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Clinical Protocol CV181169

A Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Add-On Therapy with Saxagliptin and Dapagliflozin added to Metformin compared to Add-On Therapy with Saxagliptin in combination with Metformin or Dapagliflozin in combination with Metformin in Subjects with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin Alone

Medical Monitor

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24-hr Emergency Telephone Number

[redacted]

Bristol-Myers Squibb Research and Development

[redacted]

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Original Protocol	[redacted]	Not applicable

SYNOPSIS

Clinical Protocol CV181169

Title of Study: A Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Add-On Therapy with Saxagliptin and Dapagliflozin added to Metformin compared to Add-On Therapy with Saxagliptin in combination with Metformin or Dapagliflozin in combination with Metformin in Subjects with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin Alone

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

Saxagliptin 5 mg, administered orally once daily for the 24-week double-blind treatment period.

Dapagliflozin 10 mg tablets, administered orally once daily for the 24-week double-blind treatment period.

Metformin XR 1500 - 2000 mg, administered orally once daily for the 4 week lead-in and the 24-week double-blind treatment period

Study Phase: Phase 3

Research Hypothesis:

A combination of saxagliptin and dapagliflozin added concurrently to metformin is superior to saxagliptin or dapagliflozin added to metformin in reducing HbA1c.

Primary Objective:

To compare the mean change from baseline in glycosylated hemoglobin (HbA1c) achieved with concurrent addition of saxagliptin and dapagliflozin to metformin versus (vs.) the addition of placebo and saxagliptin to metformin and vs. the addition of placebo plus dapagliflozin to metformin after 24 weeks of double-blind treatment.

Secondary Objectives:

- To compare the mean change from baseline achieved with concurrent addition of saxagliptin and dapagliflozin to metformin vs. the addition of placebo and saxagliptin to metformin and vs. the addition of placebo plus dapagliflozin to metformin after 24 weeks of double-blind treatment in:
  1. 2-hour post prandial glucose from a liquid meal tolerance test (2-h MTT)
  2. Fasting plasma glucose (FPG)
- To compare the proportion of subjects achieving therapeutic glycemic response, defined as HbA1c < 7.0%, after 24 weeks of double-blind treatment with concurrent addition of saxagliptin and dapagliflozin to metformin vs. the addition placebo and saxagliptin to metformin and vs. the addition of placebo plus dapagliflozin to metformin.
- To compare the mean change in total body weight achieved with the addition of saxagliptin and dapagliflozin to metformin vs. the addition of placebo and saxagliptin to metformin.

Other Objectives:

- To compare the percent of subjects who require glycemic rescue or discontinue study treatment for lack of efficacy with concurrent addition of saxagliptin and dapagliflozin to metformin vs. the addition

of placebo and saxagliptin to metformin and vs. the addition of placebo plus dapagliflozin to metformin after up to 24 weeks of double-blind treatment.

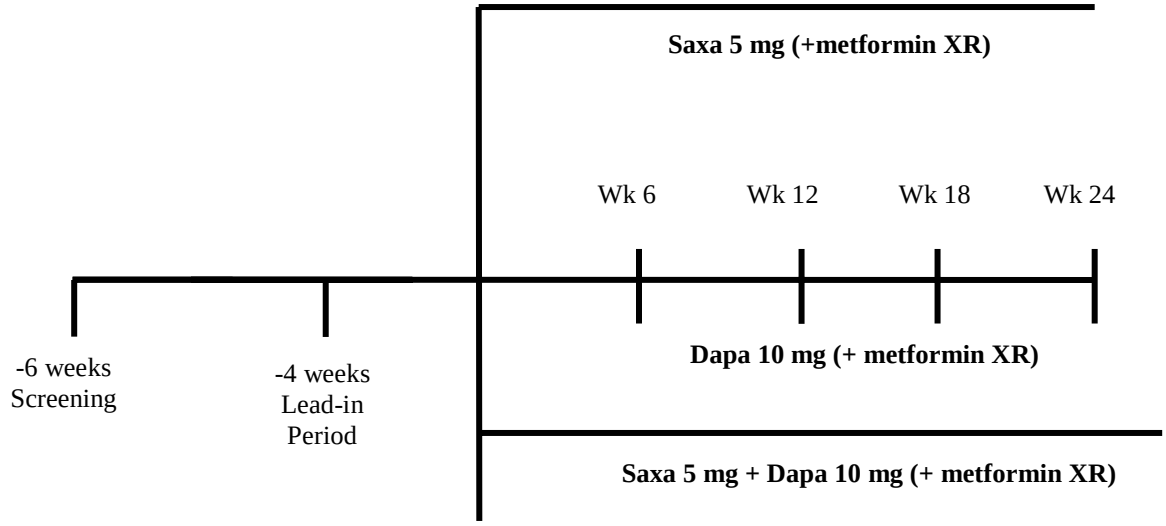
- To compare the time to glycemic rescue or discontinuation for lack of efficacy with concurrent addition of saxagliptin and dapagliflozin to metformin vs. the addition of placebo and saxagliptin to metformin and vs. the addition of placebo plus dapagliflozin to metformin after up to 24 weeks of double-blind treatment.
- To compare the mean change from baseline in AUC of glucose, AUC insulin, AUC C-peptide and AUC glucagon obtained during a MTT with concurrent addition of saxagliptin and dapagliflozin to metformin vs. the addition of placebo and saxagliptin to metformin and vs. the addition of placebo plus dapagliflozin to metformin after 24 weeks of double-blind treatment.
- To compare the mean percent change from baseline in fasting serum lipids (Total-C, LDL-C, HDL-C, TG) with concurrent addition of saxagliptin and dapagliflozin to metformin vs. the addition of placebo and saxagliptin to metformin and vs. the addition of placebo plus dapagliflozin to metformin during the double-blind treatment period.

Study Design:

Figure 1: Study Design

Stable dose of metformin (≥ 1500 mg) for ≥ 8 weeks Screening $A1_C$ ≥ 8% ≤ 12%

Metformin IR or XR will be switched to the nearest multiple of Metformin XR 500 mg tablets at week -4



Study Population:

Inclusion:

- Men and women, aged ≥ 18 years old at time of screening visit
- Subjects with T2DM with inadequate glycemic control defined as central laboratory HbA1c ≥ 8.0 and ≤ 12.0 % at the screening visit.
- Stable metformin therapy for at least 8 weeks prior to screening at a dose ≥ 1500 mg per day
- C-peptide ≥ 1.0 ng/mL (0.34 nmol/L) at screening visit
- BMI ≤ 45.0 kg/m^2 at the screening visit

Exclusion:

- Moderate or severe impairment of renal function [defined as eGFR <60mL/min/1.73 m^2 (estimated by MDRD) or serum creatinine (Scr) ≥ 1.5 mg/dL in males or ≥ 1.4 mg/dL in females]
- Uncontrolled hypertension defined as systolic blood pressure (SBP) ≥ 160 mmHg and/or diastolic blood pressure (DBP) ≥ 100 mmHg

  Note: Subjects with SBP ≥ 160mmHg and < 180mmHg or a DBP ≥ 100 mmHg and < 110 mmHg will be able to enter the lead-in period, provided their hypertension treatment is adjusted as deemed appropriate by the investigator. These subjects can not be randomized if they meet the blood pressure exclusion criterion of SBP ≥ 160 mmHg or DBP ≥ 100 mmHg measured at Day 1.
- Cardiovascular diseases within 3 months of the screening visit
- Significant hepatic disease, including, but not limited to, chronic active hepatitis and/or severe hepatic insufficiency, including subjects with ALT and/or AST > 3x ULN and or Total Bilirubin > 2.5xULN.
- Male subjects with microscopic hematuria present at week -6 or -4 AND no common cause that can be confirmed. Male subjects with a confirmed common cause can be randomized with a documented negative microscopic urinalysis.

  NOTE: *Female subjects with hematuria can be randomized, but should be investigated according to local standards and best clinical practices. (See Appendix 3).*
- Malignancy within 5 years of the screening visit (with the exception of treated basal cell or treated squamous cell carcinoma)
- Subjects who have contraindications, including but not limited to a history of serious hypersensitivity reaction to saxagliptin, as outlined in the saxagliptin and dapagliflozin Investigator Brochure, the local saxagliptin package insert or the local metformin package insert.
- Administration of any antihyperglycemic therapy, other than metformin, for more than 14 days (consecutive or not) during the 12 weeks prior to screening, as well as previous participation in any SGLT2- or DPP-4-inhibitor trial.
- Current treatment with potent cytochrome P450 3A4/5 inhibitors (in countries where dose adjustment would be required by the saxagliptin label).

Randomization Criteria

Exclusion:

- FPG >270mg/dl as measured at Week -4

Note: At Week -4 a qualification check will be performed and subjects will be excluded, if their FPG is > 270 mg/dl. A re-test will be permitted within 7 days if the initial result was > 270mg/dl but < 300 mg/dl. Subjects will be excluded if the mean value of the Week -4 result and the re-test result is > 270mg/dl.

Study Assessments:

Key assessments are:

- The central laboratory measurement of the HbA1c during the treatment period
- 2-hour post prandial glucose from a liquid meal tolerance test (2-h MTT)
- Fasting plasma glucose
- Full body weight

Statistical Methods:

The primary efficacy analysis will be performed using a longitudinal repeated measures model for the change from baseline at Week 24, with terms for treatment group, baseline value, time, the interaction of treatment and time, and the interaction of baseline value and time in the model, including observations prior to rescue. Point estimates and 95% confidence intervals will be calculated for the adjusted mean changes within each treatment group as well as for the differences in adjusted mean changes between treatment groups.

Sensitivity analyses for HbA1c will include additional repeated measures analyses and analysis of covariance (ANCOVA) analyses. The repeated measures analyses will include two separate analyses including values after rescue, including and excluding a time-dependent covariate for rescue. Two separate ANCOVA analyses of the change from baseline at Week 24 will be performed, with terms for treatment group and baseline value in the model. One analysis will be based on measurements at Week 24 (if prior to rescue, if applicable) or the last post-baseline measurement prior to Week 24 and prior to rescue (if applicable), if no Week 24 assessment is available (ie, last observation carried forward [LOCF]). The second sensitivity analysis using ANCOVA will be based on all subjects completing the short-term double-blind period without requiring glycemic rescue therapy.

The min test approach of Laska and Meisner[5] will be implemented to test the simultaneous addition of saxagliptin and dapagliflozin to metformin versus each of the individual add-on components plus placebo. Statistical significance of the primary endpoint will be claimed if the p-values for both comparisons are significant at the 2-sided, 0.05 significance level. With 163 subjects per treatment group, there will be 90% power to detect a difference in mean HbA1c of 0.4% between the saxagliptin plus dapagliflozin mg added to metformin treatment group and each of the monotherapy add-on groups, assuming a standard deviation of 1.0%. Assuming that 5% of subjects do not have a post-baseline assessment, a total of approximately 516 subjects (172 subjects per treatment arm) need to be randomized.

Assuming that 50% of screened subjects will fail to meet enrollment criteria, a total of 1032 subjects need to be screened.

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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 antihyperglycemic drugs, as most patients eventually require 2 or more agents to achieve or maintain glycemic targets. Amongst the medications approved for the treatment of T2DM, metformin is the drug of choice for initiating oral therapy, while other classes of antidiabetic agents are typically sequentially added 2nd and 3rd line. Recently 2 new classes of oral drugs, DPP4-inhibitors (Dipeptidyl Peptidase) and SGLT2-inhibitors (Sodium-Glucose Transporter 2) are emerging as new options in the management of T2DM.

1.1 Study Rationale

This study is a Phase III study, performed as part of the clinical development program for both saxagliptin, a DPP4-inhibitor, and dapagliflozin, a SGLT2-inhibitor, for the treatment of T2DM. The study is intended to compare the dual addition of saxagliptin plus dapagliflozin vs. placebo plus saxagliptin or placebo plus dapagliflozin as 2nd-line add-on therapy in subjects with T2DM who are inadequately controlled on metformin therapy.

Many medications are approved for the treatment of T2DM, however the challenge of achieving and maintaining treatment goals within the current sequential therapy approach is linked to shortcomings of older classes of drugs. These older classes of drugs are associated with undesirable side effects that can negatively affect patient compliance and limit the effectiveness of antidiabetic treatment.

There are oral and parenteral options for glycemic therapy. Injectables like insulin and GLP-1 analogs, have limitations. For example insulin has an increased risk of hypoglycemia and weight gain, and GLP-1 analogs have gastrointestinal side effects. More importantly, not all patients are able to use or willing to inject diabetes drugs.

Metformin is the oral first line gold standard agent. Metformin is a biguanide; its major mechanism of action (MOA) is to decrease hepatic glucose output thus lowering fasting hyperglycemia. Metformin is recommended as the initial pharmacological therapy

because of its glycemic efficacy, weight neutrality, low risk of hypoglycemia, good tolerability and relatively low cost.

Current sequential add-on 2nd and 3rd line oral therapy mainly includes older classes of oral drugs like sulfonylureas (SUs) and thiazolidinediones (TZDs). Some of their key limitations are weight gain and increased risk of hypoglycemia (SU only). Hypoglycemia is a clinically important barrier to optimizing treatment and there is emerging evidence that hypoglycemia is associated with negative cardiovascular outcomes. SUs (and insulin) are associated with a high risk for hypoglycemia and caution is recommended when using combination therapy with agents causing hypoglycemia if HbA1c is < 8.5 %[1]. Efforts by patients to lose weight as part of a therapeutic lifestyle program are undermined by therapies that lead to weight gain. Over 85% of patients with T2DM are overweight or obese, and additional weight gain is undesirable and often results in reduced treatment compliance by the patients. TZDs, SUs and Insulin, are all associated with a significant weight gain.

These treatment limitations of older classes of anti diabetic medicines might contribute to the poor level of glycemic control seen worldwide. In the US according to NHANES 2004 data, 44.3 % of patients with T2DM have HbA1c levels ≥ 7 %.[2] This level of poor control appears not to have improved. NHANES 2006 still showed that 40 % of patients have HbA1c > 7 % [3].

Market research data indicate that the average time for adaptation of dosing or adding additional therapy is > 2 years[4]. In the US, metformin is used as single anti-diabetic medication on average 24.4 months before a SU is added. The HbA1c at the time of addition is on average 7.7%.

This probably reflects treatment inertia in the context of the typical sequential add-on treatment approach of prescribing additional medications for those with uncontrolled HbA1c levels as well as some hesitancy based on the recommendation to be cautious, when using combination therapy with agents causing hypoglycemia.[4]

Because of this lack of, and delay in, glucose control, the progressive nature of the disease and the limitations of available oral and non-oral therapies, there is a significant medical need not only for additional oral combination treatment options for T2DM, but

also for a new approach to treatment, ie dual add-on therapy in patients who are not adequately controlled on their mono therapy.

None of the recommendations of the leading scientific societies addresses the issue of dual-add-on therapy after initial metformin therapy. In this sense a dual add-on therapy to metformin if HbA1c is ≥ 8 % represents a new treatment paradigm.

The 2 new emerging classes of oral drugs, DPP4-inhibitors and SGLT2-inhibitors, differ from the older classes in multiple ways, chiefly by their mechanism of action (MOA), their low risk for hypoglycemia and either weight neutrality or weight loss.

Saxagliptin enhances glucose-mediated insulin secretion by a glucose-dependent mechanism (via incretin effect), while dapagliflozin inhibits renal glucose reabsorption and acts independently of insulin. Therefore, both saxagliptin and dapagliflozin complement metformin's MOA. Saxagliptin and dapagliflozin have demonstrated, both individually and in combination with metformin in general a favorable safety and tolerability profile. They have shown as single agents, as well as in (initial and add-on) 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 2 glucose lowering agents simultaneously. Both drugs have either demonstrated weight neutrality (saxagliptin) or moderate weight reduction (dapaglifozin) and also do not require dose titration, simplifying therapy vs. add-on therapy with SUs or TZDs.

Thus a second-line oral dual add-on therapy with saxagliptin plus dapagliflozin could be a new option, as part of a triple combination that only includes drugs with complementary mechanisms of action, a low risk of hypoglycemia and also has the potential for moderate weight loss, thus contributing in a useful and complementary fashion to a more effective, patient friendly management of T2DM.

1.2 Research Hypothesis

A combination of saxagliptin and dapagliflozin added concurrently to metformin is superior to saxagliptin or dapagliflozin added to metformin in reducing HbA1c.

1.3 Objectives

Primary:

To compare the mean change from baseline in glycosylated hemoglobin (HbA1c) achieved with concurrent addition of saxagliptin and dapagliflozin to metformin versus (vs.) the addition of placebo and saxagliptin to metformin and vs. the addition of placebo plus dapagliflozin to metformin after 24 weeks of double-blind treatment.

Secondary:

- To compare the mean change from baseline achieved with concurrent addition of saxagliptin and dapagliflozin to metformin vs. the addition of placebo and saxagliptin to metformin and vs. the addition of placebo plus dapagliflozin to metformin after 24 weeks of double-blind treatment in:
  1. 2-hour post prandial glucose from a liquid meal tolerance test (2-h MTT)
  2. Fasting plasma glucose (FPG)
- To compare the proportion of subjects achieving therapeutic glycemic response, defined as HbA1c < 7.0%, after 24 weeks of double-blind treatment with concurrent addition of saxagliptin and dapagliflozin to metformin vs. the addition placebo and saxagliptin to metformin and vs. the addition of placebo plus dapagliflozin to metformin.
- To compare the mean change in total body weight achieved with the addition of saxagliptin and dapagliflozin to metformin vs. the addition of placebo and saxagliptin to metformin.

Other:

- To compare the percent of subjects who require glycemic rescue or discontinue study treatment for lack of efficacy with concurrent addition of saxagliptin and dapagliflozin to metformin vs. the addition of placebo and saxagliptin to metformin and vs. the addition of placebo plus dapagliflozin to metformin after up to 24 weeks of double-blind treatment.
- To compare the time to glycemic rescue or discontinuation for lack of efficacy with concurrent addition of saxagliptin and dapagliflozin to metformin vs. the addition of placebo and saxagliptin to metformin and vs. the addition of placebo plus dapagliflozin to metformin after up to 24 weeks of double-blind treatment.
- To compare the mean change from baseline in AUC of glucose, AUC insulin, AUC C-peptide and AUC glucagon obtained during a MTT with concurrent addition of

saxagliptin and dapagliflozin to metformin vs. the addition of placebo and saxagliptin to metformin and vs. the addition of placebo plus dapagliflozin to metformin after 24 weeks of double-blind treatment.

- To compare the mean percent change from baseline in fasting serum lipids (Total-C, LDL-C, HDL-C, TG) with concurrent addition of saxagliptin and dapagliflozin to metformin vs. the addition of placebo and saxagliptin to metformin and vs. the addition of placebo plus dapagliflozin to metformin during the double-blind treatment period.

Safety and tolerability:

To evaluate the safety and tolerability of dual add-on therapy (triple therapy) vs. each of the dual therapies.

1.4 Product Development Background

Metformin, the standard initial pharmacological therapy for T2DM as an adjunct to diet and exercise, should not be used in subjects with serum creatinine levels of ≥ 1.4/1.5 mg/ml for women and men respectively. Metformin's dose limiting side effect is GI tolerability. However doses ≥ 1500 mg are generally well tolerated.

Saxagliptin is a DPP4-inhibitor for the treatment of patients with T2DM. DPP4-inhibitors are a relatively new class of oral antihyperglycemic drugs that enhance glucose-mediated insulin secretion and suppress glucagon by reducing the clearance of active glucagon-like peptide 1 (GLP-1). It is approved in many countries including the US as monotherapy, and initial combination therapy with metformin and in both the EU and the US as add-on therapy to metformin. The results from the 24 week periods of the Phase 3 studies confirmed clinically meaningful benefits of saxagliptin 5 mg on HbA1c, as well as fasting plasma glucose (FPG), postprandial glucose, 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, as add-on combination treatment to metformin, insulin with or without background metformin and as initial therapy in combination with metformin. Treatment with saxagliptin led to rates of hypoglycemia that were generally similar compared to placebo. 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 patients 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 a novel antihyperglycemic agent being developed to treat T2DM as an adjunct to diet and exercise. Dapagliflozin is a highly selective and orally active inhibitor of SGLT2, the major transporter responsible for the renal glucose reabsorption. Dapagliflozin's mechanism of action (MOA) is different from, and complementary to, the mechanisms of currently available medicines, resulting in the direct and insulin-independent elimination of glucose by the kidney. 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). Therefore, the action of dapagliflozin is dependent upon the patient's baseline glycemic control and renal function, and is independent of the patient's beta cell function or insulin sensitivity, which translates into a relatively low risk of hypoglycemia. Additionally, the steady excretion of glucose due to SGLT2 inhibition results in a continual loss of calories that ultimately leads to a decrease in weight and adiposity, a supplemental benefit that addresses one of the basic underlying problems in the pathogenesis of T2DM, namely over-nutrition and caloric excess. The inhibition of sodium and glucose transport in the proximal tubule also causes a mild diuretic effect, with potential for beneficial blood pressure effects. Dapagliflozin is associated with risks related to the MOA, ie. excretion of glucose and accompanying sodium and water in the urine, potentially leading to genital infections, UTIs, hypoglycemia, and volume depletion. Glucosuria and associated physiological effects such as increased hematocrit are rapidly reversible and therefore, any side effects and/or laboratory changes related to glucosuria can be expected to normalize after stopping dapagliflozin treatment. A meta analysis of the pivotal studies was consistent with acceptable CV safety for dapagliflozin therapy and there is a low risk for drug-drug interactions with commonly prescribed therapies for T2DM or its comorbidities.

1.5 Overall Risk/Benefit Assessment

Saxagliptin has been approved as an antidiabetic agent in more than 60 countries. Considering saxagliptin's mechanism of action, the comprehensive previous clinical

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

This protocol includes also an experimental compound, dapagliflozin that is being developed as a potential new therapy for hyperglycemia in subjects with type 2 diabetes. However considering dapagliflozin's mechanism of action, the study's design features (including the inclusion, exclusion, and discontinuation criteria), and the planned safety procedures, participation in this study presents a minimal and thus acceptable risk to the individual patients that will be included. In addition, a recently concluded phase III study included combination therapy with another member of the DPP4-inhibitor class. In that study treatment with dapagliflozin as add-on to sitagliptin alone or in combination with metformin over 24 weeks was found effective in improving glycemic control in subjects with inadequate control on sitagliptin alone or in combination with metformin. As part of this dual (with metformin) or triple regimen (with the DPP4-inhibitor plus metformin) dapagliflozin treatment was found to be safe and well tolerated.[4] Consistent with other studies, addition of dapagliflozin resulted in a mean bodyweight reduction vs. placebo of about 1.9 kg vs. placebo. The rate of hypoglycemic events was low, 6 subjects in the dapagliflozin group and 4 subjects in the placebo group experienced at least 1 hypoglycemic event.

Potential risks

Both metformin and saxagliptin are widely used anti-diabetic treatments. Metformin will be prescribed according to its approved label. The potential risks associated with dapagliflozin have been identified based upon the mechanism of action, the preclinical results, and the extensive clinical experience to date, including a study combining it with another DPP4-inhibitor and / or metformin. Thus, the benefits and risks associated with the investigational drugs and metformin, are well established and presented in their approved prescribing information and investigator brochure respectively. No study procedure will put patients at a risk beyond those ordinarily encountered during the performance of routine medical examinations or tests.

Protection against risks

The present study has been designed with appropriate measures in place so as to monitor and minimize any of the potential health risks to participating patients. In order to ensure the safety of all patients participating in this study, AstraZeneca and Bristol-Myers Squibb will conduct a real-time review of all safety information from all ongoing clinical saxagliptin and dapagliflozin studies as they become available. Safety signal detection will include the integration of all available sources of safety information, including clinical study data, adverse event reports, pre-clinical data, epidemiological studies and literature reports, to identify and characterize unrecognized safety risks or changes in those which are currently expected Adverse Drug Reactions. 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. In addition, all studies which include dapagliflozin are subject to a carefully designed patient risk management plan that includes the temporary and if necessary permanent discontinuation of investigational product in individual patients in whom a potential health risk or a laboratory abnormality of clinical concern has been identified. Investigators are also provided guidance on appropriate management of potential risks such as hypoglycemia, urinary tract infections and decreased renal function and also the potential risks of saxagliptin mentioned in the Risk Management Plan.

Potential benefits to patients

All patients will receive active dual antihyperglycaemic therapy; however, a direct benefit from randomized treatment cannot be assured as two thirds of patients will receive placebo as a third agent, and the efficacy and safety of saxagliptin in combination with dapagliflozin as well as the dual add-on of both agents in this clinical setting has yet to be established, although in a previous study sequential step therapy with dapaglifozin and another DPP4-inhibitor has been shown to be efficacious and safe.[4] In the present study, the doses of saxagliptin (5 mg) and dapagliflozin (10 mg) are the usual standard doses. In addition, saxagliptin is expected to be weight neutral and dapagliflozin to reduce weight moderately, while both have shown a low risk for hypoglycemia in combination w. metformin. There is also a low risk of hypoglycemia in a triple combination of dapagliflozin including metformin and another DPP4 inhibitor.

Patients are also expected to receive some benefit in the form of increased medical care/attention when participating in study procedures, which includes multiple clinic visits and physical examinations over the 24 week study. Patients will also receive counseling on dietary and life-style modifications. It is commonly observed that even patients receiving placebo in diabetes studies show some improvement in glycemic control, likely due to their increased compliance to dietary and life-style counseling while they are participating in a clinical study.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

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

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

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

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

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

2.3 Informed Consent

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

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

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is 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 their informed consent during the study, then 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 consent form must also include a statement that BMS 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.

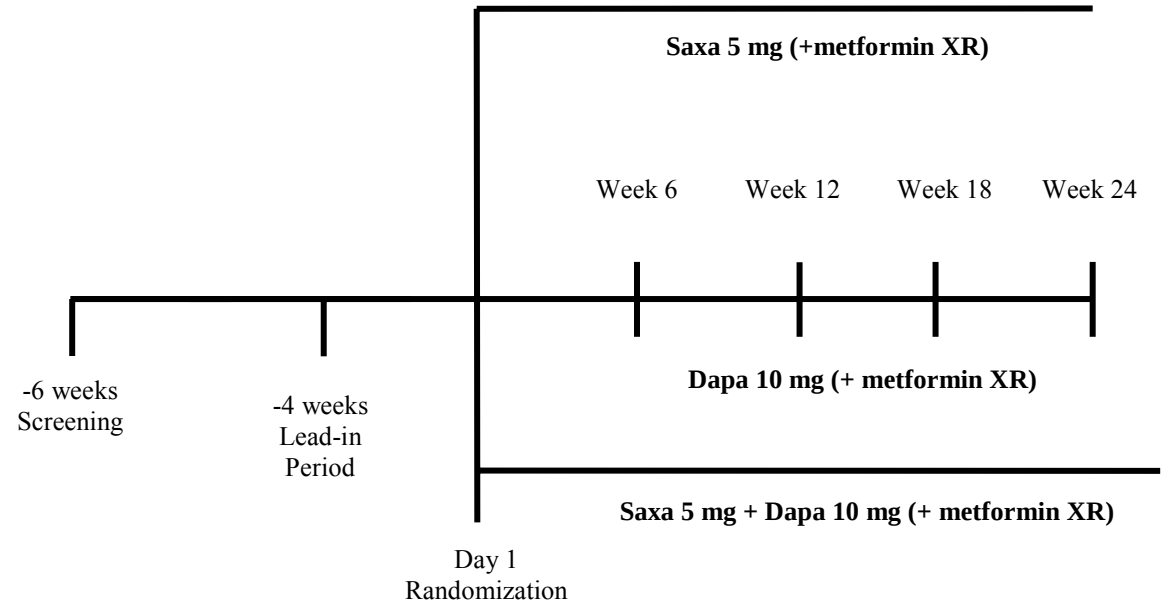
3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

Figure 3.1: Study Design

Stable dose of metformin (≥ 1500 mg) for ≥ 8 weeks Screening $A1_c \geq 8\% \leq 12\%$

Metformin IR and XR will be switched to the **nearest multiple of Metformin XR 500 mg tablets at week -4**



Date: [redacted]

3.2 Post Study Access to Therapy

At the end of the study, the sponsor will not continue to supply study drug to subjects/investigators unless the sponsor chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

3.3 Study Population

For entry into the study, the following criteria MUST be met prior to the visit at week -4.

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

Note: At Week -4 a qualification check will be performed and subjects will be excluded, if their FPG is > 270 mg/dl. A re-test will be permitted within 7 days if the initial result was > 270mg/dl but < 300mg/dl. Subjects will be excluded if the mean value of the Week -4 result and the re-test result is > 270mg/dl.

b) Stable metformin therapy for at least 8 weeks prior to screening at a dose ≥ 1500 mg per day.

c) C-peptide ≥ 1.0 ng/mL (0.34 nmol/L) at screening visit

d) BMI ≤ 45.0 kg/m^2 at the screening visit

3) Age and Reproductive Status

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

b) Women of childbearing potential (WOCBP) must be using an acceptable method of contraception to avoid pregnancy throughout the study in such a manner that

the risk of pregnancy is minimized. See Section 3.3.3 for the definition of WOCBP.

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

d) Women must not be breastfeeding.

e) Sexually active fertile men must use effective birth control if their partners are WOCBP.

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) History of diabetes insipidus.

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

c) History of diabetic ketoacidosis or hyperosmolar nonketotic coma.

2) Medical History and Concurrent Diseases

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

b) Any unstable endocrine, psychiatric or rheumatic disorders as judged by the Investigator.

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

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

Acute vascular event:

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

Note: Subjects with SBP ≥ 160mmHg and < 180mmHg or a DBP ≥ 100 mmHg and < 110mmHg will be able to enter the lead-in period, provided their hypertension treatment is adjusted as deemed appropriate by the investigator. These subjects can not be randomized if they meet the blood pressure exclusion criterion of SBP ≥ 160 mmHg or DBP ≥ 100 mmHg measured at Day 1.

f) Cardiovascular Disease within 3 months of the screening visit [ie myocardial infarction, cardiac surgery or revascularization (CABG/PTCA), unstable angina, stroke or transient ischemic attack (TIA).

g) Congestive heart failure as New York Association (NYHA) class IV (see Appendix 1), unstable or acute congestive heart failure. Note: eligible patients with congestive heart failure, especially those who are on diuretic therapy, should have careful monitoring of their volumes status throughout the study.

Renal Diseases:

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

i) Conditions of congenital renal glucosuria.

Hepatic Diseases:

j) Significant hepatic disease, including, but not limited to, chronic active hepatitis and/or severe hepatic insufficiency, including subjects with ALT and/or AST > 3x ULN and or Total Bilirubin 2.5x ULN.

Hematological/Oncological Disease/Conditions:

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

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

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

n) Donation of blood or blood products to a blood bank, blood transfusion, or participation in a clinical study requiring withdrawal of > 400 mL of blood during the 6 months prior to the screening visit.

Prohibited Treatment and Therapies:

o) Administration of any antihyperglycemic therapy, other than metformin, for more than 14 days (consecutive or not) during the 12 weeks prior to screening, as well as previous participation in any DDP-4 or SGLT2 inhibitor trial is an exclusion criterion.

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

q) Administration of any other investigational drug or participation in any interventional clinical studies within 30 days of planned screening to this study.

3) Physical and Laboratory Test Findings

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

b) Male subjects with microscopic hematuria present at week -6 or -4 AND no common cause that can be confirmed. Male subjects with a confirmed common cause can be randomized with a documented negative microscopic urinalysis. ***NOTE:*** *Female subjects with hematuria can be randomized, but should be investigated according to local standards and best clinical practices.* (See Appendix 3)

c) Other central laboratory test findings:

- Abnormal free T4 vales. *Abnormal thyroid stimulating hormone (TSH) value at screening will be further evaluated by free T4. Subjects with abnormal free T4 values will be excluded.*
- Positive for hepatitis B surface antigen
- Positive for anti-hepatitis C virus antibody

4) Allergies and Adverse Drug Reaction

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

5) Sex and Reproductive Status

a) Women who are pregnant.

6) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated.

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

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

d) Employees of BMS, AstraZeneca (AZ), or their relatives.

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.

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

3.3.2.1 Randomization Criteria

Exclusion:

- FPG >270mg/dl as measured at Week -4

Note: At Week -4 a qualification check will be performed and subjects will be excluded, if their FPG is > 270 mg/dl. A re-test will be permitted within 7 days if the initial result was > 270 mg/dl but < 300mg/dl. Subjects will be excluded if the mean value of the Week -4 result and the re-test result is > 270 mg/dl.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure 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

Women of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Post menopause is defined as:

- Amenorrhea ≥ 12 consecutive months without another cause and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL or
- Women with irregular menstrual periods and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL or (NOTE: FSH level testing is not required for women ≥ 62 years old with amenorrhea of ≥ 1 year)
- Women on hormone replacement therapy (HRT) who have prior clinical evidence of menopause based on any of the criteria above.

Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (eg, vasectomy) should be considered to be of childbearing potential.

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 both screening and treatment periods:

- Antihyperglycemic medication (other than protocol required medication and/or protocol-allowed open-label rescue medication).
- Stable weight loss medication is allowed.
- Treatment with any stable replacement or chronic corticosteroid therapy at the time of screening is permitted. During the trial (beginning with screening), new initiation of treatment with any systemic corticosteroid therapy that will involve ≥ 5 days of therapy is prohibited (inhaled and topical are allowed). The medical monitor should be consulted prior to beginning therapy with corticosteroids for subjects who require acute systemic corticosteroid treatment.
- In countries where dose adjustment would be required by the local saxagliptin label: if initiation of treatment with any potent cytochrome P450 3A4/5 inhibitors during the trial is required, the medical monitor should be consulted prior to beginning therapy with any potent cytochrome P450 3A4/5 inhibitors.

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, over-the-counter 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 (see Section 5.9.1) and to the protocol visit schedule (see Section 5.1).
- Women of child-bearing potential must immediately contact the Investigator if they suspect they might be pregnant and if they have changed or plan to change their birth control method (see Section 6.4).

3.5 Discontinuation of Subjects from Treatment

Subjects MUST discontinue investigational product (and noninvestigational product at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- 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
- Pregnancy
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- eGFR < 60 mL/min/1.73m^2 for sustained period of time (12 - 16 weeks)

Dapaglifozin based on its mechanism of action has been shown to reduce eGFR by up to 10% with initiation of therapy; however this has in general been reversible and not resulted in renal failure and eGFR values returned to baseline within 12 - 24 weeks of continued therapy.

In case of a decision to discontinue treatment the Investigator will follow the subject until the event has resolved or stabilized, however at least till week 24.

All subjects who discontinue from treatment should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

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

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

During the double-blind treatment period of the trial, subjects may be eligible for the addition of open label rescue medication (Insulin or other antidiabetic agents except GLP-1 analogs, other DPP4/SGLT2 inhibitors or metformin) to their blinded treatment regimen in order to treat ongoing hyperglycemia.

The sub-sections and table listed below define the lack of glycemic control criteria for initiation of rescue medication and subsequent dose titration of rescue medication.

3.5.1.1 Initiation of Rescue Medication

Pre-specified glycemic criteria (see Table 3.5.1.1), based upon central laboratory FPG and repeat, confirmatory FPG, have been established during the double-blind treatment period, starting at Week 6, and up to Week 24 visits, to determine eligibility for open label rescue medication.

Table 3.5.1.1: Lack of Glycemic Control Criteria for Initiation of Rescue Medication

Visit Label	Central Laboratory FPG
Week 6	FPG > 270 mg/dL (15.0 mmol/L)
After Week 6 to Week 12 (excluding Week 12)	FPG > 240 mg/dL (13.3 mmol/L)
Week 12 to Week 24	FPG > 200 mg/dL (11.1 mmol/L)

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

Subjects who meet rescue criteria in the double-blind treatment period must first complete the Rescue Visit procedures before receiving open-label rescue medication to ensure that important trial endpoint measurements are collected. (S**ee Section 5.8.3.1)**

Following completion of the Rescue Visit, rescued subjects will be given open-label antidiabetic rescue medication (Insulin or other antidiabetic agents except GLP-1 analogs, other DPP4/SGLT2 inhibitors or metformin) **to 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 double-blinded study medication. Rescued subjects will then continue in the double-blind treatment period according to their original visit schedule.

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

Following initiation of open-label rescue antidiabetic medication, rescued subjects should be scheduled for titration visits to increase their 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.

3.5.2 Discontinuation Guidelines due to Protocol-Defined Major Hypoglycemia Episode or Recurrent Non-Major Hypoglycemia Episodes

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

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

- Multiple occasions of episodes outlined below that, in the opinion of the Investigator, indicate that continued treatment with study therapy is not in the best interest of the subject. This includes, but is not limited to:
  - Symptoms suggestive of hypoglycemia (eg, sweating, shakiness, increased heart rate, confusion, dizziness, lightheadedness, or hunger) in the absence of environmental factors known to contribute to hypoglycemia (ie, excess physical activity, concurrent illness, or missed or delayed meal) **and/or**
  - Documented fingerstick glucose values ≤ 54 mg/dL (≤ 3.1 mmol/L).
- A subject may also be discontinued from the study due to severe hypoglycemia as determined by the Investigator.

Down titration of blinded study drug and/or background antihyperglycemic agent will not be allowed at any time during the study.

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

Section 5.3.1.1 provides additional guidance on management and reporting of hypoglycemia.

4 TREATMENTS

All protocol-specified investigational and noninvestigational products are considered study drug.

4.1 Study Treatments

Table 4.1: Product Description: Double Blind Treatment Period

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Dapagliflozin Tablet	10 mg	HDPE Bottle, 50 count tablets / PNL Double Blind	N/A	Green, plain, diamond shaped, film coated tablet	Store at 15-25 Degrees Celsius (59-77 Degrees Fahrenheit); Store in tightly closed container
Placebo for Dapagliflozin Tablet		HDPE Bottle, 50 count tablets / PNL Double Blind	N/A	Green, plain, diamond shaped, film coated tablet	Store at 15-25 Degrees Celsius (59-77 Degrees Fahrenheit); Store in tightly closed container
Saxagliptin Film Coated Tablet, 5 mg (as the free base)	5 mg	HDPE Bottle, 50 count tablets / PNL Double Blind	N/A	Plain, yellow, biconvex, round, film coated tablet	Store at 15-25 Degrees Celsius (59-77 Degrees Fahrenheit); Store in tightly closed container
Placebo for Saxagliptin Film Coated Tablets		HDPE Bottle, 50 count tablets / PNL Double Blind	N/A	Plain, yellow, biconvex, round, film coated tablet	Store at 15-25 Degrees Celsius (59-77 Degrees Fahrenheit); Store in tightly closed container
Metformin XR (metformin hydrochloride film-coated tablets) manufactured by Bristol-Myers Squibb	500 mg	HDPE Bottle, 100 count tablets / PNL Open Labeled		White to off-white, capsule shaped, biconvex tablets, with "BMS 6063" debossed on one side and "500" debossed across the face of the other side	Store at 20-25 Degrees Celsius (68-77 Degrees Fahrenheit). Dispense in light-resistant containers

4.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as follows:

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) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

In this protocol, investigational products (also described in Table 4.1) are: Dapagliflozin 10 mg and matching placebo tablets, saxagliptin 5 mg and matching placebo tablets, and metformin XR 500 mg tablets

4.1.2 Noninvestigational Product

Other medications used as support or escape 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.

Subjects who require rescue therapy for meeting the FPG rescue criteria shall receive open label insulin or other anti-glycemic medication (with the exception of GLP-1 analogs or other DPP-4/SGLT2 inhibitors or metformin) at the discretion of the investigator. Rescue medication will not be provided by the sponsor.

4.1.3 Handling and Dispensing

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.

The investigator should ensure that the investigational product is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor (see Table 4.1). If concerns regarding the quality or appearance of the investigational product arise, do not dispense the investigational product and contact the

sponsor immediately. Please refer to Section 9.2.2 for information on investigational product record retention and Section 4.6 for return and destruction instructions.

Storage facilities for controlled substances must be securely locked and substantially constructed, with restricted access to prevent theft or diversion, as applicable by local regulations.

4.2 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 five 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 participant.

Subjects who meet the criteria will be randomly assigned by IVRS to one of the following three double-blind treatment groups in a 1:1:1 ratio using a centralized blocked randomization schedule ratio into one of the following three blinded treatment arms:

- Saxagliptin 5 mg, dapagliflozin placebo, plus metformin XR
- Dapagliflozin 10 mg, saxagliptin placebo, plus metformin XR
- Saxagliptin 5 mg plus dapagliflozin 10 mg plus metformin XR

Randomization will be stratified by site. Randomization schedules for both subject treatment and containers will be generated and kept by Bristol-Myers Squibb and stored in a secure location with restricted access.

At all study visits when study medication is dispensed, each subject will be assigned a kit number by the IVRS. Kit numbers will be assigned randomly and will correspond to the numbers printed on the packages and kits containing study drug.

Kit numbers will be recorded on the appropriate eCRFs. The IVRS will be available 24 hours per day, 7 days per week.

4.3 Selection and Timing of Dose for Each Subject

Blinded Study Medication

Saxagliptin 5 mg tablets and matching placebo tablets, administered orally once daily for the 24-week double-blind treatment period. Saxagliptin 5 mg is the maximum

recommend daily dose as well as the usual daily dose. It is not currently labeled for triple therapy use in combination with dapagliflozin and metformin.

Dapagliflozin 10 mg tablets and matching placebo tablets administered orally once daily for the 24-week double-blind treatment period.

Dapagliflozin 10 mg is an investigational drug. Based on considerations of efficacy, pharmacodynamic, and safety data from the Phase 1 and 2 programs, daily doses up to 10mg of dapagliflozin have been chosen for the Phase 3 studies. The 10 mg dose was chosen for this study as it has been extensively studied in Phase 3 trials and is the dose expected to deliver the most favorable benefit:risk profile.

Open Label Metformin

Subjects entering the study on metformin IR will be switched to open-label metformin XR 500 mg tablets administered orally once daily with food at doses ≥ 1500 mg/day from the 4-week lead-in period. Subjects whose current therapy is not based on 500 mg metformin IR tablets will have their dose modified as noted in Appendix 4 and for the 24-week double-blind treatment period.

Subjects entering the study on metformin XR, whose current therapy is not based on 500 mg metformin XR tablets, will have their dose modified as noted in Appendix 4 for the lead-in period and for the 24-week double-blind treatment period.

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

4.4 Blinding/Unblinding

Blinding is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject, **in which knowledge of the investigational product is critical to the subject's management**, the blind for that subject may be broken by the treating physician.

Before breaking the blind of an individual subject's treatment, the investigator should have determined that the information is necessary, ie, that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not investigational product-related, the problem may be properly managed by assuming that the subject is receiving active product without the need for unblinding.

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

4.5 Treatment Compliance

Each time study medication is dispensed, compliance will be reinforced. When study medication is returned, compliance will be assessed based upon subject's interview and a count of the tablets returned. Compliance should be between ≥ 80% and ≤ 120%. The Investigator (or designee) will record the amounts of study medication dispensed and returned at each visit, as well as document reasons for non-compliance, in the source document. The dates of all study medication dosing, including interruptions, missed doses or overdose, must be recorded on the eCRF. If the subject is not > 80% compliant with recording study drug doses during the study the period of non compliance should be noted as a protocol deviation and the sponsor should be notified. The subject should be educated regarding recording these values.

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

If study drugs (those supplied by the sponsor or sourced by the investigator) are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor.

4.6.2 Return of Study Drug

Upon completion or termination of the study, all unused and/or partially used study drug that was supplied by the sponsor must be returned to BMS.

All study drug returned to BMS must be accompanied by the appropriate documentation and be clearly identified by protocol number and study site number on the outermost shipping container. Returned supplies should be in the original containers (eg, patient kits that have clinical labels attached). Empty containers should not be returned to BMS. 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. The return of unused study drug, those that were supplied by the sponsor, should be arranged by the responsible Study Monitor.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1: Flow Chart for CV181169

Procedure	Screening Period	Lead-In Period	Double-Blind Treatment Period Visit window ± 5days						Notes
	WK (-6)	WK (-4)	Day 1	WK 6	WK 12	WK 18	WK 24/ Study Termination	Rescue / Early Treatment Discontinuation	
Eligibility Assessments									
Obtain Informed Consent	X								
Review Medical History	X								
Review Eligibility Criteria	X								
Review Randomization Criteria			X						

Table 5.1: Flow Chart for CV181169

Procedure	Screening Period	Lead-In Period	Double-Blind Treatment Period Visit window ± 5days						Notes
	WK (-6)	WK (-4)	Day 1	WK 6	WK 12	WK 18	WK 24/ Study Termination	Rescue / Early Treatment Discontinuation	
General Procedures									
Brief Physical Examination		X	X	X	X	X			
Complete Physical Examination	X						X	X	
Body Weight	X	X	X	X	X	X	X	X	
Seated Blood Pressure and Heart Rate	X		X	X	X	X	X	X	
Height	X								
Body Mass Index (BMI)	X								
Waist Circumference	X		X				X		
12-Lead ECG			X				X*	X*	* Only 2 ECGs performed/subject. ECG is not required at Wk 24 if subject has been rescued or discontinued from treatment prior to Week 24

Table 5.1: Flow Chart for CV181169

Procedure	Screening Period	Lead-In Period	Double-Blind Treatment Period Visit window ± 5days						Notes
	WK (-6)	WK (-4)	Day 1	WK 6	WK 12	WK 18	WK 24/ Study Termination	Rescue / Early Treatment Discontinuation	
Review Concomitant Medications / Procedures	X	X	X	X	X	X	X	X	
Contact IVR system	X	X	X	X	X	X	X*	X**	* Call to register study termination only **Call at Rescue/ETD visit only if drug re-supply required.
Provide Diet and Exercise Counseling	X	X	X	X	X	X		X	
Provide Glucose Meter and Supplies / Instructions		X	X	X	X	X		X*	*Only if required
Provide logs / Instructions		X	X	X	X	X			
Review study logs			X	X	X	X	X	X	

Table 5.1: Flow Chart for CV181169

Procedure	Screening Period	Lead-In Period	Double-Blind Treatment Period Visit window ± 5days						Notes
	WK (-6)	WK (-4)	Day 1	WK 6	WK 12	WK 18	WK 24/ Study Termination	Rescue / Early Treatment Discontinuation	
Safety Assessment									
Assess Adverse Events, Hypoglycemia Episodes		X	X	X	X	X	X	X	
Central Laboratory									
Pregnancy Test (urine) WOCBP only	X	X	X	X	X	X	X	X	Home pregnancy test kits sent home with WOCBP to perform pregnancy tests between visits and record result in log book
Blood & Urine Standard Safety Laboratory Panels	X	X	X	X	X	X	X	X	
Dipstick Urinalysis (local)	X	X							Positive dipstick at Wk-4 will require repeat test with microscopy prior to randomization. (See Appendix 3)
Microscopic Urinalysis	X	X*			X		X	X	*Microscopic urinalysis only performed at Wk-4 if dipstick result is positive. (See Appendix 3)

Table 5.1: Flow Chart for CV181169

Procedure	Screening Period	Lead-In Period	Double-Blind Treatment Period Visit window ± 5days						Notes
	WK (-6)	WK (-4)	Day 1	WK 6	WK 12	WK 18	WK 24/ Study Termination	Rescue / Early Treatment Discontinuation	
Spot Urine Glucose Quantification and glucose:creatinine ratio			X		X		X	X	
HbA1C	X	X	X	X	X	X	X	X	
FPG	X	X*	X	X	X	X	X	X	*FPG must be >270 mg/dL. See section 3.3.1 for more details.
Assess FPG for Rescue				X	X	X		X	
Fasting C-Peptide	X								
MTT (Glucose, insulin, C-peptide, glucagon)			X				X*	X*	Subject must be fasted for at least 8 hrs prior to the MTT Subject must abstain from tobacco, alcohol and caffeine for at least 8 hrs prior to the MTT *Maximum of 2 MTTs performed/subject. MTT not conducted at Wk24 if subject has been rescued or discontinued from treatment prior to Wk 24.

Date: [redacted]

Table 5.1: Flow Chart for CV181169

Procedure	Screening Period	Lead-In Period	Double-Blind Treatment Period Visit window ± 5days						Notes
	WK (-6)	WK (-4)	Day 1	WK 6	WK 12	WK 18	WK 24/ Study Termination	Rescue / Early Treatment Discontinuation	
eGFR (MDRD) & Serum Creatinine (SCr)	X		X	X	X	X	X	X	
Fasting Serum Lipids (Total-C, LDL-C, HDL-C, TG)			X				X	X	
Hepatitis Screen Panel, TSH	X	X							
SDF-1 biomarker			X				X	X	
Drug Dispensing									
Dispense Study Medication		X*	X	X	X	X		X	*Only metformin XR dispensed at week -4.
Dispense, open-label rescue medication, as needed (if applicable				X	X	X		X	
Review Study Medication Compliance			X	X	X	X	X	X	

Date: [redacted]

5.2 Study Materials

BMS will supply the sites with the following materials:

- Blood glucose meters. One meter will be provided to each study subject at screening and one additional meter will be provided to each investigative site
- Blood glucose test strips
- Lancets
- Glucose control solutions
- Subjects logs for hypoglycemia episodes or events suggestive of hypoglycemia episodes reporting, as well as daily medication logs and pregnancy testing logs
- Electronic Case Report Forms (eCRFs).
- Patient education material and Site Support Tools
- Liquid Meal for Liquid Meal Tolerance Test (MTT)
- Study Drug logs
- Home pregnancy test kits

The central laboratory will provide all laboratory-related materials to the study site.

5.3 Safety Assessments

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

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

5.3.1 Self-Monitoring of Blood Glucose (SMBG)

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

The Sponsor recommends instructing the subjects to self-monitor their blood glucose at least one time per day, and in the occurrence of hypoglycemic symptoms, and to contact the Investigator in the event of an unusually high or low blood glucose value. In addition, study subjects should comply with site's instructions with regard to self-monitoring of blood glucose and should promptly report to the site blood glucose values and/or signs and symptoms suggestive of a hypoglycemia episode.

The memory of the glucose meter should be reviewed to compare 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.

5.3.1.1 Guidance on Management and Reporting of Hypoglycemia Episodes

Hypoglycemia may be an expected event in subjects who are treated for diabetes. Subjects and their family members must be aware of the possibility that hypoglycemia may occur and the dangers associated with low blood sugar.

Study subjects must be properly instructed on the recognition and management of hypoglycemia. Subjects should record in their logs any hypoglycemic symptoms. They should be encouraged to measure, when possible, their blood glucose values when they have symptoms of hypoglycemia. Subjects should carry with them easily ingestible forms of carbohydrate 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.

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, hypoglycemia episode or discontinuation due to hypoglycemia should not be reported on the AE eCRF page, unless the event fulfills protocol criteria for a Serious Adverse Event (see Section 6.1.1), in which case an SAE form must be completed in addition to the hypoglycemia eCRF pages for hypoglycemia.

5.3.2 Guidance on Assessment of Urinary Infections & Hematuria

5.3.2.1 Guidance on Assessment of Urinary Infections

The following is presented to assist in the classification and management of urinary tract infections. It is not intended to supplant investigators' clinical judgment:

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

It is recommended that a follow-up urine culture be obtained within 7 days of clinical recovery from all urinary tract infections. 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 Investigator's judgment and subject's medical history, related adverse events as defined in Section 6. Additional information, including but not limited to completion of supplemental eCRFs or questionnaires may be requested for certain adverse events and/or laboratory abnormalities which are reported/identified during the course of the study.

5.3.2.2 Guidance on Assessment of Hematuria

All events of hematuria (confirmed by microscopy) during the double blind phase of the study should be investigated according to local standards and best clinical practices for a possible cause. If an immediate or benign common cause is identified eg., menstruation, urinary tract infection (UTI) the cause should be treated and resolution be confirmed and documented with a microscopic urinary analysis (performed by central laboratory) at an unscheduled visit while the patient continues in the study (See appendix 3).

If **NO** common cause is identified, if a malignancy is otherwise suspected or positive hematuria (by microscopy) at the unscheduled repeat visit is found this should be captured on the nonserious AE CRF page or SAE page, as appropriate, (See section 6.3) and the supplemental hematuria CRF page, and patients should be further investigated based on American Urological Association (AUA) guidelines or equivalent local standard of care and best practices which could include referral to an urologist and undergoing evaluation that may include abdominal computed tomography (CT), urine cytology, and NMP-22 urine test. The patient should continue to receive investigational product treatment during these investigations (unless otherwise contraindicated).

It is the investigator's responsibility to report, as applicable based on Investigator's judgment and 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 Clinical Event Committee (CEC) blinded to the treatment of the subjects, will independently adjudicate certain cardiovascular adverse events, and they will operate in accordance with a dedicated Clinical Event Committee Charter/Manual of Operations.

Events related to the following will be sent to the CEC for adjudication:

- Death, including:
  - Cardiovascular Death
  - Non-cardiovascular Death
- Myocardial Infarction (MI), including:
  - ECG and/or cardiac enzymes confirmed MI
  - Sudden death
  - Percutaneous Coronary Intervention (PCI)-related MI
  - Coronary Artery Bypass Graft (CABG)-related MI
  - MI diagnosed via pathologic criteria
  - Silent MI

- Fatal and Non-fatal Stroke, including:
  - Ischemic Stroke
  - Hemorrhagic stroke
- Serious Adverse Events of the following:
  - Heart failure
  - Cardiac arrhythmia
  - Unstable angina
  - Unplanned arterial revascularization (coronary, carotid and peripheral)
  - Cardiac arrest with successful resuscitation
  - Deep vein Thrombosis and Pulmonary Emboli
  - Systemic non-stoke arterial embolism/thrombosis including systemic arterial occlusion
  - Non-traumatic amputation of the lower limb. Only events above the ankle will be considered for adjudication.

In order to provide the independent CEC with appropriate and adequate information for adjudication of the listed events, please consult the Reference Manual *Adjudication Reference Manual for Primary Investigators and Study Staff.*

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-induces liver injury (DILI) is the cause of liver-related abnormalities, included, but not limited to:

- Hepatic disorders leading to discontinuation from study treatment and/or death
- Liver laboratory abnormalities such as elevated AST and/or ALT with or without TB elevations

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

The following is presented to assist in the evaluation and management of hepatic laboratory values. It is not intended to supplant Investigators' 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 TB, including:
  - Use of suspect concomitant medication [including over-the-counter (ie acetominaphen/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 eCRF's, 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 the study medication as a result of sustained elevated liver safety abnormalities as described in Section 3.5, additional blood sampling must be done within 3 days of the confirmed laboratory results (see Appendix 5), in conjunction with an Early Treatment Discontinuation (End-of-Treatment) visit, in addition to the procedures noted above. A referral consultation to a hepatologist or gastroenterologist (specializing in liver abnormalities) should be obtained. Any additional tests and/or examinations should be carried out at the discretion of the Investigator. **Any further investigations and laboratory results for subjects with abnormal laboratory values at the follow-up visit should be made available to the Sponsor upon request.**

5.3.5 Physical Examination

- A brief physical examination should include cardiovascular, lungs, abdomen, and extremities, and any organ systems pertinent to the subject's signs, symptoms, or adverse events
- A full physical examination should include general appearance, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdomen, lymph nodes, extremities, neurological, skin, and musculoskeletal.

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

5.3.6 Blood Pressure and Heart Rate

Blood pressure (BP) and heart rate (HR) measurements must be taken consistently throughout the study. Only use either the right or the left arm when measuring these parameters. Document which arm was used along with the observer's initials; the same arm should be used for each position and at each visit. The subject should be allowed at least 5 minutes of rest before measurement. Seated 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.

Seated BP 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 3 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 blood pressure and heart rate measurements be obtained prior to the administration of blinded study medication.

5.3.7 Liquid Meal Tolerance Test (MTT)

MTTs are scheduled to occur at Day 1 visit and at Week 24 / Study Termination visit, or Rescue/ETD visit for subjects meeting criteria for rescue due to lack of glycemic control. A maximum of 2 MTTs will be performed per subject: one at the Day 1 visit and the other at either the Week 24 / Study Termination visit, or Rescue/ETD, whichever occurs first.

The MTT visit should be rescheduled within 3 days if the subject did not comply with all of the following:

- Subject fasted for at least 8 h prior to the visit
- Subject abstained from tobacco, alcohol, and caffeine for 8 h prior to the MTT.

Note: In the event more than 2 time points are missing from the Day 1 MTT, the Investigator should contact the Medical Monitor prior to proceeding with the Week 24 /

Study Termination visit, or Rescue/ETD, as there might be situations where the analysis cannot be performed in the absence of key time point expected to be obtained at Day1. In these situations, conducting a MTT at Week 24 / Study Termination visit, or Rescue/ETD may not be required.

At Day 1 (randomization), study medication is given within 2 hours AFTER MTT is complete.

- Insert saline lock, if appropriate
- Draw Time 0 blood sample for glucose, insulin, C-peptide and glucagon
- Administer the liquid meal supplement over 10 minutes, starting immediately after Time 0 blood sample is drawn
- Draw specimens for post-liquid meal glucose, insulin, C-peptide and glucagon at 30, 60, 120, and 180 minutes
- Give study medication within 2 hours **AFTER** MTT is complete.

At Week 24/Study Termination Visit (or at Rescue Visit/ETD visit), the study medication is given 1 hour BEFORE administration of the liquid meal supplement.

- Insert saline lock, if appropriate
- Draw Time -60 minutes BEFORE taking study medication
- Give study medication 1 hour BEFORE administration of the liquid meal supplement
- Draw Time 0 blood sample for glucose, insulin, C-peptide and glucagon
- Administer the liquid meal supplement over 10 minutes, starting immediately after Time 0 blood sample is drawn
- Draw specimens for post-liquid meal glucose, insulin, C-peptide and glucagon at 30, 60, 120, and 180 minutes.
- Remove saline lock.

In the event an MTT is performed during the course of a Rescue visit, first dose of rescue medication should be taken after completion of the MTT.

5.3.8 Supplemental Visits

5.3.8.1 Rescue or Early Treatment Discontinuation Visit

Subjects rescued during or discontinued from the Double-Blind Treatment Period

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

- For subjects qualifying for rescue **PRIOR** to Week 24, Rescue/ETD procedures will be performed and the subject will then continue in the study according to the regular visit schedule. The Rescue/ETD supplemental eCRF will need to be completed to collect Rescue related endpoint data. A WK24/Rescue/ETD visit laboratory kit will need to be used to collect Rescue Visit blood and urine samples
- Subjects who discontinue study medication during the double-blind treatment period should have all ETD procedures performed (Rescue/ETD visit). The Rescue/ETD supplemental eCRF will also need to be completed and a Week 24/Rescue/ET visit laboratory kit will need to be used to collect ETD Visit blood and urine samples. The subject will then continue in the study according to the regular visit schedule.

5.3.8.2 Other Supplemental (Unscheduled Visits)

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

5.4 Efficacy Assessments

Efficacy assessments consist of the central laboratory measurement of the HbA1C during the treatment period and the FPG, 2-hour post-liquid meal plasma glucose, insulin, C-peptide and glucagon throughout the treatment period.

Other efficacy assessments will also include the mean change from baseline in body weight at Week 24 with the addition of saxagliptin and dapagliflozin to metformin vs. the addition of placebo and saxagliptin to metformin.

5.5 Pharmacokinetic Assessments

Not applicable.

5.6 Biomarker Assessments

Blood will be collected on Day 1 and Week 24 to assess the effects of saxagliptin and dapagliflozin added to metformin after 24 weeks of double-blind treatment on stromal cell-derived factor-1 (SDF-1), a chemokine related to cardiovascular disease which attracts endothelial progenitor cells and induces angiogenesis..

5.7 Outcomes Research Assessments

Not applicable.

5.8 Other Assessments

5.8.1 Diet and Exercise Counseling

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

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

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

5.8.2 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.
- 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 .05 or greater, round up)

5.8.3 Waist Circumference

The waist circumference measurements will be performed at various time points during the course of the study (refer to Table 5.1). They will be measured by placing a measuring tape midway between the lower rib and iliac crest. The measuring tape should pass over the umbilicus. The waist measurement reported on the eCRF should represent the average of at least 2 measurements. The average measurement should agree with 1 cm. If not, additional measurement(s) should be taken.

5.8.4 Survey of Subject Vital Status

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

5.9 Results of Central Assessments

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

During the lead-in and double-blind treatment periods, the HbA1C, plasma glucose and insulin MTT values, and the urinary glucose values, including the urinary glucose:creatinine ratio will be masked to the Investigator and to the Sponsor. These values will be provided to the Investigator after the study has been completed.

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject

administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

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 ***serious AE (SAE)*** is any untoward medical occurrence that at <u>any dose</u>:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

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

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or event life threatening)
- 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 for purpose other than remedying ill health state and was 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, care-giver respite, family circumstances, administrative).

6.1.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure. An SAE report should be completed for any event where doubt exists regarding its status of 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 BMS (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: See Contact Information list.

SAE Facsimile Number: See Contact Information list.

For studies capturing SAEs/pregnancies 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): See Contact Information list.

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

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

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious 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.

Nonserious 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 nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

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

See Section 6.7.1; regarding the collection and reporting of non-serious events necessary to meet the postmarketing commitments required by the FDA.

6.3 Laboratory Test Abnormalities

The following laboratory abnormalities should be captured on the nonserious AE CRF page or SAE Report Form as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy.
- Any microscopic hematuria with **NO** common cause identified, if a malignancy is otherwise suspected or positive hematuria (by microscopy) at the unscheduled repeat visit (See section 5.3.2.2 & appendix 3)

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

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

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

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

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

6.5 Overdose

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

6.6 Potential Drug Induced Liver Injury (DILI)

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 DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 and Appendix 5 for more details).

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

6.7.1 AE's of Special Interest

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

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

Liver test abnormalities accompanied by jaundice or hyperbilirubinemia

This category of events includes all AEs where hepatocellular damage (with elevation of ALT or AST > 3 times the upper limit of normal) is combined with hepatic dysfunction (with elevation of total bilirubin > 2.5 times upper limits of normal) 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 multidermatomal, neurological 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 four categories, notify the Medical Monitor within 24 hours to discuss next steps in reporting.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

7.1 Cardiovascular Adjudication Committee

An Independent Adjudication Committee, blinded to the treatment of the subjects, will classify cardiovascular adverse events, such as, but not limited to, death, myocardial infarction, and stroke reported in the study. A separate Adjudication Manual will define and describe the procedure for the handling, reporting and classification of these events.

Please also refer to Section 5.3.3.

7.2 Hepatic Adjudication Committee

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

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

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The mean change from baseline in HbA1c at Week 24 will be assessed comparing the saxagliptin 5 mg plus dapagliflozin 10 mg add-on to metformin treatment group versus each of the two monotherapy add-on treatment groups (dapagliflozin 10 mg plus placebo added to metformin and saxagliptin 5 mg plus placebo added to metformin). The min test approach of Laska and Meisner [5] will be implemented to test the simultaneous addition of saxagliptin and dapagliflozin to metformin versus each of the individual add-on components plus placebo. Statistical significance of the primary endpoint will be claimed if the p-values for both comparisons are significant at the 2-sided, 0.05 significance level.

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

With 163 subjects per treatment group, there will be 90% power to detect a difference in mean HbA1c of 0.4% between the saxagliptin plus dapagliflozin mg added to metformin treatment group and each of the monotherapy add-on groups, assuming a standard deviation of 1.0%. Assuming that 5% of subjects do not have a post-baseline assessment, a total of approximately 516 subjects (172 subjects per treatment arm) need to be randomized.

Assuming that 50 % of screened subjects will fail to meet screening criteria, a total of 1032 subjects need to be screened.

8.2 Populations for Analyses

- The Enrolled Subjects Data Set will consist of all subjects who sign informed consent.
- The Randomized Subjects Data Set will consist of all randomized subjects who receive at least one dose of study medication during the double-blind treatment period. This is also known as the Intent to Treat (ITT) population. This will be the primary efficacy data set. Data in this data set will be analyzed based on randomized treatment group.
- The Evaluable Subjects Data Set will be a subset of the Randomized Subjects, with all data points collected after a relevant protocol deviation excluded from the data set. Relevant protocol deviations are defined as deviations that could potentially affect the interpretability of the study results. This is also known as the Per-protocol population. This data set will be used for sensitivity analyses of the primary efficacy endpoint if > 10% of subjects in any treatment group have relevant protocol deviations.
- The Treated Subjects Data Set will consist of all subjects who receive at least one dose of study medication during the double-blind treatment period. This will be the primary safety data set. Data in this data set will be analyzed based on randomized treatment, except in cases where a subject received a different treatment for the entire course of his/her participation in the double-blind treatment period. In this case, safety data for such a subject will be analyzed based on the first treatment the subject actually received.

8.3 Endpoint Definitions

8.3.1 Primary Efficacy Endpoint

- Mean change from baseline in HbA1c at Week 24

8.3.2 Secondary Efficacy Endpoints

- Mean change from baseline in 2-hour post-prandial glucose during a liquid meal test (2-h MTT) at Week 24
- Mean change from baseline in fasting plasma glucose (FPG) at Week 24
- Percent of subjects achieving a therapeutic glycaemic response, defined as a HbA1c < 7.0% at Week 24
- Mean change from baseline in body weight at Week 24 with the addition of saxagliptin and dapagliflozin to metformin vs. the addition of placebo and saxagliptin to metformin.

8.3.3 Exploratory Endpoints

- The percent of subjects who require glycemic rescue or discontinue study treatment for lack of efficacy up to Week 24.
- Time to glycemic rescue or discontinuation for lack of efficacy in the double-blind treatment period.
- Mean change from baseline in AUC glucose, AUC insulin, AUC C-peptide and AUC glucagon obtained during MTT at Week 24.
- Mean percent change from baseline in fasting serum lipids (Total-C, LDL-C, HDL-C, TG) during the double-blind treatment period.

8.4 Analyses

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

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized using frequency distributions and descriptive statistics using the Randomized Subjects data set, for each treatment group as well as for all subjects combined. Key baseline characteristics that will be summarized include: age, gender, race, ethnicity, geographic region, body weight, body mass index (BMI), duration of type 2 diabetes, baseline HbA1c, baseline FPG, 2-hour post-prandial glucose during a liquid meal test, metformin formulation at

screening, and metformin daily dose. Baseline is defined as the last measurement prior to the first dose of double-blind study medication. No statistical tests will be performed to compare treatment groups at baseline. Additional analyses will be performed using available data.

8.4.2 Efficacy Analyses

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

8.4.2.1 Primary Efficacy Analysis

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

Sensitivity analyses for HbA1c will include additional repeated measures analyses and analysis of covariance (ANCOVA) analyses. The repeated measures analyses will include two separate analyses including values after rescue, including and excluding a time-dependent covariate for rescue. Two separate ANCOVA analyses of the change from baseline at Week 24 will be performed, with terms for treatment group and baseline value in the model. One analysis will be based on measurements at Week 24 (if prior to rescue, if applicable) or the last post-baseline measurement prior to Week 24 and prior to rescue (if applicable), if no Week 24 assessment is available (ie. last observation carried forward [LOCF]). The second sensitivity analysis using ANCOVA will be based on all subjects completing the short-term double-blind period without requiring glycemic rescue therapy.

8.4.2.2 Secondary Efficacy Analyses

In order to protect the overall type I error rate, the interpretation of the statistical significance of treatment comparisons for each secondary efficacy endpoint will be done using a step-wise procedure. The secondary endpoints will be tested in the order in which they are listed in Section 8.3.2.

The analysis of the mean change from baseline at week 24 for 2-hour post-prandial glucose during a liquid meal test (2-h MTT) will be based on an ANCOVA model using LOCF methodology with terms for treatment group and baseline value in the model. Analyses of the mean change from baseline at week 24 for FPG, and total body weight will be performed using the same longitudinal repeated measures model as for the primary efficacy endpoint. The analysis of total body weight will compare the saxagliptin 5 mg plus dapagliflozin 10 mg add-on to metformin treatment group versus the saxagliptin 5 mg plus placebo added to metformin group only. Sensitivity analyses for FPG and total body weight will consist of ANCOVA analyses using LOCF methodology.

The proportion of subjects achieving a therapeutic glycemic response (defined as HbA1c < 7.0%) at Week 24 (LOCF) will be summarized by treatment group and compared between treatment groups using the methodology of Zhang, Tsiatis, and Davidian[6] and Tsiatis, Davidian, Zhang, and Lu[7] 95% confidence intervals for the response rate within each treatment group as well as for the difference in response rates between treatment groups will be calculated with adjustment for baseline HbA1c.

8.4.2.3 Other Efficacy Analyses

The percent of subjects who require glycemic rescue or discontinue study for lack of efficacy up to Week 24 will be assessed by summarizing the difference in percentages between treatment groups and by a time to event analysis using the Kaplan-Meier methodology.

Analyses of the mean change from baseline for continuous endpoints (AUC glucose, AUC insulin, AUC C-peptide and AUC glucagon obtained during a 2-h MTT) will be performed using the same longitudinal repeated measures model as for the primary efficacy endpoint. The percent change from baseline in lipids at Week 24 will be analyzed using a longitudinal repeated measures analysis of the logarithms of the post- to pre-treatment ratios with terms for treatment group, time, interaction of treatment and time, the natural logarithm (Ln) of the baseline measurement, and the interaction of Ln (baseline) and time the logarithms of the post-treatment to baseline ratios with terms for treatment group and the log of the baseline measurement as a covariate.

Values and changes from baseline at each scheduled time point for clinical laboratory parameters, body weight, and vital signs, including seated blood pressure and heart rate, will be summarized by treatment group using descriptive statistics.

8.4.3 Safety Analyses

The number and percent of subjects with at least one adverse event will be summarized for each treatment group, including summaries of AEs, SAEs, AEs leading to discontinuation, and AEs of special interest. Summaries will include the number of subjects with events by specified system organ classes and preferred terms.

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

Values and changes from baseline at each scheduled time point for clinical laboratory parameters and vital signs, including seated blood pressure and heart rate, will be summarized by treatment group using descriptive statistics. The normality/abnormality of electrocardiogram (ECG) tracings, as determined by the investigator, will be summarized by shift tables overall and by ECG tracing at baseline. The number and percent of subjects with laboratory values meeting marked abnormality criteria will be summarized for each treatment group. Other safety assessments including serum creatinine and eGFR by MDRD, will be summarized by treatment group using descriptive statistics of values and changes from baseline at each scheduled time point.

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

8.4.4 Pharmacokinetic Analyses

Not applicable

8.4.5 Biomarker Analyses

The exploratory biomarker measurements of SDF-1 will be summarized with descriptive statistics by treatment. Further analyses will be discussed in a separate Statistical Analysis Plan.

8.4.6 Outcomes Research Analyses

Not applicable

8.4.7 Other Analyses

Not applicable

8.5 Interim Analyses

Not applicable

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. 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
- Bristol-Myers Squibb
- 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.

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 screening.

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

9.1.2 Monitoring

Representatives of BMS 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.

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

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.3 Investigational Site Training

Bristol-Myers Squibb 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 screening of WOCBP.

9.2 Records

9.2.1 Records Retention

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

BMS 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.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by the sponsor is maintained at each study site

where study drug is inventoried and dispensed. 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 ID number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to the sponsor
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product (IP) dispensing/accountability, as per the Delegation of Authority Form.

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

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

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

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

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

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by a qualified physician who is an investigator or subinvestigator. For electronic CRFs, review and approval/signature is completed electronically through the BMS 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 training requirements and must only access the BMS electronic data capture tool using the unique user account provided by the sponsor. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

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

For this protocol, the Signatory Investigator will be selected considering the following criteria:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

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

have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or the sponsor as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)

11 LIST OF ABBREVIATIONS

HbA1c	Glycosylated hemoglobin
ADA	American Diabetes Association
AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
AM or am	Morning (ante meridian)
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUA	American Urological Association
AUC	Area under the curve
BMI	Body mass index
BMS	Bristol-Myers Squibb
BP	Blood pressure
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CDC	Center for Disease Control
CHF	Congestive heart failure
CK	Creatine Kinase
Cm	Centimeter
Cmax	Concentration maximal
CRF(s)	Case Report Form(s)
DBP	Diastolic Blood Pressure
DILI	Drug Induced Liver Injury
dl	Deciliter
DPP4	Dipeptidyl Peptidase 4 inhibitors
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture

eg	exempli gratia (for example)
ETD	Early Treatment Discontinuation
FDA	Food and Drug Administration
FFA	Free fatty acids
FPG	Fasting plasma glucose
FSH	Follicle stimulating hormone
g	Gram
GI	Gastrointestinal
GCP	Good Clinical Practice(s)
HCG	Human Chorionic Gonadotropin
HCTZ	Hydrochlorothiazide
HDL-C	High-density lipoprotein cholesterol
HOMA	Homeostasis model assessment
HR	Heart Rate
hr(s) or h	Hour(s)
HRT	Hormone replacement therapy
ICH	International Council on Harmonization
ie	id est (that is)
IEC(s)	Independent ethics committee(s)
INF	Infinity
IRB(s)	Institutional Review Board(s)
IU	International Units
IVRS	Interactive Voice Response System
kg	Kilogram
L	Liter
lb	Pound
LDL-C	Low density lipoprotein cholesterol
LOCF	Last observation carried forward

m	Meter
max	Maximum
MCH	Mean cell hemoglobin
MCHC	Mean cell hemoglobin concentration
MCV	Mean cell volume
MDRD	Modification in Diet and Renal Disease
min	minute
mg	Milligram
Mg	Magnesium
ml	Milliliter
mmHg	Millimeters of mercury
mmol	Millimole
MTT	Liquid meal tolerance test
N/A	Not Applicable
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
nmol	Nanomole
NOAEL	No-Observed-Adverse-Effect Level
NYHA	New York Heart Association
OL	Open-Label
OGTT	Oral glucose tolerance test
PAI-1	Plasminogen Activator Inhibitor 1
pH	Symbol for the negative logarithm of the H+ ion concentration
PK	Pharmacokinetics
PM or pm	Afternoon (or post meridian)
PP-C-peptide	Postprandial C-peptide
PPG	Post-prandial glucose
PTCA	Percutaneous Transluminal Coronary Angioplasty

RBC	Red Blood Cells
SA	Sickle cell trait
SAE(s)	Serious adverse event(s)
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDF-1	Stromal cell-derived factor-1
SMBG	Self -monitoring of blood glucose
Scr	Serum Creatinine
SGLT(s)	Sodium glucose transporter(s)
SGLT1	Sodium-dependent glucose transporter 1
SGLT2	Sodium-dependent glucose transporter 2
SU	Sulfanylureas
T1/2	Mean Terminal Half-Life
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
TG	Triglycerides
TIA	Transient Ischemic Attack
Tmax	Time to maximal concentration
Total-C	Total cholesterol
TSH	Thyroid Stimulating Hormone
TZD	Thiazolidinedione
U	Units
U/A	Urinalysis
UACR	Urine albumin creatinine ratio
ULN	Upper limit normal
µmol	Micromole
US	United States

WK	Week
WOCBP	Women of childbearing potential

Date: [redacted]

12 REFERENCES

1 Rodbard HW, Jellinger PS, Davidson JA, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on Type 2 Diabetes Mellitus: An Algorithm for Glycemic Control. American Association of Clinical Endocrinologists (AACE/ACE) Consensus Statement, Endocr Pract. 2009; 15:540-559.

2 Hoeger, TJ, et al., Is Glycemic Control Improving in U.S. Adults? Diabetes Care 31(1):81-86, 2008

3 Nguyen, NT, at al., Relationship Between Obesity and Diabetes in a US Adult Population: Findings from the National Health and Nutrition Examination Survey, Obes Surg 21:351-355, 2011.

4 Study D1690C00010 Report: A 24 Week, Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group International Phase III Study with a 24-week Extension Period to Evaluate the Safety and Efficacy of Dapagliflozin 10 mg Daily in Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on a DPP-4 inhibitor (Sitagliptin) Alone or in Combination with Metformin. 2012. 24 Weeks. Bristol-Myers Squibb and Astra Zeneca. Document Control Number 930056628

5 Laska EM, Meisner MJ. Testing whether an identified treatment is best. Biometrics 1989; 45(4): 1139-1151.

6 Zhang M, Tsiatis A, Davidian M. Improving efficiency of inference in randomized clinical trials using auxiliary covariates. Biometrics. Published online on January 11, 2008; Digital Object Identifier: 10.1111/j.1541-0420.2007.00976.x

7 Tsiatis A, Davidian M, Zhang M, et al. Covariate adjustment for two-sample treatment comparisons in randomized clinical trials: a principled yet flexible approach. Statistics in Medicine. Published online 2007; Digital Object Identifier: 10.1002/sim.3113

APPENDIX 1 NEW YORK HEART ASSOCIATION FUNCTIONAL CLASS

I. Patients without limitation of physical activity. Ordinary activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

II. Patients with slight limitation of physical activity who are comfortable at rest. Ordinary activity results in palpitation, dyspnea, or fatigue.

III. Patients with marked limitation of physical activity. Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.

IV. Patients with inability to carry on any physical activity without discomfort. Symptoms may be present at rest.

APPENDIX 2 CENTRAL LABORATORY ASSESSMENTS

Blood and urine samples will be obtained at specified time points for laboratory evaluations. The central laboratory for this study will perform the analysis of all scheduled laboratory tests and will provide reference ranges for these tests. All samples for clinical laboratory testing must be collected in the morning after the subject has fasted for at least 8 hours prior to collection. The detailed methods for specimen collection, handling, processing, shipping, and storage will be supplied in the Investigator's Laboratory Manual provided by the Central Laboratory. All clinical laboratory tests will be performed by the Central Laboratory or designated reference laboratory.

During the lead-in and double-blind treatment periods, the HbA1C, plasma glucose and insulin MTT values, and the urinary glucose values, including the urinary glucose:creatinine ratio will be masked to the Investigator and to the Sponsor. These values will be provided to the Investigator after the study has been completed.

The following sections indicate the laboratory tests required for this study. For countries using conventional units, the results will be reported using conventional units. For countries using SI units, the results will be reported using SI units. In cases of differences in the units as listed in this protocol compared to the units on the central laboratory reports, the units from the central laboratory reports will be used.

PROTOCOL-SPECIFIC CENTRAL LABORATORY ASSESSMENTS:

- HbA1C (%, mmol/mol)
- FPG (mg/dL, mmol/L)
- Fasting C-peptide (ng/mL, nmol/L)
- Fasting serum lipid profile:
  - Total-C (mg/dL, mmol/L)
  - Calculated LDL-C (mg/dL, mmol/L)
    - *Except screening period, reflex testing will occur for Direct LDL-C if TG > 400 mg/dL (4.52 mmol/L)*
  - HDL-C (mg/dL, mmol/L)
  - TG (mg/dL, mmol/L)
- 2-hour post meal plasma glucose, glucagon and C-peptide

Enrollment-Specific Safety Panel

- Thyroid Stimulating Hormone (TSH)
  - ♦ *Reflex Testing: Abnormal TSH value at enrollment will be further evaluated by free T4.*
- Hepatitis Screen Panel:
  - Anti-hepatitis C virus antibody
    - ♦ *Reflex Testing: HCV Ab positive results will be confirmed by HCV RIBA or HCV RNA*
  - Hepatitis B surface antigen

Specialized Liver Panel:

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

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

Liver Discontinuation Panel:

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

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

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

Biomarkers

- SDF-1

Standard Safety Laboratory Panels:

Table Appendix 2: Standard Safety Laboratory Panels

Hematology
• Hemoglobin (g/dL, g/L) • Hematocrit (%, V/V) • Red blood cell (RBC) ($x10^6$/UL, $x10^{12}$/L) *RBC count indices:* • Mean Cell Volume (MCV) (fL) • Mean Cell Hemoglobin (MCH) (pg/cell) • Mean Cell Hemoglobin Concentration (MCHC) (gHb/dL, gHb/L) • White blood cell Count and Differential • Platelet count ($x10^9$/L)
Serum Chemistry
• AST (IU/L)

Table Appendix 2: Standard Safety Laboratory Panels

- ALT (IU/L)
- ALK-P (IU/L)
- CK/CPK (IU/L). *Reflex Testing: Troponin I will be ordered if CK > 400 IU/L).*
- Total Bilirubin (mg/dL, μmol/L)
- Serum Creatinine (mg/dL, μmol/L). Glomerular Filtration Rate will be calculated by the Central Laboratory using the re-expressed abbreviated (four-variable) Modification in Diet and Renal Disease (MDRD) formula and results will be reported to the sites and the Sponsor. (*Levey AS, Coresh J, Greene T, et al. Expressing the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate with Standardized Serum Creatinine Values. Clinical Chemistry 2007; 53: 766-72*).
- Sodium (mEq/L, mmol/L)
- Potassium (mEq/L, mmol/L)
- Chloride (mEq/L, mmol/L)
- Calcium (mg/dL, mmol/L)
- Magnesium (mEq/L, mmol/L)
- Phosphorus (mg/dL, mmol/L)
- Total Protein (g/dL, g/L)
- Albumin (g/dL, g/L)
- Uric acid (mg/dL, μmol/L)

Urine Analyses

- Creatinine
- Calculated Urinary albumin:creatinine ratio (UACR)
- Urine HCG pregnancy test for WOCBP (HCG minimum sensitivity of 25 IU/L; performed at site or at home). *If a urine HCG test is positive, a blood specimen will be obtained and a serum pregnancy test will be performed by the central laboratory for confirmation.*

In addition to the above assessments, Day 1 and Week 24, Rescue/ETD visits will include the following assessments (spot urine):

- Glucose
- Urinary glucose:creatinine ratio

In addition to the above assessments, screening, Week -4, Week 12 and Week 24/Rescue/ETD visits will include the following assessments (urinalysis with microscopy):

- Hematuria

APPENDIX 3 ALGORITHM FOR MICROSCOPIC HEMATURIA

Interpretable microscopic hematuria is defined as ≥ 3 RBC/HPF without the presence of epithelial cells. Urine samples that are positive for hematuria WITH the presence of epithelial cells are not interpretable and must be repeated. For this study, the presence of epithelial cells is defined as ≥ 1+ as reported by the central laboratory.

Dipstick Urinalyses (U/A) must be evaluated at the screening visit (Week -6) and lead-in (Week -4) visit.

Microscopic Urinalyses (U/A) at central laboratory must be evaluated at the screening visit (week -6), Week 12 and Week 24 visits. Microscopic U/A will be evaluated at week -4, only if dipstick U/A is positive.

Screening evaluation

To be eligible for the study, male subjects with evidence of microscopic hematuria at week -6 or -4 must have confirmed evidence of common causes and a documented negative microscopic urinalysis.

***NOTE**: Common causes of microscopic hematuria should be checked at the time of sample collection. Common causes of microscopic hematuria include menstruation, vigorous exercise, sexual activity, urinary tract infection, kidney stones or trauma. If a common cause of microscopic hematuria is identified, at least 48 hours should be allowed after resolution of the cause, prior to repeating the U/A. A U/A following a urinary tract infection should occur no sooner than 48 hours AFTER the last dose of antibiotic. A U/A should occur no sooner than 48 hours AFTER the last day of menses*

If dipstick hematuria is present on the week -4 dipstick U/A, a microscopic evaluation at the central laboratory for microscopic hematuria must be performed. If the microscopic urinalysis is negative for hematuria, the subject may be enrolled into the study. (See section 5.3.2.2).

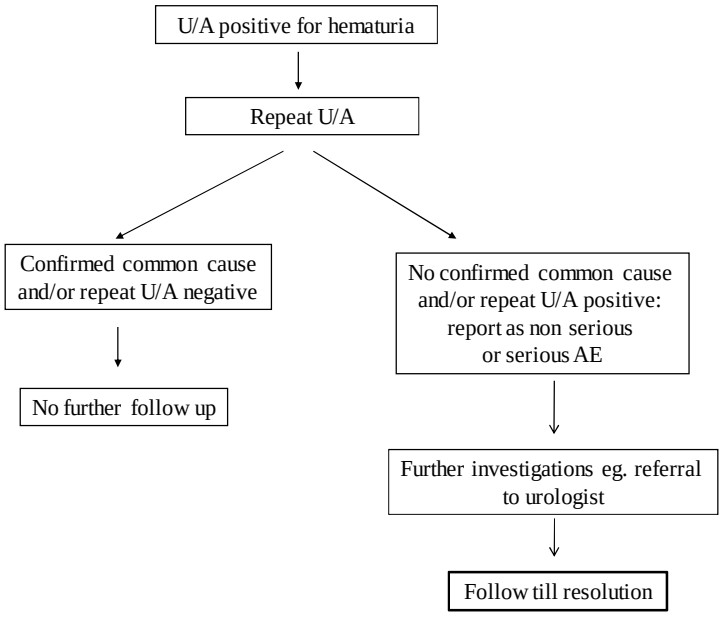
Female subjects with hematuria can be randomized, but should be investigated according to local standards and best clinical practices (see also the following paragraph for Double-blind treatment and Site and Subject blinded periods).

Double-blind treatment period Week 12 and 24 visits

If the microscopic urinalysis shows **evidence of microscopic hematuria** the algorithm below must be followed.

If **NO** common cause is identified, if a malignancy is otherwise suspected or positive hematuria (by microscopy) at the unscheduled repeat visit is found this should be captured on the nonserious AE CRF page or SAE page, as appropriate, and the supplemental hematuria CRF page (See section 6.3).

Algorithm for Protocol Specified Tests for Hematuria after Enrollment



APPENDIX 4 DOSES OF METFORMIN THERAPY

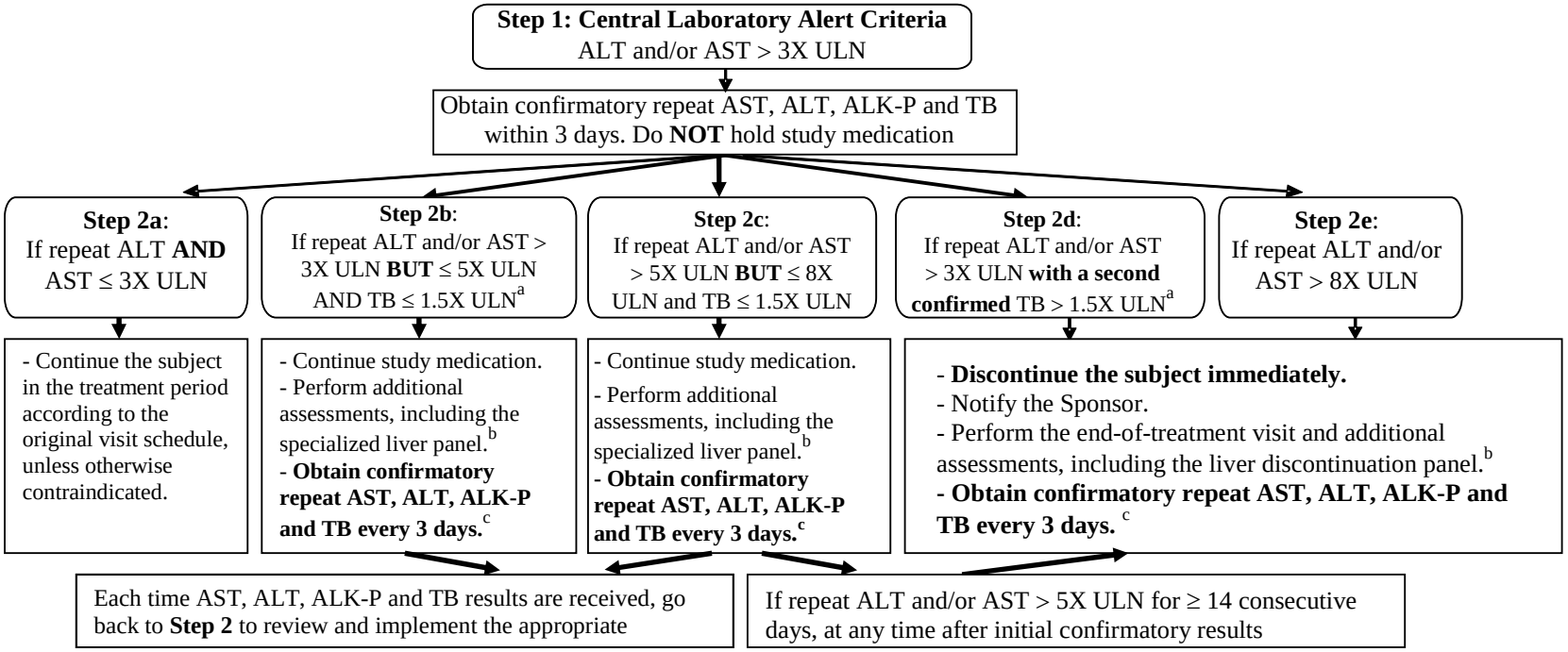
The following guideline is to be used to modify metformin (Trade name Glucophage®) therapy for the open-label drug supply with metformin 500 mg tablets.

Table Appendix 4: DOSES OF METFORMIN THERAPY

Metformin (IR or XR) dose as established at Screening	Open-Label Metformin XR dose during the study
1500 - 1700 mg	1500 mg (3 tablets)
1701 - 3000 mg	2000 mg (4 tablets)

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

APPENDIX 5 SUSTAINED ELEVATED LIVER SAFETY ABNORMALITIES FLOW CHART



[a] In subjects with repeat ALT or AST > 3X ULN but ≤ 8X ULN, only subjects with TB ≤ 1.5X ULN at Step 1 should be followed according to Step 2b. Subjects with an initial TB and confirmatory repeat TB > 1.5X ULN should be followed according to Step 2d.

[b] Refer to section 5.3.4 for details on additional assessments to be performed (AE assessment, PE, review of current medical history including focused review of risk factors for liver diseases and collection of blood samples [specialized liver panel or liver discontinuation panel]).

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

Date: [redacted]