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Clinical Protocol CV181369

A 24-week International, Multicenter, Randomized, Open-Label, Active-Controlled, Parallel Group, Phase 3b Trial with a 28-week Extension to Evaluate the Efficacy and Safety of Saxagliptin Co-administered with Dapagliflozin Compared to Insulin Glargine in Subjects with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin with or without Sulfonylurea Therapy

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Incorporates amendment(s): 01

Medical Monitor

24-hr Emergency Telephone Number

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Study being conducted by Bristol-Myers Squibb on behalf of AstraZeneca AB

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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 01	17-Mar-2016	Incorporates Amendment 01
Amendment 01	17-Mar-2016	Addition of DKA safety language, change in starting insulin dose and titration algorithm, removal of pre-randomization criteria at the lead-in visit along with other minor statistical and protocol clarifications.
Original Protocol	06-Jul-2015	Not applicable

SYNOPSIS

Clinical Protocol CV181369

Protocol Title: A 24-week International, Multicenter, Randomized, Open-Label, Active-Controlled, Parallel Group, Phase 3b Trial with a 28-week Extension to Evaluate the Efficacy and Safety of Saxagliptin Co-administered with Dapagliflozin Compared to Insulin Glargine in Subjects with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin with or without Sulfonylurea Therapy

Investigational Products, Dose and Mode of Administration, Duration of Treatment with Investigational Products: Saxagliptin 5 mg oral tablet and dapagliflozin 10 mg oral tablet will be administered once daily for a total of 52 weeks of open-label treatment. Alternatively, insulin glargine, 100 Units/ml solution, for subcutaneous injection will be administered once daily throughout 52 weeks of treatment. Dosing will be titrated based on individual subject criteria to achieve a target fasting blood glucose level using a fixed dose algorithm.

Study Phase: 3b

Research Hypothesis: In subjects with type 2 diabetes with inadequate glycemic control treated with metformin with or without sulfonylurea (SU), co-administration of saxagliptin and dapagliflozin over an open-label treatment period of 24 weeks, will result in glycemic control, measured by HbA1c,that is non-inferior compared to the addition of insulin glargine.

Objectives:

Primary Objective

- To examine whether the mean change from baseline in HbA1c with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU is non-inferior to titrated insulin glargine plus metformin with or without SU after 24 weeks of open-label treatment.

Secondary Objectives

- To compare the mean change from baseline in total body weight with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 24 weeks of open-label treatment.
- To compare the proportion of confirmed hypoglycemia [defined as: a) plasma glucose ≤ 70 mg/dL (3.9 mmol/L); or b) signs / symptoms of hypoglycemia with self-monitored blood glucose ≤ 70 mg/dL (3.9 mmol/L)] when co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU during 24 weeks of open-label treatment.
- To compare the proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, without any hypoglycemia, with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 24 weeks of open-label treatment.
- To examine whether the change from baseline in the mean value of 24-hour glucose readings measured by Continuous Glucose Monitoring (CGM) with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU is non-inferior to titrated insulin glargine plus metformin with or without SU after 2 weeks of open-label treatment.
- To examine whether the proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU is non-inferior to titrated insulin glargine plus metformin with or without SU after 24 weeks of open-label treatment.

Exploratory Objectives

- To assess the change from baseline in mean amplitude of glucose excursions (MAGE) of 24-hour glucose readings measured by CGM with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 2 weeks, 12 weeks and 24 weeks of open-label treatment.
- To assess the change from baseline in the mean value of 24-hour glucose readings measured by CGM with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 12 weeks and 24 weeks of open-label treatment.
- To assess the change from baseline within-subject, within-day standard deviation of 24 hour glucose readings measured by CGM with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 2 weeks, 12 weeks, and 24 weeks of open-label treatment.
- To assess the change from baseline in the percentage of time spent within the euglycemic target range of ≥ 71 mg/dL (3.9 mmol/L) and ≤ 180 mg/dL (10.0 mmol/L) as measured by CGM with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 2 weeks, 12 weeks and 24 weeks of open-label treatment.
- To assess the change from baseline in the percentage of time spent with glucose ≤ 70 mg/dL (3.9 mmol/L) as measured by CGM with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 2 weeks, 12 weeks, and 24 weeks of open-label treatment.
- To assess the change from baseline in the percentage of time spent with glucose ≤ 70 mg/dL (3.9 mmol/L) as measured by CGM between midnight (12:00 am) and 6:00 am with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 2 weeks, 12 weeks and 24 weeks of open-label treatment.
- To assess the mean change from baseline in HbA1c with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 52 weeks of open-label treatment.
- To assess the mean change from baseline in total body weight with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 52 weeks of open-label treatment.
- To assess the proportion of confirmed hypoglycemia [defined as: a) plasma glucose ≤ 70 mg/dL (3.9 mmol/L); or b) signs / symptoms of hypoglycemia with self-monitored blood glucose ≤ 70 mg/dL (3.9 mmol/L)] with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU during 52 weeks of open-label treatment.
- To assess the proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, without any hypoglycemia, with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 52 weeks of open-label treatment.
- To assess the proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 52 weeks of open-label treatment.
- To assess the proportion of subjects requiring rescue or discontinuation for lack of glycemic control with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU during 24 weeks and 52 weeks of open-label treatment.
- To assess the time to treatment intensification (addition of non-study insulin or other anti-diabetic therapies for rescue therapy or discontinuation for lack of glycemic control) with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU during 24 weeks and 52 weeks of open-label treatment.
- To assess the proportion of subjects achieving HbA1c ≤ 6.5% with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 24 weeks and 52 weeks of open-label treatment.

- To assess the proportion of subjects achieving HbA1c ≤ 6.5% without any hypoglycemia with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 24 weeks and 52 weeks of open-label treatment.
- To assess change from baseline in average glucose values and postprandial glucose values measured by 6-point self-monitored blood glucose (SMBG) profiles with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 12 weeks, 24 weeks and 52 weeks of open-label treatment.
- To assess changes from baseline in subject-reported treatment satisfaction, quality of life, and barriers to medication adherence achieved with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 12 weeks, 24 weeks, and 52 weeks of open-label treatment.

Safety Objective

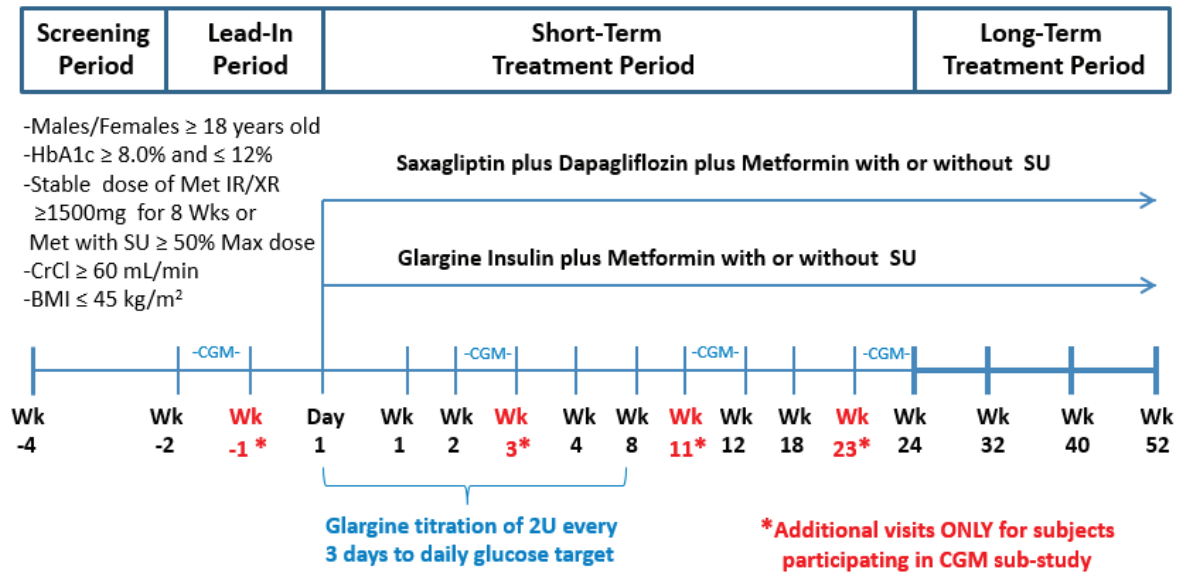
- To assess the safety and tolerability of co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 24 weeks and 52 weeks of open-label treatment.

Study Design:

- CV181369 is a randomized, open label, two arm, parallel group, active controlled, phase 3b study to evaluate the efficacy and safety of saxagliptin 5 mg co-administered with dapagliflozin 10 mg compared to titrated insulin glargine. Subjects with documented T2DM and inadequate glycemic control (central laboratory HbA1c value ≥ 8.0% and ≤ 12.0% at screening) on a stable dose of metformin ≥ 1500 mg per day for at least 8 weeks prior to screening, with or without a stable dose of sulfonylurea (SU) of at least 50% maximal dose per local label for at least 8 weeks prior to screening visit will be enrolled. Randomization will be stratified by current use of background medication (metformin alone vs metformin plus SU).
- After a 2 week Lead-in period, during which subjects will remain on their stable dose of metformin with or without SU and no study medication will be provided, eligible subjects will be randomized in a 1:1 ratio into one of the two open-label treatment arms (saxagliptin 5 mg daily (QD) and dapagliflozin 10 mg QD as a fixed dose combination or titrated insulin glargine). Subjects will receive saxagliptin 5 mg QD and dapagliflozin 10 mg QD or titrated insulin glargine for the 24 week, short-term period, followed by a 28 week, long-term period while continuing their stable dose of metformin with or without SU. Subjects will be monitored closely with regard to safety parameters, including vital signs, safety laboratory tests and adverse events. The primary endpoint of HbA1c will be assessed at 24 weeks.
- Approximately 171 sites will randomize a combined total of approximately 598 subjects (299 subjects per treatment arm). Allowing approximately 12 months of subject recruitment, this study will be conducted over 24 months.
- Continuous Glucose Monitoring (CGM) Sub-Study
- In this protocol, a sub-population of approximately 250 subjects (~125 subjects per treatment arm stratified by background SU use) who agree to participate (after signing a separate informed consent) will have a CGM sensor inserted subcutaneously to measure glucose levels in tissue fluid. The glucose sensor will be inserted and removed by trained personnel at the site. Subjects will wear the glucose sensor for 7 consecutive days at 4 different time periods during the study:
- At baseline, prior to receiving study medication, between Week -2 and Week-1
- Between Week 2 and Week 3 of treatment
- Between Week 11 and Week 12 of treatment
- Between Week 23 and Week 24 of treatment.

Subjects in the sub-study will have 4 site visits for sensor insertion–visits (at Week -1, Week 3, Week 11, and Week 23) added to the regularly scheduled visits.

Study Design Schematic:



Study Population: Males and females subjects ≥ 18 years old, with a clinical diagnosis of type 2 diabetes who have inadequate glycemic control, defined as HbA1c ≥ 8.0% and ≤ 12% at screening, a stable dose of metformin of ≥ 1500 mg/day for at least 8 weeks prior to screening visit with or without a stable dose of SU of at least 50% the maximal dose per local label for at least 8 weeks prior to screening visit. Subjects will be stratified according to whether their treatment regimen contains SU or not.

Key Inclusion Criteria

- Males and females subjects aged ≥ 18 years old at the time of screening visit.
- Subjects with T2DM with inadequate glycemic control, defined as a central laboratory HbA1c ≥ 8% and ≤ 12% obtained at the screening visit.
- Subjects must be taking a stable dose of metformin ≥ 1500 mg/day for at least 8 weeks prior to screening visit with or without a stable dose of SU of at least 50% maximal dose per local label for at least 8 weeks prior to screening visit. Subjects must not take any other antidiabetic therapy for more than 14 days (consecutive or not) during 12 weeks prior to screening.
- BMI ≤ 45.0 kg/m^2 at the screening visit.
- Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of hCG) at screening and within 24hours prior to the start of study drug.

Key Exclusion Criteria:

- Clinical diagnosis of Type 1 Diabetes.
- History of diabetic ketoacidosis
- History of unstable or rapidly progressing renal disease, hepatic insufficiency or current, acute or chronic pancreatitis.
- Any of the following cardiovascular/vascular diseases within 3 months of enrollment visit: myocardial infarction (MI), coronary arterial bypass graft (CABG), percutaneous coronary intervention (PCI), valvular disease or repair, unstable angina or unstable congestive heart failure (CHF), transient ischemic attack

(TIA), Class III or IV heart failure, known left ventricular ejection fraction of < 40%, or significant cerebrovascular disease.

- Impairment of renal function (defined as creatinine clearance [CrCl] < 60 mL/min [estimated by Cockcroft-Gault] or serum creatinine [SCr] ≥ 1.5 mg/dL in male subjects or ≥ 1.4 mg/dL in female subjects).
- Hematuria (confirmed by microscopy at screening) with no explanation as judged by the investigator up to randomization.
- Bladder cancer
- Other hematological or oncological diseases or conditions.
- Participation in a commercial weight loss program or history of bariatric surgery.
- Replacement or chronic systemic corticosteroid therapy.
- Administration of any other investigational drug or participation in any interventional clinical study within (30) days prior to screening for this study.

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

Study Drug for CV181369		
Medication	**Potency**	**IP/Non-IP**
Saxagliptin	5 mg	IP
Dapagliflozin	10 mg	IP
Glargine insulin	100 Units / ml	IP

Study Assessments:

Efficacy assessments consist of the central laboratory measurement of HbA1c during the treatment period, central laboratory and self-monitored glucose values to assess hypoglycemia and hyperglycemia, measurement of total body weight and CGM, measured in the sub-study, throughout the study treatment period.

Safety assessments will include adverse event (AE) reporting, clinical laboratory tests, electrocardiograms (ECG), vital signs, and physical examination findings.

Patient-reported outcomes (satisfaction, quality of life and barriers to medication adherence) will also be assessed by questionnaire at several timepoints throughout the study.

Statistical Considerations:

Sample Size:

The change from baseline in HbA1c at Week 24 will be assessed comparing co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU.

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 (ANCOVA) using last observation carried forward (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.

To demonstrate non-inferiority of saxagliptin plus dapagliflozin to insulin for changes from baseline to week 24 in HbA1c within a non-inferiority margin of 0.30%, assuming a standard deviation 1.1%, and at a one-sided significance level of 0.025, 284 evaluable subjects will be needed in each treatment group to provide approximately 90% power (given a true difference of zero between the 2 treatment groups). Assuming that 5% of subjects do not have a post-baseline assessment, a total of approximately 598 subjects (299 subjects per treatment arm) need to be randomized. Assuming that 50% of screened subjects will fail to meet screening criteria, a total of 1196 subjects need to be screened.

Endpoints:

Primary Endpoint(s)

Change from baseline in HbA1c at Week 24.

Secondary Endpoint(s)

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

1) Change from baseline in total body weight at Week 24
2) Proportion of subjects with confirmed hypoglycemia [defined as: a) plasma glucose ≤ 70 mg/dL (3.9 mmol/L); or b) signs / symptoms of hypoglycemia with self-monitored blood glucose ≤ 70 mg/dL (3.9 mmol/L)] at Week 24
3) Proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, without any reported hypoglycemia (for the duration of the Short-term Period) at Week 24
4) In a sub-study, change from baseline in the mean value of 24-hour glucose readings measured by Continuous Glucose Monitoring (CGM) at Week 2
5) Proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0% at Week 24

Analyses:

The primary endpoint will be tested for non-inferiority for saxagliptin plus dapagliflozin versus insulin at the alpha = 0.025 level (one sided). The primary analysis of the change in HbA1c from baseline at Week 24 visit will be based on a longitudinal repeated measures analysis using 'direct likelihood' using the randomized subject data set. The SAS procedure PROC MIXED will be used. The preferred model will include the fixed categorical effects of treatment, week, randomization stratification factor (background medication of metformin alone vs metformin + SU) and treatment-by-week interaction as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction. Point estimates and 95% confidence intervals for the mean change within each treatment group as well as the difference in mean change between the saxagliptin and dapagliflozin versus insulin will be calculated. If the upper limit of the 95% confidence interval is < 0.3%, then saxagliptin plus dapagliflozin as add-on therapy to metformin with or without SU will be considered to be non-inferior to insulin as add-on therapy to metformin with or without SU. The analysis will be repeated using Evaluable Subjects data set. Several other sensitivity analyses, including an analysis using the Evaluable Subjects data set and data regardless of rescue or treatment discontinuation, will also be performed for the primary efficacy endpoint to assess the robustness of the results.

If non-inferiority is demonstrated for the primary endpoint, the statistical tests for the secondary efficacy endpoints will be performed. The secondary endpoints then will be tested sequentially in the order that they appear in the objectives section of the protocol. Each comparison will be tested at the alpha = 0.05 (two-sided) level (one-sided alpha = 0.025 will be used for the non-inferiority test).

The continuous secondary endpoints (ie, the change from baseline in total body weight, the change from baseline at Week 24 visit in the mean value of 24-hour glucose readings obtained from CGM, and the change from baseline in amplitude of glucose excursion of 24-hour glucose readings obtained from CGM) will be analyzed using a longitudinal repeated measures analysis, similarly to the one used for primary efficacy analysis. The binary endpoints (eg, the proportion of subjects achieving HbA1c < 7.0%; hypoglycemia endpoint; and composite response endpoints of glycemic control with hypoglycemia) will be analyzed using logistic regression with adjustment for baseline HbA1c value and/or the stratification factor. In addition to point estimates and 95% confidence intervals, p-values will be calculated for all secondary endpoints. However, no claim will be based on endpoints for which the statistical testing is not performed for the endpoint as per the sequential testing strategy.

For the non-inferiority endpoints, the analysis will be repeated using evaluable subjects data set to examine the robustness of the results. For the non-inferiority secondary endpoint (for the sub-study) of change from baseline in mean 24-hour glucose readings measured by Continuous Glucose Monitoring (CGM) at Week 24, the non-inferiority margin used for testing will be 12 mg/dL. For the non-inferiority secondary endpoint of the proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0% at Week 24, the non-inferiority margin used for testing will be 10%.

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

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1 INTRODUCTION AND STUDY RATIONALE

Type 2 diabetes mellitus (T2DM) is a chronic progressive disease, characterized by hyperglycemia and an increased risk of microvascular and macrovascular complications. Achieving and maintaining the glycemic treatment goal is challenging. Typically the treatment paradigm consists of a step-wise addition of different classes of anti-hyperglycemic 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 anti-diabetic agents are typically added sequentially as second and third-line agents. Despite multiple drugs and classes being available, many patients are still inadequately controlled. An optimal add-on to metformin would provide strong HbA1c reduction in the absence of hypoglycemia through complementary mechanisms of action (MoA), accompanied by weight loss.

1.1 Study Rationale

This Phase 3 study is part of a clinical program to support the development of a saxagliptin 5 mg and dapagliflozin 10 mg fixed-dose combination (FDC) therapy for the treatment of T2DM. In subjects with T2DM who are inadequately controlled on metformin therapy with or without a sulfonylurea (SU), this study will compare the efficacy and safety of the addition of saxagliptin-dapagliflozin versus the addition of titrated insulin glargine. The complementary mechanisms of action of saxagliptin and dapagliflozin, in combination with metformin, have been shown in previous studies to provide superior HbA1c reduction compared to either of the individual agents alone in subjects with inadequately controlled T2DM.

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 (GLP-1) and gastric inhibitory polypeptide (GIP). By inhibiting the enzyme DPP4, saxagliptin potentiates active endogenous GLP-1 concentrations, augmenting the physiological mechanism of insulin secretion and decreasing glucagon release, thereby reducing postprandial and fasting glucose levels in patients with T2DM.

The results from 8 Phase 2b and 3 clinical studies of saxagliptin in over 4600 subjects, combined with the results from clinical pharmacology studies, support the oral dose of saxagliptin 5 mg once daily in a wide range of subjects with T2DM, as either monotherapy, add-on combination therapy with metformin, a thiazolidinedione (TZD), a sulfonylurea, insulin or initial combination therapy with metformin. The results from the Phase 3 studies confirmed clinically meaningful benefits of saxagliptin 5 mg on HbA1c, as well as on fasting plasma glucose (FPG), postprandial glucose (PPG), insulin, C-peptide, and glucagon concentrations.

Dapagliflozin (BMS-512148) 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 consisted of 5 core Phase 2b studies and 16 core Phase 3 studies of 11,801 subjects, along with data from a wide range of clinical pharmacology studies which support the oral dose of dapagliflozin 10 mg once daily. 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. Treatment with dapagliflozin also results in a persistent loss of calories associated with glucose loss in the urine, resulting in a consistent and maintained reduction of the total body weight. Dapagliflozin also has a mild diuretic effect, which in combination with weight loss, has the potential to reduce blood pressure. Dapagliflozin 10 mg consistently provided clinically meaningful reductions in HbA1c in a wide range of subjects with T2DM, as either monotherapy, add-on combination therapy with metformin, a TZD, a SU, a DPP4 inhibitor, insulin or initial combination therapy with metformin.

As a FDC therapy, saxagliptin-dapagliflozin differ from the other classes of T2DM by their MoA, their low risk for hypoglycemia and either weight neutrality or weight loss. Dapagliflozin inhibits renal glucose reabsorption and acts independently of insulin, while saxagliptin enhances glucose-mediated insulin secretion by a glucose-dependent mechanism (via incretin effect). Saxagliptin and dapagliflozin have demonstrated, both individually, in combination and in combination with metformin with or without SU, a favorable safety and tolerability profile.[1 2 3] They have shown as single agents, as well as in combination with metformin, a low propensity for hypoglycemia consistent with their respective glucose dependent mechanism of action, therefore addressing a potential key concern when adding a glucose lowering agent. Both drugs have either demonstrated moderate weight reduction (dapagliflozin) or weight neutrality (saxagliptin) and do not require dose titration, simplifying therapy compared to insulin.

While insulin is an effective treatment for T2DM, insulin is associated with several undesirable side effects that can negatively affect patient compliance and limit its effectiveness. These include increased risk of hypoglycemia and weight gain. Hypoglycemia is a clinically important barrier to optimizing treatment and there is emerging evidence that hypoglycemia is associated with negative cardiovascular outcomes. Over 85% of patients with T2DM are overweight or obese[4], and additional weight gain is undesirable and often results in reduced treatment compliance by the patients. In addition, not all patients are willing or able to inject insulin and keep up with the regular blood glucose monitoring required by insulin regimens.

1.2 Research Hypothesis

In subjects with type 2 diabetes with inadequate glycemic control treated with metformin with or without SU, co-administration of saxagliptin and dapagliflozin over an open-label treatment period of 24 weeks will result in glycemic control, measured by HbA1c that is non-inferior compared to the addition of insulin glargine.

1.3 Objectives

1.3.1 Primary Objective

- To examine whether the mean change from baseline in HbA1c with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU is non-inferior

to titrated insulin glargine plus metformin with or without SU after 24 weeks of open-label treatment.

1.3.2 Secondary Objectives

- To compare the mean change from baseline in total body weight with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 24 weeks of open-label treatment.
- To compare the proportion of confirmed hypoglycemia [defined as: a) plasma glucose ≤ 70mg/dL (3.9 mmol/L); or b) signs / symptoms of hypoglycemia with self-monitored blood glucose ≤ 70 mg/dL] with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU during 24 weeks of open-label treatment.
- To compare the proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, without any hypoglycemia, with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 24 weeks of open-label treatment.
- To examine whether the change from baseline in the mean value of 24-hour glucose readings measured by Continuous Glucose Monitoring (CGM) with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU is non-inferior to titrated insulin glargine plus metformin with or without SU after 2 weeks of open-label treatment.
- To examine whether the proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU is non-inferior to titrated insulin glargine plus metformin with or without SU after 24 weeks of open-label treatment.

1.3.3 Exploratory Objectives

- To assess the change from baseline in mean amplitude of glucose excursions (MAGE) of 24-hour glucose readings measured by CGM with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 2 weeks, 12 weeks and 24 weeks of open-label treatment.
- To assess the change from baseline in the mean value of 24-hour glucose readings measured by CGM with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 12 weeks and 24 weeks of open-label treatment.
- To assess the change from baseline within-subject, within-day standard deviation of 24 hour glucose readings measured by CGM with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 2 weeks, 12 weeks and 24 weeks of open-label treatment.
- To assess the change from baseline in the percentage of time spent within the euglycemic target range of ≥ 71 mg/dL (3.9 mmol/L) and ≤ 180 mg/dL (10.0 mmol/L) as measured by CGM with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or

without SU versus titrated insulin glargine plus metformin with or without SU after 2 weeks, 12 weeks and 24 weeks of open-label treatment.

- To assess the change from baseline in the percentage of time spent with glucose ≤ 70 mg/dL (3.9 mmol/L) as measured by CGM with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 2 weeks, 12 weeks and 24 weeks of open-label treatment.
- To assess the change from baseline in the percentage of time spent with glucose ≤ 70 mg/dL (3.9 mmol/L) as measured by CGM between midnight (12:00 am) and 6:00 am with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 2 weeks, 12 weeks and 24 weeks of open-label treatment.
- To assess the mean change from baseline in HbA1c with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 52 weeks of open-label treatment.
- To assess the mean change from baseline in total body weight with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 52 weeks of open-label treatment.
- To assess the proportion of confirmed hypoglycemia [defined as: a) plasma glucose ≤ 70 mg/dL (3.9 mmol/L); or b) signs / symptoms of hypoglycemia with self-monitored blood glucose ≤ 70 mg/dL (3.9 mmol/L)] with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU during 52 weeks of open-label treatment.
- To assess the proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, without any hypoglycemia, with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 52 weeks of open-label treatment.
- To assess the proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 52 weeks of open-label treatment.
- To assess the proportion of subjects requiring rescue or discontinuation for lack of glycemic control with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU during 24 weeks and 52 weeks of open-label treatment.
- To assess the time to treatment intensification (addition of non-study insulin or other anti-diabetic therapies for rescue therapy or discontinuation for lack of glycemic control) with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU during 24 weeks and 52 weeks of open-label treatment.
- To assess the proportion of subjects achieving HbA1c ≤ 6.5% with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 24 weeks and 52 weeks of open-label treatment.

- To assess the proportion of subjects achieving HbA1c ≤ 6.5% without any hypoglycemia with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 24 weeks and 52 weeks of open-label treatment.
- To assess change from baseline in average glucose values and postprandial glucose values measured by 6-point self-monitored blood glucose (SMBG) profiles with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 12 weeks, 24 weeks and 52 weeks of open-label treatment.
- To assess changes from baseline in subject-reported treatment satisfaction, quality of life, and barriers to medication adherence achieved with co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 12 weeks, 24 weeks and 52 weeks of open-label treatment.

1.3.4 Safety Objective

- To assess the safety and tolerability of co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU after 24 weeks and 52 weeks of open-label treatment.

1.4 Product Development Background

Saxagliptin is a DPP4-inhibitor for the treatment of patients with T2DM. DPP4-inhibitors enhance glucose-mediated insulin secretion and suppress glucagon by reducing the clearance of active glucagon-like peptide 1 (GLP-1). Saxagliptin is approved for the treatment of T2DM in many countries including in the US and EU. The results of many Phase 3 studies have confirmed clinically meaningful benefits of saxagliptin 5 mg on HbA1c, as well as FPG, postprandial glucose (PPG), insulin, C-peptide, and glucagon levels. In an extensive Phase 2b/3 program, the majority of 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 or in combination with other antidiabetic agents. Treatment with saxagliptin led to rates of hypoglycemia that were generally similar compared to placebo. 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. The adverse reactions most frequently reported in subjects treated with saxagliptin in a pooled analysis of 5 pivotal placebo-controlled clinical studies of saxagliptin were: upper respiratory tract infection, urinary tract infection, sinusitis, gastroenteritis, vomiting, and headache.

Dapagliflozin is an SGLT2 inhibitor, the major transporter responsible for renal glucose reabsorption, resulting in the direct, and insulin-independent, elimination of glucose by the kidney. Dapagliflozin is approved for the treatment of T2DM in many countries including the US and EU. Urinary glucose excretion induced by dapagliflozin depends upon the amount of

glucose filtered by the kidney. This filtered load is the product of the plasma glucose concentration and the glomerular filtration rate (GFR).

Phase 3 study results have shown clinically significant reductions in HbA1c, FPG, PPG, and total body weight with dapagliflozin 10 mg treatment. Reductions in blood pressure are also consistently observed with dapagliflozin treatment, attributed to its mild diuretic effect. The majority of reported AEs in clinical studies of dapagliflozin were non-serious and did not require discontinuation of treatment. Dapagliflozin has a low intrinsic risk of hypoglycemia, due to its insulin independent mechanism of action. The adverse reactions most frequently reported in a pooled analysis of (12) placebo-controlled clinical studies of dapagliflozin were: female genital mycotic infections, nasopharyngitis, urinary tract infections, back pain, increased urination, male genital mycotic infections, nausea, influenza, dyslipidemia, constipation, discomfort with urination and pain in extremity.

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

In the saxagliptin 5 mg - dapagliflozin 10 mg FDC development program, 3 Phase 3 studies have been completed: CV181169, a 24-week study of 534 subjects; CV181168, a 52-week study of 315 subjects; and, MB102129, a 52-week study of 320 subjects. All three studies demonstrated that treatment with saxagliptin and dapagliflozin, added to metformin as triple therapy, provided a greater reduction in HbA1c than either saxagliptin or dapagliflozin alone added to metformin as double therapy in subjects with inadequately controlled T2DM. The saxagliptin/dapagliflozin combination has raised no new safety concerns. Most AEs in these studies were not serious and did not require discontinuation of treatment. There were no new safety issues seen in the studies of the FDC that had not been identified previously in the individual clinical development programs for saxagliptin or dapagliflozin alone.

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.

Potential Risks

Saxagliptin, dapagliflozin, metformin, SU and insulin are widely used anti-diabetic treatments. All will be prescribed according to their approved labels. The potential risks associated with

saxagliptin and dapagliflozin have been identified based upon their mechanism of action, preclinical results, and extensive clinical experience to date, including other studies of saxagliptin plus dapagliflozin added to metformin with or without SU. Thus, the benefits and risks associated with these investigational drugs are well established and presented in their approved prescribing information and investigator brochures respectively. No study procedure will put subjects at risk beyond those ordinarily encountered during the performance of routine medical examinations or tests.

Continuous Glucose Monitoring (CGM)

A subset of study subjects will be enrolled in the CGM sub-study. 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).

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 subject safety, AstraZeneca (AZ) and Bristol-Myers Squibb (BMS) will conduct a real-time review of all safety information from all ongoing clinical saxagliptin plus 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.

Potential benefits to subjects

All subjects will receive active antihyperglycemic therapy. Insulin glargine is an approved medication for the treatment of T2DM, and the efficacy and safety of saxagliptin in combination with dapagliflozin has been recently established. A Phase 3 study (CV181169) demonstrated that early combination treatment with saxagliptin and dapagliflozin, added to 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 52 week 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 Harmonization (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 at the specific institution.

All potential serious GCP breaches (defined below) must be reported to BMS (or designee) 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 subject(s) of the study and/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

Before 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 BMS/AZ 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 BMS/AZ 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 to subjects, their legally acceptable representatives (as per country guidelines) must be clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS (or designee) will provide the investigator with an appropriate (eg, 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 most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or 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 (ICF) and, in the USA the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS/AZ 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.

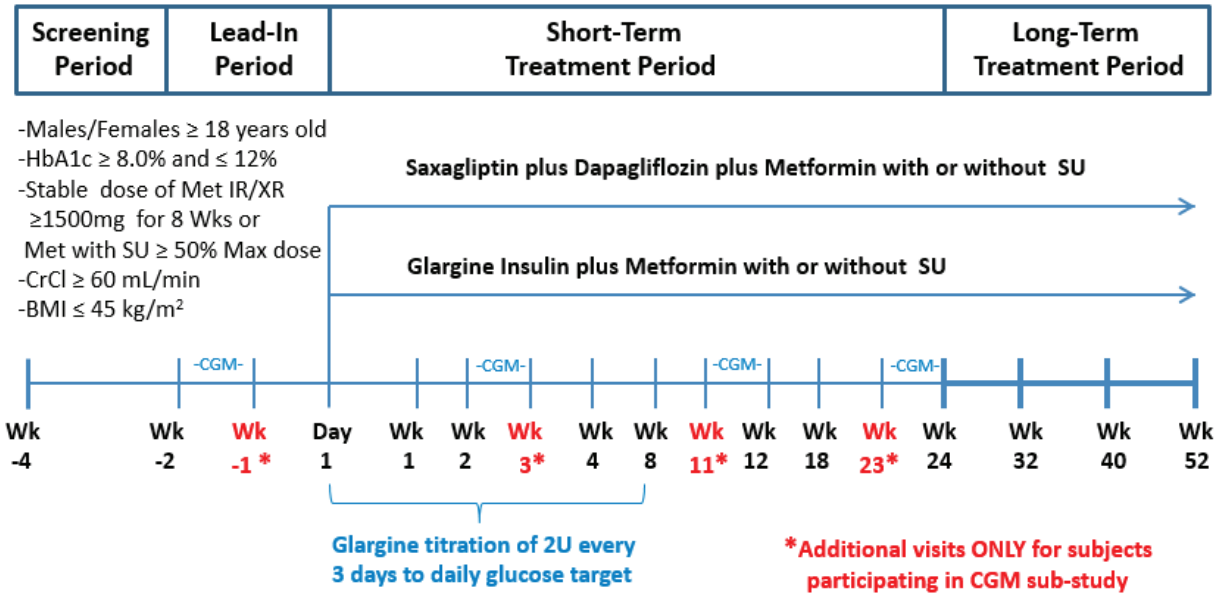
3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

The CV181369 study is a randomized, open-label, two arm, parallel group, active-controlled, multicenter, Phase 3b study to evaluate the efficacy and safety of saxagliptin co-administered with dapagliflozin compared to insulin glargine. Subjects with documented T2DM and inadequate glycemic control (central laboratory HbA1c value ≥ 8% and ≤ 12% at screening) on a stable dose of metformin ≥ 1500 mg/day for at least 8 weeks prior to screening visit with or without a stable dose of SU of at least 50% the maximal dose per local label for at least 8 weeks prior to screening visit will be enrolled. The primary endpoint of HbA1c will be assessed at 24 weeks; however, the trial will continue to 52 weeks as a long-term extension.

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

Figure 3.1-1: Study Design Schematic



Approximately 171 sites will randomize a combined total of approximately 598 subjects (299 subjects per treatment arm). Allowing approximately 12 months for patient recruitment, this study will be conducted over 24 months.

Subjects who are identified for evaluations must sign the protocol-specific informed consent prior to undergoing any study-specific procedures. **Only subjects who sign the protocol-specific informed consent form are considered enrolled and will have a subject number assigned by the IVRS.**

The study design as shown in Figure 3.1-1 includes the following four study periods:

3.1.1 Screening Period

Subjects with documented T2DM and inadequate glycemic control (central laboratory HbA1c value ≥ 8% and ≤ 12% at screening) on a stable dose of metformin ≥ 1500 mg/day for at least 8 weeks prior to screening visit with or without a stable dose of a SU of at least 50% the maximal dose per local label will be eligible for protocol-specific assessment during the Screening Period. Signature of the protocol-specific informed consent form constitutes the first procedure of the Screening Period, followed by the assignment of a unique subject number by the IVRS. Protocol-specific procedures may then be performed, as part of the screening visit, to evaluate the subject's eligibility. The screening visit procedures may be completed on one or more days during the Screening Period, which lasts for 14 days.

Subjects will be instructed to continue their current metformin and, if applicable, SU treatment at the same dose level during Screening Period. The end of Screening Period/entry into Lead-in Period (Week -2) visit will be scheduled once all the inclusion and exclusion criteria have been

evaluated. Entry into Lead-in Week -2 visit should be scheduled within 14 days of the screening central laboratory samples collection. The Medical Monitor should be contacted if the Week -2 visit is planned to be scheduled more than 14 days after the screening central laboratory samples collection. The end of the Screening Period is the same day as the entry into Lead-in Period.

3.1.2 Lead-In Period

Eligible subjects who complete the Screening Period will enter the 2-week Lead-in Period. Subjects will continue to receive their stable dose of metformin with or without SU throughout the study. Subjects will be instructed on diet and exercise in accordance with the American Diabetes Association (ADA) recommendations, or similar local guidelines, by a qualified member of the study staff for the duration of the study, beginning with the Lead-In visit. Home glucose meters will be dispensed to subjects and self-monitoring blood glucose (SMBG) requirements and procedures will be explained. Subjects should demonstrate the ability to correctly perform SMBG during the Lead-in Period, and complete their subject diary, as required per protocol (see Section 5.3.1.1). Visits should occur within +/- 5 day window of the protocol designated visit schedule, based on the screening date. Subjects should arrive at the site between 6:00 AM and 10:00 AM, should be in a fasting state (at least 8 hours) for all regularly scheduled visits and avoid alcohol, caffeine and tobacco prior to the visit (at least 8 hours).

All subjects will be instructed to perform 6-point SMBG profiles consisting of 3 glucose measurements obtained pre-prandially (within 15 minutes prior to meal) and 3 glucose measurements obtained post-prandially (1.5 - 2 hours after the meal) for the 3 main meals of the day. The initial pre-prandial glucose measurement on the 6-point SMBG day should be a fasting plasma glucose reading. All subjects should perform 6-point SMBG on any 3 days (do not have to be on consecutive days) during the Lead-in Period: Week (- 2) to Week (- 1).

Subjects will also be given a diary and instructed to use it to record SMBG results each day and meal times (during periods of 6-point SMBG and CGM, if applicable) during the Lead-in Period. Subjects will also be instructed to always self-monitor their blood glucose for hypoglycemia and to record any hypoglycemia episodes (time, symptoms and SMBG values) in the diary.

Eligible subjects with an enrollment HbA1c $\geq$ 8.0 % and $\leq$ 12.0 % should complete the Lead-in Period in 14 $\pm$ 5 days.

3.1.3 Short-term Treatment Period

On the Day 1 visit, subjects who meet all protocol enrollment and randomization criteria will be randomized into one of the two open-label treatment arms, in a 1:1 ratio:

- Saxagliptin 5 mg QD and Dapagliflozin 10 mg QD
- Titrated insulin glargine

Randomization will be stratified by current use of background medication (metformin alone vs metformin plus SU) at baseline to ensure equal representation across all treatment groups and

also within the CGM sub-study. Subjects will continue to receive their stable dose of metformin with or without SU throughout the study.

At the Day 1 visit and all other subsequent visits, the subject's current dietary and exercise behavior will be reviewed and guidelines reinforced. The investigator will review the subject's diary entries between visits to identify any hypoglycemic events, including symptoms with or without SMBG ≤ 70 mg/dL (see Section 5.3.1.3). Visits should occur within +/- 5 day window of the protocol designated visit schedule, based on the Day 1 visit date. Subjects should arrive at the site between 6:00 AM and 10:00 AM, should be in a fasting state (at least 8 hours) for all regularly scheduled visits and avoid alcohol, caffeine and tobacco prior to the visit (at least 8 hours).

Subjects will be instructed to continue recording in their diary their fasting SMBG twice daily, study medication dosing, any hypoglycemia episodes, and meal times (during periods of 6-point SMBG and CGM, if applicable).

All subjects will be instructed to perform 6-point SMBG profiles consisting of 3 glucose measurements obtained pre-prandially (within 15 minutes prior to meal) and 3 glucose measurements obtained post-prandially (1.5 - 2 hours after the meal) for the 3 main meals of the day. The initial pre-prandial glucose measurement on the 6-point SMBG day should be a fasting plasma glucose reading. All subjects should perform 6-point SMBG on any 3 days (do not have to be on consecutive days) during the Short-term Period: Week 11 to Week 12 and Week 23 to Week 24.

During the first 12 weeks following randomization, there will be no protocol specified rescue criteria. During this time, subjects receiving open-label insulin glargine will have their dosage titrated to FPG target of ≤ 100 mg/dL (5.5 mmol/L), which is driven over an 8 week period, then at Investigator's discretion with minimal adjustment at 12 and 18 weeks. Titration of open-label saxagliptin and dapagliflozin will not be allowed at any time during the study.

Insulin Titration during the Short-term Treatment Period

Subjects randomized to open-label treatment with insulin glargine will be recommended to start on Day 1 with an initial dose of 0.2U/kg bodyweight or at least 10 Units of insulin per day according to the discretion of the Investigator. A FPG target of ≤ 100 mg/dL (5.5 mmol/L) will guide insulin glargine titration, based on daily glucose monitoring (see Appendix 6 for details). Subjects will self-titrate their insulin dose in 2 Unit increments every 3 days (based on the FPG average for the previous 3 days) until Week 8 of the study. Investigators may modify the fixed dosing titration steps, scheduled in the first eight weeks, to optimize titration for individual patients in order to reach the target goal. At the Week 8 and Week 12 visit, the Investigator, at his/her discretion, can decide whether to increase the daily dose of insulin, based on FPG and SMBG values. If there have been any unexplained hypoglycemic events (glucose ≤ 70 mg/dL [3.9 mmol/L] during the last 3 days of SMBG readings, insulin glargine will not be up-titrated until there are 3 days without hypoglycemia. The insulin titration will be checked at each site visit and the Investigator can provide recommendations of higher doses at his/her discretion between Weeks 8-12. The goal is to reach an acceptable and stable dose by Week 12 Any insulin

dose increases after Week 12 should be discussed with the Medical Monitor. Attempts should be made to minimize changes to the daily insulin dose for the remainder of the study.

After Week 12, subjects with confirmed central laboratory measured FPG values > 200 mg/dL (11.1 mmol/L), without an obvious explanation, will be eligible for open-label rescue medication (including further up-titration of daily insulin dose) (see Section 3.5.4). Down-titration of insulin after Week 8 will be allowed only as necessary to prevent low blood glucose or hypoglycemia (see Section 3.5.5).

Subjects will be followed in the Short-term Period for a total of 24 Weeks. The primary endpoint of HbA1c will be assessed at 24 weeks.

3.1.4 Long-term Treatment Period

Subjects who complete the Short-term Treatment Period will continue into the Long-term Period taking the same open-label study medication (saxagliptin 5 mg QD and dapagliflozin 10 mg QD or insulin glargine) to which they were randomized on study Day 1. Subjects will continue to receive their stable dose of metformin with or without SU throughout the study. Visits should occur within +/- 5 day window of the protocol designated visit schedule, based on the screening date. Subjects should arrive at the site between 6:00 AM and 10:00 AM, should be in a fasting state (at least 8 hours) for all regularly scheduled visits and avoid alcohol, caffeine and tobacco prior to the visit(at least 8 hours).

The investigator will review the subject's diary entries between visits to identify any hypoglycemic events, including symptoms with or without SMBG ≤ 70 mg/dL (see Section 5.3.1.3).

All subjects will be instructed to perform 6-point SMBG profiles consisting of 3 glucose measurements obtained pre-prandially (within 15 minutes prior to meal) and 3 glucose measurements obtained post-prandially (1.5 - 2 hours after the meal) for the (3) main meals of the day. The initial pre-prandial glucose measurement on the 6-point SMBG day should be a fasting plasma glucose reading.

All subjects should perform 6-point SMBG on any 3 days (do not have to be on consecutive days) during the Long-term Period: Week 51 to Week 52 (see Section 5.3.1.2). Subjects will be instructed to continue recording in their diary their fasting SMBG, study medication dosing, hypoglycemia episodes, and meal times (applicable during periods of and 6-point SMBG).

After Week 24, subjects with HbA1c > 8.0% will be eligible for open-label rescue medication (including further up-titration of daily insulin dose) (see Section 3.5.4).

Subjects will be followed in the Long-term Period for an additional 28 weeks. All endpoints assessed at Week 52 will be exploratory.

3.1.5 Continuous Glucose Monitoring (CGM) Sub-Study

CGM is a useful technology to qualitatively as well as quantitatively, monitor the quality of glycemic control, including 24-hour average glucose and time spent in the euglycemic target range of > 70 mg/dl (3.9 mmol/L) and ≤ 180 mg/dL (10 mmol/L).

In this protocol, a sub-population of approximately 250 subjects with valid CGM data at the baseline assessment performed at Week -2 (~125 subjects per treatment arm stratified by background SU use) who agree to participate (separate informed consent) will have a CGM sensor inserted subcutaneously to measure glucose levels in tissue fluid. The glucose sensor will be inserted and removed by trained personnel at the site. Subjects will wear the glucose sensor for 7 consecutive days at 4 different time periods during the study:

- At baseline, prior to receiving study medication, between Week -2 and Week-1
- Between Week 2 and Week 3 of treatment
- Between Week 11 and Week 12 of treatment
- Between Week 23 and Week 24 of treatment.

Subjects in the sub-study will have 4 site visits added to the regularly scheduled visits (Week -1, Week 3, Week 11, and Week 23). If CGM recording is insufficient at any of these timepoints, subjects may be asked to wear the glucose sensor for an additional 7 day period to obtain sufficient data.

Subjects in the CGM sub-study will be required to perform a 4-point SMBG profile on days of CGM monitoring when they are not performing the 6-point SMBG profile (see Section 5.3.1.2). This 4-point SMBG should be performed at the approximate times: before breakfast, before lunch, before dinner and before bedtime and the values recorded in the subject's diary.

Detailed procedures (including calibration, insertion/removal and upload of data) will be described in an operations manual and site staff will be trained on the use of the CGM. Subjects will be instructed on use of the device according to the manufacturer's instructions (see Section 5.9 for additional information).

3.2 Post Study Access to Therapy

There will be no post study access to study medication after the end of the study (Week 52). BMS/AZ will not continue to provide study medication to subjects/investigators unless BMS/AZ chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care for T2DM thereafter.

3.3 Study Population

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

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent

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

2) Target Population

a) Subjects who are T2DM with inadequate glycemic control, defined as a central laboratory HbA1c ≥ 8.0 % and ≤ 12.0 % obtained at the screening visit.

b) Subjects must be taking a stable dose of metformin ≥ 1500 mg/day for at least 8 weeks prior to screening visit with or without a stable dose of SU of at least 50% maximal dose

per local label for at least 8 weeks prior to screening visit. Subjects must not take any other antidiabetic therapy for more than 14 days (consecutive or not) during 12 weeks prior to screening.

c) Body Mass Index (BMI) ≤ 45.0 kg/m2 at the screening visit.

d) Subject re-enrollment: This study does not permit the re-enrollment of a subject who has discontinued the study as a Screening or Lead-in failure.

3) Age and Reproductive Status

a) Males and female subjects aged ≥ 18 years old at the time of 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) at screening and within 24 hours prior to the start of study drug (Day 1).

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for a highly effective method of contraception for the duration of treatment with study drugs: saxagliptin, and dapagliflozin, and insulin plus 5 half-lives of study drugs: saxagliptin, dapagliflozin, and insulin 33 days plus 30 days (duration of ovulatory cycle) for a total of 63 days post-treatment completion.

e) 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 who are sexually active on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP who are sexually active on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% 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
- Vasectomized 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 is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. (See Appendix 5).

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) Clinical diagnosis of Type 1 diabetes, known diagnosis of mature onset diabetes of youth (MODY), secondary diabetes mellitus, or diabetes insipidus.

b) History of diabetic ketoacidosis

2) Medical History and Concurrent Diseases

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

i) Myocardial infarction

ii) Cardiac surgery or revascularization (coronary artery bypass surgery [CABG]/percutaneous coronary intervention [PCI])

iii) Valvular disease/ repair

iv) Unstable angina

v) Unstable congestive heart failure (CHF)

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

vii) Unstable or previously undiagnosed arrhythmia

viii) Congestive heart failure* (see Appendix 1), 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%.

* Eligible subjects 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:

ix) History of unstable or rapidly progressing renal disease

x) Impairment of renal function (defined as creatinine clearance [CrCl] < 60 mL/min [estimated by Cockcroft-Gault] or serum creatinine [SCr] ≥ 1.5 mg/dL [133 μmol/L] in male subjects or ≥ 1.4 mg/dL [124 μmol/L] in female subjects).

xi) Hematuria, defined as ≥ 3 RBC/HPF (red blood cells per high powered field) without the presence of epithelial cells (confirmed by microscopy at screening) with no explanation as judged by the investigator up to randomization. If bladder cancer is identified, subject is not eligible to participate.

c) Hepatic diseases:

xii) Severe hepatic insufficiency

xiii) 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. Subjects who have isolated positive anti-hepatitis B antibodies (ie, indicating immunity to hepatitis B infection or previous vaccination) may be included.

xiv) Documented history of hepatotoxicity with any medication

d) Pancreatic disease

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

e) Hematological and oncological disease/conditions:

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

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

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

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

f) Prohibited treatments and/or therapies:

i) Administration of any antidiabetic therapy, other than metformin and SU, for more than 14 days (consecutive or not) during the 12 weeks prior to screening.

ii) 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. NOTE: *Topical or inhaled corticosteroids are allowed*.

iii) Active participation a commercial weight loss program with ongoing weight loss, or on an intensive exercise program.

iv) History of bariatric surgery or lap band procedure.

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

3) Physical and Laboratory Test Findings

a) Aspartate aminotransferase (AST) > 3x upper limit of normal (ULN)

b) Alanine aminotransferase (ALT) > 3x ULN.

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

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

e) Subjects with 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 Medical Monitor 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 study identification number will however remain the same as initially assigned.)

f) 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.

4) 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 insulin glargine or metformin or SU package insert, including current treatment with potent cytochrome P4503A4/5 inhibitors (in countries where dose adjustment would be required by the local saxagliptin label).

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

d) 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.

e) 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.

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

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

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

i) Previous randomization in the present study.

j) Administration of any other investigational drug or participation in any interventional clinical study within (30) days prior to screening for this study.

k) 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.

l) For women only - currently pregnant (confirmed with positive pregnancy test) or breastfeeding.

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 Women 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 > 40mIU/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, Lead-in, or open-label Short-term and Long-term Treatment Periods:

- Treatment with any antihyperglycemic medication (other than protocol required medication and/or protocol allowed open-label rescue medication). Temporary insulin use is acceptable during hospitalizations if study medication is interrupted.
- Treatment with potent cytochrome P450 3A4/5 inhibitors (in countries where dose adjustment would be required by the local saxagliptin label).

Newly initiated treatment with any systemic corticosteroid therapy that will involve ≥ 5 days of therapy is not permitted (inhaled and topical corticosteroids are allowed). The 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 5.8.1 and Tables in 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 6.4 and Appendix 5).

3.5 Discontinuation of Subjects following any Treatment with Study Drug

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the Investigator) for any of the following reasons:

- Subject decision to withdraw for any reason (withdraw of informed consent in writing). The subject is at any time free to discontinue study treatment without prejudice to further 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 Sponsors (BMS/AZ)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Severe non-compliance to protocol, as judged by the investigator and/or Sponsors (BMS/AZ).
- Safety reasons as judged by the investigator and/or Sponsors (BMS/AZ).
- Incorrect enrollment (ie, the subject does not meet the protocol-defined inclusion/exclusion criteria) (see Section 3.5.3)
- Pregnancy (see Section 6.4)
- CrCl < 60 mL/min (estimated by Cockcroft-Gault) for a sustained period of time (12-16 weeks).
- Sustained elevated serum creatinine (see Section 3.5.1)
- Sustained elevated liver function tests (see Section 3.5.2 and Appendix 4)
- Protocol-defined lack of glycemic control (see Section 3.5.4)
- If ketoacidosis is suspected, discontinuation or temporary interruption of dapagliflozin should be CONSIDERED and the patient promptly evaluated (see Section 3.5.6)
- Protocol-defined severe or recurrent hypoglycemia episodes (see Section 3.5.5)

In the case of pregnancy, the investigator must immediately notify the Medical Monitor of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the Medical Monitor must occur.

All subjects who discontinue study treatment should return and complete procedures described for the End of Treatment (EOT) visit (as outlined in Section 5.3.10.1). EOT visit should be scheduled as soon as possible. All subjects who discontinue study medication should continue in the study, and complete all study visits following the EOT visit, returning for their next regularly scheduled study visits until all study visits are completed. All protocol specified procedures should be performed at these visits with the exception of study drug management. Subjects who have discontinued study treatment will also not be required to complete 6-point SMBG and CGM procedures (if applicable) following study treatment discontinuation. The only exception to these follow-up requirements 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).

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.

All subjects who prematurely discontinue from the study may be contacted after discontinuation from the study, to collect vital status information.

3.5.1 Discontinuation Guidelines due to Sustained Elevated Serum Creatinine

Subjects with serum creatinine (SCr) ≥ 1.5mg/dL (133 μmol/L) in males or ≥ 1.4 mg/dL (124 μmol/L) in females will have open-label metformin withheld and a confirmatory repeat SCr drawn within (1) week.

- If the repeat SCr is < 1.5 mg/dL (133 μmol/L) in male subjects or < 1.4 mg/dL (124 μmol/L) in female subjects, metformin may be resumed unless contraindicated.
- If the repeat SCr is ≥ 1.5 mg/dL (133 μmol/L) in males, or ≥ 1.4 mg/dL (124 μmol/L) in females, the subject must be immediately discontinued from study medication, the Medical Monitor notified, and the end of treatment visit performed (see Section 5.3.10.1). The Investigator will follow the subject until the event resolves or stabilizes.

3.5.2 Discontinuation Guidelines due to Sustained Elevated Liver Function Tests

The monitoring for liver safety will be performed using the serum levels of AST, ALT and total bilirubin (TB).

- Subjects with central laboratory ALT and/or AST > 3x ULN will be scheduled for a follow-up visit within 3 days following receipt of the initial laboratory results, to obtain

repeat central laboratory ALT, AST, TB and Alkaline Phosphatase (ALK-P) (see Appendix 4 for further guidance). In the event that the repeat laboratory assessments cannot be obtained within 3 days, the Investigator is encouraged to discuss possible alternatives with the Medical Monitor. Subjects should remain on study medication until confirmatory results are obtained, unless otherwise contraindicated.

- Subjects should be discontinued from study treatment if the initial and repeat laboratory tests meet any of the following criteria:
  - ALT and/or AST are > 3x ULN and (TB) > 2x ULN.
  - ALT and/or AST are > 5x ULN for ≥ 14 consecutive days, at any time after initial confirmatory results.
  - ALT and/or AST are ≥ 10x ULN.

The Investigator will follow the subject (according to the flowchart in Appendix 4), until the event of elevated liver function test(s) has resolved or stabilized.

3.5.3 Procedures for Handling Subjects 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 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 Medical Monitor is to ensure all such contacts with the investigator and such decisions are appropriately documented.

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

During the trial, subjects may be eligible for rescue treatment (the addition of open-label rescue medication to their treatment regimen or increase in the dose of their current antiglycemic background medications) in order to treat ongoing hyperglycemia.

During the first 12 weeks following randomization, there will be no protocol specified rescue criteria. During this time, subjects receiving open-label insulin glargine will be titrated to target, which is driven over an 8 week period, then at Investigator's discretion with minimal adjustment

at 12 and 18 weeks (see Appendix 6). A fasting plasma glucose (FPG) target of ≤ 100 mg/dL (5.5 mmol/L) will guide insulin glargine titration.

Pre-specified glycemic criteria (see Table 3.5.4-1), based upon central laboratory measurements, have been established during the treatment period, starting after Week 12, and up to Week 52 visit, to determine eligibility for open-label rescue medication.

Table 3.5.4-1: Lack of Glycemic Control Criteria for Initiation of Rescue Medication

Visit Label	Central Laboratory FPG/HbA1c
After Week 12 to Week 24 (including Week 24)	FPG > 200 mg/dL (11.1 mmol/L)
After Week 24 to Week 52	HbA1c > 8.0% (prior to Week 52)

Subjects with a central laboratory FPG value > 200 mg/dL (11.1 mmol/L) after Week 12 and up to and including Week 24, 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 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 with a central laboratory HbA1c value > 8% after Week 24 and prior to Week 52 must be rescued (no repeat confirmation is required).

Subjects who meet rescue criteria must first complete the Rescue/End of Treatment (EOT) visit procedures before receiving open-label rescue medication to ensure that important trial endpoint measurements are collected.

Following completion of the Rescue/EOT visit, rescued subjects will be given open-label antidiabetic rescue medication 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 assigned open-label study medication. Insulin (initiation or up-titration) is recommended as the first-line rescue therapy (either initiation of basal insulin, modification of basal insulin or addition of prandial insulin). If a subject refuses treatment with insulin or is not a candidate for insulin, other antiglycemic agents can be considered. However, initiation of a DPP4 inhibitor, initiation of a SGLT2 inhibitor, initiation of any GLP-1 or GLP-1 analog, initiation or dose modification of SU and dose modification of metformin are not permitted for rescue therapy. Rescued subjects will then continue in the treatment period according to their original visit schedule.

Note: Rescue medication will NOT be provided by the Sponsor in this study.

Following initiation of open-label rescue antidiabetic medication, rescued subjects should be scheduled for titration visits as needed, as unscheduled visits in addition to their regularly scheduled study 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.

3.5.5 Discontinuation Guidelines due to Protocol-Defined Hypoglycemia Episodes

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

Clinical indications for discontinuation due to hypoglycemia may include the following:

- Multiple episodes of hypoglycemia, as outlined below that, in the opinion of the investigator, indicate the 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 plasma or capillary glucose values ≤ 70 mg/dL (3.9 mmol/L).
  - Severe hypoglycemia (see definition in Section 5.3.1.2), as determined by the investigator.

Subjects who record two or more SMBG readings of ≤ 70 mg/dL (≤ 3.9 mmol/L) in one week, should be instructed to contact the Investigator at the time they obtain the readings.

If finger stick glucose values recorded in the subject diary 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 5.3.1.3 provides additional guidance on management and reporting of hypoglycemia.

Down-titration of study drugs and/or background antihyperglycemic agents during the study.

Down-titration of saxagliptin, dapagliflozin or metformin will not be allowed at any time during the study.

Down-titration of insulin after Week 8 in subjects randomized to receive open-label insulin glargine will be allowed only as necessary to prevent low blood glucose or hypoglycemia, at the discretion of the Investigator. Any changes in insulin glargine dose must be recorded in the eCRF.

If applicable, the SU dose can be down-titrated in response to hypoglycemic events, at the discretion of the Investigator. It is recommended that any SU down-titration be discussed with the Medical Monitor. Any changes in SU dose must be recorded in the eCRF.

3.5.6 Discontinuation Guidelines due to Ketoacidosis

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. Contact the medical monitor to discuss treatment options.

3.6 Post-Study Drug 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 investigational product during the 24 week, Short-term treatment period or during the 28 week, 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 3.1 and study flowchart (Tables in section 5.1), with the exception of study drug management. Subjects who have discontinued study treatment will also not be required to complete 6-point SMBG and CGM procedures (if applicable) following study treatment discontinuation. If continued study participation according to the protocol schedule is not possible, the investigator should contact the Medical Monitor to discuss alternatives (eg, contact by telephone every 4 weeks after discontinuation of study drug to perform safety assessments for adverse events 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 complete all protocol-specified visits and 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 3 documented phone calls, faxes, or emails, as well as lack of response by the subject to 1 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.

4 STUDY DRUG

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/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, or rescue medications)

Table 4-1: Study Drugs for CV181369

Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Saxagliptin	5 mg	IP	Open-Label	Plain, yellow, biconvex, round, film-coated tablet HDPE Bottle	Store at 15-25°C (59-77°F). Store in tightly closed container
Dapagliflozin	10 mg	IP	Open-Label	Green, plain, diamond-shaped, film-coated tablet HDPE Bottle	Store at 15-25°C (59-77°F). Store in tightly closed container
Insulin Glargine	100 Units/ml	IP	Open-Label	Clear, colorless and free of particles insulin solution 3ml disposable insulin device	<u>Un-Opened Device</u> Store in refrigerator 2-8°C (35.6-46.4°F). Do not freeze or place next to the freezer compartment or a freezer pack. Keep the device in the outer carton in order to protect from light. <u>In-Use Devices</u> Device should NOT be refrigerated but should be kept at room temperature (not above 25°C (77° F) and away from direct heat or direct light. The opened (in-use) device must be discarded after 28 days. The cap must be put back on the device after each injection in order to protect from light.

4.1 Investigational Product

An investigational product, also known as investigational medicinal product 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.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, unblinded IP is saxagliptin 5 mg tablets and dapagliflozin 10 mg tablets, administered orally for the 52-week treatment period (24 week Short-term Period and 28 week Long-term Period). No titration of either saxagliptin or dapagliflozin will be allowed. In addition, insulin glargine will be supplied in 100 Units/ml solution for subcutaneous injection and dosing will be based on individual subject criteria. Instructions are provided in Section 4.5 and Appendix 6 on use and dosing regimen.

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-investigational products.

In this protocol, non-investigational product(s) are metformin and SU. BMS/AZ will not be providing these medications as they are considered standard of care. Instructions are provided in Section 4.5 on use and dosing regimen.

In addition, any rescue therapies required will be managed by the Investigator's discretion and will not be supplied by BMS/AZ but may be reimbursed through the investigational site on an as needed basis.

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 BMS/AZ or manufacturer's instruction. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS (or designee) immediately.

Study drug not supplied by BMS/AZ will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS/AZ 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

At the screening visit, each subject will be assigned a unique sequential subject number by the Interactive Voice Response System (IVRS). The subject number will consist of (5) digits which are assigned sequentially (00001, 00002, 00003, etc.) by the IVRS. This number will be used for identification throughout the study and will not be used for any other subject.

Randomized schedules will be generated and kept by BMS (or designee). Subjects will be randomly assigned to one of two open-label treatment groups by the IVRS in a 1:1 ratio. Subjects will be stratified according to whether their treatment regimen contains SU or not for both the main study and sub-study.

4.5 Selection and Timing of Dose for Each Subject

- Saxagliptin 5 mg tablets, will be administered orally once daily in the AM for the 52 week treatment period (24 week Short-term period and 28 week Long-term period). Saxagliptin 5 mg is the maximum recommended daily dose. No up or down-titration of saxagliptin will be allowed.
- Dapagliflozin 10 mg tablets will be administered orally once daily in the AM for the 52 week treatment period (24 week Short-term period and 28 week Long-term period). Dapagliflozin 10 mg is the maximum recommended daily dose. No up or down-titration of dapagliflozin will be allowed.
- Metformin 500mg tablets will be administered orally, per Investigator direction, at a dose of no less than 1,500 mg per day and not to exceed 2,500 mg per day (or maximum locally approved dose) based on the subject's qualifying dose at screening. No titration of metformin will be allowed.
- Sulfonylurea - Subjects randomized with a background therapy of SU ≥ 50% maximal oral daily dose per local label, will continue on the same stable dose throughout the study based on their qualifying dose at screening. No up-titration of SU will be allowed. If applicable, the SU dose can be down-titrated in response to hypoglycemic events, at the discretion of the Investigator. It is recommended that any SU down-titration be discussed with the Medical Monitor
- Insulin glargine - Subjects randomized to the insulin glargine arm should administer subcutaneously once a day at the same time every day and follow Investigator instructions and training. All subjects will start with an initial dose of 0.2U/kg bodyweight or at least 10 Units of insulin per day (per local label). Subjects will self-titrate the dose of insulin glargine over the first (8) weeks of the study based on daily glucose monitoring with the goal of achieving a fasting blood glucose target level of ≤ 100 mg/dL (5.5 mmol/L). Investigators may modify the fixed dosing titration steps, scheduled in the first eight weeks, to optimize titration for individual patients in order to reach the target goal. Investigator has the discretion to modify insulin dose, based on his/her assessment, between Week 8 and Week 12, with the goal to reach an acceptable and stable insulin dose by Week 12 (see Appendix 6 for details).

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

Each time study medication is dispensed, compliance will be reinforced. Study medication is to be returned at each study visit, and compliance will be assessed based upon subject's interview, a count of the tablets and insulin returned. Compliance should be between ≥ 80% and ≤ 120% of prescribed dosing. The Investigator (or designee) will record the amounts of study medication dispensed and returned at each visit, as well as review the subject logbook to capture reasons for non-compliance in the source document. The dates of all study medication dosing, including interruptions, missed doses or overdose, must be recorded on the eCRF. If the subject is not ≥ 80% compliant with recording study drug doses during the study, then the period of non-compliance should be noted as a protocol deviation and BMS (or designee) 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 BMS/AZ or sourced by the Investigator) such as partially used study drug containers, and/or insulin supplies may be destroyed on site.

Any unused study drugs can only be destroyed only 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 SOPs and a copy provided to BMS (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 study 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 BMS/AZ must be returned to BMS/AZ. 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.

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 & Lead In Visit Flow Chart for Protocol CV181369[a]

Procedure	Screening Period (Week-4)	Lead-In Period (Week -2)	Lead-In Period (Week -1) CGM Subjects Only	Notes
Eligibility Assessment:				
Main Informed Consent	X			MUST be signed prior to any study related procedures are performed
CGM Informed Consent	X	X		Only required for subjects participating in the CGM sub-study
Review Inclusion/Exclusion Criteria	X			MUST have documentation of stable dosing of metformin ≥ 1500 mg/day for at least 8 weeks prior to screening with or without a stable dose of SU of at least 50% maximal dose per local label for at least 8 weeks prior to screening and no other anti-hyperglycemic therapy > 14 days during 12 weeks prior to screening
Review Medical History	X			
Contact IXRS	X	X		All patients
General Procedures:				
Complete Physical Examination		X		Refer to Protocol Section 5.3.5
Brief Physical Examination	X			Refer to Protocol Section 5.3.5
Vital Signs (Seated BP & Heart Rate)	X	X	X	Refer to Protocol Section 5.3.6 Note: Measurements must be taken prior to administration of study medication
Body Weight	X	X		Refer to Protocol Section 5.8.2
Height	X			Refer to Protocol Section 5.8.3

Table 5.1-1: Screening & Lead In Visit Flow Chart for Protocol CV181369[a]

Procedure	Screening Period (Week-4)	Lead-In Period (Week -2)	Lead-In Period (Week -1) CGM Subjects Only	Notes
Body Mass Index (BMI)	X			Refer to Protocol Section 5.8.3
Review Concomitant Medications	X	X		Refer to Protocol Section 3.4
Diet & Exercise Counseling		X		Refer to Protocol Section 5.8.1
Subject Diary & Instructions		X		Refer to Protocol Sections 5.2 and 9.2.4
Review Subject Diary/Coaching			X	Refer to Protocol Sections 5.2 and 9.2.4
Glucose Meter/Supplies & Instructions		X		Refer to Protocol Sections 5.2 and 5.3.1.1
6 Point SMBG Profile		X[b]		Refer to Protocol Section 5.3.1.2
Safety Assessment:				
Review for Adverse Events	X	X	X	Refer to Protocol Section 6
Review for Hypoglycemia Episodes	X	X	X	Refer to Protocol Section 5.3.1.2
Central Laboratory Tests:				
Blood & Urine Standard Safety Panels	X			
Urine Pregnancy Test (WOCBP Only)	X			
Hematuria Dipstick Urinalysis	X			Positive dipstick result requires repeat test with microscopy (Refer to Protocol Section 5.3.2.2 & Appendix 3 for guidance)
Hematuria Microscopic Urinalysis	X*			*Only performed if dipstick urinalysis is positive (Refer to Section 5.3.2.2 of Protocol & Appendix 3for further directions)
HbA1c	X			

Table 5.1-1: Screening & Lead In Visit Flow Chart for Protocol CV181369[a]

Procedure	Screening Period (Week-4)	Lead-In Period (Week -2)	Lead-In Period (Week -1) CGM Subjects Only	Notes
FPG	X			
CrCL (Cockcroft-Gault) & Serum Creatinine (SCr)	X			
Hepatitis Screen Panel & TSH	X			
Fasting Serum Lipids (Total -C, LDL-C, HDL-C and TG)	X			
Continuous Glucose Monitoring:				ONLY for those subjects electing to participate in the sub-study and have signed CGM ICF
CGM Device Training/Instruction		X		CGM device to be worn for 7 consecutive days (Refer to Section 5.9 of protocol for detailed instructions)
Insertion/Calibration of CGM Sensor		X		Refer to Section 5.9 of protocol for detailed instructions
Removal of Sensor & Data Upload of CGM & Glucose Meter Values			X	Refer to Section 5.9 of protocol for detailed instructions
4- Point SMBG Profile		X[c]		Refer to Protocol Section 5.9

[a] All visits should occur on the designated visit day +/- a 5 day visit window (based on the screening date).

[b] ALL subjects will perform a 6 Point SMBG profile for any 3 days (not required to be consecutive) during Week (-2) to Week (-1), Week 11-12, Week 23-24 and Week 51-52. Blood glucose readings will consist of 3 pre-prandial measurements (1-15 minutes before breakfast, 1-15 minutes before lunch, and 1-15 minutes before dinner) AND 3 post-prandial measurements (1~1-2 hours after breakfast, 1~1-2 hours after lunch, and 1~1-2 hours after dinner).). The initial pre-prandial 6-point glucose measurement on the SMBG day should be a fasting plasma glucose reading.

[c] CGM Only subjects will also perform a 4 Point SMBG Profile daily while wearing the CGM sensor and when not performing the 6-point SMBG testing. Blood glucose readings will consist of 4 measurements (1-15 minutes before breakfast, 1-15 minutes before lunch, 1-15 minutes before dinner and 1-15 minutes before bedtime).

Table 5.1-2: Short-Term Visit Procedural Flow Chart for Protocol CV181369[a]

Procedure	Day 1	Wk 1	Wk 2	Wk 3 *CGM Only	Wk 4	Wk 8	Wk 11 *CGM Only	Wk 12	Wk 18	Wk23 *CGM Only	Wk 24 or Rescue or EOT	Notes
Eligibility Assessment:												
Review Inclusion/Exclusion Criteria	X											Refer to Protocol Section 3.3.1 and 3.3.2
Review Discontinuation Criteria		X	X		X	X		X	X		X	Refer to Protocol Section 3.5
Review Rescue Criteria									X		X	Refer to Protocol Section 3.5.2
Contact IXRS-Oral Saxa/Dapa	X										X	*Saxa/Dapa dispensed ONLY Day 1 for ST period and Week 24 for LT period ONLY
Contact IXRS-Insulin	X				X	X		X	X		X	Insulin glargine is dispensed sufficient for 4 weeks as needed per subjects individual dosing regimen. Refer to Protocol Section 4).
General Procedures:											X	
Complete Physical Examination											X	Refer to Protocol Section 5.3.5
Brief Physical Examination	X	X	X		X	X		X	X			Refer to Protocol Section 5.3.5

Table 5.1-2: Short-Term Visit Procedural Flow Chart for Protocol CV181369[a]

Procedure	Day 1	Wk 1	Wk 2	Wk 3 *CGM Only	Wk 4	Wk 8	Wk 11 *CGM Only	Wk 12	Wk 18	Wk23 *CGM Only	Wk 24 or Rescue or EOT	Notes
12 Lead ECG	X										X	Refer to Protocol Section 5.3.9
Vital Signs (Seated BP & Heart Rate)	X	X	X	X	X	X	X	X	X	X	X	Refer to Protocol Section 5.3.6 Note: Measurements must be taken prior to administration of study medication
Body Weight	X				X	X		X	X		X	Refer to Protocol Section 5.8.2
Review Concomitant Medications	X	X	X		X	X		X	X		X	Refer to Protocol Section 3.5.2
Diet & Exercise Counseling	X	X	X		X	X		X	X		X	Refer to Protocol Section 5.8.1
Review Subject Diary/Coaching	X	X	X	X	X	X	X	X	X	X	X	Refer to Protocol Section 5.2 and 9.2.4
Review Glucose Meter & Supplies	X	X	X		X	X		X	X		X	Refer to Protocol Section 5.2 and 5.3.1.1
Review for Adverse Events	X	X	X	X	X	X	X	X	X	X	X	Refer to Protocol Section 6
Review for Hypoglycemic Episodes	X	X	X	X	X	X	X	X	X	X	X	Refer to Protocol Section 5.3.1.2

Table 5.1-2: Short-Term Visit Procedural Flow Chart for Protocol CV181369[a]

Procedure	Day 1	Wk 1	Wk 2	Wk 3 *CGM Only	Wk 4	Wk 8	Wk 11 *CGM Only	Wk 12	Wk 18	Wk23 *CGM Only	Wk 24 or Rescue or EOT	Notes
6 Point SMBG Profile						X[b]			X[b]			Refer to Protocol Section 5.3.1.2
Central Laboratory Tests:												
Blood & Urine Standard Safety Panels	X	X	X		X	X		X	X		X	
Urine Pregnancy Test	X											Positive dipstick result MUST be confirmed with Central Lab pregnancy (serum) test
Provide Home Pregnancy Tests	X											Home pregnancy test to be sent home with WOCBP subjects to perform pregnancy test only when pregnancy is suspected. Verify expiration date is acceptable. Subject should contact site immediately if positive test.

Table 5.1-2: Short-Term Visit Procedural Flow Chart for Protocol CV181369[a]

Procedure	Day 1	Wk 1	Wk 2	Wk 3 *CGM Only	Wk 4	Wk 8	Wk 11 *CGM Only	Wk 12	Wk 18	Wk23 *CGM Only	Wk 24 or Rescue or EOT	Notes
Hematuria Dipstick Urinalysis	X							X			X	Positive dipstick result requires repeat test with microscopy (Refer to Protocol Section 5.3.2.2 & Appendix 3 for guidance)
Hematuria Microscopic Urinalysis	X*							X*			X*	*Only performed if dipstick urinalysis is positive (Refer to Protocol Section 5.3.2.2 & Appendix 3 for further directions)
HbA1c	X				X	X		X	X		X	
FPG	X	X	X		X	X		X	X		X	
CrCL (Cockcroft-Gault) & Serum Creatinine (SCr)	X	X	X		X	X		X	X		X	
Fasting Serum Lipids (Total-C, LDL-C, HDL-C and TG)	X							X			X	

Table 5.1-2: Short-Term Visit Procedural Flow Chart for Protocol CV181369[a]

Procedure	Day 1	Wk 1	Wk 2	Wk 3 *CGM Only	Wk 4	Wk 8	Wk 11 *CGM Only	Wk 12	Wk 18	Wk23 *CGM Only	Wk 24 or Rescue or EOT	Notes
Clinical Drug Supplies:												
Review Study Medication Compliance		X	X	X	X	X	X	X	X	X	X	Refer to Protocol Section 4.7
Dispense Study Medication (Oral medication or insulin glargine)	X*				X	X		X	X		X*	*Saxa/Dapa dispensed at ONLY Day 1 for ST period and Week 24 for LT period ONLY. Insulin glargine is dispensed sufficient for 4-6 weeks as needed per subject's individual dosing regimen. Refer to Protocol Section 4. Last dose of ST period Saxa/Dapa should be taken from their current bottle.
Insulin Administration Instructions	X											ONLY Subjects in Insulin Arm
Insulin Titration Review/Guidance	X	X[c]	X[c]		X[c]	X[c]		X[c]				ONLY Subjects in Insulin Arm. Refer to Appendix 6

Table 5.1-2: Short-Term Visit Procedural Flow Chart for Protocol CV181369[a]

Procedure	Day 1	Wk 1	Wk 2	Wk 3 *CGM Only	Wk 4	Wk 8	Wk 11 *CGM Only	Wk 12	Wk 18	Wk23 *CGM Only	Wk 24 or Rescue or EOT	Notes
Continuous Glucose Monitoring:												Only for those subjects electing to participate in the sub-study and have signed CGM ICF
Insertion/Calibration of CGM Sensor			X				X			X		Refer to Protocol Section 5.9
Removal of Sensor/ Data upload & review of CGM				X				X			X	Refer to Protocol Section 5.9
4- Point SMBG Profile			X[d]				X[d]			X[d]		Refer to Protocol Section 5.9
Health Outcome Assessment:												
PRO Questionnaire	X							X			X	Refer to Protocol Section 5.7.1 for detailed instructions

[a] All visits should occur on the designated visit day +/- a 5 day visit window (based on the Day 1 visit date).

[b] ALL subjects will perform a 6 Point SMBG profile for any 3 days (not required to be consecutive) during Week (-2) to Week (-1), Week 11-12, Week 23-24 and Week 51-52. Blood glucose readings will consist of 3 pre-prandial measurements (1-15 minutes before breakfast, 1-15 minutes before lunch, and 1-15 minutes before dinner) AND 3 post-prandial measurements (1~1-2 hours after breakfast, 1~1-2 hours after lunch, and 1~1-2 hours after dinner). The first pre-prandial measurement should be a fasting plasma glucose.

[c] Insulin titration should be based on the protocol specified fixed dose algorithm as described in Protocol Section 4.3 to achieve daily FPG < 100mg/dL (5.5 mmol/L). Refer to Appendix 6. Investigator has the discretion to modify insulin dose during the fixed dosing schedule as well as during Week 8-Week 12 to achieve target daily FPG.

[d] CGM Only subjects will also perform a 4 Point SMBG Profile daily while wearing the CGM sensor and when not performing the 6-point SMBG testing. Blood glucose readings will consist of 4 measurements (1-15 minutes before breakfast, 1-15 minutes before lunch, 1-15 minutes before dinner and 1-15 minutes before bedtime).

Table 5.1-3: Long-Term Visit Procedural Flow Chart for Protocol CV181-369[a]

Procedure	Week 32	Week 40	Week 52 or Rescue or EOT	Notes
Eligibility Assessment:				
Review Discontinuation Criteria	X	X		Refer to Protocol Section 3.5
Review Rescue Criteria	X	X		Refer to Protocol Section 3.5.2
Contact IXRS-Insulin	X	X	X	Insulin supplies provided should be sufficient for 8 weeks *ALL patients should register Week 52/Rescue/EOT in IXRS.
General Procedures:				
Complete Physical Examination			X	Refer to Protocol Section 5.3.5
Brief Physical Examination	X	X		Refer to Protocol Section 5.3.5
12 Lead ECG			X	Refer to Protocol Section 5.3.9
Vital Signs (Seated BP & Heart Rate)	X	X	X	Refer to Protocol Section 5.3.6 Note: Measurements must be taken prior to administration of study medication
Body Weight	X	X	X	Refer to Protocol Section 5.8.2
Review Concomitant Medications	X	X	X	Refer to Protocol Section 3.4
Diet & Exercise Counseling	X	X		Refer to Protocol Section 5.8.1
Review Subject Diary/Coaching	X	X		Refer to Protocol Section 9.2.4
Subject Diary Collection			X	Refer to Protocol Section 9.2.4

Table 5.1-3: Long-Term Visit Procedural Flow Chart for Protocol CV181-369[a]

Procedure	Week 32	Week 40	Week 52 or Rescue or EOT	Notes
Review Glucose Meter & Supplies	X	X	X*	*Glucose meters and supplies do NOT need to be returned by subject at the final visit(based on local regulations)
Review for Adverse Events	X	X	X	Refer to Protocol Section 6
Review for Hypoglycemic Episodes	X	X	X	Refer to Protocol Section 5.3.1.2
6 Point SMBG Profile		X[b] [b]		Refer to Protocol Section 5.3.1.2
Central Laboratory Tests:				
Blood & Urine Standard Safety Panels	X	X	X	
Provide Home Pregnancy Tests				Home pregnancy test to be sent home with WOCBP subjects to perform pregnancy test only when pregnancy is suspected. Verify expiration date is acceptable. Subject should contact site immediately if positive test.
Hematuria Dipstick Urinalysis	X	X	X	Positive dipstick result requires repeat test with microscopy (Refer to Protocol Section 5.3.2.2 & Appendix 3 for guidance)
Hematuria Microscopic Urinalysis	X*	X*	X*	*Only performed if dipstick urinalysis is positive (Refer to Section 5.3.2.2 of Protocol & Appendix 3for further directions)
HbA1c	X	X	X	
FPG	X	X	X	
CrCL (Cockcroft-Gault) & Serum Creatinine (SCr)	X	X	X	

Table 5.1-3: Long-Term Visit Procedural Flow Chart for Protocol CV181-369[a]

Procedure	Week 32	Week 40	Week 52 or Rescue or EOT	Notes
Fasting Serum Lipids (Total-C, LDL-C, HDL-C and TG)	X	X	X	
Clinical Drug Supplies:				
Review Study Medication Compliance	X	X	X	Refer to Protocol Section 4.7
Dispense Study Medication	X	X		Saxa/Dapa dispensed at Week 24 ONLY. First dose of LT period Saxa/Dapa should be taken day after final ST visit. Insulin glargine is dispensed sufficient for 8-12 weeks as needed per subject's individual dosing regimen. Refer to Protocol Section 4.
Collection of Study Medication			X	Last dose of study medication should occur on the day of the final visit following completion of all visit procedures.
Verify Post-Study Medication Support			X	Per Investigator's Instructions
Health Outcome Assessment:				
PRO Questionnaire			X	Refer to Protocol Section 5.7.1

[a] All visits should occur on the designated visit day +/- a 5 day visit window (based on the Day 1 visit date).

[b] ALL subjects will perform a 6 Point SMBG profile for any 3 days (not required to be consecutive) during Week (-2) to Week (-1), Week 11-12, Week 23-24 and Week 51-52. Blood glucose readings will consist of 3 pre-prandial measurements (1-15 minutes before breakfast, 1-15 minutes before lunch, and 1-15 minutes before dinner) AND 3 post-prandial measurements (1~1-2 hours after breakfast, 1~1-2 hours after lunch, and 1~1-2 hours after dinner). The first pre-prandial measurement should be a fasting plasma glucose.

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)

Retesting is limited to these specific laboratory parameters and/or assessments:

- Subjects with an abnormal TSH value at screening 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 Medical Monitor prior to re-testing. The subject must have all screening procedures and laboratory assessments performed as part of this re-test, and all of these must meet enrollment eligibility criteria. The subject's study identification number will however remain the same as initially assigned).

5.2 Study Materials

BMS/AZ 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) reader with software to upload data will be provided to each investigative site
- Glucose test strips
- Lancets
- Glucose control solutions
- CGM sensors with applicator will be provided to only those subjects participating in the CGM sub-study along with adapter and software to download data will be provided to each investigative site
- Insulin device lancets, alcohol wipes and sharps container (only in those subjects randomized to insulin)
- Patient Reported Outcomes software and training will be provided to each investigative site
- Subject education and site support materials (eg, CGM instruction manuals)
- Electronic Case Report Forms (eCRFs) [Serious Adverse Events Forms, Pregnancy Surveillance Forms, Events of Special Interest]
- 12 Lead ECG machine (will not be supplied, but required by site)
- Subject alert cards
- Pill counting tray
- Study drug inventory control forms
- Site file
- Subject diary (see Section 9.2.4 for additional information):
  - 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, and meal times (applicable during periods of 6-point SMBG and CGM). Electronic case report form (eCRF) pages will be provided to the sites so they can record the data obtained from the diaries into the study database.

- Subjects should self-monitor their blood glucose approximately 2 times per day.
- 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 will be reviewed by site staff (according to Section 5.3.1.3).
- 6-point SMBG profiles: Subjects will be instructed to perform and record in their diaries the results for their 6-point SMBG profiles (see Section 5.3.1.2 for details). Subjects should also record their meal times in their diary on the days that they perform 6-point SMBG.
- CGM Sub-study
  - During CGM monitoring, subjects will record the times of their three main meal and any snacks in their diary.
  - The dates and number of tablets of study medication and /or Units of insulin, taken by the subject are to be recorded in the study diary.

- 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 (AE) reporting, clinical laboratory tests, ECGs, vital signs, and physical examination findings. 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 as needed to allow for all daily blood glucose assessments (~ 2 tests / day) with a minimum fasting plasma glucose test each morning for the duration of the study. Additional supplies will be provided to perform the required 6-point SMBG profile (see Section 5.3.1.2). The Investigator may require more or less frequent readings based on local clinical practice and supplies will be adjusted accordingly. 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 (as allowed by local laws), 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. 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 fingertip), or concomitant medications. 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 6-point SMBG profiles

All subjects will be instructed to perform 6-point SMBG profiles consisting of 3 glucose measurements obtained pre-prandially (within 15 minutes prior to the start of each meal) and 3 glucose measurements obtained post-prandially (1.5 - 2 hours after the start of each 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, according to the schedules presented in study flow chart/time and event schedule (see tables in section 5.1):

- Between Week - 2 and Week - 1 (eg, prior to the Day 1 randomization visit)
- Between Week 11 and Week 12 (eg, prior to Week 12 visit)
- Between Week 23 and Week 24 (eg, prior to Week 24 visit)
- Between Week 51 and Week 52 (eg, prior to Week 52 visit)

Subjects are to record their meal times in their diary on the days that they perform 6-point SMBG. 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. A minimum of 2 days of 6-point SMBGs is required to complete the 6-point SMBG profile for each period.

5.3.1.3 Guidance on Management and Reporting of Hypoglycemia Episodes

Mild hypoglycemia may occur in subjects who are treated for T2DM, particularly those treated with an insulin secretagogue (eg, SU) or insulin. Subject's should be instructed to contact the investigator for advice if they record two or more self-monitored blood glucose (SMBG) readings ≤ 70 mg/dL (3.9 mmol/L) in one week. Down-titration of insulin and/or SU at the

investigator's discretion will be allowed as necessary to prevent low blood sugar or hypoglycemia. Any changes in insulin or SU doses must be captured on the eCRF and discussed with the Medical Monitor prior to change. Dose titration of saxagliptin, dapagliflozin or metformin will not be allowed.

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 diaries. 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.

- **Other:** Any hypoglycemic event that cannot be placed into one of the above defined categories.

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), 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 information is provided 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[5,6] 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 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 6.2). 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 during the course of the study.

5.3.2.2 Guidance on Assessment of Hematuria

All events of hematuria defined as ≥ 3 RBC/HPF (red blood cells per high power field) without the presence of epithelial cells (microscopic and/or macroscopic) 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 study medication during these investigations (unless otherwise contraindicated). All confirmed events of bladder cancer should lead to the discontinuation of study medication (See Appendix 3 for definition and treatment algorithm).

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 3.5.2), 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

The individual performing the physical examinations must be licensed by state law (or applicable local law) to perform this procedure.

- 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.

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 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 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 Ketoacidosis

There have been post-marketing reports of ketoacidosis, including diabetic ketoacidosis, in patients with type 1 and type 2 diabetes mellitus taking dapagliflozin and other SGLT2 inhibitors, although a causal relationship has not been established. Dapagliflozin is not indicated for the treatment of patients with type 1 diabetes mellitus. Patients treated with dapagliflozin who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise, and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL). If ketoacidosis is suspected, discontinuation or temporary interruption of dapagliflozin should be considered and the patient should be promptly evaluated. Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (e.g., type 1 diabetes, history of pancreatitis, or pancreatic surgery), insulin dose reduction, reduced caloric intake, or increased insulin requirements due to infections, illness or surgery and alcohol abuse. Dapagliflozin should be used with caution in these patients. Contact the medical monitor to discuss treatment options.

5.3.9 Electrocardiograms

ECGs must be performed after the subject has been supine for at least 5 minutes. ECG must be reviewed by a qualified physician or cardiologist at the research site. ECG machines will not be supplied, but required by the site.

5.3.10 Supplemental Visits

5.3.10.1 Rescue or Discontinuation of Treatment Visit

Subjects rescued during or discontinued from study treatment

Any subject who qualifies for rescue or discontinues from study treatment must have all Rescue/End of Treatment (EOT) visit procedures performed at the time of rescue or study scheduled as soon as possible.

The IVRS must be called to record the subject status (ie, rescue or study drug treatment discontinuation status). All subjects who are rescued or who discontinue study drug should remain in the study and follow the normal visit schedule. Subjects who have discontinued study treatment will not be required to complete 6-point SMBG and CGM procedures (if applicable) following study treatment discontinuation.

- Subjects qualifying for rescue or discontinuing PRIOR to Week 24 will use the Week 24/Rescue/EOT visit laboratory kit to collect the blood and urine samples.
- Subjects qualifying for rescue or discontinuing AFTER Week 24 but PRIOR to Week 52 will use the Week 52/Rescue/EOT visit laboratory kit to collect the blood and urine samples.

5.3.10.2 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 during the treatment period, central laboratory and self-monitored glucose values to assess hypoglycemia, measurement of total body weight and CGM, measured in the sub-study, throughout the study treatment period.

5.5 Pharmacokinetic Assessments

Not Applicable

5.6 Biomarker Assessments

Not Applicable

5.7 Outcomes Research Assessments

5.7.1 Patient-reported outcomes (PRO)

The Phase V® health outcomes information system diabetes module will be used for the patient reported outcomes (PRO) assessments.[7] The self-administered pro questionnaires consist of validated generic and diabetes-specific modules of treatment satisfaction, quality of life, and barriers to medication adherence and weight perception.

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 24, and Week 52, as well as the Rescue/End of Treatment 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.

5.8 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 Survey of Subject Vital Status

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

5.9 Continuous Glucose Monitoring (CGM) Sub-study

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.

In this protocol, a sub-population of approximately 250 subjects with valid CGM data at the baseline assessment performed at Week -2 (~ 125 subjects per treatment arm) who agree to participate (separate informed consent) will have a CGM sensor inserted subcutaneously to measure glucose levels in tissue fluid. The glucose sensor will be inserted and removed by trained personnel at the site. Subjects will wear the glucose sensor for 7 consecutive days at 4 different time periods during the study:

- At baseline, prior to receiving study medication, between Week -2 and Week-1
- Between Week 2 and Week 3 of treatment
- Between Week 11 and Week 12 of treatment
- Between Week 23 and Week 24 of treatment.

Subjects in the sub-study will have (4) site visits added to the regularly scheduled visits (at Week -1, Week 3, Week 11 and Week 23) for CGM monitoring. If CGM recording is insufficient at any of these timepoints, subjects may be required to wear the glucose sensor for an additional (7) day period to obtain sufficient data

CGM data will not be available to the subject or the Investigator during the recording.

Subjects in the CGM sub-study will be required to perform a 4-point SMBG profile on days of CGM monitoring that they are not performing the 6-point SMBG profile (see Section 5.3.2.2). This 4-point SMBG should be performed at the approximate times: before breakfast, before lunch, before dinner and before bedtime. During each day that the CGM sensor is worn, subjects will document their (3) main meal times and any snacks, along with their blood glucose meter readings in the subject diaries. The CGM data will be uploaded, along with the blood glucose meter data to the Phase V® Health Outcomes Information System Diabetes Module.

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

5.10 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. HbA1c values will be available to the Investigator during the Screening Period (Week -4 to Week -2) for assessment of eligibility criteria. During the short-term treatment period (Day 1 to Week 24), the HbA1c values will not be available to the investigator. HbA1c values will be provided to the investigator during the long-term treatment period (after Week 24 through Week 52) for assessment of lack of glycemic control for initiation of rescue medication (see Section 3.5.4).

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting 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 5.3.4 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 6.4 for reporting pregnancies).
- Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details).

NOTE: The following hospitalizations are not considered SAEs in this 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 assessment 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).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

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 serious adverse events 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 must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report must 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 AZ (or designee) within 24 hours of awareness of the event. 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: Refer to Contact Information list

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 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)**:** Refer to 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 must be updated and submitted within 24 hours to the AZ (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.2 Non-serious Adverse Events

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

6.2.1 Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin at initiation of study drug. Non-serious AE information should also be collected from the start of a placebo Lead-in period or other observational period intended to establish a baseline status for the subjects.

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 AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 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.

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).

6.4 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 after product administration, the investigator must immediately notify the Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to AZ within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS/AZ, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject

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 Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to AZ (or designee) within (24) hours of awareness of the event and in accordance with SAE reporting procedures (as described in Section 6.1.1).

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

6.5 Overdose

For the purpose of this study, an overdose is defined as “a dose of study medication in excess of that specified in the protocol”. All cases of overdose should be reported as an SAE, if considered both excessive and medically important (see Section 6.1.1 for reporting details).

6.6 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:

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

AND

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

AND

3) 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.

6.7 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.

6.7.1 AEs of Special Interest

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

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 lab 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 multi-dermatomal, 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 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 congestive 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 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.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The change from baseline in HbA1c at Week 24 will be assessed comparing co-administered saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU versus titrated insulin glargine plus metformin with or without SU.

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 (ANCOVA) using last observation carried forward (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.

To demonstrate non-inferiority of saxagliptin plus dapagliflozin to insulin for changes from baseline to Week 24 in HbA1c within a non-inferiority margin of 0.30%, assuming a standard deviation 1.1%, and at a one-sided significance level of 0.025, 284 evaluable subjects will be needed in each treatment group to provide approximately 90% power (given a true difference of zero between the 2 treatment groups). Assuming that 5% of subjects do not have a post-baseline assessment, a total of approximately 598 subjects (299 subjects per treatment arm) need to be randomized. Assuming that 50% of screened subjects will fail to meet screening criteria, a total of 1196 subjects need to be screened.

8.2 Populations for Analyses

- Enrolled subject data set: all subjects who sign informed consent.
- Lead-in subject data set: The lead-in subject data set includes data collected from all subjects who have at least one vital sign measurement during Lead-in Period.
- Randomized subject data set: The randomized subject data set will consist of all randomized subjects. Whenever using the randomized subject data set, subjects will be presented in the treatment group to which they were randomized at the start of the Short-term treatment Period (even if the treatment they received was different or even if they did not receive treatment at all). This is also known as the Intent-to-Treat (ITT) population. This will be the primary efficacy data set.
- Evaluable subject data set: The evaluable subject data set will be a subset of the randomized subject data set. It will exclude primary efficacy variable data which may have been affected by protocol deviations as determined by the Medical Monitor. All decisions to exclude data from the randomized subject data set to form the evaluable subject data set will be made prior to database lock. This is also known as the per-protocol population.
- Treated subject data set: The treated subject data set consists of all subjects who received at least one dose of study medication during the Short-term treatment Period. This will be the primary safety data set. The treated subject data set includes any subject who accidentally received study medication but was not randomized in the study. These subjects will be included in analyses using the treated subject data set in the treatment they received. For randomized subjects, all analyses using the treated subject data set will be presented by randomized treatment group, except in cases where information was available which indicated that a subject received a different treatment for the entire course of their participation in the study (or period). In this case, the safety data for those subjects will be presented by the treatment actually received. In case a subject never received the treatment as assigned by randomization, then the safety data for that subject will be presented by the first treatment received.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

Change from baseline in HbA1c at Week 24.

8.3.2 Secondary Endpoint(s)

The secondary efficacy endpoints for the Short-term treatment Period include:

1) Change from baseline in total body weight at Week 24
2) Proportion of subjects with confirmed hypoglycemia [defined as: a) plasma glucose ≤ 70 mg/dL (3.9 mmol/L); or b) signs / symptoms of hypoglycemia with self-monitored blood glucose ≤ 70 mg/dL] at Week 24
3) Proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, without any reported hypoglycemia (for the duration of the Short-term Period) at Week 24
4) In a sub-study, change from baseline in the mean value of 24-hour glucose readings measured by Continuous Glucose Monitoring (CGM) at Week 2
5) Proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0% at Week 24

8.3.3 Exploratory Endpoint(s)

1) In a sub-study, change from baseline in mean amplitude of glucose excursions (MAGE) of 24 hour glucose readings measured by Continuous Glucose Monitoring (CGM) at Week 2, Week 12, and Week 24
2) In a sub-study, change from baseline in the mean value of 24 hour glucose readings measured by Continuous Glucose Monitoring (CGM) at Week 12 and Week 24
3) In a sub-study, change from baseline within-subject, within-day in the standard deviation of 24 hour glucose readings measured by Continuous Glucose Monitoring (CGM) at Week 2, Week 12 and Week 24
4) In a sub-study, change from baseline in the percentage of time spent in the euglycemic target range of ≥71 mg/dL (3.9 mmol/L) and ≤ 180 mg/dL (10.0 mmol/L) as measured by CGM at Week 2, Week 12, and Week 24
5) In a sub-study, change from baseline in the percentage of time spent with glucose ≤ 70 mg/dL (3.9 mmol/L) as measured by CGM at Week 2, Week 12, and Week 24
6) In a sub-study, change from baseline in the percentage of time spent with glucose ≤ 70 mg/dL (3.9 mmol/L) as measured by CGM between midnight (12:00am) and 6:00 am at Week 2, Week 12, and Week 24
7) Change from baseline in HbA1c at Week 52.
8) Change from baseline in total body weight at Week 52
9) Proportion of subjects with confirmed hypoglycemia [defined as: a) plasma glucose ≤ 70 mg/dL (3.9 mmol/L); or b) signs / symptoms of hypoglycemia with self-monitored blood glucose ≤ 70 mg/dL (3.9 mmol/L)] at Week 52

10) Proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, without any hypoglycemia, at Week 52
11) Proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%, at Week 52
12) Proportion of subjects requiring rescue or discontinuation for lack of glycemic control) at Week 24 and Week 52
13) Time to treatment intensification (addition of non-study insulin or other anti-diabetic therapies for rescue therapy or discontinuation for lack of glycemic control) at Week 24 and Week 52
14) Proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c ≤ 6.5%, at Week 24 and Week 52
15) Proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c ≤ 6.5%, without any hypoglycemia at Week 24 and Week 52
16) Change from baseline in average glucose values and postprandial glucose values measured by 6-point SMBG profiles at Week 12, Week 24, and Week 52
17) Change from baseline in patient-reported treatment satisfaction, quality of life, and barriers to medication adherence at Week 2, Week 24 and Week 52

8.4 Analyses

8.4.1 Subject Disposition

The disposition of subjects for each study period will be summarized using the enrolled subjects data set for pre-treatment, lead-in subject data set for end of lead in status, and randomized subjects data set for the short-term period. Reasons for discontinuation from the study period will be tabulated and listed.

8.4.2 Demographics and Baseline Characteristics

Frequency distributions and summary statistics for demographic and baseline variables summarized in efficacy analyses, will be computed by treatment group as well as for all subjects combined for the randomized subjects data set. No statistical test will be carried out for comparison of any baseline measurement among the treatment groups.

8.4.3 Concomitant medications

Concomitant medications will be summarized using the treated subject data set by drug class and (generic) drug name. The WHO dictionary is used to code the non-study medication.

8.4.4 Extent of Exposure

The extent of exposure to open-label study medication will be summarized by treatment group using the treated subject data set.

8.4.5 Efficacy Analyses

Efficacy analyses will be run for the randomized subject data set. For the non-inferiority endpoints, the analysis will also be performed using the evaluable subject data set. All analyses

included in the hierarchical testing below, including the primary analysis, will use the randomized subject data set. The analyses using the evaluable subject data set will not be included in the hierarchical testing.

All analyses will be conducted using values prior to rescue/intensification of treatment. Values collected after this time will be excluded from analyses. Several sensitivity analyses, including the sensitivity analyses using data regardless of rescue, will also be performed for the primary efficacy endpoint to assess the robustness of the primary efficacy results.

8.4.5.1 Primary Efficacy Analyses

The primary endpoint is the change in HbA1 from baseline at Week 24 visit. The primary endpoint will be tested for non-inferiority for saxagliptin plus dapagliflozin versus insulin at the alpha = 0.025 level (one sided). The primary analysis of the change in HbA1c from baseline at Week 24 visit will be based on a longitudinal repeated measures analysis using 'direct likelihood'. The model will use subjects in the primary efficacy data set (ie, randomized subjects data set) who have a baseline assessment and at least one post-baseline open-label treatment period assessment. The SAS procedure PROC MIXED will be used. The preferred model will include the fixed categorical effects of treatment, week, randomization stratification factor (background medication of metformin alone vs metformin + SU) and treatment-by-week interaction as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction. An unstructured matrix for the within-subject error variance-covariance will be used. The denominator degrees of freedom will be calculated according to the Kenward-Roger method. A number of back-up models will be defined in the statistical analysis plan in case of non-convergence of the preferred model or other issues. Point estimates and 95% confidence intervals for the mean change within each treatment group as well as the difference in mean change between the saxagliptin plus dapagliflozin versus insulin will be calculated. If the upper limit of the 95% confidence interval is < 0.3%, then saxagliptin plus dapagliflozin as add-on therapy to metformin with or without SU will be considered to be non-inferior to insulin as add-on therapy to metformin with or without SU. The analysis will be repeated using Evaluable Subjects data set. Several other sensitivity analyses, including the analysis using the Evaluable Subjects data set and data regardless of rescue or treatment discontinuation, will also be performed for the primary efficacy endpoint to assess the robustness of the results.

Sensitivity analyses for the primary analysis of change in HbA1c will include:

- Repeat MMRM Analyses of the primary endpoint using Evaluable Subjects data set.
- Repeat MMRM Analyses of the primary endpoint using all available values (ie, including values regardless of rescue or treatment discontinuation).
- ANCOVA analyses of the primary endpoint using values prior to rescue (and within 8 days of treatment discontinuation) using last observation carried forward (LOCF) to impute missing values.
- A pattern mixture model (which does not assume missing at random) will be fit to the data prior to rescue (and within 8 days of treatment discontinuation).

8.4.5.2 Secondary Efficacy Analyses

If non-inferiority is demonstrated for the primary endpoint, the statistical tests for the secondary efficacy endpoints will be performed. The secondary endpoints then will be tested sequentially in the order that they appear in the objectives section of the protocol. Each comparison will be tested at the alpha = 0.05 (two-sided) level (one-sided alpha = 0.025 will be used for the non-inferiority test). Statistical tests between the dapagliflozin plus saxagliptin group and insulin group will be only performed for a given secondary endpoint if all previous sequential tests are statistically significant. Otherwise, the testing procedure will stop at the secondary endpoint that does not reach statistical significance.

The continuous secondary endpoints (ie, the change from baseline in total body weight, the change from baseline at Week 24 visit in the mean value of 24-hour glucose readings obtained from CGM, and the change from baseline in amplitude of glucose excursion of 24-hour glucose readings obtained from CGM) will be analyzed using a longitudinal repeated measures analysis, similarly to the one used for primary efficacy analysis. The binary endpoints (ie, the proportion of subjects achieving HbA1c < 7.0%; hypoglycemia endpoint; and composite response endpoints of glycemic control with hypoglycemia) will be analyzed using logistic regression with adjustment for baseline HbA1c value and/or the stratification factor. In addition to point estimates and 95% confidence intervals, p-values will be calculated for all secondary endpoints. However, no claim will be based on endpoints for which the statistical testing is not performed for the endpoint as per the testing strategy as described above. No claims can be made based on these p-values. A clear distinction will be made between p-values whereby claims can and cannot be made. All secondary efficacy analyses will use subjects in the primary efficacy data set (ie, randomized subjects data set) who have a baseline assessment and any post-baseline open-label treatment period assessment.

For the non-inferiority endpoints, the analysis will be repeated using evaluable subjects data set to examine the robustness of the results. For the non-inferiority secondary endpoint (for the sub-study) of change from baseline in mean 24-hour glucose readings measured by Continuous Glucose Monitoring (CGM) at Week 24, the non-inferiority margin used for testing will be 12 mg/dL. For the non-inferiority secondary endpoint of the proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0% at Week 24, the non-inferiority margin used for testing will be 10%.

8.4.5.3 Exploratory Efficacy Analyses

Analyses for other efficacy objectives will use the same methodology for binary and continuous endpoints as described above. 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 24 / 52 weeks, all subjects will be censored at 24 / 52 weeks if treatment intensification has not occurred by then. Subjects rescued at Week 24 / 52 will be counted as having an event for the analysis. Composite response endpoints (glycemic control without

hypoglycemia), will be analyzed using logistic regression with adjustment for baseline HbA1c value and/or the stratification factor. None of the exploratory endpoints will be statistically tested.

8.4.6 Safety Analyses

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

The number and percent of subjects with at least one AE will be summarised by treatment group, including summaries of AEs, SAEs, AEs leading to discontinuation of study medication, and adverse events of special interest (AEOSI). Summaries will include the number of subjects with events by specified system organ classes and preferred terms for AEs and SAEs, and by preferred term for AEOSI.

The proportion of subjects with at least one hypoglycemia will be summarized by treatment group and by the severity of the events. The frequency of the hypoglycemia will also be summarized. The percentage of patients withdrawing from the study due to hypoglycaemia will also be presented descriptively by treatment group.

Summary statistics will be presented at each assessment visit for the continuous laboratory parameters. Descriptive statistics of changes from baseline by study visits will also be presented. A frequency table of results of categorical laboratory parameters will be produced. The number and percent of subjects with laboratory values meeting marked abnormality criteria will be summarized for each treatment group. Laboratory data will be listed with abnormal values flagged for the subjects with marked abnormalities.

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

Descriptive statistics of the continuous ECG parameters will be presented by treatment group and overall, at each assessment visit for the raw data and change from baseline data respectively. The incidence of clinically notable ECG abnormalities will be summarized.

8.4.7 Pharmacokinetic Analyses

Not applicable

8.4.8 Biomarker Analyses

Not applicable.

8.4.9 Outcomes Research Analyses

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, week, randomization stratification factor (background medication of metformin alone vs metformin + SU) and treatment-by-week interaction as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction. The model will use data 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. No p-values will be generated.

Phase V® is collecting the data for patient reported outcomes in this study.

8.4.10 Subgroup Analysis

The primary efficacy endpoint of HbA1c will be summarized for the following subgroups: age, gender, race, female age, region, baseline eGFR and baseline HbA1c category and the stratification factor.

8.4.11 Other Analysis

Not applicable.

8.5 Interim Analyses

There will be produced one study report at the end of Short-term Period and a second study report at the end of Short-term plus Long-term period. Analyses will not be performed by treatment arm until the Short-term database lock.

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 BMS (or designee). 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
- BMS or 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 BMS/AZ.

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

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

Representatives of BMS or Sponsor 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.

In addition, the study may be evaluated by BMS or Sponsor 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 BMS (or designee) promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS (or designee).

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

Bristol-Myers Squibb or 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 BMS/AZ, whichever is longer. The investigator must contact BMS/AZ prior to destroying any records associated with the study.

BMS/AZ 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 BMS/AZ.

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 investigational product and the following non-investigational product(s) saxagliptin, dapagliflozin and glargine insulin. 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 BMS/AZ
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS/AZ 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 BMS (or designee) 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 BMS (or designee).

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 BMS (or designee) 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 BMS (or designee) training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.2.4 Subject Diaries

Subject diaries are a data collection tool intended to capture information that normally would not be included in a subject's chart and to capture study-related activities or events between study visits. The investigator is responsible for maintaining accurate source documentation to support any data reported on CRFs throughout this trial and verifying that all source documentation is accurate, complete, and kept up-to-date by reviewing subject diaries at each visit. Subject diaries must be collected as part of the subject's medical records upon completion of study activity, expected to provide access to these original records collected, as part of the overall monitoring plan and included as part of the Investigator files maintained after study completion.

The information below describes the use of paper subject diaries in this study. Diaries should be reviewed for completeness at each visit. Incomplete records, missing diaries and retraining should be noted in source records. Ensure all hypoglycemic episodes noted on the diary are also captured in the eCRF as per instructions. Diaries that are too neat, all look the same or have inconsistent handwriting should be investigated to determine validity.

Subject diaries are to be completed by the subject and reviewed by clinical staff to collect the following types of information:

- Symptoms , episodes or activities associated with potential hypoglycemic events
- Use of the study medication, to monitor compliance and /or dosing regimen
- Home glucose monitoring readings*, the time of glucose measurements and meal times.
- Pregnancy testing

*Note: *Glucose reading values captured in the subject diary should not be used as the primary reference value. All reported blood glucose values should be collected from glucose meter data*

and not from patient reported values. Patient recorded values should be used an indicator of potential events, timing of events or as supplemental information to support meter recorded information.

All subject diaries will be provided by the sponsor and must be IRB/EC approved prior to distribution to subjects. Documentation of site training on how to instruct the subject to complete the diary should be available in the On-Site Investigator File (eg, Investigator Meeting Presentation, detailed instructions, or instruction manual). Documentation of subject training or re-training on diary completion should also be noted in the source records. This training should include at a minimum:

- Expectation for frequency and time of completion
- Importance of legibility
- Completeness, how to correct incorrect entries to the diary if needed (eg, cross out, date and initial)
- What to do if an expected entry is missed or unknown
- What to do if diary is lost
- How often the subject should bring the diary back to the site for review.

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:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Subject recruitment (ie, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (ie, 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 BMS/AZ. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS/AZ at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or BMS/AZ as related to the investigational product.
Complete Abstinence	Complete avoidance of heterosexual intercourse. Complete abstinence is an acceptable form of contraception. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (ie, 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. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence
Serious Adverse Event	Serious adverse event defined as 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; 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.). For reporting purposes only, BMS also considers the occurrence of pregnancy, overdose (regardless of association with an AE), and cancer as important medical events.
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (ie, Investigator Brochure for an unapproved investigational product).

11 LIST OF ABBREVIATIONS

Term	Definition
Ab	Antibody
ADA	American Diabetes Association
ADR	adverse drug reaction
AE	adverse event
AEOSI	adverse events of special interest
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AZ	AstraZeneca
β-HCG	beta-human chorionic gonadotrophin
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
Ca++	calcium
CABG	coronary artery bypass graft
CBC	complete blood count
CDE	Certified Diabetes Educator
CFR	Code of Federal Regulations
CGM	continuous glucose monitoring
CHF	congestive heart failure
CI	confidence interval
C1-	chloride

Term	Definition
Cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CNS	Central nervous system
CRC	Clinical Research Center
CrCl	creatinine clearance
CRF	Case Report Form, paper or electronic
CT	computerized tomography
CTA	clinical trial agreement
CYP	cytochrome p-450
D/C	discontinue
DILI	drug-induced liver injury
dL	deciliter
DMC	data monitoring committee
DPP4	dipeptidyl peptidase-4
DSMB	Data safety monitoring board
EC	European Commission
ECG	electrocardiogram
eCRF	Electronic Case Report Form
ect.	et cetera
EDC	Electronic Data Capture
eg,	exempli gratia (for example)
eGFR	estimated glomerular filtration rate
EOT	end of treatment
EHR	electronic health records
EMR	electronic medical records
EU	European Union
ESR	Expedited Safety Report
FDA	Food and Drug Administration
FDC	fixed dose combination
FPG	fasting plasma glucose

Term	Definition
FSH	follicle stimulating hormone
G	gram
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GIP	gastric inhibitory polypeptide
GFR	glomerular filtration rate
GLP-1	glucagon-like peptide-1
H	hour
HbA1c	Hemoglobin A1c
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HCO3-	bicarbonate
HDL	high-density lipoprotein
HDPE	High density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator Brochure
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDSA	Infectious Disease Society of America
Ie	id est (that is)
IEC	Independent Ethics Committee
IgM	imunoglobulin
IMP	investigational medicinal products
In	inches

Term	Definition
IND	Investigational New Drug Exemption
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
ITT	intent to treat
IU	International Unit
IUD	interuterine device
IV	intravenous
IVRS	Interactive Voice Response System
K+	potassium
Kg	kilogram
L	liter
Lb	pounds
LDL	Low-density lipoprotein
LFT	liver function test
LOCF	last observation carried forward
MAGE	mean amplitude of glucose excursion
Max	maximum
Mg	milligram
Mg++	magnesium
Min	minute
m^2	meter squared
mL	milliliter
Mm	millimeter
mmHg	millimeters of mercury
MoA	mechanism of action
MODY	mature onset diabetes of youth
µg	microgram
N	number of subjects or observations
Na+	sodium

Term	Definition
N/A	not applicable
Ng	nanogram
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
OTC	over the counter
PCI	percutaneous coronary intervention
PPG	post-parandial glucose
PRO	patient reported outcome
PD	pharmacodynamics
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PT	prothrombin time
PTT	partial thromboplastin time
QC	quality control
QD, qd	quaque die, once daily
RBC	red blood cell
SAE	serious adverse event
SCr	Serum creatinine
SD	standard deviation
SE	standard error
SGLT2	sodium glucose transporter-2
SMBG	Self-monitored blood glucose
SOP	Standard Operating Procedures
SU	sulfonylurea
T	temperature
T	time
TIA	transient ischemic attack
TIBC	total iron binding capacity
T2DM	type 2 diabetes mellitus
TG	triglyceride

Term	Definition
TSH	Thyroid stimulating hormone
TZD	thiazolidinedione
U	units
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
Wk	week
°	degree
%	percent
>	greater than
<	less than
≥	greater than or equal
≤	less than or equal

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STUDY ACKNOWLEDGMENT/DISCLOSURE

I understand that this protocol contains information that is confidential and proprietary to Bristol-Myers Squibb Company (BMS). Any supplemental information that may be added to this document is also confidential and proprietary to BMS 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 BMS 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 BMS. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to BMS 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 BMS, with or without cause.

Original Protocol ☐ Revised protocol ☒ Amendment ☐

Protocol Number: CV181369 Site Number: _____

Date of Protocol: 17 MARCH 2016

IND Number: 63,634 EUDRACT Number: 2015-001702-33

Investigator _____ Date _____
(signature)

_____
(printed name)

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

Medical Monitor/Study Director PPD Date Mar 29/2016
(If required by applicable regulatio

Protocol Number: CV181369
IND Number: 63,634
EUDRACT Number 2015-001702-33
Date: 17-Mar-2016

Protocol CV181369: A 24-week International, Multicenter, Randomized, Open-Label, Active-Controlled, Parallel Group, Phase 3b Trial with a 28-week Extension to Evaluate the Efficacy and Safety of Saxagliptin Co-administered with Dapagliflozin to Insulin Glargine in Subjects with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin with or without Sulfonylurea Therapy

Amendment Number 01
Site Number: All

Medical Monitor

PPD

24-hr Emergency Telephone Number:

PPD

Bristol-Myers Squibb Research and Development

PPD

This protocol amendment contains information that is confidential and proprietary to Bristol-Myers Squibb (BMS).

This amendment must be maintained with the referenced protocol.

Amendment Rationale:

- Added language to allow insulin titration to be initiated at 0.2 U/kg body weight in addition to the previous starting dose of 10U of glargine insulin. This change will only affect new subjects assigned to the insulin arm of the study.
- Removal of the Week -2 (Lead-In) qualification requirement to have a central laboratory fasting plasma glucose (FPG) ≤ 270 mg/dL (5.5 mmol/L) performed. This change will only affect new subjects enrolling in to the study.
- Added section on assessment of ketoacidosis and urosepsis. This will affect all subjects.
- Update criteria for highly effective methods of contraception.This will affect all subjects.
- Added clarification of visit window to be +/- 5 days. This will affect all subjects.
- A number of typographical edits and addtional statistical clarifications to the protocol.

Changes to the Protocol:

1. Protocol, Section 1.1.3 Exploratory Objectives, Third bullet, First sentence: Added within-subject, within-day to definition.
2. Protocol, Section 1.1.3 Exploratory Objectives, Fourth bullet, First sentence: Changed definition to: percentage of time spent within the euglycemic target range of ≥ 71 mg/dL (3.9 mmol/L) to definition, and as measured by CGM.
3. Protocol, Section 1.1.3 Exploratory Objectives, Fifth bullet, First sentence: Changed definition to: percentage of time spent with glucose of ≤ 70 mg/dL (3.9 mmol/L) as measured by CGM to definition.
4. Protocol, Section 1.1.3 Exploratory Objectives, Sixth bullet, First sentence: Changed definition to: percentage of time spent with glucose of ≤ 70 mg/dL (3.9 mmol/L) as measured by CGM between midnight 12:00 Aam and 6:00 am to definition.
5. Protocol Section 1.2, Product Development Background, Fourth parapgraph, added: There have been post marketing reports of ketoacidosis, including diabetic ketoacidosis, in patientswith type 1 and type 2 diabetes mellitus taking dapagliflozin and other SGLT2 inhibitors, although a causal relationship has not been established.
6. Protocol Section 1.2, Product Development Background, Fifth parapgraph, Third sentence, added sentence: The saxagliptin/dapagliflozin combination has raised no new safety concerns.
7. Protocol Section 1.3, Overall Risk/Benefit Assessment, Fifth paragraph: Potential benefits to subjects, Sixth sentence, added 52 week duration of the study.
8. Protocol Section 2.3, Infromed Consent, Second paragraph, first sentence; must be.
9. Protocol Section 3.1.1, Screening Period, First paragraph, Last sentence: which lasts for 14 days.
10. Protocol Section 3.1.1, Screening Period, Second paragraph, Second sentence,removed: and the requirements for entry into the Lead-In period have been met.

11. Protocol Section 3.1.2, Lead-In Period, First paragraph, Last sentence, removed: as required per protocol (see Section 5.3.1.1) and added: and complete their subject diary as required per protocol (see Section 5.3.1.1). Visits should occur within +/- 5 day window of the protocol designated visit schedule, based on the screening date. Subjects should arrive at the site betwen 6:00 AM and 10:00 AM, should be in a fasting state (at least 8 hours) for all regularly scheduled visits and avoid alcohol, caffeine and tobacco prior to the visit(at least 8 hours).
12. Protocol Section 3.1.2, Lead-In Period, Second paragraph, Second sentence, added: The initial pre-parandial glucose measurement on the 6-point SMBG day should be a fasting plasma glucose reading.
13. Protocol Section 3.1.2, Lead-In Period, Fourth paragraph, change: Lead-In period ± 5 days.
14. Protocol Section 3.1.3, Short-term Treatment Period, Second paragragh, Second sentence, added: Visits should occur within +/- 5 day window of the protocol designated visit schedule, based on Day 1 visit date. Subjects should arrive at the site between 6:00 AM and 10:00 AM, should be in a fasting state (at least 8 hours) for all regularly scheduled visits and avoid alcohol, caffeine and tobacco prior to the visit (at least 8 hours).
15. Protocol Section 3.1.3, Short-term Treatment Period, Fourth paragragh, Second sentence, added: The initial pre-prandial glucose measurement on the 6-point SMBG day should be a fasting plasma glucose reading.
16. Protocol Section 3.1.3, Short-term Treatment Period, Fifth paragragh, Second sentence, added: have their dosage titrated to FPG target of ≤ 100 mg /dL (5.5 mmol/L).
17. Protocol Section 3.1.3, Short-term Treatment Period, Insulin Titration during the Short-term Treatment Period, First paragraph, First sentence, added: be recommended to start Day 1 with an initial dose of 0.2U/kg bodyweight or at least 10 Units of insulin per day according to the discretion of the Investigator.
18. Protocol Section 3.1.3, Short-term Treatment Period, Insulin Titration during the Short-term Treatment Period, First parapgraph, Sixth sentence, added: If there have been any unexplained hypoglycemic events (glucose ≤ 70 mg/dL (3.9 mmol/L) during the last 3 days of SMBG readings, insulin glargine will not be uptitrated until there are 3 days without hypoglycemia. The insulin titration will be checked at each site visit and the Investigator can provide recommendations of higher doses at his/her discretion between Weeks 8-12. The goal is to reach an acceptable and stable dose by Week 12.
19. Protocol Section 3.1.3, Short-term Treatment Period, Insulin Titration during the Short-term Treatment Period, Second parapgraph, First sentence, added:without an obvious explanation.
20. Protocol Section 3.1.4, Long-term Treatment Period, First parapgraph, Third sentence, added: Visits should occur within +/- 5 day window of the protocol designated visit schedule, based on Day 1 visit date. Subjects should arrive at the site between 6:00 AM and 10:00 AM, should be in a fasting state (at least 8 hours) for all regularly scheduled visits and avoid alcohol, caffeine and tobacco prior to the visit (at least 8 hours).
21. Protocol Section 3.1.4, Long-term Treatment Period, Third parapgraph, Second sentence, added: The initial pre-prandial glucose measurementr on the 6-point SMBG day should be a fasting plasma glucose reading.
22. Protocol Section 3.1.5, Continuous Glucose monitoring (CGM) Sub-Study, Second parapgraph, added: with valid CGM data at the baseline assessment performed at the Week -2.

23. Protocol Section 3.2, Post Study Access to Therapy, First parapgraph, Second sentence, removed: to treat the condition under study and added: for T2DM thereafter.
24. Protocol Section 3.3.1, Inclusion Criteria, 2) Target Population, a) deleted: Note: At Week -2 (Lead-In), a central laboratory fasting plasma glucose (FPG) qualification check will be performed. Subjects will only be randomized on Day 1 if their FPG is ≤ 270 mg/dL (15 mmol/L) at the Week -2 qualification check. A re-test will be permitted within 7 days if the Week -2 central lab result was > 270 mg/dL (15 mmol/L) but < 300 mg/dL (16.6 mmol/L). Subjects will be excluded if the central lab FPG value at Week -2 (Lead-In) is ≥ 300 mg/dL (16.6 mmol/L) or if the central lab FPG value at Week -2 (Lead-In) and the re-test FPG value are both > 270 mg/dL (15 mmol/L).
25. Protocol Section 3.3.1, Inclusion Criteria, 2) Target Population, Section HIGHLY EFFECTIVE METHODS OF CONTRACEPTION: Removed first bullet: Male condoms with spermacide, added second bullet: Progestogen only hormonal contraception associated with inhibition of ovulation., third bullet, added: containinig a combination of estrogen + progesterone, added fourth bullet: Nonhormonal IUDs, added fifth bullet: Bilateral tubal occulsion, added sixth bullet: Vasectomized partner with documented azoospemia 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 recieived medical assessment of the surgical success., removed seventh bullet: IUDs, such as ParaGard®,removed eighth bullet: Tubal ligation, removed ninth bullet: Vasectomy, and added 10th buller: Inrauterine hormone-releasing system (IUS).
26. Protocol Section 3.4.1 Prohibited and/or Restricted Treatments, First bullet, Second sentence added: Temporary insulin use is acceptable during hospitalizations if study medication is interrupted.

- Protocol Section 3.5 Discontinuation of Subjects following any Treatment with Study Drug, Thirteenth bullet, added: If ketoacidosis is suspected, discontinuation or temporary interruption of dapagliflozin should be CONSIDERED and the patient promptly evaluated (see Section 3.5.6).

27. Protocol Section 3.5 Discontinuation of Subjects following any Treatment with Study Drug, Third paragraph, Third sentence, added: and complete all study visits.
28. Protocol Section 3.5.4 Rescue Guidlelines for Subjects with Protocol-Defined Lack of Glycemia Control, Table 3.5.4-1, Second sentence under Visit Label, removed: (including Week 52) and added under Central Laboratory FPG/HbA1c: (prior to Week 52).
29. Protocol Section 3.5.6, Discontinuation Guidelines due to Ketoacidosis, new section and paragraph added: 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. Contact the medical monitor to discuss treatment options.
30. Protocol Section 4.5 Selection and Timing of Dose for Each Subject, Fourth bullet, First sentence, added: per local label.

31. Protocol Section 4.5 Selection and Timing of Dose for Each Subject, Fourth bullet, Second sentence, added: 0.2U/kg of body weight or at least and (per local label). Third and fourth sentence added: Investigators may modify the fixed dosing titration steps, scheduled in the first eight weeks, to optimize titration for individual patients in order to reach the target goal. Investigator has the discretion to modify insulin dose, based on his/her assessment, between Week 8 and Week 12, with the goal to reach an acceptable and stable insulin dose by Week 12 (see Appendix 6 for details).
32. Section 5.1 Flow Chart/Time and Events Schedule, 5.1-1, Screening & Lead-In Visit Flow Chart for Protocol CV181369, Subscript section a) added: All visits should occur on the designated visit day +/- a 5 day window (based on the screening date) and Subscript section b), last sentence, added: The initial pre-prandial 6-point glucose measurement on the SMBG day should be a fasting plasma glucose reading.
33. Section 5.1 Flow Chart/Time and Events Schedule, 5.1-1, Screening & Lead-In Visit Flow Chart for Protocol CV181369, Procedures, CGM Informed Consent procedure added to Screening Period (Week -4), FPG procedure removed for Lead-In (Week-2) along with notes,Vital Signs (seated BP & Heart Rate procedure), notes added: Note: Measurement must be taken prior to administration of study medication.
34. Section 5.1 Flow Chart/Time and Events Schedule, 5.1-2, Short-term Visit Procedures Flow Chart for Protocol CV181369, Subscript section a) added: All visits should occur on the designated visit day +/- a 5 day window (based on the screening date), Subscript section b), last sentence, added: The initial pre-prandial 6-point glucose measurement on the SMBG day should be a fasting plasma glucose reading, Subscript section c) added third sentence: Investigator has the discretion to modify insulin doses during the fixed dosing schedule as well as during Week 8-Week 12 to achieve target daily FPG.
35. Section 5.1 Flow Chart/Time and Events Schedule, 5.1-2, Short-term Visit Procedures Flow Chart for Protocol CV181369, Procedures, Contact IXRS-Oral Saxa/Dapa procedure at Day 1 with note added: Saxa/Dapa dispensed ONLY Day1 for ST period and Week 24 for LT period ONLY., Contact IXRS-Insulin procedure added at Week 4, Week 8 with note added: Insulin glargine is dispensed sufficent for 4 weeks as needed per subject's individual dosing regimen. refer to Protocol Secton 4, Vital Signs(Seated BP & Heart Rate) procedure, note added: Note: Measurements must be taken prior to administration of study medication, Dispense Study Medication(Oral medication or insulin) procedure, added note: Last dose of ST period Saxa/Dapa should be taken from their current bottle.
36. Section 5.1 Flow Chart/Time and Events Schedule, 5.1-3, Long-Term Procedural Flow Chart for Protocol CV181369, Subscript section a) added: All visits should occur on the designated visit day +/- a 5 day window (based on the screening date) and Subscript section b), last sentence, added: The initial pre-prandial 6-point glucose measurement on the SMBG day should be a fasting plasma glucose reading.

37. Section 5.1 Flow Chart/Time and Events Schedule, 5.1-3, Long-Term Procedural Flow Chart for Protocol CV181369, Procedures, Contact IVRS procedure modified to Contact IXRS-Insulin with notes added: Insulin supplies should be sufficent for 8 weeks. *All patients should register Week 52/Rescue/EOT in IXRS, Vital Signs (Seated BP & Heart Rate) procedure, note added: Note: Measurement must be taken prior to administration of study medication, Dispense Study Medication (insulin glargine only) procedure, (insulin glargine only) was removed and note added: First dose of LT period Saxa/Dapa should be taken the day after the final ST visit, Collection of Study Medication procedure, note changed to Last dose of study medicationshould occur on the last day of the final visit foloowing completion of all visit procedures.
38. Protocol Section 5.3.1.2, 6-point SMBG profiles, first sentense added: (within 15 minutes prior to the start of each meal) and (1.5-2 hours after the start of each meal), Second paragraph, sentence added: A minimum of 2 days of 6-point SMBGs is required to complete the 6-point SMBG profile for each period.
39. Protocol Section 5.3.2.1, Guidance on Assessment of Urinary Tract Infections, Second paragraph added: **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.
40. Protocol Section 5.38 added for Ketoacidosis with addtional paragraph text: There have been post-marketing reports of ketoacidosis, including diabetic ketoacidosis, in patients with type 1 and type 2 diabetes mellitus taking dapagliflozin and other SGLT2 inhibitors, although a causal relationship has not been established. Dapagliflozin is not indicated for the treatment of patients with type 1 diabetes mellitus. Patients treated with dapagliflozin who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise, and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL). If ketoacidosis is suspected, discontinuation or temporary interruption of dapagliflozin should be considered and the patient should be promptly evaluated. Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (e.g., type 1 diabetes, history of pancreatitis, or pancreatic surgery), insulin dose reduction, reduced caloric intake, or increased insulin requirements due to infections, illness or surgery and alcohol abuse. Dapagliflozin should be used with caution in these patients. Contact the medical monitor to discuss treatment options.
41. Protocol Section 5.7.1 Patient reported outcomes (PRO), First prargraph, re-worded text to: The Phase V® health outcomes information system diabetes module will be used for the patient reported outcomes (PRO) assessments. The self-administered pro questionnaires consist of validated generic and diabetes-specific modules of treatment satisfaction, quality of life, and barriers to medication adherence and weight perception.
42. Protocol Section 5.9, Continuous Glucose Monitoring (CGM) Sub-Study, Second paragraph, First sentence, added text: with valid CGM data at the baseline assessment at Week -2.
43. Protocol Section 7.2 Hepatic Adjudication Committee, First sentence, removal of text: discontinuation from study treatment and/or.
44. Protocol Section 8.3.3 Exploratory Endpoint(s), Bullet number 1) add text: mean.

45. Protocol Section 8.3.3 Exploratory Endpoint(s), Bullet number 3) add text: within-subject, within-day as well as Week 2, Week 12.
46. Protocol Section 8.3.3 Exploratory Endpoint(s), Bullet number 4) revised sentence to: In a sub-study, change from baseline in the percentage of time spent in the euglycemic target range of ≥ 71 mg/dL (3.9 mmol/L) and ≤ 180 mg/dL (10.0 mmol/L) as measured by CGM at Week 2, Week 12 and Week 24.
47. Protocol Section 8.3.3 Exploratory Endpoint(s), Bullet number 5) revised sentence to: In a sub-study, change from baseline in the percentage of time spent with glucose ≤ 70 mg/dL (3.9 mmol/L) as measured by CGM at Week 2, Week 12 and Week 24.
48. Protocol Section 8.3.3 Exploratory Endpoint(s), Bullet number 6) revised sentence to: In a sub-study, change from baseline in the percentage of time spent with glucose ≤ 70 mg/dL (3.9 mmol/L) as measured by CGM between midnight (12:00 AM) and 6:00 am at Week 2, Week 12 and Week 24.
49. Protocol Section 8.3.3 Exploratory Endpoint(s), Bullet number 17) added text :Week 2, Week 24.
50. Protocol Section 8.4.5.1 Primary Efficacy Analyses, Sentence 12, added textor treatment discontinuation. Also added new paragraph after last sentence to read: Sensitivity analyses for the primary analysis of the change in HbA1c will include: Bullet 1-Repeat MMRM Analyses of the primary endpoint using values regardless of rescue. Bullet 2- Repeat MMRM Analyses of the primary endpoint using all available values (i.e., including values regardless of rescue or discontinuation). Bullet 3-ANCOVA analyses of the primary endpoint using values prior to rescue (and within 8 days of treatment discontinuation) using last observation carried forward (LOCF) to impute missing values. Bullet 4- A pattern mixture model (which does not assume missing at random) will be fit to the data prior to rescue (and within 8 days of treatment discontinuation).
51. Protocol Section 8.4.5.2 Secondary Efficacy Analyses, Second paragraph, Second sentence, remove text: the methodology of Zhang, Tsiatis and Davidson and Tsiatis, Davidson, Zhang and Lu and replace with: logisitic regression.
52. Protocol Section 8.4.5.3 Exploratory Efficacy Analyses, Sixth sentence, remove text: the methodology of Zhang, Tsiatis and Davidson and Tsiatis, Davidson, Zhang and Lu and replace with: logisitic regression.
53. Protcol Section 8.4.9 Outcomes Research Analyses, Add sentence at the end of the paragraph: Phase V® is collecting the data for patient reported outcomes in this study.
54. Protocol Section 8.4.10 Subgroup analysis, add text: baseline eGFR.
55. Protocol Section 11, List of Abbreviations, Removed term PCTA-percutaneous transluminal coronary angioplasty and replaced it with PCI-percutanious coronary intervention.
56. Protocol Section 12, References, remove reference numbers 5 & 6: 5) Kestelman P. et. al., Efficacy of the Simultaneous Use of Condoms and Spermicides Family Planning Perspectives.Vol 23 (5); October 1991 and 6) Gabbay MB, Thomas J, Gibbs A, Hold P. A Randomized Crossover Trial of The Impact of Additional Spermicide on Condom Failure Rates. Sex Transm Dis 2008; 35: 862-8.

57. Protocol Section Appendix 2, Central Laboratory Assessments, Standrard Safety Laboratory Panels, Table Appendix 2, Urine Analyses, Urinalysis with microscopy, revised text: Hematuria urinalysis with microscopy, Bullet 1-Hematuria (completed only upon request) and Hematuria Dispstick analysis, Bullet 1-Postive result requires repeat microscopy.
58. Protocol Section Appendix 5, Guidance on Contraception, Table Acceptable Highly Effective Methods of Contraception, table revised to text: Progestogen only hormonal contraception associated with inhibition of ovulation[a]. Non-hormonal IUD[b]. Vasectomy[c]. Bilateral tubal occlusion. Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen + progesterone, vaginal ring, injectable, and implants and intrauterine devices (IUDs). Intrauterine hormone-releasing system (IUS). Complete abstinenece[d]. Footnotes include: a-A highly effective method of birth control with a failure rate of less than 1% per year. b- IUDs used shaould have a failure rate less than 1% (highly effective method) such as Mirena and ParaGard. c-Must be at least 90 days from the date of surgery with a semen analysis documenting azoospermia. d-Complete abstinence is defined as complete avoidance if heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnanct tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
59. Protocol Section Appendix 7, Insulin Glargine Fixed Dose Titration Schedule, Second paragraph, Dosing should follow this fixed titration schedule, revised bullets 1-5, Bullet 1-Subjects will self-titrate their insulin dose in 2 Unit increments every 3 days (based on the FPG average from the previous 3 days) until Week 8 of the study. Note: Subjects must have at least 2 SMBG readings in order to titrate their insulin dose. Bullet 2- Subjects randomized to receive open-label insulin glargine will start on Day 1 with an initial dose of 0.2U/kg bodyweight or a 10 Unit dose (per local label directions), based on the discretion of the Investigator, administered subcutaneously once a day, at the same time every day, following Investigator instructions and training. Bullet 3-At Week 8 through Week 12, the Investigator has the discretion to increase or decrease the daily dose of insulin based on FPG and SMBG values, with the goal to reach an acceptable and stable insulin dose after 12 weeks of titration. Bullet 4-All attempts should be made to minimize changes after Week 12 to the daily insulin dose for the remainder of the study.
60. Protocol Section Appendix 7, Insulin Glargine Fixed Dose Titration Schedule, For the first 56 days of the study, First bullet, Second sentence added: A minimum of 2 daily FPG values are required before dose adjustment. Third bullet was deleted.

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 *Medical Monitor/Study Director*	Mar 29/2016 *Date*

(If required by applicable regulations and guidelines.)

Protocol Number: CV181369
Site Number:
Amendment Number: 01