dapagliflozin in Combination with Metformin Compared to Glimepiride in Combination with Metformin in Adult Patients with Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Therapy Alone.

Amendment Number 03
Site Number: All

Medical Monitor

24-hr Emergency Telephone Number:

Bristol-Myers Squibb Research and Development
Cardiovascular Clinical Research and Development
Route 206 & Province Line Road
Lawrenceville, NJ 08543
Avenue de Finlande 4
B-1420 Braine-l'Alleud, Belgium

This amendment must be maintained with the referenced protocol.

Amendment Rationale:

The primary purpose of this amendment is to revise the CrCl discontinuation criteria. In addition the following changes were made to accommodate internal feedback and comments made by regulatory institutions.

- Updated stability data that has been accumulated to allow the revision of the glimepiride storage conditions.
- Emphasis and clarification to the overall 'half-life' of the treatments utilized in this study; denoting a computation of 30 days
- Clarify the definition of abstinence throughout the protocol
- Provide further details to define Adverse Event reporting.

Changes to the Protocol:

Secondary reasons for this amendment include:

1) Grammatical and spelling corrections throughout the document.
2) Synopsis (Safety Objectives): clarified 'self monitored' blood glucose.
3) In Section 1.3.4 (Exploratory Safety Objectives): clarified 'self monitored' blood glucose.
4) In Section 2.3 (Informed Consent) (1): removed 'most'.
5) In Section 3.1 (Study Design and Duration/Dose and Treatment Regimens Blinded Study Medication): replace language for glimepiride IP dosing.
6) In Section 3.3.1 (Inclusion Criteria) (3) Age and Reproductive Status bullets (d) and (e): removed text.
7) In Section 3.3.1 (Inclusion Criteria) (3) Age and Reproductive Status bullets (f) and (g): replaced 33 day half-life to 30 days. Resulting in Total durations of 60 days and 123 days respectively.
8) In Section 3.3.1 (Inclusion Criteria) (3) Age and Reproductive, Highly Effective Methods of Contraception: Expanded language on Complete Abstinence.
9) In Section 3.4.1 (Prohibited and/or Restricted Treatments: removed 6th bullet (Acetaminophen (paracetamol) containing medications (such as Tylenol) while using the CGM device and 24 hours prior to insertion).
10) In Section 3.5 (Discontinuation of Subjects following any Treatment with Study Drug) 9th bullet: amended CrCl criteria for discontinuation.
11) Table 4.1 (Study Drug for CV181-365): updated storage conditions for glimepiride and placebo for glimepiride.
12) Section 4.5 (Selection and Timing of Dose for Each Subject) 3rd paragraph: replace language for glimepiride IP dosing.
13) Table 5.1-1 (Screening Procedural Outline Flow Chart for Protocol CV181-365) Procedure, FPG: amended < 270 mg/dL to ≤ 270 mg/dL.
14) Table 5.1-1 (Screening Procedural Outline Flow Chart for Protocol CV181-365) footnote: amended lead-in to week-1.

15) Table 5.1-2 (Short-term Procedural Outline Flow Chart for Protocol CV181-365) Procedure, MRI-PDFF: added additional note to reflect process when a subject has been rescued or undergone early termination
16) Table 5.1-2 (Short-term Procedural Outline Flow Chart for Protocol CV181-365) Procedure, Assess FPG for Rescue: removed Week 6 time-point visit.
17) Table 5.1-2 (Short-term Procedural Outline Flow Chart for Protocol CV181-365): amended procedure title to read "Dispense blinded glimepiride or blinded placebo and titrate during titration period (Weeks 3-12)".
18) Table 5.1-2 (Short-term Procedural Outline Flow Chart for Protocol CV181-365) footnote: included MRI in Week 51 visit.
19) Table 5.1-3 (Long-term Procedural Outline Flow Chart for Protocol CV181-365) Procedure, Provide glucose meter supplies / instructions: removed Week 156 time-point visit.
20) Table 5.1-3 (Long-term Procedural Outline Flow Chart for Protocol CV181-365) Procedure, Provide logs / instructions: removed Week 156 time-point visit.
21) Table 5.1-4 footnote: amended to state Week 26
22) In Section 6.1.1 (Serious Adverse Event Collection and Reporting): added clarification of reporting including 'Safety reporting to local regulatory authorities' plus 'Safety reporting to investigational review boards/ethics committees and investigators' paragraphs
23) In Section 7.1 (Cardiovascular Adjudication Committee): removed 'congestive'.
24) Appendix 5 (Guidance on Contraception) : Removed
25) Addition of other minor clarifications and correction of typographical errors.

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.

AMENDMENT ACKNOWLEDGMENT

I have read this Amendment and agree that it contains all necessary details for carrying out the changes described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion by all necessary Health Authorities before implementation unless to eliminate an immediate hazard to subjects.

If this Amendment substantially alters the study design or increases potential risk to subjects, the consent form will be revised and submitted to the Institutional Review Board/Independent Ethics Committee for approval/positive opinion. I will use the new consent form for any new subjects prior to enrollment, and for subjects currently enrolled in the study if they are affected by the Amendment.

_____ _____

Investigator's printed name and signature *Date*

PPD _____ 14-Aug-2015

Medical Monitor/Study Director *Date*
(If required by applicable regulations and guidelines.)

Protocol Number: CV181365
Site Number:
Amendment Number: 03

Protocol Number: CV181365
IND Number: 63,634
EUDRACT Number 2014-003721-18
Date: 27-May-2016

Protocol CV181365: A 52-week International, Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel Group, Phase 3bTrial with a Blinded 104-week Long -term Extension Period to Evaluate the Efficacy and Safety of Saxagliptin Co-administered with Dapagliflozin in Combination with Metformin Compared to Glimepiride in Combination with Metformin in Adult Patients with Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Therapy Alone.

Amendment Number 04
Site Number: All

Study Director / Central Medical Monitor

PPD

24-hr Emergency Telephone Number:

PPD

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden
Study being conducted by Bristol-Myers Squibb on behalf of AstraZeneca AB

Bristol-Myers Squibb Research and Development
Metabolics Clinical Research and Development
Route 206 & Province Line Road
Lawrenceville, NJ 08543
Avenue de Finlande 4
B-1420 Braine-l'Alleud, Belgium

This amendment must be maintained with the referenced protocol.

Amendment Rationale:

The purpose of this amendment is to provide an update of the safety language for the investigational product, contraceptive language changes, and a clarification regarding the evaluable data in the sub-study populations to include the following:

- Provided updated safety information and protocol guidance regarding ketoacidosis, urosepsis, and pyelonephritis.
- Updated the contraceptive section. Removed condoms as a highly effective method and provided clarification of language for other highly effective methods of contraception.
- Addressed sub-study language to allow sites to provide additional patients in the sub-studies if a subject has unevaluable data at baseline.
- Additional administrative corrections (typos, etc.):

This amendment should be implemented upon receipt of IRB/IEC/HA approval.

This amendment applies to all subjects participating in this study.

Changes to the Protocol:

1. Updated Cover Page: Updated the name and contact information for the person responsible for the medical and safety oversight of the study
2. Section 1.5: Overall Risk/Benefit - Dapagliflozin - Updated UTI language and added DKA language.
3. Section 3.3.1: Inclusion Criteria - 3. Age and Reproductive Status - Updated WOCBP language and contraception language:
4. Section 3.5.4: Added section - Discontinuation Guidelines due to Ketoacidosis
5. Section 5.3.2.1: Guidance on Assessment of Urinary Tract Infections - Added urosepsis and pyelonephritis language
6. Section 5.3.4: Guidance on Assessment of Hepatic Laboratory Abnormalities - Clarification of discontinuation language.
7. Section 5.8.6: Magnetic Resonance Imaging (MRI) - Added clarification on evaluable data and continuation in base study.
8. Section 5.8.7: Continuous Glucose Monitoring (CGM) - Added clarification on evaluable data and continuation in base study.
9. Section 7.2: Hepatic Adjudication Committee - Clarification of discontinuation language.
10. Additional minor typo and administrative updates

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.

AMENDMENT ACKNOWLEDGMENT

I have read this Amendment and agree that it contains all necessary details for carrying out the changes described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion by all necessary Health Authorities before implementation unless to eliminate an immediate hazard to subjects.

If this Amendment substantially alters the study design or increases potential risk to subjects, the consent form will be revised and submitted to the Institutional Review Board/Independent Ethics Committee for approval/positive opinion. I will use the new consent form for any new subjects prior to enrollment, and for subjects currently enrolled in the study if they are affected by the Amendment.

Investigator's printed name and signature	*Date*
PPD	June 9 /2016
Medical Monitor/Study Director *(If required by applicable regulations and guidelines.)*	*Date*

Protocol Number: CV181365
Site Number:
Amendment Number: 04

Protocol Number: CV181365
AstraZeneca AB Protocol Number: D1689C00013
IND Number: 63,634
EUDRACT Number 2014-003721-18
Date: 08-Feb-2018

Protocol CV181365: A 52-week International, Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel Group, Phase 3bTrial with a Blinded 104-week Long-term Extension Period to Evaluate the Efficacy and Safety of Saxagliptin Co-administered with Dapagliflozin in Combination with Metformin Compared to Glimepiride in Combination with Metformin in Adult Patients with Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Therapy Alone.

Amendment Number 05
Site Number: All

Study Director / Central Medical Monitor

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

This amendment must be maintained with the referenced protocol.

Amendment Rationale:

The purpose of this amendment is to provide an update on language for safety (including details regarding the recording and adjudication of diabetic ketoacidosis [DKA] events), adverse events (AEs; including AEs leading to amputation and potential risk factor AEs for amputations affecting lower limbs), confirmed hypoglycemia, magnetic resonance imaging (MRI), pregnancy, blinding, investigational medicinal products (IMPs), efficacy analyses, rescue therapies, and prohibited treatments; to define the end of the study; and to incorporate administrative changes to include the following:

- Provided details of the DKA Adjudication Committee and DKA Adjudication Manual for Sites
- Clarified the collection and reporting of AEs, including those leading to amputation and potential risk factor AEs for amputations
- Definition updated for confirmed hypoglycemia
- MRI language updated, including the addition of liver volume at Week 122, amending the final MRI-proton density fat fraction (PDFF) to Week 122 ± 4 weeks, and to provide clarification of blinding
- Clarified that study drug will be permanently discontinued in any subjects that become pregnant during the study
- Clarified blinding of laboratory results during the study and that local laboratory results will be monitored for liver function test (LFT) abnormalities
- Clarified the metformin dose, permitted dose adjustments for glimepiride, and storage conditions for the IMPs
- Zhang's method removed from any statistical analyses
- Clarified the pre-specified glycemic control criteria, permitted rescue therapies, prohibited corticosteroid therapy, and initiation of rescue therapies
- Definition provided for the end of the study
- Additional minor typo and administrative updates.

This amendment should be implemented upon receipt of IRB/IEC/HA approval.

This amendment applies to all subjects participating in this study.

Changes to the Protocol:

1. Synopsis:
    - Definition for confirmed hypoglycemia updated to clarify it relates to blood glucose ≤ 70 mg/dL (3.9 mmol/L) recorded in the hypoglycemia module of the electronic Case Report Form (eCRF)
    - Clarified that subjects will continue to receive background metformin ≥1500 mg/day throughout the duration of the study, unless metformin treatment is temporarily withheld due to decreased creatinine clearance (CrCl)
    - Clarified that the glimepiride dose can be down titrated from Week 12 onwards (maintenance period) if hypoglycemic events occur
    - Clarified that MRI-PDFF investigations include an assessment of liver volume at Week 122, that the MRI analysis will be performed using semi-automated software, and amended the final MRI-PDFF assessment and related exploratory objective to Week 122
    - Text of 'Study medication should be discontinued if the estimated CrCl falls below 60 ml/min (by Cockcroft-Gault) for a sustained period of time (12-16 weeks)' deleted
    - Analysis of the therapeutic glycemic response revised to remove Zhang's method and to include logistic regression and odds ratio for the response rate
    - Administrative updates
2. Section 1.1, Study Rationale; Section 1.5: Overall Risk/Benefit Assessment, MRI; and Section 5.8.6: Magnetic Resonance Imaging (MRI) - Clarified that the MRI-PDFF investigations include an assessment of liver volume at Week 122.
3. Section 1.1, Study Rationale; Section 1.3.3: Exploratory Objectives, Long-term; Section 3.1: Study Design and Duration, MRI-PDFF; Section 5: Study Assessments and Procedures, Table 5.1-3: Long-term Procedural Outline for Protocol CV181365 (104-week) Subject- and Site-Blinded Treatment (Period D Week 52 to Week 156); Section 5.8.6: Magnetic Resonance Imaging (MRI); and Section 8.3.3: Exploratory Endpoint(s) - final MRI-PDFF assessment and associated objective / endpoint amended to Week 122 (± 4 weeks).
4. Section 1.3.4: Exploratory Safety Objectives – Definition for confirmed hypoglycemia updated to clarify it relates to blood glucose ≤ 70 mg/dL (3.9 mmol/L) recorded in the hypoglycemia module of the eCRF.
5. Section 1.5: Overall Risk/Benefit Assessment, MRI and Section 5.8.6: Magnetic Resonance Imaging (MRI) – Clarified that the MRI investigations will be performed to assess subcutaneous and visceral adipose tissue volume.
6. Section 3.1: Study Design and Duration – Clarified that subjects will continue to receive background metformin ≥1500 mg/day throughout the duration of the study, unless metformin treatment is temporarily withheld due to decreased CrCl.
7. Section 3.1: Study Design and Duration; Section 3.5.3: Discontinuation Guidelines due to Protocol-Defined Hypoglycemia Episodes; and Section 4.5: Selection and Timing of Dose for Each Subject – Clarified that the glimepiride dose can be down titrated from Week 12 onwards (maintenance period) if hypoglycemic events occur.
8. Section 3.4.1: Prohibited and/or Restricted Treatments – Clarified permitted rescue therapies and prohibited corticosteroid therapy.

9. Section 3.5: Discontinuation of Subjects following any Treatment with Study Drug and Section 6.5: Pregnancy – Clarified that study drug will be permanently discontinued in any subjects that become pregnant during the study.
10. Section 3.5.2: Rescue Guidelines for Subjects with Protocol-Defined Lack of Glycemic Control – Clarified when glycosylated hemoglobin (HbA1c) or fasting plasma glucose are to be used as the basis for the pre-specified glycemic control criteria; when rescue medication should be initiated; and that reimbursement will be provided for insulin rescue medication.
11. Section 3.5.3: Discontinuation Guidelines due to Protocol-Defined Hypoglycemia Episodes and Section 3.5.4: Discontinuation Guidelines due to Ketoacidosis – Text relating to down-titration of blinded study drug and/or background antihyperglycemic agent during the study due to hypoglycemic events moved from Section 3.5.4 to 3.5.3. Clarified that the background antihyperglycemic agent related to metformin which can be down-titrated if hypoglycemic events occur, but that the dose of metformin must be ≥ 1500 mg/day, unless metformin treatment is temporarily withheld due to CrCl < 60 mL/min (estimated by Cockcroft-Gault).
12. Section 3.5.4: Discontinuation Guidelines due to Ketoacidosis – Cross-reference added to Section 7.3, providing details of DKA event recording and adjudication.
13. Section 3.7: End of Study – New section added to define the end of the study.
14. Section 4: Study Drug, Table 4-1: Study Drugs for CV181365: Product Description: Short-term Double-Blinded Treatment Period and Long-term Subject- and Site-Blinded Treatment Period and Section 4.1: Investigational Product – Storage conditions updated.
15. Section 4: Study Drug, Table 4-2 and Section 4.1: Investigational Product: Contents of Blinded Glimepiride 2-Bottle kit – Table deleted and reference to Table 4-2 removed.
16. Section 5.2: Study Materials – Confirmation that a DKA Adjudication Manual for Sites will be provided.
17. Section 5.8.6: Magnetic Resonance Imaging (MRI) - Clarified that a) during the short-term treatment period, the MRI results will be blinded to recruiting sites, investigators, the MRI sites, the subjects, and the Sponsor, but would not be blinded to the Sponsor after Week 52, b) the Sponsor will not provide MRI results to subjects or investigators at the conclusion of the study, unless specifically requested by the subject, and c) MRI analysis will be performed using semi-automated software.
18. Section 5.9: Results of Central Assessments and Appendix 2: Central Laboratory Results – Clarified which laboratory results were blinded in either the short or long term treatment periods during the study.
19. Section 6.2.1: Non-serious Adverse Event Collection and Reporting – Clarified the collection and reporting of AEs.
20. Section 6.3: Adverse Events (AEs) Leading to Amputation and Potential Risk Factor AEs for Amputations Affecting Lower Limbs ("Preceding Events") – New section added to clarify the collection and reporting of AEs leading to amputation and potential risk factor AEs for amputations.
21. Section 6.8.1: AEs of Special Interest, Liver function test (LFT) abnormalities accompanied by jaundice or hyperbilirubinemia – clarified that local laboratory results will also be monitored for LFT abnormalities.
22. Section 7.3: Diabetic Ketoacidosis Adjudication Committee – New section included to provide details on the DKA Adjudication Committee.

23. Section 8.4.2.2: Secondary Efficacy Analyses and Section 8.4.2.3: Other Efficacy Analyses – Analysis of the therapeutic glycemic response and composite response endpoints revised to remove Zhang's method; analysis of the therapeutic glycemic response amended to include logistic regression and odds ratio.
24. Additional administrative corrections made throughout the documents as needed, including: details relating to Bristol-Myers Squibb deleted following transition of the study to AstraZeneca AB; references to Bristol-Myers Squibb removed throughout the document, and replaced with AstraZeneca AB or the Sponsor as appropriate; AstraZeneca AB protocol number added to the title page; update to the number of MRI sites the sub-study will be conducted at; removal of the 24 hour emergency telephone numbers as these are provided in the patient identification cards, minor text and formatting changes, amending typos etc.

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with AZ.

AMENDMENT ACKNOWLEDGMENT

I have read this Amendment and agree that it contains all necessary details for carrying out the changes described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion by all necessary Health Authorities before implementation unless to eliminate an immediate hazard to subjects.

If this Amendment substantially alters the study design or increases potential risk to subjects, the consent form will be revised and submitted to the Institutional Review Board/Independent Ethics Committee for approval/positive opinion. I will use the new consent form for any new subjects prior to enrollment, and for subjects currently enrolled in the study if they are affected by the Amendment.

Investigator's printed name and signature — *Date*

PPD — 8 Feb 2018

Medical Monitor — *Date*

(If required by applicable regulations and guidelines.)

Protocol Number: CV181365
AstraZeneca AB Protocol Number: D1689C00013
Site Number:
Amendment Number: 05