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Clinical Protocol MB102013

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin as Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control with Diet and Exercise

Revised Protocol Number: 02
Incorporates amendment(s) 04

Central Medical Monitor
[redacted]

Clinical Protocol Manager
[redacted]

24-hr Emergency Telephone Number
USA: [redacted]
International: [redacted]

Bristol-Myers Squibb Research and Development
[redacted]

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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 02	[redacted]	Incorporates Amendment 04
Amendment 04	[redacted]	The purpose of this amendment is to modify the discontinuation guidelines for subjects rescued during the short-term treatment period. 1) Adjustments to the secondary objectives for the study (addition of a new objective and the removal of another). 2) The clarification in secondary analyses. 3) Administrative changes that resulted from the change to discontinuation criteria for short-term rescued subjects. 4) Clarification of verbiage in Section 1.5 Overall Risk/Benefit Assessment 5) Clarification of verbiage in Section 6.3.2 Guidance on Assessment of Urinary and Genital Infections. 6) Additional changes to the sponsor's protocol template.
Revised Protocol 01	[redacted]	Incorporates Amendment 03
Amendment 03	[redacted]	The purpose of this amendment is to modify selected exclusion criteria to allow the evaluation of a more representative population of subjects, to incorporate additional measures of safety, and to address comments received by the United States Food and Drug Administration (FDA). 1) Change exclusion criteria for AST/ALT from 2.5X ULN to 3X ULN. 2) Change exclusion criteria for CK from ≥ 3X ULN to > 3X ULN. 3) Exclusion criteria related to history of chronic hemolytic anemia will be modified to not exclude sickle cell trait, thalassemia minor; or chronic or recurrent hemolysis. 4) Exclusion criteria related to unstable dose of teriparatide (Forteo®), bisphosphonates and/or calcitonin will be removed. 5) Exclusion criteria will be added for history of bariatric surgery or lap band procedure. 6) Measurement of 25-hydroxy vitamin D will be added at Day 1, Week 24, Week 50 and Week 102. 7) Discontinuation criterion related to major

Document	Date of Issue	Summary of Change
		hypoglycemia episodes will be modified to include provision for subjects with recurrent non-major hypoglycemia episodes. 8) Discontinuation criteria related to AST, ALT and TB values will be specified. 9) A discontinuation criterion will be added for elevated CK values. 10) A discontinuation criterion related to hyponatremia will be added. 11) An independent Adjudication Committee, blinded to the treatment of individual subjects, will be implemented to classify cardiovascular events. 12) The protocol section providing guidance on the assessment of urinary and genital infections will be modified to include a recommendation for the Investigator's proactive inquiry for urinary and/or genital infections. 13) Subjects who receive rescue medication during the short-term treatment period will be discontinued from the study when they reach Week 24, and will not be eligible to enter the long-term treatment period. 14) Change medical monitor and contact information from [redacted] to [redacted] and change if fax number for protocol manager. 15) Clarification of the criteria for safety monitoring of serum creatinine. 16) Clarification of the criteria for discontinuation due to lack of glycemic control. 17) Clarification of one secondary objective and one exploratory objective. 18) Clarification on protocol-allowed re-test of central laboratory A1C and/or calcium value(s) obtained at the enrollment visit. 19) Clarification of the number of tablets per bottle of study medication. 20) The deletion of the 30 day window related to the collection of enrollment laboratory samples related to Day 1 visit. 21) Additional guidance related to self-monitoring of blood glucose. 22) Clarification to the analysis section in regard to the A1C value. 23) Additional guidance related to diet and exercise counseling as it relates to calcium intake.

Document	Date of Issue	Summary of Change
		24) Update to SAE contact information. 25) Clarification of the formula used by the central laboratory for the assessment of the glomerular filtration rate. 26) Addition of Appendix 5, hyponatremia algorithm 27) Correction of the original protocol issue date in the document history section. 28) Correction of typographical errors.
Original Protocol	[redacted]	Not Applicable

SYNOPSIS

Clinical Protocol MB102013

Title of Study: Protocol MB102013: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin as Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control with Diet and Exercise

Estimated Number of Study Centers and Countries/Regions: Approximately 100 sites in USA, Canada, Mexico and Russia.

Study Phase: 3

Research Hypothesis: After 24 weeks of oral daily administration, there will be a greater mean reduction from baseline in glycosylated hemoglobin (A1C) achieved with dapagliflozin AM dosing compared to placebo in drug naive subjects with type 2 diabetes who have inadequate glycemic control with diet and exercise.

Primary Objective: To compare the change from baseline in A1C achieved with each dapagliflozin AM dosing treatment group versus placebo, after 24 weeks of oral administration of double-blind treatment

Study Design: The MB102013 trial is a randomized, double-blind, seven arm, parallel group, placebo-controlled, multicenter trial. Subjects with enrollment A1C ≥ 10.1 and ≤ 12.0% may be eligible for randomization into one of two non-placebo controlled active treatment arms. The long-term treatments will be blinded to sites and subjects but will be unblinded to the Sponsor after the database for the 24-week treatment period has been locked.

Figure A: Study Schematic

Qualification Period (up to 14 days)	7 to 14-day Lead-In Period§	24-WEEK Short-Term DB Treatment Period	78-WEEK Long-Term Site and Subject Blinded Treatment Period
		Group 1 (Enrollment AIC ≥ 7.0% and ≤ 10.0%) • DB Dapagliflozin 2.5 mg (QAM) • DB Dapagliflozin 2.5 mg (QPM) • DB Dapagliflozin 5 mg (QAM) • DB Dapagliflozin 5 mg (QPM) • DB Dapagliflozin 10 mg (QAM) • DB Dapagliflozin 10 mg (QPM) • DB Dapagliflozin matching placebo (QAM and QPM) **Group 2 (Enrollment AIC ≥ 10.1% and ≤ 12.0%)** • DB Dapagliflozin 5 mg (QAM) • DB Dapagliflozin 10 mg (QAM) **All arms may include the addition of open-label metformin as rescue medication in eligible subjects.**	**Group 1 (Enrollment AIC ≥ 7.0% and ≤ 10.0%)** • DB Dapagliflozin 2.5 mg (QAM) plus metformin matching placebo • DB Dapagliflozin 2.5 mg (QPM) plus metformin matching placebo • DB Dapagliflozin 5 mg (QAM) plus metformin matching placebo • DB Dapagliflozin 5 mg (QPM) plus metformin matching placebo • DB Dapagliflozin 10 mg (QAM) plus metformin matching placebo • DB Dapagliflozin 10 mg (QPM) plus metformin matching placebo • DB Dapagliflozin placebo (QAM) plus metformin 500 mg **Group 2 (Enrollment AIC ≥ 10.1% and ≤ 12.0%)** • DB Dapagliflozin 5 mg (QAM) • DB Dapagliflozin 10 mg (QAM) **All arms may include the addition of open-label metformin as rescue medication in eligible subjects.**

Diet and Exercise Counseling

Day -14: Entry into lead-in

Enrollment

Scheduled Visits: WEEKS 1, 2, 4*, 8*, 12*, 16*, 20*, and 24*
*Assess glycemic parameters to determine eligibility for addition of rescue medication.

Day 1: Randomization

Scheduled Visits: WEEKs 37*, 50*, 63*, 76*, 89*, and 102
*Assess glycemic parameters to determine eligibility for addition of rescue medication

WEEK 24: End of Short-Term / Entry into Long-Term Treatment Period

§ Eligible subjects with an enrollment A1C ≥ 10.1 and ≤ 12.0% should have the Day 1 randomization visit scheduled within 7 ± 5 days of the Day - 14 entry into lead-in visit, provided short-term treatment period drug supplies have been received at the site. Eligible subjects with an enrollment A1C ≥ 7.0 and ≤ 10.0 % should have the Day 1 randomization visit scheduled within 14 ± 5 days of the Day -14 entry into lead-in period visit.

Study Periods:

1. Qualification Period

Drug naive subjects will be eligible for protocol-specific assessment during the qualification period. Drug naive subjects are defined as subjects who have never received prescription medications for diabetes or who have received prescription medications for diabetes for < 24 weeks since the original diagnosis, have not received antihyperglycemic therapy for more then 14 days (consecutive or not) during the 12 weeks prior to enrollment, and who have not received any antihyperglycemic therapy, during the 4 weeks prior to the enrollment visit. Signature of the protocol-specific informed consent form constitutes the first procedure of the qualification period, followed by the assignment of a unique subject number by the Interactive Voice Response System (IVRS). Protocol-specific procedures may then be performed, as part of the enrollment visit, to evaluate the subject's eligibility.

When all inclusion and exclusion criteria have been evaluated and the requirements for entry into the lead-in period have been met, the end of qualification period/entry into lead-in period Day -14 visit will be scheduled. The end of qualification period is the same day as the entry into lead-in period.

2. Lead-In Period

The lead-in period is a 2-week single-blind placebo period during which subjects will receive diet and exercise counseling, consistent with the American Diabetes Association (ADA) recommendations or similar local guidelines. Diet and exercise counseling will be provided for the duration of the study. Upon entry in the lead-in period, subjects will also be given a blood glucose meter and instructed on its use by site personnel. Eligible subjects with an enrollment A1C ≥ 7.0 and ≤ 10.0 % should complete the lead-in period in 14 ± 5 days. Eligible subjects with an enrollment A1C ≥ 10.1 and ≤ 12.0 % should complete the lead-in period in 7 ± 5 days. Single-blind placebo will be used to assess subject's compliance with treatment

3. Short-Term Double-Blind Treatment Period

Eligible subjects will enter in the randomized, short-term, double-blind, treatment period as follows:

Group 1: Subjects with an enrollment A1C ≥ 7.0% and ≤ 10.0%

The IVRS will assign subjects with an enrollment A1C ≥ 7.0% and ≤ 10.0% to randomly receive one of the following blinded treatment regimens in a 1:1:1:1:1:1:1 ratio:

- Dapagliflozin 2.5 mg QAM
- Dapagliflozin 2.5 mg QPM
- Dapagliflozin 5 mg QAM
- Dapagliflozin 5 mg QPM
- Dapagliflozin 10 mg QAM
- Dapagliflozin 10 mg QPM
- Dapagliflozin Matching Placebo AM and PM

Group 2: Subjects with an enrollment A1C ≥ 10.1 and ≤ 12.0%

The IVRS will assign subjects with an enrollment A1C ≥ 10.1% and ≤ 12.0% to randomly receive one of the following blinded treatment regimens in a 1:1 ratio:

- Dapagliflozin 5 mg (QAM)
- Dapagliflozin 10 mg (QAM)

Subjects will be followed for a total of 24 weeks on double-blind study medication. Scheduled visits will occur at Week 1, 2, 4, 8, 12, 16, 20 and 24. Subjects in all treatment arms will maintain the same treatment regimen. From Week 4 to 24, glycemic parameters will be assessed to determine eligibility for rescue during the short-term treatment period.

Subjects with lack of glycemic control during the short-term treatment period (Week 4 to Week 24) may be eligible to receive open-label rescue medication. Rescue medication means the addition of an approved oral antihyperglycemic agent, used according to conventional standards of care, to treat hyperglycemia which may therefore allow the subject to remain in the trial.

The rescue medication provided by the Sponsor will be metformin. During the short-term treatment period, all rescue decisions will be based on central laboratory Fasting Plasma Glucose (FPG) and repeat confirmatory FPG. If subjects meet the protocol-specified glycemic criteria based on FPG (see Table 1 below), they will be considered for rescue medication.

Table 1: Lack of Gycemic Control Criteria for Initiation of Rescue Medication During the Short-Term Treatment Period

Short-Term Treatment Period Visit	Central Laboratory Fasting Plasma Glucose
From Week 4 to Week 8 (excluding Week 8)	FPG > 270 mg/dL (15.0 mmoll/L)
From Week 8 to Week 12 (excluding Week 12)	FPG > 240 mg/dL (13.3 mmol/L)
From Week 12 to Week 24 **(including** Week 24)	FPG > 200 mg/dL (11.1 mmol/L)

Subjects who meet the glycemic rescue criteria in the short-term phase will first have a rescue visit completed. Rescue medication will then be added and the subjects will continue their original schedule for the short-term treatment period visits.

Eligible subjects will be rescued by receiving open-label metformin 500mg, which can be titrated as needed up to 2000 mg by the Investigator, to obtain glycemic control. Rescued subjects with central laboratory A1C values consistently greater than A1C values specified per protocol, for 12 weeks despite a maximum tolerated dose of rescue medication, will be discontinued from the study and referred for additional antihyperglycemic therapy.

4. Long-Term Site and Subject Blinded Treatment Period

During the long-term treatment period, subjects will be followed for a total of 78 weeks on site and subject blinded study medication. Scheduled visits will occur at Weeks 37, 50, 63, 76, 89, and 102.

Subjects who enter the long-term phase of the study will be treated as follows:

- Subjects who did not receive rescue medication during the 24 week short-term treatment period:
  - Subjects with enrollment A1C ≥ 7.0 and ≤ 10.0% who received double-blind dapagliflozin during the short-term treatment period will remain on the same treatment plus double-blind metformin - matching placebo.

- Subjects with enrollment A1C ≥ 7.0 and ≤ 10.0% who received double-blind placebo during the short-term treatment period will remain on the same treatment plus double-blind metformin 500 mg.
- Subjects with enrollment A1C ≥ 10.1 and ≤ 12.0% will remain on the same treatment.

- **Subjects who received rescue medication during the 24 week short-term treatment period:**
  - Subjects who received rescue medication during the short-term treatment period will remain on the same treatment assigned to them in the short-term treatment period throughout the long-term treatment period, but will receive open-label rescue metformin in addition to their blinded study medication regimen.

Subjects with lack of glycemic control who were not rescued during the short-term treatment period may be eligible to receive open-label rescue medication (metformin) during the long-term treatment period to manage uncontrolled hyperglycemia, based on pre-specified criteria. During the long-term treatment period, all rescue decisions will be based on central laboratory A1C (see Table 2).

Table 2: Lack of Glycemic Control Criteria for Initiation of Rescue Medication During the Long-Term Treatment Period (in Subjects not Previously Rescued During the Short-Term Treatment Period)

Lack of Glycemic Control Criteria for Initiation of Rescue Medication During the Long-Term Treatment Period (in Subjects not Previously Rescued During the Short-Term Treatment Period)	
Long-Term Treatment Period Visit	**Central Laboratory A1C**
After Week 24 to Week 50 (including Week 50)	A1C > 8.0%
After Week 50 to Week 76 (including Week 76)	A1C > 7.5%
After Week 76 to Week 102 (**excluding** Week 102)	A1C > 7.0%

Eligible subjects will be rescued by receiving open-label metformin 500mg, which can be titrated as needed up to 2000 mg by the Investigator, to obtain glycemic control. Rescued subjects with central laboratory A1C values consistently greater than A1C values specified per protocol, for 12 weeks despite a maximum tolerated dose of rescue medication, will be discontinued from the study and referred for additional antihyperglycemic therapy.

Duration of Study: 33 months (8 months for enrollment plus 25 months for study participation)

Number of Subjects per Group:

Group 1: Subjects with enrollment A1C ≥ 7.0 and ≤ 10.0% (target population): Approximately 70 subjects per treatment arm (Total n = 490) will be randomized in a 1:1:1:1:1:1:1 ratio to receive double-blind dapagliflozin 2.5 mg, dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo. Subjects will be randomized to receive dapagliflozin 2.5 mg, 5.0 mg, or 10.0 mg, in the AM or PM; and placebo in the AM and PM

Group 2: Subjects with enrollment A1C ≥ 10.1 and ≤ 12.0%: Approximately 35 subjects per treatment arm (Total n = 70) will be randomized in a 1:1 ratio to receive double-blind dapagliflozin 5 mg or dapagliflozin 10 mg in the AM. The total number of subjects per arm in these 2 treatment arms may be less than 70, in the event the target population arms complete enrollment earlier.

Study Population: Males and females with type 2 diabetes, ≥ 18 to ≤ 77 years old, who are drug naive (never received prescription medications for diabetes or received prescription medications for diabetes for

< 24 weeks since the original diagnosis) and received < 14 days of prescription medication for diabetes in the 12 weeks prior to enrollment); and have inadequate glycemic control with diet and exercise, defined as A1C ≥ 7.0 % and ≤ 10%. In addition, administration of any antihyperglycemic therapy, at any dose, within the 4 weeks prior to the enrollment visit, is an exclusion criterion. Subjects with an enrollment A1C ≥ 10.1 % and ≤ 12.0 % who meet all other selection criteria may be eligible for randomization to dapagliflozin 5 mg or 10 mg (non-target-patient population) treatment arms. Subjects must also have a body mass index (BMI) ≤ 45.0 kg/m^2 and an enrollment central laboratory C-peptide value ≥ 1.0 ng/mL (0.34 nmol/L).

Exclusion Criteria Include:

- Urine albumin:creatinine ratio (UACR) > 1,800 mg/g (203.4 m/mmol/Cr).
- Aspartate Aminotransferase (AST) > 3X upper limit of normal (ULN).
- Alanine Aminotranferase (ALT) > 3X ULN.
- Serum total bilirubin (TB) > 2 mg/dL (34.2 μmol/L).
- Serum Creatinine (S_{cr}) ≥ 1.50 mg/dL (133 μmol /L) for male subjects; S_{cr} ≥ 1.40 mg/dL (124 μmol /L) for female subjects.
- Calcium value outside of the central laboratory normal reference range. ***Note: A one-time central laboratory re-test of calcium is allowed in subjects with an out of range initial central laboratory calcium value who are otherwise eligible as determined by the Investigator.***

  In situations where both the central laboratory A1C and the calcium values meet criteria for re-test, such re-tests of both the A1C and calcium values are allowed provided the subject is otherwise fully eligible, as determined by the Investigator.

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

- Blinded dapagliflozin tablets, 2.5 mg, 5 mg, 10 mg administered orally for the 24-week double-blind, short-term treatment period, and the 78-week site and subject blinded, long-term treatment period of the study.
- Matching placebo for dapagliflozin tablets, 2.5 mg, 5 mg, and 10 mg, administered orally for the 2-week lead-in period, the 24-week double-blind, short-term treatment period, and the 78-week site and subject blinded, long-term treatment period of the study.
- Matching placebo for metformin 500 mg tablets, administered orally for the 78-week site and subject blinded, long-term treatment period of the study.
- Blinded metformin 500 mg tablets, administered orally for the 78-week site and subject blinded, long-term treatment period of the study.
- Open-label rescue metformin 500 mg tablets, administered orally based on rescue criteria, during the 24-week double-blind, short-term treatment period and/or during the 78-week site and subject blinded long-term treatment period of the study.

Study Assessments and Primary Endpoints: The primary endpoint is the change from baseline in A1C at Week 24, or the last post-baseline measurement prior to Week 24, (if no Week 24 assessment is available) in the short-term treatment period. For rescued subjects, measurements obtained after initiation of rescue medication will not be considered in calculating the primary endpoint.

Statistical Methods:

The primary analysis for the change in A1C from baseline at Week 24 or the last post-baseline measurement prior to Week 24 if no Week 24 assessment is available, will be performed on subjects with enrollment A1C between 7% - 10% inclusive, and who are randomized to dapagliflozin AM dosing or placebo group. It will be based on an analysis of covariance (ANCOVA) model with treatment group as an effect and baseline value as a covariate. Point estimates and 95% confidence intervals for the means within each treatment group as well as for the differences between each of the dapagliflozin AM dosing treatment groups (2.5 mg QAM, 5 mg QAM, 10 mg QAM) and placebo will be estimated. In addition, for each comparison, statistical significance will be claimed if the p-value for the comparison between the dapagliflozin AM dosing treatment group and placebo group < 0.019 two sided, using Dunnett's adjustment. This maintains the overall Type-1 error rate at 0.05.

With 67 subjects per treatment group with post-baseline measurements, there is 90% power to detect a difference in means of 0.7% between each dapagliflozin AM dosing treatment group and placebo, assuming a standard deviation (SD) of 1.1%. Assuming that 5% of subjects do not have a post-baseline assessment, a total of 490 subjects (70 subjects per treatment arm), with enrollment A1C between 7% - 10% inclusive, need to be randomized to the dapagliflozin AM dosing, dapagliflozin PM dosing or placebo group. In addition, 70 subjects (35 subjects on each dapagliflozin treatment arm (5 mg and 10 mg)) with enrollment A1C between 10.1% - 12% inclusive will also be randomized to obtain initial efficacy and safety data in this population.

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1 INTRODUCTION AND STUDY RATIONALE

1.1 Research Hypothesis

After 24 weeks of oral daily administration, there will be a greater mean reduction from baseline in glycosylated hemoglobin (A1C) achieved with dapagliflozin AM dosing compared to placebo in drug naive subjects with type 2 diabetes who have inadequate glycemic control with diet and exercise.

1.2 Investigational Product Development Rationale

The treatment of diabetes is an important health concern and despite a wide range of available therapies, the epidemic continues. Type 2 diabetes is a progressive disease caused by insulin resistance and decreased pancreatic β-cell function.[1] Insulin is produced by the pancreatic β-cell and mediates cellular glucose uptake and clearance. Insulin resistance is characterized by the lack of response to the actions of this hormone which results in decreased cellular clearance of glucose from the circulation and overproduction of glucose by the liver.

Worldwide, there are an estimated 150 million people who have type 2 diabetes.[1] According to the Centers for Disease Control (CDC) in 2005, seven percent of the United States (U.S.) population has diabetes, of whom approximately 15 million have been diagnosed.

The currently available therapies to treat type 2 diabetes augment the action or delivery of insulin to lower blood glucose. However, despite therapy, many patients do not achieve control of their type 2 diabetes. According to the National Health and Nutrition Examination Survey (NHANES) III, only 36% of subjects with type 2 diabetes achieve glycemic control defined as a A1C < 7.0% with current therapies.[2] In an effort to treat type 2 diabetes, aggressive therapy with multiple pharmacologic agents may be prescribed. However, despite this increased use of aggressive therapy, there has been a decline in glycemic control. Therefore, additional therapies are warranted.

Dapagliflozin has been designed as a potent and selective inhibitor of the renal sodium-glucose transporter, SGLT2. This compound is being developed as an orally active agent for the treatment of type 2 diabetes, and represents a novel therapeutic approach for the treatment of this disorder. Intestinal absorption and renal reabsorption of glucose are mediated through sodium-glucose transporters (SGLT).[3] Two sodium-dependent glucose transporters, SGLT1 and SGLT2, have been identified as the major transporters of glucose in the human.[4,5] SGLT1 is expressed in the gastrointestinal tract, heart, skeletal muscle, liver, lung, and kidney, while SGLT2 is expressed almost exclusively in the kidney. SGLT2 expression is localized to the S1 segment of the proximal tubule, where > 90% of renal glucose reabsorption occurs.[6] Human mutations in SGLT2 are associated with familial renal glucosuria.[7,8] These patients present with glucosuria secondary to a decrease in glucose reabsorption in the proximal tubule. They have normal plasma glucose levels. From the information available, these patients have a normal life-span and the majority of them have no other abnormalities other than the increased urinary glucose excretion. Thus SGLT2 appears to be the major transporter responsible for renal glucose transport, mediating glucose re-uptake from the glomerular filtrate.

1.3 Summary of Results of Investigational Program

Dapagliflozin has undergone considerable *in vitro* and *in vivo* evaluation in a wide variety of preclinical models; these findings are detailed in the Investigator brochure.

1.3.1 Non-Clinical Toxicology

Dapagliflozin was well tolerated when given orally to dogs for up to 12 months (≤ 120 mg/kg/day) (1520 - 1540 μg•h/mL AUC) and in rats when given orally for up to 6 months (≤ 25 mg/kg/day) (160-310 μg•h/mL AUC). Drug-related changes considered secondary to anticipated pharmacology observed in both species included dose-dependent reversible increases in food and water intake and increases in urine parameters (volume, glucose, calcium and phosphorus), as well as decreases in urine osmolality and minimal decreases in body-weight gain compared to controls (males). The no-observed-adverse-effect level (NOAEL) in dogs was 120 mg/kg/day based on the lack of target organ toxicity and adverse clinical pathology at the high dose. Despite elevated total urine protein levels (up to 7x) at the high dose, no adverse renal histologic or clinical

pathologic findings were observed in dogs. Similarly, no renal histopathologic findings were observed up to 25 mg/kg/day in the 6-month rat study, despite elevations in total urine protein (up to 5x). Importantly, although total urinary protein was increased, the concentration of urinary protein was not significantly increased in either the 12-month dog or 6-month rat studies. The NOAEL in the 6-month rat study was 25 mg/kg/day based primarily on tissue mineralization including bone changes, urothelial hyperplasia with mineral deposition in collecting ducts and tubular dilatation in the kidney, and vascular mineralization observed at the high dose (150 mg/kg/day). Non-reversible bone changes, characterized by increased thickness of primary trabeculae, and tissue mineralization associated with hypercalciuria and hypercalcemia were noted only in high-dose rats at very high exposure multiples (1945 - 2846x) relative to the human area under the curve (AUC) at a clinical dose of 10 mg. Preliminary evidence suggests that these rat-specific findings at the high dose (150 mg/kg/day) are consistent with the dysregulation of calcium homeostasis due to an off-target inhibitory effect on SGLT-1, leading to an increased absorption of calcium from the GI tract rather than mobilization of calcium from bone. Animal-to-human exposure multiples at the NOAEL in the pivotal toxicology studies were 318 and 621x for rats (male and female, respectively) and approximately 3004 and 3044x for dogs (male and female respectively) based on the 10 mg clinical dose.

1.3.2 Pharmacokinetics/Pharmacodynamics

A total of 6 clinical pharmacology studies (5 Phase 1 studies and 1 Phase 2a study), which evaluated the safety, tolerability, and pharmacokinetics (PK) of dapagliflozin have been completed. In brief, the pharmacokinetics of dapagliflozin are characterized by rapid absorption after oral administration, with peak plasma concentrations (Cmax) usually attained within 2 hours after administration in the fasted state. Administration of food appears to increase the time to Cmax (Tmax) to approximately 4 hours after dosing but has no effect on exposure (AUC). In general, the Cmax and AUC values for dapagliflozin increased approximately equal to the increment in dose. Following single oral doses of 100 mg dapagliflozin in the fasted state, the mean terminal half-life (T1/2) for dapagliflozin was 15.9 hours. Consistent with these T1/2 values, approximately 30% accumulation of dapagliflozin (Accumulation Index of 1.3) was observed upon repeated once-daily dosing of dapagliflozin.

Following oral administration, approximately 65% of a dapagliflozin dose is eliminated in the urine as a glucuronide metabolite, BMS-801576. Preliminary data indicate that BMS-801576 is pharmacologically inactive (> 1000x less potent in inhibiting SGLT2 than parent). BMS-801576, though inactive towards SGLT2, was only recently discovered and further characterization of this compound's pharmacokinetics is ongoing.

In a Phase 2a study that administered 5, 25 or 100 mg dapagliflozin to Type 2 diabetic subjects for 14 days, doses of 25 and 100 mg dapagliflozin appeared to provide the maximal percent inhibition of renal glucose reabsorption. Subjects administered 25 or 100 mg dapagliflozin for 1 and 14 days appeared to have greater cumulative 24 h urinary glucose excretion (approximately 75 gram of glucose per day) compared to subjects administered 5 mg dapagliflozin for 1 and 14 days (approximately 40 grams per day). The average mean urinary glucose excretion rate for subjects administered 25 or 100 mg dapagliflozin (3 g/h) was generally higher compared to subjects administered 5 mg (2 g/h).

1.3.3 Summary of Clinical Efficacy

1.3.3.1 MB102008

Three-hundred eighty-nine (389) subjects with type 2 diabetes were studied in a Phase 2b multicenter, randomized, seven-arm, parallel group, placebo controlled trial (MB102008). Subjects were randomly assigned to 1 of 5 daily doses of dapagliflozin (2.5, 5, 10, 20 or 50 mg), metformin extended release (XR), (1500 mg) or placebo for 12 weeks (MB102008). Statistical comparisons for efficacy parameters were performed only for comparison between the dapagliflozin treatment arms and the placebo arm.

Subjects who completed the double-blind treatment period, or discontinued this period early, entered a 4-week follow-up period. No study medication was provided during the follow-up period but subjects were permitted to begin treatment with an oral antihyperglycemic agent.

An analysis was conducted to evaluate data up to and including the primary endpoint of A1C, measured after 12 weeks of therapy. There was a statistically significant decrease in A1C in all dapagliflozin arms as compared with the placebo arm. There was also a dose-

dependent decrease in fasting plasma glucose (FPG) from baseline to week 12 in all doses of dapagliflozin. There was a statistically significant difference in mean change from baseline in FPG in each of the dapagliflozin 5 mg, 10 mg, 20 mg, and 50 mg arms compared to placebo. Increased total urinary glucose excretion was observed at all dapagliflozin doses, consistent with the mechanism of action of this compound. The maximum increase in glucose excretion was observed at dapagliflozin doses ≥ 20 mg.

The proportion of dapagliflozin-treated subjects achieving a therapeutic glycemic response (defined as A1C < 7%) at week 12 ranged from 40% to 59%. A statistically significant difference compared to placebo was attained only at the 50 mg dose of dapagliflozin. There were reductions in postprandial glucose (area under the curve) from baseline, compared to placebo, for all doses of dapagliflozin. Declines in total body weight from baseline in all dapagliflozin arms were greater than placebo. The percent decrements from baseline were comparable for the 2.5 mg to 10 mg arms, and larger for the 20 mg and 50 mg doses, where they were likewise comparable.

1.3.3.2 MB102003

Data from a multiple dose study (MB102003) in subjects with type 2 diabetes indicate that after 14 days of treatment, fasting and post-prandial serum glucose levels decrease significantly in subjects randomized to dapagliflozin in doses of 5, 25 and 100 mg/day as compared with placebo-treated subjects. The area under the curve (AUC) for the serum glucose levels during the oral glucose tolerance test (OGTT) had a similar decrease in all 3 dapagliflozin treatment arms. The average amount of glucose excreted in 24 hours on Day 14 was approximately 21, 71, and 66 g for the 5, 25, and 100 mg once-daily doses of dapagliflozin, respectively. Therefore, it appears that the maximal peak effect on urinary glucose excretion in diabetic subjects is observed at doses of 25 mg/day and higher. In addition, the magnitude of peak effect in diabetic subjects is similar to that observed in healthy volunteers.

1.3.4 Summary of Clinical Safety

The clinical safety experience to date is based on a phase 2b study as well as 5 Phase 1 and 1 Phase 2a clinical pharmacology studies.

1.3.4.1 MB102008

This study has recently been concluded and the results, currently undergoing review, are summarized below.

No deaths occurred during this phase 2b study. Six (6) SAEs occurred in 5 subjects (4 unrelated and 2 unlikely related to study medication). AEs were experienced by 177 (63.4%) of subjects treated with dapagliflozin, 38 (67.9%) of subjects treated with metformin, and 29 (53.7%) of the subjects receiving placebo.

Dapagliflozin increased the urinary excretion of glucose, a potential substrate for urinary and vaginal pathogens. The following table summarizes the percentage of reports of adverse events related to urinary and genital infections, according to their preferred terms, for all subjects receiving dapagliflozin, placebo, and metformin.

Table 1.3.4.1: Distribution of Adverse Events by Treatment Allocation

Adverse Events	Dapagliflozin (%)	Placebo (%)	Metformin (%)
Urinary Tract Infection	7.5	5.6	7.1
Cystitis	1.4	0.0	1.8
Escherichia Urinary Tract Infection	0.4	0.0	0.0
Urinary Tract Infection Fungal	0.4	0.0	0.0
Vulvovaginal Mycotic Infection	1.8	0.0	0.0
Vaginal Infection	1.1	0.0	0.0
Vulvitis	0.0	0.0	1.8
Vaginitis Bacterial	0.4	0.0	0.0
Penile Infection	0.4	0.0	0.0

Changes in mean serum creatine kinase compared to baseline were small, and inconsistent, in all treatment arms. The maximum increment in mean serum creatine kinase was 25 mEq/L, seen in the 10 mg dapagliflozin treatment arm at two weeks. The

adverse event of an increase in blood creatine phosphokinase was reported in 2.5% of the subjects treated with dapagliflozin, and was not reported in subjects who received either placebo or metformin. There were no marked abnormalities defined as creatinine kinase (CK) ≥ 10X ULN reported in this study. No cases of acute renal failure were reported. There were no apparent drug related effects with respect to AST, ALT, or bilirubin.

Dapagliflozin has a potential diuretic action due to its effects on sodium and glucose transport. Dapagliflozin-treated subjects exhibited dose-related increases in mean 24-hour urine volume compared to baseline. These increments ranged from 107 mL (at the 2.5 mg dose) to 470 mL (at the 50 mg dose), compared with decreases of 112 mL for subjects receiving placebo, and 96 mL for those receiving metformin.

Negative fluid balance could result in manifestations attributable to reductions in extracellular fluid volume. Reductions in plasma volume due to diuresis may be reflected by increases in hematocrit. After 12 weeks of treatment, dapagliflozin treated subjects exhibited dose-related mean increments in hematocrit ranging from 1.5% at the 2.5 mg dose to 2.9% at the 50 mg dose, compared with decrements in mean hematocrit of 0.1% in subjects receiving placebo and 1.1% in those receiving metformin.

With baseline ratios of serum blood urea nitrogen (BUN) (mg/dL) to creatinine (mg/dL) of 17 - 19, dapagliflozin-treated subjects exhibited increases in this ratio of 10 - 18% compared to baseline, in contrast with a decrease of 3.9% in subjects treated with placebo, and an increase of 2.8%, in subjects treated with metformin. Increased serum creatinine was reported in one subject receiving 50 mg/day of dapagliflozin (0.4% of all subjects receiving dapagliflozin), and in no subjects receiving placebo or metformin. No subjects had the marked abnormality of either serum creatinine ≥ 2.5 mg/dL or BUN ≥ 60 mg/dL. Renal failure was not reported as an adverse event in any subject.

Mean standing systolic blood pressures decreased from baseline by 4 - 5 mmHg in the 10 - 50 mg dapagliflozin treatment arms, and by 2 - 3 mmHg at the lower doses; while the placebo group changed by + 0.8 mmHg and the metformin group by -0.3 mmHg. Mean changes in standing diastolic blood pressures ranged from - 2.5 mmHg to + 0.8 mmHg, without relationship to dose; while changes of + 1.0 mmHg and 0 mmHg were seen in the placebo and metformin groups. Orthostatic hypotension was reported in one subject receiving dapagliflozin at the 50 mg dose (0.4% of all dapagliflozin-treated

subjects), and in no subjects receiving placebo or metformin. Hypotension was reported in one subject each receiving placebo (1.9%) and metformin (1.8%), and in no subjects receiving dapagliflozin.

Dizziness was reported in 5.0% of the subjects receiving dapagliflozin, in 1.9% of the subjects receiving placebo, and 3.6% of the subjects receiving metformin. Presyncope was reported in 0.7% of the subjects receiving dapagliflozin and no subjects receiving either placebo or metformin. Syncope was reported in 1.8% of metformin-treated subjects, and was not reported in subjects receiving dapagliflozin or placebo.

Disturbances in serum electrolyte concentrations were infrequent. Hypokalemia and hyponatremia were both reported in one subject receiving dapagliflozin, (0.4% each of all subjects receiving dapagliflozin), and hypokalemia was reported in one subject on placebo (1.9% of subjects receiving placebo). The marked abnormality of hypokalemia (serum potassium ≤ 2.5 mEq/L) was seen in 2 subjects receiving the 50 mg dose, and no subjects in any other study arm. Dapagliflozin was associated with increased prevalence compared to placebo of the marked abnormality of hyperphosphatemia (serum phosphorous ≥ 5.0 mg/dL). This abnormality was observed in 17% of subjects receiving 20 mg of dapagliflozin and 20% of subjects at the 50 mg of dapagliflozin, versus 10% of the subjects receiving with placebo. Mean serum phosphorus compared to baseline increased by 0.2 mg/dL at the 20 mg and 50 mg doses; 0.1 mg/dL at the 5 mg and 10 mg doses; and was unchanged at the 2.5 mg dose. Mean serum magnesium concentrations increased by up to 0.2 mEq/L. Mean serum uric acid concentrations declined by approximately 1 mg/dL at all dapagliflozin doses. Neither urolithiasis nor acute gouty arthritis was reported.

There were no confirmed hypoglycemic events, defined as a documented blood glucose of ≤ 50 mg/dL (2.8 mmol/L). The reported incidence of unconfirmed hypoglycemic events ranged from 6.4% to 10.3% of subjects on dapagliflozin, without relationship to dose, compared to 3.7% of subjects receiving placebo and 8.9% receiving metformin.

Markers of bone metabolism, urinary C-telopeptide and deoxypyridinolone excretions, and serum osteocalcin concentration, increased compared to baseline in subjects treated with dapagliflozin. There were small increments in mean serum parathyroid hormone

concentration without apparent relationship to dose. The clinical significance of these findings is unknown.

1.3.4.2 Clinical Pharmacology Studies

A total of 6 clinical pharmacology studies (5 Phase 1 studies and 1 Phase 2a study), which evaluated the safety, tolerability, and pharmacokinetics (PK) of dapagliflozin have been conducted. A summary of clinical pharmacology safety to date is included below. For more detailed information on the safety of dapagliflozin in clinical pharmacology trials, please refer to the Investigator Brochure.

Safety assessments in all clinical pharmacology studies included a medical review of adverse events (AEs), findings from physical examinations, vital sign and electrocardiogram (ECG) measurements, and clinical laboratory tests. All subjects who received study drug (dapagliflozin or placebo) were included in the safety evaluation.

At least 154 subjects have received dapagliflozin in clinical pharmacology studies. One hundred sixteen (116) healthy subjects and at least 38 subjects with type 2 diabetes have received at least 1 single oral dose (2.5 to 500 mg and 5 to 100 mg, respectively) of dapagliflozin. Multiple daily oral doses (2.5 to 100 mg) of dapagliflozin were administered to 30 healthy subjects for up to 14 days, and at least 38 subjects with type 2 diabetes received multiple oral daily doses (5 to 100 mg) for up to 14 days.

When administered in clinical pharmacology studies, all doses of dapagliflozin have been safe and generally well tolerated. No deaths have been reported. One (1) serious adverse event (SAE) of psychological stress was reported in 1 healthy volunteer in the MB102001 trial. This event was determined to be unrelated to study drug.

To date, adverse events of clinical interest in clinical pharmacology studies include hypoglycemia episodes and vulvovaginal mycotic infection. In subjects treated with dapagliflozin, symptoms suggestive of hypoglycemia have been reported by 1 healthy volunteer (treated with dapagliflozin 20 mg) and 2 subjects with type 2 diabetes (1 treated with dapagliflozin 5 mg and metformin and 1 subject treated with dapagliflozin 25 mg and metformin). All cases of hypoglycemia in subjects who received dapagliflozin resolved within 25 minutes, were categorized to be of mild or moderate intensity, and

considered possibly related to the study drug by the Investigator. Vulvovaginal mycotic infection has been reported by 2 subjects, both with type 2 diabetes, who received dapagliflozin (1 treated with dapagliflozin 100 mg and metformin and 1 subject treated with dapagliflozin 25 mg). The events were judged by the Investigator to be mild in intensity and unlikely related to study drug. Laboratory data indicated the amount of glucose excreted in the urine by these subjects was not substantially higher than the mean amount of glucose excreted by other subjects in the same randomization groups. Both subjects participated at the same clinical site.

Laboratory assessments in clinical pharmacology trials have included analysis of biomarkers for general renal tubular function, potential renal toxicity and bone metabolism abnormalities, as well as urinary and serum electrolytes. No apparent changes in any of these parameters have been observed and no laboratory AEs have been reported in any trial. In addition, healthy volunteers and subjects with type 2 diabetes who were treated with dapagliflozin (despite having significantly higher urinary glucose excretion than subjects treated with placebo) did not have higher urinary volumes than subjects treated with placebo in any clinical pharmacology study conducted to date.

There were no clinically relevant vital sign abnormalities, ECG abnormalities or physical examination findings noted in any study.

1.3.5 Other Clinical Studies

The MB102004 study was an open-label, randomized, 3-period, 3-treatment, crossover study in healthy subjects to evaluate the potential for a PK interaction between dapagliflozin and hydrochlorothiazide (HCTZ). Preliminary data indicate that the PK of dapagliflozin and HCTZ were not substantially different compared to each agent administered alone to healthy subjects. No dosage adjustment of either drug is anticipated on the basis of their PK when they are co-administered.

MB102007 is an open-label, parallel, single-dose study which is currently ongoing. This trial is designed to assess the single-dose PK of dapagliflozin in subjects with type 2 diabetes with mild or moderate renal impairment compared to subjects with type 2 diabetes and healthy subjects with normal renal function. Approximately 32 subjects will

receive a single oral dose of dapagliflozin 50 mg. The results of this study are not yet available.

MB102009 is an ongoing Phase 2b study in subjects with type 2 diabetes treated with insulin and oral hypoglycemic agents (metformin and/or a thiazolidinedione [TZD]). Approximately 80 subjects will be randomized to 1 of 2 daily doses of dapagliflozin (10 or 20 mg) or placebo for a 12-week treatment period. The results of this study are not yet available.

1.4 Study Rationale

1.4.1 Rationale for Study Design

The current trial is designed to demonstrate the efficacy and safety of dapagliflozin when used as monotherapy in subjects with type 2 diabetes inadequately controlled with diet and exercise.

There is an unmet need with the current pharmacologic treatment of type 2 diabetes mellitus. Despite the currently available therapies, many subjects are still not reaching glycemic control goals. Many subjects treated with insulin secretagogues experience significant side effects including weight gain, hypoglycemia, and insulin resistance. Agents that affect insulin resistance alone often do not provide the desired decrease in A1C when used alone, and sometimes have clinically important side effects such as weight gain, fluid retention and cardiac dysfunction. An agent with a different mechanism of action, which can be used either in monotherapy or in addition to existing treatments, is warranted. Dapagliflozin, through its novel mode of action, is such an agent. In the dose-ranging, phase 2b MB102008 trial, dapagliflozin reduced both fasting and postprandial blood glucose. The MB102008 trial results suggest dapagloflozin's potential use as a monotherapy alternative to currently available treatments, and support the design of the MB102013 trial.

In this trial, dapagliflozin doses of 2.5 mg, 5 mg and 10 mg will be assessed versus placebo. The use of a placebo control affords the clearest opportunity to further establish dapagliflozin's efficacy and safety profile by distinguishing the effect of pharmacologic interventions from other interventions such as diet and exercise counseling.

Subjects will be carefully monitored at frequent intervals. Subjects who experience continued or worsening hyperglycemia may be eligible to receive additional antihyperglycemic therapy (rescue medication), based on pre-specified criteria, through conventional oral anti-diabetic medication. Moreover, the administration of blinded metformin to subjects in the placebo arm, during the long-term treatment period, in conjunction with progressively strict rescue criteria, will help ensure that subjects are not exposed to prolonged excessive hyperglycemia.

Inclusion of subjects with an enrollment A1C ≥ 10.1% and ≤ 12.0%, in active blinded treatment arms of either dapagliflozin 5 mg QAM or dapagliflozin 10 mg QAM, may permit subjects with inadequate control to experience a therapeutic benefit of active study medication. Such benefits, when expressed as absolute reductions in A1C, are typically greater in subjects with higher baseline A1C. Furthermore, treatment arms including these subjects with higher baseline A1C values will afford an opportunity to observe the safety of dapagliflozin in subjects who may have substantial glucosuria prior to drug administration.

1.4.1.1 Rationale for AM and PM Dosing:

Subjects assigned to active treatment with dapagliflozin will be randomized to receive their once daily dose of study drug either with the morning (AM) or evening (PM) meal. In single ascending dose studies in healthy volunteers, a glucosuric response to dapagliflozin was evident by four hours after dose administration, for all doses, and lasted greater than 24 hours for the 5 and 10 mg doses. Assessment of differences in responses to dapagliflozin administered either in the AM or PM is important in evaluating its efficacy and safety in patients who choose either AM or PM dosing to coincide with the co-administration of additional prescription medications, including other antidiabetic drugs, and will support a determination whether dosing of dapagliflozin at any time of the day is acceptable in terms of efficacy and tolerability for all doses.

1.4.2 Rationale for Dose Selection

Based on a consideration of efficacy, pharmacodynamic, and safety data from the Phase 1 and Phase 2 programs, the dapagliflozin Phase 3 program will study daily doses of

2.5 mg, 5 mg, and 10 mg, in subjects with type 2 diabetes. This dose range is supported by the following assessments:

- In the Phase 1 and 2a program, maximal glucosuria was seen at the 10 mg dose. Doses ≥ 20 mg only increased the duration of glucosuria.
- In the Phase 2b study (MB102008), dapagliflozin improved glycemic parameters throughout the dose range of 2.5 mg to 50 mg daily, with most of the efficacy realized within the dose range of 2.5 mg to 10 mg. There was no apparent dose relationship beyond 10 mg for A1C or for postprandial glucose AUC, though there was evidence for a continued dose-response relationship up to 50 mg with respect to FPG.
- Adverse events of dizziness, hypoglycemia, and genitourinary infections did not appear to be related to dose.
- Urinary glucose excretion and weight loss were seen at all doses. There was an apparent relationship to dose for these parameters, with a step-up seen at doses greater than 10 mg. There was also a step-up seen in the incidence of the marked laboratory abnormality of hyperphosphatemia with increasing dose throughout the dose range. Dose-related increases in mean hematocrit were also observed.

Based on the data from the Phase 2b trial, doses greater than 10 mg increase the potential risks of fluid losses, hemoconcentration, and hyperphosphatemia, without the promise of substantially greater glycemic efficacy.

1.5 Overall Risk/Benefit Assessment

This protocol includes an experimental compound, dapagliflozin, being developed as a potential new therapy for hyperglycemia in subjects with type 2 diabetes. Other conventional treatments are currently available for subjects with type 2 diabetes and include insulin therapy and oral medications. Each of these conventional therapies entails risks and side effects that will not be reviewed here.

In the phase 1 and 2 clinical studies, dapagliflozin was generally safe and well-tolerated. In the phase 2a study in subjects with type 2 diabetes, the most commonly reported AEs included diarrhea, nausea, headache, dizziness, and weakness. In the phase 1 study (MB102001), only one SAE was reported, which was considered by the investigator not to be related to study medication.

In the phase 2B study MB102008 of subjects with type 2 diabetes, adverse events related to urinary tract and genital infections were somewhat more frequent in dapagliflozin-treated subjects. Clinical and laboratory manifestations consistent with a diuretic effect of the drug were also observed.

Dapagliflozin administration was associated with increases in mean serum concentrations of phosphorus and magnesium, and decreases in uric acid, within their normal ranges. While there were more unconfirmed hypoglycemic events in dapagliflozin-treated subjects in comparison with placebo, there were no confirmed hypoglycemic events in any treatment arm.

Subjects receiving dapagliflozin, in comparison to placebo, exhibited declines in A1C and dose-related decrements in FPG. Dapagliflozin administration was associated with reductions in postprandial glycemia, an increment in the proportion of subjects attaining therapeutic glycemic goal, and decrements in total body weight.

In this trial, the doses of dapagliflozin have been chosen to provide efficacy in reducing hyperglycemia while mitigating the potential for fluid and electrolyte imbalance. The trial also includes pre-specified criteria for adding open-label rescue therapy for subjects who experience continued or worsened hyperglycemia.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To compare the change from baseline in A1C achieved with each dapagliflozin AM dosing treatment group versus placebo after 24 weeks of oral administration of double-blind treatment.

2.2 Secondary Objectives

- To compare the change from baseline in FPG for each dapagliflozin AM dosing treatment group versus placebo after 24 weeks of oral administration of double-blind treatment.

- To compare the proportion of subjects achieving a therapeutic glycemic response, defined as A1C < 7.0%, for each dapagliflozin AM dosing treatment group versus placebo after 24 weeks of oral administration of double-blind treatment.
- To compare the change from baseline in total body weight, for each dapagliflozin AM dosing treatment group versus placebo after 24 weeks of oral administration of double-blind treatment.
- To compare the change from baseline in FPG for each dapagliflozin AM dosing treatment group versus placebo after 1 week of oral administration of double-blind treatment.
- To compare the change from baseline in A1C in subjects with baseline A1C ≥ 9% for each dapagliflozin AM dosing treatment group versus placebo after 24 weeks of oral administration of double-blind treatment.
- To compare the change from baseline in A1C in subjects with baseline BMI ≥ 27 kg/m2 for each dapagliflozin AM dosing treatment group versus placebo after 24 weeks of oral administration of double-blind treatment.
- To compare the change from baseline in total body weight achieved in subjects with baseline BMI ≥ 27 kg/m^2 for each dapagliflozin AM dosing treatment group versus placebo after 24 weeks of oral administration of double-blind treatment.
- To compare the proportion of subjects achieving a therapeutic glycemic response, defined as A1C ≤ 6.5% for each dapagliflozin AM dosing treatment group versus placebo after 24 weeks of oral administration of double-blind treatment.

2.3 Exploratory Objectives

- To assess the change from baseline in A1C for each dapagliflozin PM dosing treatment group versus placebo after 24 weeks of oral administration of double-blind treatment.
- To assess the change from baseline in FPG at Week 1 and Week 24, the change from baseline in total body weight, at week 24, the proportion of subjects achieving a therapeutic glycemic response, defined as A1C < 7.0 % at week 24, and the proportion of subjects achieving a therapeutic glycemic response, defined as A1C ≤ 6.5% at Week 24, for each dapagliflozin PM dosing treatment group versus placebo.
- To assess the change from baseline in A1C in subjects with baseline A1C ≥ 9%, the change from baseline in A1C in subjects with baseline BMI ≥ 27 kg/m2, and the change from baseline in A1C in subjects with baseline BMI ≥ 30 kg/m2 for each dapagliflozin PM dosing treatment group versus placebo after 24 weeks of oral administration of double-blind treatment.

- To assess the percent change from baseline in total body weight, for each dose of dapagliflozin (AM dosing and PM dosing) versus placebo after 24 weeks of oral administration of double-blind treatment.
- To characterize the distributions of change from baseline in AIC, FPG, and body weight for each treatment group.
- To assess the proportion of subjects achieving a therapeutic glycemic response, defined by each of the sub-groups below, for each dose of dapagliflozin (AM dosing and PM dosing) versus placebo after 24 weeks of oral administration of double-blind treatment:
  - A1C decrease from baseline ≥ 0.5%
  - FPG < 110 mg/dL (6.1 mmol/L)
  - FPG < 126 mg/dL (7.0 mmol/L)
- To assess the changes from baseline for each dose of dapagliflozin (AM dosing and PM dosing) versus placebo after 24 weeks of oral administration of double-blind treatment for the following parameters:
  - β-cell function (as measured by Homeostasis Model Assessment 2 [HOMA-2])
  - Insulin resistance (as measured by HOMA-2))
- To assess the change from baseline for each dose of dapagliflozin (AM dosing and PM dosing) versus placebo after 24 weeks of oral administration of double-blind treatment for the following parameters:
  - Body Mass Index (BMI)
  - Waist Circumference
  - Fasting C-peptide
  - Metabolic Surrogate Markers:
    - High-sensitivity C-reactive protein [hs-CRP]
    - Plasminogen activator inhibitor 1 [PAI-1]
    - Fibrinogen
    - Serum uric acid
- To assess the percent change from baseline in fasting lipids (total cholesterol [Total-C], low-density lipoprotein [LDL-C], high-density lipoprotein cholesterol [HDL-C] and triglycerides [TG]) for each dose of dapagliflozin (AM dosing and PM dosing) versus placebo after 24 weeks of oral administration of double-blind treatment.
- To assess the percent change from baseline in free fatty acids (FFA) for each dose of dapagliflozin (AM dosing and PM dosing) versus placebo after 24 weeks of oral administration of double-blind treatment.

- To assess the proportion of subjects discontinued or rescued for failing to achieve pre-specified glycemic targets based on pre-specified rescue criteria, at Weeks 4, 8, 12, 16, 20 and 24, for each dose of dapagliflozin (AM dosing and PM dosing) versus placebo.
- To assess the change from baseline in A1C according to baseline A1C category (A1C < 8%, A1C ≥ 8% and < 9%, A1C ≥ 9%) for each dose of dapagliflozin (AM dosing and PM dosing) versus placebo after 24 weeks of oral administration of double-blind treatment.
- To assess the glycemic parameters, for each dose of dapagliflozin, (AM dosing and PM dosing) in the long-term treatment period.
- To assess the change from baseline in seated systolic blood pressure and seated diastolic blood pressure in subjects with baseline seated systolic blood pressure >140 mmHg for each dose of dapagliflozin (AM dosing and PM dosing) versus placebo after 24 weeks of oral administration of double-blind treatment.

2.4 Pharmacokinetic Objective

- To explore the relationships between exposure measures and efficacy endpoints such as reduction in A1C from baseline.

2.5 Safety Objectives

- To assess the safety and tolerability of each dose of dapagliflozin (AM dosing and PM dosing) after up to 24 weeks of oral administration of double-blind treatment.
- To assess the safety and tolerability of dapagliflozin 5 mg QAM and 10 mg QAM after up to 24 weeks of oral administration in subjects with enrollment A1C ≥ 10.1 and ≤ 12.0%.
- To assess the safety and tolerability of each dose of dapagliflozin (AM dosing and PM dosing) after up to 102 weeks of oral administration of either double-blind or site and subject blinded treatment.

3 ETHICAL CONSIDERATIONS

3.1 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.

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).

Systems with procedures that assure the quality of every aspect of the study will be implemented.

3.2 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.

3.3 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. Freely given written informed consent must be obtained from every subject or, in those situations where consent cannot be given by subjects, their legally acceptable representative, prior to clinical study participation, including informed consent for any screening procedures conducted to establish subject eligibility for the study.

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

Appendix 1 contains BMS procedures on obtaining informed consent from subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representative prior to participating in a clinical study. Procedures are described for all subjects, including those who are unable to give informed consent. The relevant procedures must be used whenever they are applicable (see subject selection criteria in Sections 4.2.1 and 4.2.2).

4 INVESTIGATIONAL PLAN

4.1 Study Design and Duration

This is a Phase III trial to evaluate the antihyperglycemic effect of three different doses (2.5, 5 and 10 mg) of dapagliflozin, randomized in a blinded manner for QAM or QPM dosing, in subjects with type 2 diabetes who have inadequate glycemic control, defined as an A1C $\geq$ 7.0% and $\leq$ 10.0% evaluated at the enrollment visit by the central laboratory (group 1). Subjects with an enrollment A1C $\geq$ 10.1 % and $\leq$ 12.0 %, who meet all other selection criteria may be eligible for randomization into one of the two active blinded

treatment arms of either dapagliflozin 5 mg QAM or dapagliflozin 10 mg QAM (group 2)**.**

Approximately 100 sites will randomize a minimum combined total of 560 subjects (70 subjects/treatment arm) in group 1 and up to 35 subjects/treatment arm in group 2. Allowing approximately 8 months for patient recruitment, this study will be conducted over 33 months. The end of treatment date of this study will be the date the last subject takes the last dose of study medication during the treatment period. The end of the study will be the date of the last visit of the last subject participating in the study (end of the long-term treatment period).

A pre-enrollment informed consent form sample will be provided by the Sponsor to all the sites, and implemented locally, when possible, based on all applicable regulatory requirements and laws. When used, written pre-enrollment informed consent form must be obtained prior to conducting pre-screening activities. For the purpose of this trial, pre-screening activities may include review of medical history and concomitant medications, local laboratory analyses, and vital signs (including calculation of the BMI) to evaluate prospective subjects. Laboratory tests obtained locally and procedures conducted under the pre-enrollment consent will be used only to evaluate a potential subject's eligibility. All subjects who are pre-screened should be listed by date of birth, date of pre-screen, and gender, on the pre-screening log.

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

The study design includes the following four study periods:

1) Qualification Period (up to 14 days following enrollment central laboratory samples collection) ***Note: The single-blind lead-in study medication and all the enrollment visit central laboratory results must have been received at the site prior to completing the entry into lead-in Day -14 visit.***
2) Lead-In Period (7-14 days)
   – Eligible subjects with an enrollment A1C ≥ 7.0 and ≤ 10.0 % (Group 1) should complete the lead-in period in 14 ± 5 days.

– Eligible subjects with an enrollment A1C ≥ 10.1 and ≤ 12.0 % Group 2) should complete the lead-in period in 7 ± 5 days.

3) Short-Term Treatment Period (24 weeks)
4) Long-Term Treatment Period (78 weeks)

4.1.1 Qualification Period

Signature of the protocol-specific informed consent form constitutes the first procedure of the qualification period, followed by the assignment of a unique subject number by the IVRS. Protocol-specific procedures may then be performed, as part of the enrollment visit, to evaluate the subject's eligibility. The enrollment visit procedures may be completed on one or more days during the qualification period.

The end of qualification period/entry into the lead-in period (Day -14) visit will be scheduled once all the inclusion and exclusion criteria have been evaluated and the requirements for entry into the lead-in period have been met. Entry into lead-in Day -14 visit should be scheduled within 14 days of the enrollment central laboratory samples collection. **The Sponsor should be contacted if the Day -14 visit is planned to be scheduled more than 14 days after the enrollment central laboratory samples collection.**

4.1.2 Lead-In Period

Eligible subjects who complete the qualification period will be eligible to enter the lead-in period. The lead-in period is a 7 - 14 day placebo lead-in period during which subjects will receive diet and exercise counseling consistent with the American Diabetes Association (ADA) recommendations or similar local guidelines. Diet and exercise counseling will be provided for the duration of the study. A Registered Dietitian, Registered Nurse, Physician, Certified Diabetes Educator or Nutritionist will provide this counseling.

- Subjects with an enrollment A1C ≥ 7.0 and ≤ 10.0 % (Group 1) should complete the lead-in period in 14 ± 5 days.
- Subjects with an enrollment A1C ≥ 10.1 and ≤ 12.0 % (Group 2) should complete the lead-in period in 7 ± 5 days.

Upon entry in the lead-in period, subjects will also be given a blood glucose meter and instructed on its use by site personnel. Subjects should demonstrate the ability to correctly perform self-monitoring of blood glucose (SMBG) during the lead-in period, as required per protocol (see section 6.3.1).

Single-blind placebo will be used to assess subject's compliance with treatment. Subjects should demonstrate good compliance with study medication (≥ 70% and ≤ 130%) during the lead-in period to be eligible for entry into the short-term treatment period. **For subjects with a compliance between ≥ 70% AND < 80% or > 120% AND ≤ 130%, the Investigator should ensure that there are no systematic factors which may result in unacceptable compliance with study medication during the treatment periods of the trial. Such cases should be discussed with the Medical Monitor prior to randomization.**

4.1.3 Short-Term Treatment Period

Eligible subjects will enter in the randomized, short-term, double-blind, treatment period.

Group 1: Subjects with an enrollment A1C ≥ 7.0% and ≤ 10.0%

The IVRS will assign subjects with an enrollment A1C ≥ 7.0% and ≤ 10.0% to randomly receive one of the following blinded treatment regimens in a 1:1:1:1:1:1:1 ratio:

- Dapagliflozin 2.5 mg QAM
- Dapagliflozin 2.5 mg QPM
- Dapagliflozin 5 mg QAM
- Dapagliflozin 5 mg QPM
- Dapagliflozin 10 mg QAM
- Dapagliflozin 10 mg QPM
- Dapagliflozin Matching Placebo AM and PM

Group 2: Subjects with an enrollment A1C ≥ 10.1 and ≤ 12.0%

The IVRS will assign subjects with an enrollment A1C ≥ 10.1% and ≤ 12.0% to randomly receive one of the following blinded treatment regimens in a 1:1 ratio:

- Dapagliflozin 5 mg (QAM)
- Dapagliflozin 10 mg (QAM)

Subjects will be followed for a total of 24 weeks on double-blind study medication.

Dose titration of blinded study medication is not permitted at any time during the study. Any changes in the dose (s) of blinded study medication may result in discontinuation from the study.

4.1.3.1 Rescue Medication due to Lack of Glycemic Control in the Short-Term Treatment Period

Subjects with lack of glycemic control during the short-term treatment period may be eligible to receive open-label rescue medication, in addition to their current double-blind treatment. The rescue medication provided by the Sponsor will be metformin. **Rescue medication means the addition of an approved oral antihyperglycemic agent, used according to conventional standards of care, to treat hyperglycemia which may therefore allow the subject to remain in the trial.** During the short-term treatment period, all rescue decisions will be based on the central laboratory FPG and confirmatory FPG results. If subjects meet the protocol-specified glycemic criteria based on FPG (see Table 4.2.3.2A), they will be considered for rescue medication.

Titration of open-label rescue metformin will be permitted as described in Section 4.2.3.2

4.1.4 Long-Term Treatment Period

Eligible subjects completing the 24-week short-term treatment period will continue into the site and subject blinded long-term treatment period. During the long-term treatment period, subjects will be followed for a total of 78 weeks on blinded study medication.

Sites and subjects will be blinded to treatment assignment, but the Sponsor will not be blinded.

The IVRS will assign site and subject blinded treatment in the long-term treatment period as follows:

In subjects who did not receive rescue medication during the 24 week short-term treatment period:

- Subjects with enrollment A1C ≥ 7.0 and ≤ 10.0% who received double-blind dapagliflozin during the short-term treatment period will remain on the same treatment plus double-blind meformin matching placebo in the long-term treatment period.
- Subjects with enrollment A1C ≥ 7.0 and ≤ 10.0% who received double-blind placebo during the short-term treatment period will remain on the same treatment plus double-blind metformin 500 mg in the long-term treatment period.
- Subjects with enrollment A1C ≥ 10.1 and ≤ 12.0% will remain on the same treatment in the long-term treatment period.

In subjects who received rescue medication during the 24 week short-term treatment period:

- Subjects who received rescue medication during the short-term treatment period will remain on the same blinded treatment assigned to them in the short-term treatment period throughout the long-term treatment period, and will continue to receive open-label rescue medication.

Dose titration of blinded study medication is not permitted at any time during the study. Any changes in the dose(s) of blinded study medication may result in discontinuation from the study.

4.1.4.1 Rescue Medication due to Lack of Glycemic Control in the Long-Term Treatment Period

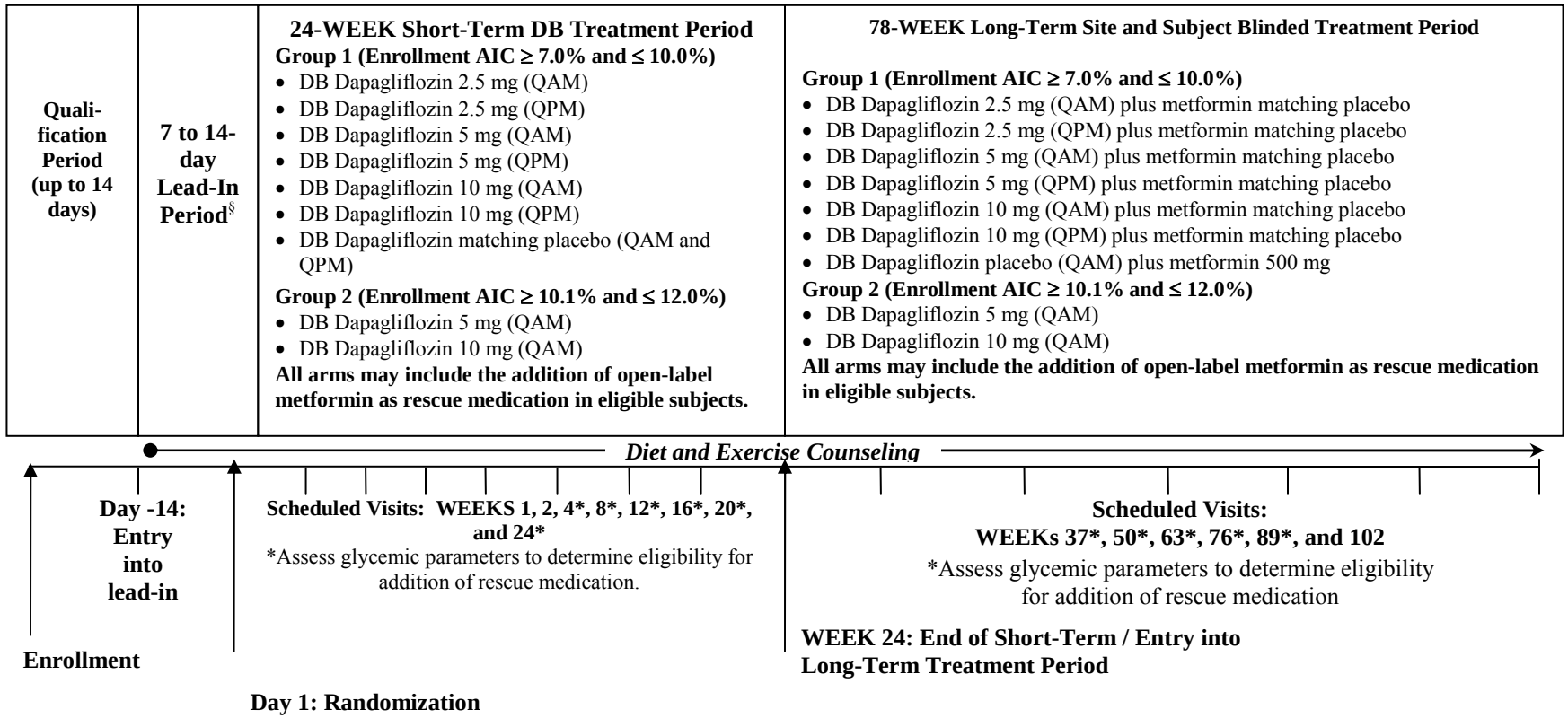
Subjects with lack of glycemic control during the long-term treatment period, who were not previously rescued during the short-term treatment period, may be eligible to receive open-label rescue medication in addition to their site and subject blinded treatment.

During the long-term treatment period, all rescue decisions will be based on central laboratory A1C. If subjects meet the protocol-specified glycemic criteria based on A1C (see Table 4.2.3.2B), they will be considered for rescue medication.

Titration of open-label rescue metformin will be permitted as described in Section 4.2.3.2

4.1.5 Study Schematic

Figure 4.1.5: Study Schematic



§ Eligible subjects with an enrollment A1C ≥ 10.1 and ≤ 12.0% should have the Day 1 randomization visit scheduled within 7 ± 5 days of the Day - 14 entry into lead-in visit, provided short-term treatment period drug supplies have been received at the site. Eligible subjects with an enrollment A1C ≥ 7.0 and ≤ 10.0 % should have the Day 1 randomization visit scheduled within 14 ± 5 days of the Day -14 entry into lead-in period visit.

4.2 Study Population

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

4.2.1 Inclusion Criteria

Signed Written Informed Consent

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

Target Population

2) Subjects must have type 2 diabetes with inadequate glycemic control, defined as:
   - **Group 1:** Central laboratory A1C ≥ 7.0 and ≤ 10.0% obtained at the enrollment visit. ***Note: A one-time central laboratory re-test of the A1C is allowed in subjects with an initial central laboratory A1C of 6.8 or 6.9% who are otherwise eligible, as determined by the Investigator.***

     In situations where both the central laboratory A1C and the calcium values meet criteria for re-test, such re-tests of both the A1C and calcium values are allowed provided the subject is otherwise fully eligible, as determined by the Investigator.

     OR;

   - **Group 2**: Subjects with an enrollment A1C ≥ 10.1 and ≤ 12.0%, who meet all other selection criteria may be eligible for randomization into one of the two active blinded treatment arms of either dapagliflozin 5 mg QAM or dapagliflozin 10 mg QAM.
3) Subjects should be drug naive. Drug naive subjects are defined as subjects who have never received prescription medications for diabetes or have received prescription medications for diabetes for < 24 weeks since the original diagnosis.

   Note: Also refer to exclusion criterion no. 36 for additional related exclusion criterion.
4) C-peptide ≥ 1.0 ng/mL (0.34 nmol/L) at enrollment visit.
5) BMI ≤ 45.0 kg/m^2 at the enrollment visit.

Age and Sex

6) Men and women, ages ≥ 18 to ≤ 77 years old at the time of enrollment visit.
   Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study in such a manner that the risk of pregnancy is minimized.

   WOCBP 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 (defined as amenorrhea ≥ 12 consecutive months; or women on hormone replacement therapy [HRT] with documented serum follicle stimulating hormone [FSH] level > 35 mIU/mL). Even 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.

   WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of investigational product.

4.2.2 Exclusion Criteria

Sex and Reproductive Status

1) WOCBP who are **unwilling or unable** to use an acceptable method to avoid pregnancy for the entire study period.
2) Women who are pregnant or breastfeeding.
3) Women with a positive pregnancy test on enrollment or prior to investigational product administration.

Central Laboratory Test Findings at Enrollment

4) UACR > 1,800 mg/g (203.4 mg/mmol/Cr).
5) Aspartate Aminotransferase (AST) > 3X upper limit of normal (ULN).
6) Alanine Aminotransferase (ALT) > 3X ULN.
7) Serum total bilirubin (TB) > 2 mg/dL (34.2 μmol/L).
8) Serum creatinine S_{cr} ≥ 1.50 mg/dL (133 μmol/L) for male subjects; S_{cr} ≥ 1.40 mg/dL (124 μmol/L) for female subjects.

9) Calcium value outside of the central laboratory normal reference range. ***Note: A one-time central laboratory re-test of calcium is allowed in subjects with an out of range initial central laboratory calcium value who are otherwise eligible as determined by the Investigator.***

   In situations where both the central laboratory A1C and the calcium values meet criteria for re-test, such re-tests of both the A1C and calcium values are allowed provided the subject is otherwise fully eligible, as determined by the Investigator.

10) Positive for hepatitis B surface antigen.
11) Positive for anti-hepatitis C virus antibody.
12) Hemoglobin ≤ 11.0 g/dL (110 g/L) for men; hemoglobin ≤ 10.0 g/dL (100 g/L) for women.
13) Creatine kinase (CK) > 3X ULN.
14) Abnormal free T4 values. *Abnormal thyroid stimulating hormone (TSH) value at enrollment will be further evaluated by free T4. Subjects with abnormal free T4 values will be excluded.*

Target Disease Exceptions

15) History of diabetes insipidus.
16) 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 three months prior to enrollment, or other signs and symptoms.
17) History of diabetic ketoacidosis or hyperosmolar nonketotic coma.

Medical History and Concurrent Diseases

CV/Vascular Diseases:

18) Severe uncontrolled hypertension defined as systolic blood pressure (SBP) ≥180 mmHg and/or diastolic blood pressure (DBP) ≥110 mmHg. ***Note: A one-time retest may be allowed, as determined by the Investigator, after a minimum of 2 weeks following the initiation or adjustment of antihypertensive medication. Such cases should be discussed with the Sponsor prior to re-testing the blood pressure.***

Any of the following CV/Vascular Diseases within 6 months of the enrollment visit:

19) Myocardial infarction.
20) Cardiac surgery or revascularization (CABG/PTCA).
21) Unstable angina.
22) Unstable congestive heart failure (CHF).
23) CHF New York Heart Association (NYHA) Class III or IV (See Appendix 3).

24) Transient ischemic attack (TIA) or significant cerebrovascular disease.
25) Unstable or previously undiagnosed arrhythmia.

Renal Diseases:

26) History of unstable or rapidly progressing renal disease.
27) Conditions of congenital renal glucosuria.

Hepatic Diseases:

28) Significant hepatic disease, including, but not limited to, chronic active hepatitis and/or severe hepatic insufficiency.
29) Documented history of hepatotoxicity with any medication.
30) Documented history of severe hepatobiliary disease.

Hematological and Oncological Diseases/Conditions:

31) History of hemoglobinopathy, with the exception of sickle cell trait (SA) or thalassemia minor; or chronic or recurrent hemolysis.
32) 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 weeks prior to the enrollment visit.
33) Malignancy within 5 years of the enrollment visit (with the exception of treated basal cell or treated squamous cell carcinoma).
34) Known immunocompromised status, including but not limited to, individuals who have undergone organ transplantation or who are positive for the human immunodeficiency virus.

Allergies and Adverse Drug Reactions:

35) Allergies or contraindication to the contents of dapagliflozin tablets or metformin.

Prohibited Treatments and/or Therapies

36) Any administration of antihyperglycemic therapy for more then 14 days (consecutive or not) during the 12 weeks prior to enrollment. **In addition, administration of any antihyperglycemic therapy, at any dose, at any time during the 4 weeks prior to the enrollment visit, is an exclusion criterion.**
37) Replacement or chronic systemic corticosteroid, defined as any dose of systemic corticosteroid taken for > 4 weeks within 3 months prior to enrollment visit.

NOTE: Topical or inhaled corticosteroids are allowed.

38) History of bariatric surgery or lap-band procedure.
39) Administration of sibutramine, phentermine, orlistat, rimonabant, benzphetamine, diethylpropion, methamphetamine, and/or phendimetrazine, within 30 days of the enrollment visit.

Other Exclusion Criteria

40) Any unstable endocrine, psychiatric, rheumatic disorders as judged by the Investigator.
41) Subject is, in the judgment of the Investigator, unlikely to comply with the protocol or has any severe concurrent medical or psychological condition that may affect the interpretation of efficacy or safety data.
42) Subject who, in the judgment of the Investigator, may be at risk for dehydration or volume depletion that may affect the interpretation of efficacy or safety data.
43) 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.
44) Subject is currently abusing alcohol or other drugs or has done so within the last 6 months.
45) Subject is a participating investigator, study coordinator, employee of an investigator or immediate family member of any of the aforementioned.
46) Previous participation in a clinical trial with dapagliflozin (BMS-512148) and/or with any other SGLT2 inhibitors.
47) Administration of any other investigational drug within 30 days of planned enrollment to this study.
48) Prisoners or subjects who are involuntarily incarcerated
49) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

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.

Criteria for Entry into the Short-Term Treatment Period

For entry into the short-term treatment period, the following criteria **MUST** be met:

- All non-central laboratory-related selection criteria evaluated at the enrollment visit have been met and have continued to be met throughout the lead-in period, and up to

the Day 1 Randomization visit. Central laboratory values that meet selection criteria at the enrollment visit are not required to meet the selection criteria at the entry into lead-in Day -14 visit. **However, in the event of new laboratory abnormalities noted at entry into lead-in Day -14 visit, the Investigator should ensure that they do not represent new and significant comorbidity that would preclude safe participation in the protocol. Such cases should be discussed with the medical monitor.**

- No clinical conditions or clinically significant abnormalities, in any laboratory value(s) collected after enrollment and prior to randomization and/or ECG, which, in the Investigator's judgment, should preclude entry into the treatment period.
- Subjects should demonstrate good compliance with the administration of study medication (≥ 70% and ≤ 130%) during the lead-in period **For subjects with a compliance between ≥ 70% AND < 80% or > 120% AND ≤ 130%, the Investigator should ensure that there are no systematic factors which may result in unacceptable compliance with study medication during the treatment periods of the trial. Such cases should be discussed with the Medical Monitor prior to randomization.**
- Subjects demonstrated ability to perform SMBG as required per protocol (see Section 6.3.1.)

4.2.3 Discontinuation of Subjects from Treatment

Subjects MUST discontinue study treatment (investigational or noninvestigational treatment) 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 (see Section 7.6.2)
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness

Subjects MAY discontinue study treatment (investigational **and/or** open-label rescue medication, if applicable) for any of the following reasons:

- Sustained elevated S_{cr} (See Section 4.2.3.1)
- Protocol-defined lack of glycemic control (See Section 4.2.3.2)
- Protocol-defined major hypoglycemia episode or recurrent non-major hypoglycemia episodes (See Section 4.2.3.3)
- Sustained elevated Liver Function Tests (see Section 4.2.3.4)
- Sustained elevated CK (see Section 4.2.3.5)
- Sustained hyponatremia (see Section 4.2.3.6)

All subjects who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 6. 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.

4.2.3.1 Discontinuation Guidelines due to Sustained Elevated Serum Creatinine

Subjects with a $S_{cr} \geq 1.50$ mg/dL (133 μmol/L) (males) or ≥ 1.40 mg/dL (124 μmol/L) (females) **OR subjects (male or female) with an increase from baseline in S_{cr} of > 0.50 mg/dL (44.2 μmol/L),** will have study medication and rescue medication (if applicable) withheld and a confirmatory, repeat S_{cr} drawn within one week.

- If the repeat S_{cr} is < 1.50 mg/dL (133 μmol/L) (males) or < 1.40 mg/dL (124 μmol/L) (females), study medication and rescue medication (if applicable) may be resumed unless otherwise contraindicated.
- If the repeat S_{cr} is ≥ 1.50 mg/dL (133 μmol/L) (males) or ≥ 1.40 mg/dL (124 μmol/L) (females), the subject should be immediately discontinued from the study, the

Sponsor notified, and the end-of-period visit will be performed (see section 6.3.6.1). **The Investigator will follow the subject until the event has resolved or stabilized.**

4.2.3.2 Discontinuation Guidelines due to Protocol-Defined Lack of Glycemic Control

During the short-term and long-term treatment periods of the trial, subjects may be eligible for the addition of open-label rescue medication (metformin) to their blinded treatment regimen in order to treat ongoing hyperglycemia. Subjects for whom metformin is not otherwise contraindicated may receive open-label metformin added onto, but not as a replacement for, their current study medication regimen.

The sub-sections and tables listed below define the lack of glycemic control criteria for initiation of rescue medication, subsequent dose titration of rescue medication as well as discontinuation from the study.

Protocol-Defined Lack of Glycemic Control Criteria for Initiation of Rescue Medication

Pre-specified glycemic criteria (see table 4.2.3.2A), based upon central laboratory FPG and confirmatory, repeat FPG, have been established during the short-term treatment period, starting at Week 4, and up to Week 24 visits, to determine eligibility for open-label rescue metformin medication.

Table 4.2.3.2A: Lack of Glycemic Control Criteria for Initiation of Rescue Medication (Short-Term Treatment Period)

Visit Label	Central Laboratory FPG
From Week 4 to Week 8 (excluding Week 8)	FPG > 270 mg/dL (15.0 mmol/L)
From Week 8 to Week 12 (excluding Week 12)	FPG > 240 mg/dL (13.3 mmol/L)
From Week 12 to Week 24 (**including** 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 can be rescued.**

Subjects who meet rescue criteria in the short-term treatment period must first complete the Week 24 "Rescue" visit procedures before receiving open-label rescue medication (metformin) to ensure that important trial endpoint measurements are collected. (see Section 6.3.6.1)

Following completion of the Week 24 "Rescue" visit, rescued subjects will be given open-label metformin, 500 mg tablets, **to be initiated at the lowest starting dose based on the approved product label in the applicable country,** in addition to their blinded study medication. Rescued subjects will then continue in the short-term treatment period according to their original visit schedule. Once a subject is rescued, the central laboratory A1C values measured at visits occurring after the rescue visit has been completed will be unblinded to ensure proper follow-up of rescued subjects.

Pre-specified glycemic criteria (Table 4.2.3.2B), based upon central laboratory A1C, have also been established during the long-term treatment period to determine eligibility for open-label rescue medication, metformin, for **subjects not previously rescued.**

Table 4.2.3.2B: Lack of Glycemic Control Criteria for Initiation of Rescue Medication During the Long-Term Period (in subjects not Previously Rescued During the Short term Treatment Period)

Visit Label	Central Laboratory A1C
After Week 24 to Week 50 (including Week 50)	A1C > 8.0%
After Week 50 to Week 76 (including Week 76)	A1C > 7.5%
After Week 76 to Week 102 (**excluding** Week 102)	A1C > 7.0%

Subjects who meet rescue criteria in the long-term treatment period, and who are not already on rescue medication, must first complete the Week 102 "Rescue" visit procedures before they can receive open-label metformin, to ensure that important trial endpoint measurements are collected (see section 6.3.6.1).

Following completion of the Week 102 "Rescue" visit, rescued subjects will be given open-label metformin 500 mg tablets, **to be initiated at the lowest starting dose based on the approved product label in the applicable country,** in addition to their blinded study medication. **Rescued subjects will then continue in the long-term treatment period according to their original visit schedule.**

Protocol-Defined Lack of Glycemic Control Criteria for Dose Titration of Rescue Medication

Open-label metformin should be initiated and titrated in accordance with the approved product label for that specific country.

Rescued subjects will be given open-label metformin 500 mg tablets in addition to their blinded study medication. The appropriate medication will be dispensed by calling the IVRS. Metformin should be started at 500 mg daily in the morning with breakfast. Following initiation of open-label rescue metformin, rescued subjects should be scheduled for titration visits to increase the metformin dose, as tolerated and in accordance with the approved product label for that country, up to a maximum of 2000 mg, as indicated by their glycemic response and as per the Investigator's judgment.

Protocol-Defined Lack of Glycemic Control Criteria for Discontinuation from the Study

Rescued subjects with central laboratory A1C values consistently greater than A1C values specified in Table 4.2.3.2C, for 12 weeks despite a maximum tolerated dose of metformin will be discontinued from the study and referred for additional antihyperglycemic therapy.

Table 4.2.3.2C: Lack of Glycemic Control Criteria for Discontinuation from the Study

Visit Label	Central Laboratory A1C
Short-Term Treatment Period Visits (including Week 24)	A1C > 8.0%
After Week 24 to Week 50 (including Week 50)	A1C > 8.0%
After Week 50 to Week 76 (including Week 76)	A1C > 7.5%
After Week 76 to Week 102 (**excluding** Week 102)	A1C > 7.0%

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

Subjects will be discontinued from study medication if they experience severe and/or frequent hypoglycemia episodes, defined as ≥ 1 major episode or recurring non-major episodes in the event where the possibility of down-titration of contributing concomitant medication(s), (other than blinded study medication) and/or other contributing factors (e.g. excessive physical activity) have been evaluated and corrected. ***NOTE: Dose titration of blinded study medication is not permitted at any time during the study.***

- Major Episodes are defined as symptomatic episodes requiring external (3rd party) assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value < 3 mmol/L (< 54 mg/dL) and prompt recovery after glucose or glucagon administration.
- Recurring Non-Major Episodes are defined as any recurrent hypoglycemia episodes, as determined by the Investigator, not meeting the definition of Major Episodes.

Section 6.3.1.1 provides additional guidance on management and reporting of hypoglycemia. **It is the Investigator's clinical assessment whether subjects who experience non-recurrent and non-major episodes of hypoglycemia should be discontinued from study medication.**

4.2.3.4 Discontinuation Guidelines due to Sustained Elevated Liver Safety Abnormalities

The monitoring for liver safety will be performed using the serum levels of AST, ALT and TB. Based on the test results for the above parameters, two signals for safety monitoring are identified, as follows:

Safety Monitoring Signal 1: Elevation of ALT and/or AST > 3X ULN AND increase of TB > 1.5X ULN:

Subjects with an ALT and/or AST > 3X ULN AND TB > 1.5 X ULN will have blinded study medication withheld and confirmatory, repeat liver function tests, drawn within one week.

- If the repeat ALT and/or AST are ≤ 3X ULN and/or ≤ 1.5X ULN (TB), blinded study medication may be resumed unless otherwise contraindicated.
- If the repeat ALT and/or AST are > 3X ULN AND TB > 1.5 X ULN, the subject must be immediately discontinued from the study, the Sponsor notified and the end-of-period visit performed (see section 6.3.6.1). **The Investigator will follow the subject until the event has resolved or stabilized.**

Safety Monitoring Signal 2: Elevation of ALT and/or AST >5X ULN:

Subjects with an ALT or AST > 5X ULN will have blinded study medication withheld and confirmatory, repeat liver function tests, drawn within one week.

- If the repeat ALT and AST are ≤ 5X ULN, blinded study medication may be resumed unless otherwise contraindicated.
- If the repeat ALT or AST is > 5X ULN, the subject must be immediately discontinued from the study, the Sponsor notified and the end-of-period visit performed (see section 6.3.6.1). The Investigator will follow the subject until the event has resolved or stabilized.

4.2.3.5 Discontinuation Guidelines due to Sustained Elevated Creatinine Kinase

Subjects with a CK > 10X ULN will have blinded study medication withheld and a confirmatory, repeat CK, drawn upon receipt of the initial laboratory result (within 24 hours as much as possible and no later than within 3 days following receipt of the initial laboratory result).

- If the repeat CK is ≤ 10X ULN, blinded study medication may be resumed unless otherwise contraindicated.
- If the repeat CK > 10X ULN, the subject must be immediately discontinued from the study, the Sponsor notified and the end-of-period visit performed (see section 6.3.6.1). **The Investigator will follow the subject until the event has resolved or stabilized.**

4.2.3.6 Discontinuation Guidelines due to Hyponatremia

Subjects with a serum sodium ≤ 125 mEq/L (125 mmol/L) will have blinded study medication withheld and a confirmatory, repeat serum sodium, drawn within 3 days.

- If the repeat serum sodium is ≥ 130 mEq/L (130 mmol/L):
  - Blinded study medication may be resumed unless otherwise contraindicated.
  - Serum sodium should be re-tested within one week after resuming the blinded study medication
    - If the repeat of serum sodium, obtained within one week after resuming blinded study medication, is < 130 mEq/L (130 mmol/L), the subject must be immediately discontinued from the study, the Sponsor notified and the end-of-period visit performed (see section 6.3.6.1). **The Investigator will follow the subject until the event has resolved or stabilized.**
    - If the repeat of serum sodium, obtained within one week after resuming blinded study medication, is ≥ 130 mEq/L (130 mmol/L), the subject may continue in the study and will be followed according to the protocol. Additional monitoring of serum sodium may be performed according to the local practice or Investigator's judgment.
- If the repeat serum sodium is < 130 mEq/L (130 mmol/L) **AND** there is no suspected new, temporary and reversible cause of hyponatremia based on clinical assessment (other than the administration of blinded study medication), the subject must be immediately discontinued from the study, the Sponsor notified and the end-of-period visit performed (see section 6.3.6.1). **The Investigator will follow the subject until the event has resolved or stabilized.**
- If the repeat serum sodium is < 130 mEq/L (130 mmol/L) **AND** there is a suspected new, temporary and reversible cause of hyponatremia based on clinical assessment (other than the administration of blinded study medication):
  - Blinded study medication will continue to be withheld.
  - The suspected cause of hyponatremia should be identified and corrected.
  - Serum sodium should be re-tested within one week after the first repeat:
    - If the repeat of serum sodium, obtained within one week after the first repeat, is < 130 mEq/L (130 mmol/L):
      - The subject must be immediately discontinued from the study, the Sponsor notified and the end-of-period visit performed (see section 6.3.6.1). **The Investigator will follow the subject until the event has resolved or stabilized.**

- If the repeat of serum sodium, obtained within one week after the first repeat, is ≥ 130 mEq/L (130 mmol/L):
  - Blinded study medication may be resumed unless otherwise contraindicated.
  - Serum sodium should be re-tested within one week after resuming blinded study medication,
  - The subject may continue in the study and will be followed according to the protocol. Additional monitoring of serum sodium may be performed according to the local practice or Investigator's judgment.

For subjects whose serum sodium is between 126 and 129 mEq/L (126 and 129 mmol/L), the Investigator's clinical judgment should apply concerning whether such subjects should be followed according to the above algorithm. (see Appendix 5 for algorithm flow chart).

5 TREATMENTS

5.1 Study Treatment

5.1.1 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 product(s) is/are:

- Dapagliflozin 2.5 mg tablets
- Dapagliflozin 5 mg tablets
- Dapagliflozin 10 mg tablets

- Dapagliflozin 2.5/5 mg matching placebo tablets
- Dapagliflozin 10 mg matching placebo tablets
- Metformin 500 mg tablet
- Placebo matching metformin 500mg tablet

5.1.2 Noninvestigational Product

Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, are considered noninvestigational products.

The rescue medication provided by the Sponsor for this trial will be metformin 500 mg tablets. Rescue medication means the addition of an approved oral antihyperglycemic agent, used according to conventional standards of care, to treat uncontrolled hyperglycemia, which may therefore allow the subject to remain in the trial.

5.1.3 Identification

The following Investigational and Non-Investigational Product(s) will be supplied by Bristol-Myers Squibb Research and Development.

Table 5.1.3: Investigational and Non-Investigational Products

PRODUCT	POTENCY	APPEARANCE
Dapagliflozin-2.5 mg tablet	2.5 mg	Green, plain, diamond-shaped, film-coated tablet
Dapagliflozin-5 mg tablet	5 mg	Green, plain, diamond-shaped, film-coated tablet
Dapagliflozin-10 mg tablet	10 mg	Green, plain, diamond-shaped, film-coated tablet
Placebo for dapagliflozin tablet (matches 2.5/5 strengths)	N/A	Green, plain, diamond-shaped, film-coated tablet
Placebo for dapagliflozin tablet (matches 10 mg strength)	N/A	Green, plain, diamond-shaped, film-coated tablet
Metformin 500 mg tablet	500 mg	White to off-white, round, tablet

Table 5.1.3: Investigational and Non-Investigational Products

PRODUCT	POTENCY	APPEARANCE
Placebo to match Metformin 500 mg tablet	N/A	White to off-white, round, tablet
Glucophage® (metformin hydrochloride film-coated tablets)	500 mg	White to off-white, round, tablet

5.1.4 Packaging and Labeling

5.1.4.1 Blinded Study Medication

Single-Blind Placebo Lead-In Medication

Upon entry in the lead-in period, each subject will be assigned a Patient Kit containing 4 bottles (Bottles A, B, C, D). Each Patient Kit will be labeled with a 2-Panel, single-blind label, printed in black with spaces to complete the subject number and date dispensed on Panel 1 and Panel 2. In addition, the protocol number, batch number, the number of bottles, route of administration, directions for use, storage conditions, and use date, will be indicated. Upon dispensing, the Investigator will complete the subject number and date dispensed on Panels 1 and 2. Panel 2, which contains the drug identity and potency, will be detached and affixed to the appropriate drug label page.

Bottles A, B, C and D will contain 17 tablets per bottle. Each bottle will be labeled with a 1-Panel, blinded label printed in black. The protocol number, batch number, the number of tablets, route of administration, directions for use, storage conditions, and use date, will be indicated on each bottle.

Each kit will contain sufficient product for the 2-week, single-blind, lead-in period with overage.

Group 1: Double-Blind Short-Term Treatment Period Medication

Upon randomization and throughout the short-term treatment period, each subject will be assigned a total of 2 Patient Kits consisting of 4 bottles each, (Bottles A, B, C, D). Each Patient Kit will be labeled with a 3-Panel, double-blind label, printed in black with spaces

to complete the subject number and date dispensed on Panel 1 and Panel 2. In addition, the protocol number, batch number, the number of bottles, route of administration, directions for use, storage conditions, and use date, will be indicated. Upon dispensing, the Investigator will complete the subject number and date dispensed on Panels 1 and 2. Panels 2 and 3 will be detached and affixed to the appropriate drug label page.

Bottles A, B, C and D will contain 100 tablets per bottle. Each bottle will be labeled with a 1-Panel, blinded label printed in black. The protocol number, batch number, the number of tablets, route of administration, directions for use, storage conditions, and use date, will be indicated on each bottle. Each kit will contain sufficient product for a 12-week, double-blind, treatment period with overage.

Group 1: Site and Subject Blinded Long-Term Treatment Period Medication

Upon entry into the long-term treatment period, and continuing throughout the long-term treatment period, each subject will be assigned a total of 6 Patient Kits consisting of 4 bottles each, (Bottles A, B, C, D). Each Patient Kit will be labeled with a 3-Panel, double-blind label, printed in black with spaces to complete the subject number and date dispensed on Panel 1 and Panel 2. In addition, the protocol number, batch number, the number of bottles, route of administration, directions for use, storage conditions, and use date, will be indicated. Upon dispensing, the Investigator will complete the subject number and date dispensed on Panels 1 and 2. Panels 2 and 3 will be detached and affixed to the appropriate drug label page.

Bottles A, B, C, and D will contain 100 tablets per bottle. Each bottle will be labeled with a 1-Panel, blinded label printed in black. The protocol number, batch number, the number of tablets, route of administration, directions for use, storage conditions, and use date, will be indicated on each bottle. Each kit will contain sufficient product for a 12-week, double-blind, treatment period with overage.

In addition to the patient kit, each subject will be assigned a total of 6 double-blind bottles. Each bottle will be labeled with a 3-Panel, double-blind label, printed in black with spaces to complete the subject number and date dispensed on Panel 1 and Panel 2. In addition, the protocol number, batch number, the number of bottles, route of administration, directions for use, storage conditions, and use date, will be indicated.

Upon dispensing, the Investigator will complete the subject number and date dispensed on Panels 1 and 2. Panels 2 and 3 will be detached and affixed to the appropriate drug label page. Each one of these bottles will be labeled with a 1-Panel, blinded label printed in black. The protocol number, batch number, the number of tablets, route of administration, directions for use, storage conditions, and use date, will be indicated on each bottle. Each kit will contain sufficient product for a 12-week, double-blind, treatment period with overage.

Group 2: Double-Blind Short-Term Treatment Period and Site and Subject Blinded Long -Term Treatment Period - Subjects with Enrollment AIC ≥ 10% and ≤ 12%

Upon entry into the short-term treatment period and continuing into the long-term treatment period, each subject will be assigned a total of 8 Patient Kits containing 2 bottles each, (Bottle A and Bottle B). Each Patient Kit will be labeled with a 3-Panel, double-blind label, printed in black with spaces to complete the subject number and date dispensed on Panel 1 and Panel 2. In addition, the protocol number, batch number, the number of bottles, route of administration, directions for use, storage conditions, and use date, will be indicated. Upon dispensing, the Investigator will complete the subject number and date dispensed on Panels 1 and 2. Panel 2 and Panel 3, which contains the drug identity and potency in a blinded fashion, will be detached and affixed to the appropriate drug label page.

Bottles A, and B will contain 100 tablets per bottle. Each bottle will be labeled with a 1-Panel, blinded label printed in black. The protocol number, batch number, the number of tablets, route of administration, directions for use, storage conditions, and use date, will be indicated on each bottle.

Each kit will contain sufficient product for a 12-week, double-blind, treatment period with overage.

5.1.4.2 Open-Label Rescue Metformin

Upon completion of the appropriate "Rescue" visit (see section 6.3.6.1) and continuing throughout the trial, each rescued subject will be allocated open-label metformin 500 mg tablets as needed based on glycemic control.

Each bottle will contain 100 tablets and will be labeled with a 2-Panel, open label booklet label printed in BLACK ink with spaces to complete the subject number, date dispensed, and directions for use on Panel 1, and the subject number and date dispensed on Panel 2. In addition, the container number, batch number, product identity and potency, number of tablets, storage conditions, and route of administration will be indicated.

Upon dispensing, the investigator will complete the subject number, date dispensed, and dosing instructions on Panel 1, and the subject number and date dispensed on Panel 2. Panel 2 is then detached and affixed to the appropriate drug label page(s).

5.1.5 Handling and Dispensing

Bristol-Myers Squibb will be responsible for assuring that the quality of the Investigational Product is adequate for the duration of the trial. All Investigational Products should be stored at 15° - 25°C (59° - 77°F) in tightly closed containers.

Metformin should be stored at 20° - 25°C (68° – 77° F); excursions permitted to 15° - 30° C (59° – 86° F).

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. 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 9.3 for return and destruction instructions**.**

5.2 Method of Assigning Subjects to a Treatment

At the enrollment visit, each subject will be assigned a unique sequential subject number by the 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.

At the time of entry into the single-blind placebo lead-in period, the site will call IVRS in order for the single-blind lead-in medication to be assigned and dispensed.

Subjects who successfully complete the single-blind placebo lead-in period and meet the criteria for entry into the short-term treatment period (see Section 4.2), will be assigned as follows:

Group 1: Subjects with an enrollment A1C ≥ 7.0% and ≤ 10.0%

The IVRS will assign subjects with an enrollment A1C ≥ 7.0% and ≤ 10.0% to randomly receive one of the following blinded treatment regimens in a 1:1:1:1:1:1:1 ratio:

- Dapagliflozin 2.5 mg QAM
- Dapagliflozin 2.5 mg QPM
- Dapagliflozin 5 mg QAM
- Dapagliflozin 5 mg QPM
- Dapagliflozin 10 mg QAM
- Dapagliflozin 10 mg QPM
- Dapagliflozin Matching Placebo AM and PM

Group 2: Subjects with an enrollment A1C ≥ 10.1 and ≤ 12.0%

The IVRS will assign subjects with an enrollment A1C ≥ 10.1% and ≤ 12.0% to randomly receive one of the following blinded treatment regimens in a 1:1 ratio:

- Dapagliflozin 5 mg (QAM)
- Dapagliflozin 10 mg (QAM)

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. A site will be assigned a block of random subject treatment assignments when calling to randomize the first site's subject, or when calling to randomize a subject and there is no open pending subject treatment block for this site.

At all study visits when study medication is dispensed, each subject will be assigned a Patient Kit number by the IVRS. Patient Kit numbers will be assigned randomly and will correspond to the numbers printed on the packages and bottles containing study drug. Patient Kit numbers will be recorded on the appropriate drug label page. The IVRS will be available 24 hours per day, 7 days per week.

The IVRS will also be used to assign each subject open-label metformin which will be provided as rescue medication in subjects eligible based on rescue criteria.

Eligible subjects completing the 24-week short-term double-blind treatment period will continue into the site and subject blinded long-term treatment period. During the long-term treatment period, subjects will be followed for a total of 78 weeks on blinded study medication. During the long-term period, treatments will be blinded to the sites and subjects but will be unblinded to the sponsor after the database for the 24-week treatment period has been locked. The IVRS will assign site and subject blinded treatment in the long-term treatment period as follows:

Subjects who did not receive rescue medication during the 24 week short-term treatment period:

- Subjects with enrollment A1C ≥ 7.0 and ≤ 10.0% who received double-blind dapagliflozin during the short-term treatment period will remain on the same treatment plus double-blind meformin -matching placebo in the long-term treatment period.
- Subjects with enrollment A1C ≥ 7.0 and ≤ 10.0% who received double-blind placebo during the short-term treatment period will remain on the same treatment plus double-blind metformin 500 mg in the long-term treatment period.
- Subjects with enrollment A1C ≥ 10.1 and ≤ 12.0% will remain on the same treatment assigned to them in the short-term treatment period throughout the long-term treatment period.

Subjects who received rescue medication during the 24 week short-term treatment period:

- Subjects who received rescue medication during the short-term treatment period will remain on the same treatment assigned to them in the short-term treatment period throughout the long-term treatment period and will continue to receive open-label rescue metformin.

5.3 Selection and Timing of Dose for Each Subject

Blinded Dapagliflozin or Matching Placebo

Upon entry into the lead-in period, each subject will be provided a kit containing 4 bottles (Bottles A, B, C, D) with enough medication for 2 weeks plus overage. **Subjects will be instructed to take 1 tablet from Bottle A and 1 tablet from Bottle B every day with the morning meal and 1 tablet from Bottle C and 1 tablet from Bottle D every day with the evening meal.**

Throughout the short-term treatment period, each subject in group 1 will be provided a total of 2 double-blind study medication kits, each containing 4 bottles (Bottles A, B, C, D). Each bottle will contain enough medication for 3 months worth of dosing plus overage. **Subjects will be instructed to take 1 tablet from Bottle A and 1 tablet from Bottle B every day with the morning meal and 1 tablet from Bottle C and 1 tablet from Bottle D every day with the evening meal.**

Each subject in group 2 will be allotted a total of 2 double-blind study medication kits, each containing 2 bottles (Bottle A and Bottle B). Each bottle will contain enough medication for 3 months worth of dosing plus overage. **Subjects will be instructed to take 1 tablet from each bottle every day with the morning meal.**

Throughout the long-term treatment period, each subject in group 1 will be provided a total of 6 blinded study medication kits, each containing 4 bottles (Bottles A,B,C,D) along with 6 bottles of blinded medicine. Each bottle will contain enough medication for 3 months worth of dosing plus overage. **Subjects will be instructed to take 1 tablet from Bottle A and 1 tablet from Bottle B from the kit and 1 tablet from the blinded**

bottle every day with the morning meal and 1 tablet from Bottle C and 1 tablet from Bottle D every day with the evening meal.

Each subject in group 2 will be allotted a total of 2 double-blind study medication kits, each containing 2 bottles (Bottle A and Bottle B). Each bottle will contain enough medication for 3 months of dosing plus overage. **Subjects will be instructed to take 1 tablet from each bottle every day with the morning meal.**

Open-Label Rescue Metformin

Open-label metformin will be provided by the Sponsor and dispensed as 500 mg tablets. Each bottle will contain 100 tablets. Initially, rescued subjects should be instructed to take 1 tablet of metformin per day, in the morning, in accordance with the product label for the appropriate country. Following initiation of open-label rescue metformin, rescued subjects should be scheduled for titration visits to increase the metformin dose, as tolerated and in accordance with the approved product label for that country, up to a maximum of 2000 mg as indicated by their glycemic response and as per the Investigator's judgment.

5.3.1 Dose Modifications

Dose titration of blinded study medication is not permitted at any time during the study. Any changes in the dose(s) of blinded study medication may result in discontinuation from the study.

Titration of open-label rescue metformin to control hyperglycemia should occur in accordance with the approved product label in the applicable country.

5.4 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.

The need to break the blind must first be discussed with the responsible medical monitor and then the best method to do this will be determined.

5.5 Concomitant Treatments

5.5.1 Prohibited and/or Restricted Treatments

5.5.1.1 Prohibited Treatments

Once enrolled, subjects may not receive any of the following for the duration of the study:

- Antihyperglycemic medication (other than protocol required medication as described in inclusion criterion no. 3, and/or open-label rescue medication)
- Treatment with any systemic corticosteroid therapy that will involve ≥ 5 days of therapy. The BMS medical monitor should be consulted prior to beginning therapy with corticosteroids for subjects who require systemic corticosteroid treatment.
- Administration of sibutramine, phentermine, orlistat, rimonabant, benzphetamine, diethylpropion, methamphetamine, and/or phendimetrazine.

5.5.1.2 Restricted Treatments

The following can be administered provided the dose was stable prior to enrollment and is maintained stable for the duration of the study:

- Herbal/over-the-counter preparations:
  - St. John’s Wort
  - Fenugreek
  - Flaxseed
  - Chromium

- Ginseng
- Natural agents marketed for lowering blood sugar such as Antibetic™, Alphabetic™, Diabetics™, DB-7™, Diabetica™, Diabetiks™, Dia-Comp™, Dia Vite™, GlucoCare™, Gluotize™, GlycoNase™, SugarMax™ or Sugar Loss™.

5.5.2 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 prior to initiation 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 6.9.1) and to the protocol visit schedule (see section 6.1.1).
- 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 7.6). During the long-term treatment period, women of childbearing potential should perform pregnancy test monthly using the home-use pregnancy kits provided for this study.
- See also Prohibited Therapies and Restricted Therapies (see Sections 5.5.1.1 and 5.5.1.2).

5.6 Treatment Compliance

Each time study medication (blinded study medication, and open-label rescue metformin, if applicable) 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 CRF.

6 STUDY ASSESSMENTS AND PROCEDURES

6.1 Flow Chart/Time and Events Schedule

Table 6.1A: Flow Chart for Protocol MB102013-Qualification ,Lead-in and Short-Term Treatment Periods

Procedure	Qualification Period (Period A)[a] Enrollment (A01)	Lead-In Period (Period B)[b,c] Day -14 (B01)	Short-Term Double-Blind Treatment Period[c,d] (Period C)									Protocol Section
			Day 1[e] (C01)	WK 1[f] (C02)	WK 2[f] (C03)	WK 4[f] (C04)	WK 8[f] (C05)	WK 12[f] (C06)	WK 16[f] (C07)	WK 20[f] (C08)	WK 24[f] (C99)	
Eligibility Assessments												
Obtain Informed Consent[g]	X											3.3
Review Medical History	X											4.2
Review Selection Criteria	X	X										4.2
Review Randomization Criteria			X									4.2
General Procedures												
Brief Physical Examination	X		X	X	X	X	X	X	X	X		6.3.3
Complete Physical Examination		X									X	6.3.3
Body Weight	X	X	X	X	X	X	X	X	X	X	X	6.4.2.2
Seated Blood Pressure and Heart Rate	X	X	X	X	X	X	X	X	X	X	X	6.3.4.1

Table 6.1A: Flow Chart for Protocol MB102013-Qualification ,Lead-in and Short-Term Treatment Periods

Procedure	Qualification Period (Period A)[a] Enrollment (A01)	Lead-In Period (Period B)[b,c] Day -14 (B01)	Short-Term Double-Blind Treatment Period[c,d] (Period C)									Protocol Section
			Day 1[e] (C01)	WK 1[f] (C02)	WK 2[f] (C03)	WK 4[f] (C04)	WK 8[f] (C05)	WK 12[f] (C06)	WK 16[f] (C07)	WK 20[f] (C08)	WK 24[f] (C99)	
Orthostatic Blood Pressure and Heart Rate			X	X				X			X	6.3.4.2
Height	X											6.9.3
Body Mass Index (BMI)	X											6.9.2
Waist Circumference		X	X								X	6.4.3.2
12-Lead ECG		X[h]									X	6.3.5
Review Concomitant Medications / Procedures	X	X	X	X	X	X	X	X	X	X	X	4.2/5.5
Contact IVR system	X[i]	X[j]	X[k]					X[l]			X[m]	5.2
Provide Diet and Exercise Counseling		X	X		X	X	X	X	X	X	X	6.9.1
Dispense Glucose Meter and Supplies / Provide Instructions		X	X		X	X	X	X	X	X	X	6.3.1
Dispense logs / Provide Instructions		X	X	X	X	X	X	X	X	X	X	6.2/6.3.1

Table 6.1A: Flow Chart for Protocol MB102013-Qualification ,Lead-in and Short-Term Treatment Periods

Procedure	Qualification Period (Period A)[a] Enrollment (A01)	Lead-In Period (Period B)[b,c] Day -14 (B01)	Short-Term Double-Blind Treatment Period[c,d] (Period C)									Protocol Section
			Day 1[e] (C01)	WK 1[f] (C02)	WK 2[f] (C03)	WK 4[f] (C04)	WK 8[f] (C05)	WK 12[f] (C06)	WK 16[f] (C07)	WK 20[f] (C08)	WK 24[f] (C99)	
Review study logs			X	X	X	X	X	X	X	X	X	6.2/6.3.1
Safety Assessment												
Assess Adverse Events		X	X	X	X	X	X	X	X	X	X	7
Assess Genitourinary symptoms	X	X	X	X	X	X	X	X	X	X	X	6.3.2
Assess Hypoglycemia Episodes		X	X	X	X	X	X	X	X	X	X	4.2.3.3/ 6.3.1
Central Laboratory												
Pregnancy Test (urine) WOCBP only	X	X	X	X	X	X	X	X	X	X	X	App. 4
Blood Standard Safety Laboratory Panel	X	X	X	X	X	X	X	X	X	X	X	App. 4
Urine Standard Safety Laboratory Panel	X	X	X	X	X	X	X	X	X	X	X	App. 4

Table 6.1A: Flow Chart for Protocol MB102013-Qualification ,Lead-in and Short-Term Treatment Periods

Procedure	Qualification Period (Period A)[a] Enrollment (A01)	Lead-In Period (Period B)[b,c] Day -14 (B01)	Short-Term Double-Blind Treatment Period[c,d] (Period C)									Protocol Section
			Day 1[e] (C01)	WK 1[f] (C02)	WK 2[f] (C03)	WK 4[f] (C04)	WK 8[f] (C05)	WK 12[f] (C06)	WK 16[f] (C07)	WK 20[f] (C08)	WK 24[f] (C99)	
Spot Urine Glucose Quantification and glucose:creatinine ratio		X	X								X	App. 4
A1C	X	X	X			X	X	X	X	X	X	App. 4
FPG	X	X	X	X	X	X	X	X	X	X	X	App. 4
Assess FPG for Rescue						X	X	X	X	X	X	App. 4
Fasting C-peptide	X		X								X	App. 4
Cystatin-C			X								X	App. 4
Fasting Serum Lipids (Total-C, LDL-C, HDL-C, TG)			X								X	App. 4
FFA			X								X	App. 4
Pre-dose PK sample collection									X	X	X	6.5

Table 6.1A: Flow Chart for Protocol MB102013-Qualification ,Lead-in and Short-Term Treatment Periods

Procedure	Qualification Period (Period A)[a] Enrollment (A01)	Lead-In Period (Period B)[b,c] Day -14 (B01)	Short-Term Double-Blind Treatment Period[c,d] (Period C)									Protocol Section
			Day 1[e] (C01)	WK 1[f] (C02)	WK 2[f] (C03)	WK 4[f] (C04)	WK 8[f] (C05)	WK 12[f] (C06)	WK 16[f] (C07)	WK 20[f] (C08)	WK 24[f] (C99)	
Post-dose PK sample collection at 60 min and 180 min			X							X		6.5
Metabolic Surrogate Markers (hs-CRP, PAI-1,Fibrinogen)			X								X	App. 4
Parathyroid hormone (PTH)			X					X			X	App. 4
Dynamic Serum Bone Metabolism Markers (Osteocalcin, P1NP, CTx, NTx)			X					X			X	App. 4
25-hydroxy vitamin D			X								X	App. 4
Hepatitis Screen Panel and TSH[n]	X											App. 4

Table 6.1A: Flow Chart for Protocol MB102013-Qualification ,Lead-in and Short-Term Treatment Periods

Procedure	Qualification Period (Period A)[a] Enrollment (A01)	Lead-In Period (Period B)[b,c] Day -14 (B01)	Short-Term Double-Blind Treatment Period[c,d] (Period C)									Protocol Section
			Day 1[e] (C01)	WK 1[f] (C02)	WK 2[f] (C03)	WK 4[f] (C04)	WK 8[f] (C05)	WK 12[f] (C06)	WK 16[f] (C07)	WK 20[f] (C08)	WK 24[f] (C99)	
Drug Dispensing												
Dispense Study Medication[o]		X	X					X			X[p]	5.1
Re-dispense Study Medication				X	X	X	X		X	X		5.1
Dispense or re-dispense open-label rescue metformin as needed (if applicable)[q]						X	X	X	X	X	X	5.1.4.2
Review Study Medication Compliance[r]			X	X	X	X	X	X	X	X	X	5.6

[a] Screening procedures required as part of the enrollment visit can be completed over multiple visits, provided all enrollment visit procedures have been completed, with the results reviewed, prior to entry into Lead-in Day -14 visit. Enrollment central laboratory samples should be collected in a fasting state (at least 8 hours prior to the study visit) and should be seen between 6 AM and 10 AM. Subjects should refrain from tobacco, caffeine and alcohol for 8 hours prior to study visit.

[b] Subjects should have their entry into lead-in Day -14 visit completed within 14 days following enrollment central laboratory samples collection. ***Note: The single-blind lead-in study medication and all the enrollment visit central laboratory results must have been received at the site prior to completing the entry into lead-in Day -14 visit.***

[c] Subjects should be in a fasting state (at least 8 hours prior to the study visit) and should be seen between 6 AM and 10 AM. Subjects should refrain from tobacco, caffeine and alcohol for 8 hours prior to study visits. Ensure to collect all fasting blood samples prior to the morning dose(s) of blinded study medication, and open-label rescue metformin (if applicable). Doses of study medication on the day of the visits should be taken upon completion of study visit procedures.

[d] Short-term treatment period visits should be scheduled according to the randomization visit date (Day 1), with a protocol-allowed visit window of ± 5 days. Subjects will bring their glucose meter and study supplies to the site at all visits.

[e] Subjects with an enrollment A1C ≥ 7.0 and ≤ 10.0 % should complete the lead-in period in 14 ± 5 days. Subjects with an enrollment A1C ≥ 10.1 and ≤ 12.0 % should complete the lead-in period in 7 ± 5 days.

[f] Randomized subjects not completing the treatment period, or requiring initiation of rescue medication should have Week 24 procedures done at the time of study discontinuation or rescue. **In subjects discontinuing the study due to AE/SAE, the Investigator will follow the subjects until the event has resolved or stabilized. In addition, subjects who prematurely discontinue from the study may be contacted after discontinuation from the study, to collect vital status information.**

[g] The start of enrollment is defined by the signature of the Protocol-Specific Informed Consent Form by the prospective subject. When only the Protocol-Specific Informed Consent is signed, and all other enrollment visit procedures are completed at a later time, the date on which the enrollment central laboratory samples are collected will serve to determine the date and window for the entry into lead-in / Day -14 visit.

[h] The 12-lead ECG should be performed entry into lead-in Day -14. The results from this ECG should to be available, assessed, and initialed and dated by the Investigator prior to Day 1 Randomization visit.

[i] All subjects who sign the Protocol-Specific Informed Consent form must be registered in the IVRS. Upon registration of the enrollment visit, a unique subject number will be assigned to each subject.

[j] Call IVRS to register entry into lead-in Day-14 visit and to obtain single-blind study medication kit. Call IVRS if the subject is discontinued prior to randomization.

[k] Call IVRS to register Day 1 randomization visit and to obtain double-blind study medication kit.

[l] Call IVRS to register Week 12 visit and to obtain double-blind study medication kit.

[m] Call IVRS to register Week 24 visit and to obtain double-blind study medication kit. Call the IVRS if the subject is rescued to register the rescue visit and to obtain open-label rescue metformin, Call the IVRS if the subject discontinues or completes the short-term treatment period.

[n] Includes Hepatitis B surface antigen and anti-hepatitis C virus antibody.

[o] Labels from dispensed study medication kits and /or bottles will be detached and affixed to the appropriate section of the Drug Label pages.

[p] At Week 24, blinded study medication kit will only be dispensed to eligible subjects entering the long-term treatment period. The first dose of **long-term** treatment period study medication should correspond to the Week 24 visit date. The last dose of **short-term** treatment period study medication should correspond to the day prior to the Week 24 visit.

[q] Subjects should have Week 24 procedures completed if rescued (Week 24 "Rescue" visit) during the short-term treatment period .Rescue medication should only be dispensed in eligible subjects upon completion of the Week 24 "Rescue" visit.

[r] Review study medication compliance, as assessed based upon subject's interview and a count of the tablets returned.

Table 6.1B: Flow Chart for Protocol MB102013 (Long-Term Treatment Period)[a,b]

Procedure	WK 37 (D01)	WK 50 (D02)	WK 63 (D03)	WK 76 (D04)	WK 89 (D05)	WK 102 (D99)	Protocol Section
General Procedures							
Brief Physical Examination	X	X	X	X	X		6.3.3
Complete Physical Examination						X	6.3.3
Body Weight	X	X	X	X	X	X	6.4.2.2
Seated Blood Pressure and Heart Rate	X	X	X	X	X	X	6.3.4.1
Orthostatic Blood Pressure and Heart Rate		X				X	6.3.4.2
Waist Circumference		X		X		X	6.4.3.2
12-Lead ECG		X				X	6.3.5
Review Concomitant Medications / Procedures	X	X	X	X	X	X	4.2/5.5
Contact IVR system [c,d]	X	X	X	X	X	X	5.2
Provide Diet and Exercise counseling	X	X	X	X	X		6.9.1
Dispense Glucose Meter and Supplies / Provide Instructions	X	X	X	X	X		6.3.1
Dispense logs / Provide Instructions	X	X	X	X	X		6.2/6.3.1

Table 6.1B: Flow Chart for Protocol MB102013 (Long-Term Treatment Period)[a,b]

Procedure	WK 37 (D01)	WK 50 (D02)	WK 63 (D03)	WK 76 (D04)	WK 89 (D05)	WK 102 (D99)	Protocol Section
Review study logs	X	X	X	X	X	X	6.2/6.3.1
Safety Assessment							
Assess Adverse Events	X	X	X	X	X	X	7
Assess Genitourinary symptoms	X	X	X	X	X	X	6.3.2
Assess Hypoglycemia Episodes	X	X	X	X	X	X	4.2.3.3/ 6.3.1
Central Laboratory							
Pregnancy Test (urine) WOCBP only[e]	X	X	X	X	X	X	App. 4
Blood Standard Safety Laboratory Panel	X	X	X	X	X	X	App. 4
Urine Standard Safety Laboratory Panel	X	X	X	X	X	X	App. 4
Spot Urine Glucose Quantification and glucose:creatinine ratio		X				X	App. 4
A1C	X	X	X	X	X	X	App. 4

Table 6.1B: Flow Chart for Protocol MB102013 (Long-Term Treatment Period)[a,b]

Procedure	WK 37 (D01)	WK 50 (D02)	WK 63 (D03)	WK 76 (D04)	WK 89 (D05)	WK 102 (D99)	Protocol Section
Assess A1C for Rescue Criteria	X	X	X	X	X		App. 4
FPG	X	X	X	X	X	X	App. 4
Fasting C-peptide						X	App. 4
Fasting Serum Lipids (Total-C, LDL-C, HDL-C, TG)		X		X		X	App. 4
FFA						X	App. 4
Cystatin-C						X	App. 4
PTH		X				X	App. 4
Dynamic Serum Bone Metabolism Markers (Osteocalcin, P1NP, CTx, NTx)		X				X	App. 4
25-hydroxy vitamin D		X				X	App. 4
Drug Dispensing							
Dispense Study Medication[f]	X	X	X	X	X		5.1

Table 6.1B: Flow Chart for Protocol MB102013 (Long-Term Treatment Period)[a,b]

Procedure	WK 37 (D01)	WK 50 (D02)	WK 63 (D03)	WK 76 (D04)	WK 89 (D05)	WK 102 (D99)	Protocol Section
Dispense or re-dispense open-label rescue metfomin IR, as needed, (if applicable)	X	X	X	X	X		4.2.3.2/5.1
Review Medication Compliance[g]	X	X	X	X	X	X	5.6

[a] Subjects should have Week 102 procedures completed if rescued during the long-term treatment period **and** at the time of study completion or discontinuation. **In subjects discontinuing the study due to AE/SAE, the Investigator will follow the subjects until the event has resolved or stabilized. In addition, subjects who prematurely discontinue from the study may be contacted after discontinuation from the study, to collect vital status information.**

[b] The long-term treatment period visits should be scheduled according to the randomization visit date (Day 1), with a protocol-allowed visit window of ± 10 days. Subjects will bring their glucose meter to the site at all visits. Subjects should be in a fasting state (at least 8 hours prior to the study visits) and should be seen between 6 AM and 10 AM. Subjects should refrain from tobacco, caffeine and alcohol for 8 hours prior to study visits. Ensure to collect all fasting blood samples prior to the morning dose(s) of blinded study medication, and open-label rescue metformin (if applicable). Doses of study medication on the day of the visits should be taken upon completion of study visit procedures.

[c] Call IVRS to register visit and to obtain blinded study medication kit.

[d] Call IVRS if subject is rescued or discontinues.

[e] Home pregnancy kits will be provided to subjects in the long-term phase. Pregnancy tests should be performed by the subject at monthly intervals between visits.

[f] Labels from dispensed study medication kits and /or bottles will be detached and affixed to the appropriate section of the Drug Label page.

[g] Review study medication compliance, as assessed based upon subject's interview and a count of the tablets returned.

6.1.1 Visit Scheduling and Visit Windows

Scheduled study visits will occur at:

- Enrollment (corresponding to "screening" when calling into the IVRS)
- Entry into Lead-in Day -14 (corresponding to "enrollment" when calling into the IVRS)
  - Entry into Lead-in Day -14 visit should be completed up to 14 days following enrollment central laboratory samples collection. ***Note: The single-blind lead-in study medication and all enrollment visit central laboratory results must have been received at the site prior to completing entry into lead-in Day -14 visit.***
- Day 1 Randomization of the short-term treatment phase (corresponding to "randomization" when calling into the IVRS)
  - Subjects with an enrollment A1C ≥ 7.0 and ≤ 10.0 % (Group 1) should complete the lead-in period in 14 ± 5 days.
  - Subjects with an enrollment A1C ≥ 10.1 and ≤ 12.0 % (Group 2) should complete the lead-in period in 7 ± 5 days.
- Weeks 1, 2, 4, 8, 12, 16, 20 and 24 of the short-term treatment phase
  - Throughout the short-term treatment period, study visits should occur on the designated visit day ± 5 days (**based on Day 1 visit date**).
- Weeks 37, 50, 63, 76, 89 and 102 of the long-term treatment phase
  - Throughout the long-term treatment period, study visits should occur on the designated visit day ± 10 days (**based on Day 1 visit date**).

All attempts should be made to schedule study visits within protocol-allowed window and to maintain visit week schedule.

6.1.2 Subject Preparation

If any of the following requirements is not fulfilled, the study visit should be rescheduled:

- Subjects should arrive at the site between 6 AM and 10 AM.
- Subjects should be in a fasting state (at least 8 hrs) for all regularly scheduled clinic visits.
- Subjects should refrain from tobacco, caffeine and alcohol for 8 hours prior to study visits.

- Subjects should take study medication, and open-label rescue metformin (if applicable) on the day preceding the study visit.
- Subjects should withhold their dose of study medication and of open-label rescue metformin on the visit date.

6.2 Study Materials

BMS will supply the sites with the following materials:

- Blood glucose meters. One meter will be provided to each study subject at Day -14 and one additional meter will be provided to each investigative site.
- Blood glucose test strips.
- Lancets.
- Glucose control solutions.
- Subject logs for hypoglycemia episodes or events suggestive of hypoglycemia episodes reporting.
- Paper Case Report Forms (CRFs) and/or Electronic Case Report Forms (eCRFs). [note: Paper CRF pages will be used for items such as Serious Adverse Events Forms, Pregnancy Surveillance Forms, and Drug Label Pages].
- Sample Source Documentation Worksheets.
- Patient education material and Site Support Tools.
- Study Drug inventory control forms.
- Pre-Screening Logs.
- Blood Pressure Monitor.

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

6.3 Safety Assessments

Safety Assessments will include adverse events reporting as well as marked abnormalities in clinical laboratory tests. Please refer to Appendix 4 for details on central laboratory assessments.

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.

The following procedures will also be completed to ensure subject's safety.

6.3.1 Self-Monitoring of Blood Glucose (SMBG)

Glucose meters will be supplied to each study site. At the entry into Lead-in / Day -14 visit, subjects will receive a glucose meter, supplies and instruction on their use. Supplies will be provided to allow for approximately 60 blood glucose assessments per month for the duration of the study. **The Investigator may require more frequent readings based on local clinical practice.** Subjects should bring their glucose meter with them to each study visit to ensure that it is functioning properly. Subjects may keep the glucose 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 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.

6.3.1.1 Guidance on Management and Reporting of Hypoglycemia Episodes

Hypoglycemia may be an expected event in subjects who are treated for diabetes. These 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 personal log books any hypoglycemic symptoms.** They should be encouraged to measure, when possible, their blood glucose values when they have symptoms of hypoglycemia. In accordance with ADA standards of treatment,[9] 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 hypoglycemia **as assessed by the Investigator** should be documented and reported on the appropriate eCRF page.

Hypoglycemia CRF 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 7.1.1), in which case an SAE form must be completed in addition to the hypoglycemia eCRF pages for hypoglycemia.

6.3.2 Guidance on Assessment of Urinary and Genital Infections

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

Asymptomatic bacteriuria is defined as the presence of $\geq 10^5$ colony forming units/mL of bacteria, in a properly collected voided urine specimen, without signs or symptoms typically attributed to urinary tract infection.[10] Asymptomatic bacteriuria is prevalent among diabetic women, and is associated with pyuria in 70% of cases.[10] Neither the Infectious Diseases Society of America nor the U.S. Preventive Services Task Force recommends screening for, or treatment of, asymptomatic bacteriuria in non-pregnant diabetic patients.[10,11] In this study, the central laboratory will not routinely report the results of urinary dipstick tests for leukocyte esterase as a screening test for pyuria in surveillance urine examinations.

At every scheduled visit, the investigator will question subjects about symptoms of **urinary tract infections**, including but not limited to pain or burning or uncomfortable pressure in the lower abdomen/pelvic area while passing urine, blood in the urine, and symptoms of urinary urgency (a strong and uncontrolled urge to pass urine). If based on the response to these questions or other suggestive signs or symptoms the investigator believes that a urinary tract infection may be present, local laboratory urine cultures should be obtained to confirm a presumptive diagnosis of cystitis, urinary tract infection, or pyelonephritis. Mid-stream clean catch urine collections are recommended. Clinical judgment and local standards of care should apply to decisions concerning therapy

Study drug should be held in subjects with clinical evidence of upper tract UTI (e.g. 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 urinary tract infection. Whether additional therapy is prescribed because of culture results should be determined by Investigator judgment, after consultation with the Medical Monitor.

In addition, at every scheduled study visit, the investigator will question subjects about symptoms of **genital infections** including but not limited to itching, soreness or redness in the genital area and a change or increase in genital discharge. The diagnosis of vaginitis, vulvovaginitis, vulvitis or balanitis can be made based on physical examinations, culture of secretions or a therapeutic response to treatment of fungal or other vaginal pathogens. A urine culture is not required for diagnosis of genital infections.

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 7.0). Additional information, including but not limited to completion of supplemental eCRFs may be requested for certain adverse events and/or laboratory abnormalities which are reported/identified during the course of the study.

In subjects with signs or symptoms, including dysuria, urgency or frequency of urination, suprapubic or perineal discomfort, flank, back, or abdominal pain, costo-vertebral angle tenderness, nausea, vomiting, fever, chills, or sepsis, urine cultures should be obtained to confirm presumptive diagnoses of cystitis, urinary tract infection, pyelonephritis, or prostatitis. Mid-stream clean catch urine collections are recommended. Clinical judgment and local standards of care should apply to decisions concerning therapy.

No urine culture is required when a diagnosis of vaginitis, vulvovaginitis, vulvitis, or balanitis is confirmed by physical examination, culture of secretions, or a therapeutic response to treatment of fungal or other vaginal pathogens.

6.3.3 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.

6.3.4 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.

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

6.3.4.1 Seated Blood Pressure and Heart Rate

Seated BP and HR will be measured at every visit, using an automated blood pressure monitor and according to the manufacturer's instructions.

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 three replicate measurements and reported in the eCRF.

6.3.4.2 Orthostatic Blood Pressure and Heart Rate

At selected visits where orthostatic blood pressure and heart rate are measured, measurements should be obtained following completion of seated blood pressure and heart rate measurement.

The supine BP and HR must be measured prior to the standing BP. The subject should rest in the supine position for at least 5 minutes prior to measurement of BP and HR. Supine BP will be determined from three replicate measurements obtained at least 1 minute apart. The average BP and HR will be determined from these three replicate measurements and reported in the eCRF.

The subject will then stand for 2 to 3 minutes. After this time, measure the BP with the arm supported at the antecubital fossa at heart level. Standing 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 three replicate measurements and reported in the eCRF.

6.3.5 12-Lead Electrocardiogram (ECG)

The Investigator or a sub-Investigator should review and assess all ECGs for any clinically significant abnormalities, and initial and date. The Day -14 ECG must be assessed, and initialed and dated by the Investigator prior to Day 1 Randomization visit.

In preparation for the ECG, ensure there is minimal interference between the skin surface and the electrode. Use alcohol to prepare the skin at each electrode site. Thick chest hair should be shaved to ensure sufficient contact.

Before attaching electrodes to pick-up points, spread the electrode with electrode gel. Place the electrodes on bony areas, avoiding large muscle masses, to achieve better tracings as described below. The subject must be supine and should refrain from movement during the ECG recording. Ensure that the subject and the electrodes (including the neutral electrode) are not exposed to conducting objects, even if grounded.

- RL: On the right leg (inside calf, midway between knee and ankle)
- LL: On the left leg (inside calf, midway between knee and ankle)
- RA: Right arm (on the inside)
- LA: Left arm (on the inside)
- V1: 4th intercostal space, at right sternal margin
- V2: 4th intercostal space, at left sternal margin
- V3: Midway between V2 and V4
- V4: 5th intercostal space at left midclavicular line
- V5: Same transverse level at V4, at anterior axillary line
- V6: Same transverse level at V4, at left midaxillary line

- Keep one original ECG print-out in the medical chart, ensuring a copy, assessed, initialed and dated by the Investigator, is maintained in the source documents for the study.

6.3.6 Supplemental Visits

6.3.6.1 Rescue or Early Termination Visit

Subjects rescued during or discontinued from the Short-Term Treatment Period

- Any subject who is rescued during or discontinued from the short-term treatment period must have all Week 24 visit procedures performed at the time of study discontinuation or rescue. The IVRS must be called to record the subject status (i.e., rescue, or discontinuation status).
  - For subjects rescued during the short-term treatment period, the IVRS will dispense the appropriate kit(s) and bottle(s) at the time of the Week 24 "Rescue" visit. The subject will then continue in the short-term treatment period according to the regular short-term treatment period visit schedule. A supplemental CRF will need to be completed to collect Week 24 "Rescue" related endpoint data. A "Rescue" visit laboratory kit will need to be used to collect Week 24 "Rescue" visit blood and urine samples.
  - For subjects discontinuing early from the short-term treatment period, the Investigator will discharge the subject from the study and arrange appropriate follow-up care, if applicable. The Week 24 CRF will then need to be completed.

Subjects rescued or discontinued from the Long-Term Treatment Period

- Any subject who is rescued during or discontinues from the long-term treatment period must have Week 102 visit procedures performed at the time of study discontinuation or rescue. The IVRS must be called to record the subject status (i.e., rescue or discontinuation status).
  - For subjects rescued during the long-term treatment period, the IVRS will dispense the appropriate kit(s) and bottle(s), at the time of the Week 102 "Rescue" visit. The subject will then continue in the long-term treatment period according to the regular long-term treatment period visit schedule. A supplemental CRF will need to be completed to collect Week 102 "Rescue" related endpoint data. A "Rescue" visit laboratory kit will need to be used to collect Week 102 "Rescue" visit blood and urine samples.

– For subjects discontinuing early from the long-term treatment period, the Investigator will discharge the subject from the study and arrange appropriate follow-up care, if applicable. The Week 102 CRF will then need to be completed.

6.3.6.2 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.

6.4 Efficacy Assessments

6.4.1 Primary Efficacy Assessment

The primary efficacy assessment consists of the central laboratory measurement of the A1C during the short-term treatment period.

6.4.2 Secondary Efficacy Assessments

6.4.2.1 Fasting Plasma Glucose and A1C

Secondary efficacy assessments include the central laboratory measurements of the FPG as well as of the A1C throughout the short-term treatment period.

6.4.2.2 Total Body Weight

Secondary objectives will also include the assessment of the change in total body weight:

- Total Body Weight will be measured throughout the short-term treatment period
- Measurement of weight should be performed with the subject dressed in indoor clothing, shoes removed, and bladder empty. Subjects should be weighed on the same scale at all visits.

6.4.3 Exploratory Efficacy Assessments

6.4.3.1 Beta-Cell Function and Insulin Resistance

- C-peptide
- β-cell function (as measured by HOMA-2)
- Insulin resistance (as measured by HOMA-2))

6.4.3.2 Waist Circumference

The waist should be measured in the standing position at the natural waist (smallest waist circumference). If there is no natural waist, the measurement should be made at the level of the umbilicus. Measurements should be made at the end of normal inspiration.

6.4.3.3 Additional Exploratory Efficacy-Related Central Laboratory Measurements

The following central laboratory parameters will be measured at various times and be assessed as exploratory endpoints:

- Fasting C-Peptide
- Metabolic Surrogate Markers
  - High-sensitivity C-reactive protein [hs-CRP]
  - Plasminogen activator inhibitor 1 [PAI-1]
  - Fibrinogen
  - Serum uric acid
- Fasting lipids
  - Total-C
  - LDL-C
  - HDL-C
  - TG
- FFA

6.5 Pharmacokinetic Assessments

Plasma samples for analysis of dapagliflozin will be obtained **immediately prior to dosing** at each of the Week 16, Week 20 and Week 24 visits. Additionally, PK samples will be obtained at Day 1, and Week 20 at 60 minutes **post dose,** and 180 minutes **post dose.**

Please refer to the central laboratory instructions for sample collection and processing.

6.6 Pharmacodynamic Assessments

Not Applicable

6.7 Pharmacogenomics/Pharmacogenetics Assessments

Pharmacogenetic samples may be collected as covered in the Pharmacogenetic blood sample amendment (Amendment 01), where applicable.

6.8 Outcomes Research Assessments

Not Applicable

6.9 Other Assessments

6.9.1 Diet and Exercise Counseling

Starting at Entry into Lead-In Day - 14 visit, 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.

6.9.2 Body Mass Index

The BMI will be calculated at the Enrollment visit to determine subject's eligibility. The BMI is determined by weight (kg) divided by height (m) squared, as described below:

- Use actual height and weight
- If the subject was not weighed in kg, convert pounds (lbs) to kilograms (kg = lb / 2.2)
- Similarly, convert inches (in) to centimeters (cm = in X 2.54)
- BMI = (weight in kg) / (height in cm/100)^2
- Round to one decimal place (if 0.05 or greater, round up)

Additional calculations for BMI will be derived internally by BMS using the weight at the specified time point, to be assessed as exploratory endpoints, and the height at enrollment.

6.9.3 Height Measurement

- 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.

6.9.4 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.

7 ADVERSE EVENTS

7.1 Definitions

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.

7.1.1 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 for exceptions)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (note: reports of congenital anomalies/birth defects must also be reported on the Pregnancy Surveillance Form [see Section 7.6])
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

  For reporting purposes, BMS also considers the occurrence of pregnancy (see Section 7.6), overdose (regardless of association with an AE), and cancer as important medical events. An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important.

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)

7.1.2 Non-Serious Adverse Events

All AEs that are not classified as serious.

7.2 Assignment of Adverse Event Intensity and Relationship to Investigational Product

The following categories and definitions of intensity as determined by a physician should be used for all BMS clinical study AEs:

- Mild (Grade 1) - Awareness of event but easily tolerated
- Moderate (Grade 2) - Discomfort enough to cause some interference with usual activity
- Severe (Grade 3) - Inability to carry out usual activity
- Very Severe (Grade 4) - Debilitating, significantly incapacitates subject despite symptomatic therapy

The following categories and definitions of causal relationship to investigational product as determined by a physician should be used for all BMS clinical study AEs:

- Certain: There is a reasonable causal relationship between the investigational product and the AE. The event responds to withdrawal of investigational product (dechallenge), and recurs with rechallenge when clinically feasible.
- Probable: There is a reasonable causal relationship between the investigational product and the AE. The event responds to dechallenge. Rechallenge is not required.
- Possible: There is reasonable causal relationship between the investigational product and the AE. Dechallenge information is lacking or unclear.
- Not likely: There is a temporal relationship to investigational product administration, but there is not a reasonable causal relationship between the investigational product and the AE.
- Not related: There is not a temporal relationship to investigational product administration (too early, or late, or investigational product not taken), or there is a reasonable causal relationship between noninvestigational product, concurrent disease, or circumstance and the AE.

7.3 Collection and Reporting

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.)

If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs: onset, duration, intensity, seriousness, relationship to investigational product, action taken, and treatment required. If treatment for the AE was administered, it should be recorded on the appropriate CRF page. The investigator shall supply the sponsor and Ethics Committee with any additional requested information, notably for reported deaths of subjects.

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

7.3.1 Serious Adverse Events

Following the subject's written consent to participate in the study, all SAEs must be collected, including those thought to be associated with clinical study procedures. All SAEs must be collected that occur within 30 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy). The investigator should notify BMS of any SAE occuring after this time period that is believed to be certainly, probably or possibly related to the investigational product.

Serious adverse events, whether related or unrelated to investigational product, must be recorded on the SAE page of the CRF and reported expeditiously to BMS (or designee) to comply with regulatory requirements. An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

All SAEs must be immediately reported by confirmed facsimile transmission (fax) and mailing of the completed SAE page (top, white, original). In some instances where a facsimile machine is not available, overnight express mail may be used. 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.) In selected circumstances, the protocol may specify conditions that require additional telephone reporting. The SAE electronic CRF in the electronic data capture tool should not be used.

If the investigator believes that an SAE is not related to the investigational product, 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 page of the CRF.

If an ongoing SAE changes in its intensity or relationship to the investigational product, a follow-up SAE report should be sent immediately to the sponsor. As follow-up information becomes available it should be sent immediately using the same procedure used for transmitting the initial SAE report. Supporting documentation such as hospital discharge summaries and autopsy reports should be forwarded to BMS in the same manner. All SAEs should be followed to resolution or stabilization.

SAE FACSIMILE TRANSMISSION:

For US Sites: Central Facsimile Station:
[redacted]

Local Contact: See Appendix 2

SAE MAILING ADDRESS:

For all sites:
Use the special SAE envelopes pre-addressed to the SAE Central Mailbox:
[redacted]

SAE TELEPHONE CONTACT

Name: [redacted]
Office:
24 Hour: [redacted] / International: [redacted]

7.3.2 Handling of Expedited Safety Reports

In accordance with local regulations, BMS will notify investigators of all SAEs that are suspected (certainly, probably, or possibly related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).

Other important findings which may be reported by the sponsor as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a

study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the Investigator Brochure. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

7.3.3 Nonserious Adverse Events

The collection of nonserious AE information should begin at initiation of investigational product. 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.

If an ongoing AE changes in its intensity or in its perceived relationship to investigational product, a new AE entry for the event should be completed. Adverse events should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 7.3.1). Follow-up is also required for AEs that cause interruption or discontinuation of investigational product, or those that are present at the end of study participation. Subjects with AEs at study completion should receive post-treatment follow-up as appropriate.

All identified nonserious AEs must be recorded and described on the appropriate nonserious AE page of the CRF (paper or electronic).

7.4 Laboratory Test Abnormalities

All laboratory test values captured as part of the study should be recorded on the appropriate laboratory test results pages of the CRF, or be submitted electronically from a

central laboratory. In addition, the following laboratory abnormalities should also be captured on the nonserious AE CRF page (paper or electronic) or SAE paper CRF page 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 the investigational product discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy

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).

7.5 Overdose

An overdose is defined as the accidental or intentional ingestion 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 7.3.1 for reporting details.)

7.6 Pregnancy

Sexually active WOCBP must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized (See Section 4.2.1 for the definition of WOCBP).

Before enrolling WOCBP in this clinical study, investigators must review the sponsor-provided information about study participation for WOCBP. The topics include the following:

- General Information
- Informed Consent Form
- Pregnancy Prevention Information Sheet
- Drug Interactions with Hormonal Contraceptives

- Contraceptives in Current Use
- Guidelines for the Follow-up of a Reported Pregnancy

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

7.6.1 Requirements for Pregnancy Testing

All WOCBP MUST have a **negative** pregnancy test within 72 hours as specified in Section 6.1 **prior** to receiving the investigational product. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the subject must not receive the investigational product and must not continue in the study.

Pregnancy testing must also be performed throughout the study as specified in Section 6.1 (see flow chart/time and events schedule) and the results of all pregnancy tests (positive or negative) recorded on the CRF or transferred electronically.

In addition, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual period) at any time during study participation.

7.6.2 Reporting of 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). Exceptions to the investigational product discontinuation may be considered for life-threatening conditions only after consultation with the BMS medical monitor or as otherwise specified in this protocol. The investigator must immediately notify the BMS medical monitor of this event, record the pregnancy on the Pregnancy Surveillance Form. Initial information on a pregnancy must be reported

immediately to BMS and the outcome information provided once the outcome is known. Forward these forms to BMS according to SAE reporting procedures described in Section 7.3.1.

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

For male subjects, the reporting of a female partner's pregnancy may be requested if animal toxicology studies show concern for reproductive risk.

7.7 Other Safety Considerations

Any significant changes 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 on the appropriate nonserious AE page of the CRF (paper or electronic) or SAE paper CRF page.

Completion of supplemental CRFs may be requested for adverse events and/or laboratory abnormalities which are reported/identified during the course of the study.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The primary endpoint is the change in A1C from baseline at Week 24, or the last post-baseline measurement prior to Week 24 if no Week 24 assessment is available. For rescued subjects, measurements obtained after initiation of rescue medication, will not be considered in calculating the primary endpoint.

The primary comparisons are between each of the three dapagliflozin AM dosing treatment groups and the placebo group in subjects with enrollment A1C between 7% and 10% inclusive. Each comparison between dapagliflozin AM dosing treatment groups and

placebo group will be carried out at the 0.019 level using Dunnett's adjustment so that the overall type I error rate is controlled at the 0.05 significance level.

With 67 subjects per treatment group with post-baseline measurements, there is 90% power to detect a difference in means of 0.7% between each dapagliflozin AM dosing treatment group and placebo, assuming a standard deviation (SD) of 1.1%[12]. Assuming that 5% of subjects do not have a post-baseline assessment, a total of 490 subjects (70 subjects per treatment arm), with enrollment A1C between 7% - 10% inclusive, need to be randomized to dapagliflozin AM dosing, dapagliflozin PM dosing or placebo group. This also provides 90% power for the comparison of each dapagliflozin PM dosing treatment group and placebo assuming 0.7% difference in means and a SD of 1.1%. In addition, 70 subjects (35 subjects on each dapagliflozin treatment arm (5mg and 10mg) with enrollment A1C between 10.1% - 12% inclusive will also be randomized to obtain initial efficacy and safety data in this population.

8.2 Populations for Analyses

Two efficacy data sets are specified for this study:

- The primary efficacy data set will consist of all randomized subjects who receive at least one dose of double-blind study medication. In addition, randomized subjects must have both a baseline and at least one post-baseline measurement for the time point under consideration to be included in the efficacy analysis of change or percent change from baseline.
- The secondary efficacy data set is a subset of the primary data set consisting of subjects who do not violate the terms of the protocol which may affect the primary efficacy endpoint significantly as determined by the Medical Monitor. All decisions to exclude subjects from the primary data set will be made prior to the unblinding of the study.

The primary efficacy variable of change from baseline in A1C will be reanalyzed using the secondary efficacy data set if more than 10% of the subjects in any regimen are found to significantly violate the terms and conditions of the protocol. Otherwise, efficacy analysis will be restricted to the primary efficacy data set.

Safety analysis will be based on the safety data set which consists of all subjects who received at least one dose of study medication.

8.3 Endpoint Definitions

The primary endpoint is the change in A1C from baseline at Week 24, or the last post-baseline measurement prior to Week 24 if no Week 24 assessment is available. For rescued subjects, measurements obtained after initiation of rescue medication will not be considered in calculating the primary endpoint.

The secondary endpoints include the change in FPG and total body weight from baseline at Week 24, or the last post-baseline measurement prior to Week 24 if no Week 24 assessment is available, the change in FPG from baseline at Week 1, the proportion of subjects achieving a therapeutic glycemic response, defined as A1C < 7.0% at Week 24, or the last post-baseline measurement prior to Week 24 if no Week 24 assessment is available and the proportion of subjects achieving a therapeutic glycemic response, defined as A1C ≤ 6.5% at Week 24, or the last post-baseline measurement prior to Week 24 if no Week 24 assessment is available. For rescued subjects, measurements obtained after initiation of rescue medication will not be considered in calculating the secondary endpoints.

8.4 Analyses

Analyses of the data from the 24 Week short-term treatment period will be performed after all subjects have completed or have been discontinued from this period. In addition, all relevant queries must be resolved and the database must be locked for this 24-Week period prior to unblinding and analyses.

8.4.1 Demographics and Baseline Characteristics

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

8.4.2 Safety Analyses

The incidence of adverse events and of marked abnormalities in clinical laboratory tests will be summarized by treatment group.

All adverse events that are serious or that result in discontinuation of study therapy will be described in depth. Changes from baseline at each of the scheduled time points in each clinical laboratory parameters will be summarized by treatment group.

8.4.3 Efficacy Analyses

Unless otherwise specified, for all changes (or percent changes) from baseline to a specific time point post-baseline as well as for glycemic response definitions, analyses will be based on measurements available at that time point or the last post-baseline measurement prior to the time-point, if no measurement is available at that time point, i.e., last observation carried forward (LOCF). For subjects who started rescue medication on the day of, or prior to, the specific time point, their last post-baseline measurement prior to the time and date of the first dose of rescue medication will be used.

8.4.3.1 Primary Analysis

The primary efficacy analysis will compare the change in A1C from baseline at Week 24, in subjects with enrollment A1C between 7% and 10% inclusive for each of the three dapagliflozin AM dosing treatment groups and the placebo group. Each comparison will be performed at the 0.019 significance level (2-sided) using Dunnett's adjustment so that the overall type I error rate will be controlled at 0.05 significance level.

The primary analysis of the change in A1C from baseline at Week 24 will be based on an analysis of covariance (ANCOVA) model with treatment group as an effect and baseline value as a covariate. Point estimates and 95% confidence intervals for the mean change within each treatment group as well as the differences in mean change between each of the dapagliflozin AM dosing treatment groups and placebo will be calculated.

8.4.3.2 Secondary Analyses

If at least one of the primary comparisons between the dapagliflozin AM dosing treatment groups and the placebo group is significant at the 0.019 level for the primary endpoint, all statistical tests for the secondary efficacy endpoints will be performed and nominal p-values will be reported. However, in order to protect the overall type I error rate across the primary and key secondary endpoints, the interpretation of the statistical significance of treatment comparisons for each secondary efficacy endpoint will be done using a step-wise procedure which will be defined in the statistical analysis plan, prior to unblinding of treatment assignments.

The change from baseline in FPG at Week 1 and Week 24, and the change from baseline at Week 24 in the total body weight will be analyzed using an ANCOVA model with treatment group as an effect and baseline value as a covariate as used for the primary analysis of A1C. In addition to point estimates and 95% confidence intervals, p-values will be calculated to compare the treatment effect of each of the dapagliflozin AM dosing treatment groups versus placebo group.

The change from baseline in A1C at Week 24 in subjects with baseline A1C $\geq$ 9%, the change from baseline in total body weight at Week 24 in subjects with baseline BMI $\geq$ 27 kg/m^2, and the change from baseline in A1C at Week 24 in subjects with baseline BMI $\geq$ 27 kg/m^2 will be analyzed using an ANCOVA model with treatment group as an effect and baseline value as a covariate as used for the primary analysis of A1C. In addition to point estimates and 95% confidence intervals, p-values will be calculated to compare the treatment effect of each of the dapagliflozin AM dosing treatment groups versus placebo group.

The proportion of subjects achieving a therapeutic glycemic response defined as A1C < 7.0% at Week 24, and the proportion of subjects achieving a therapeutic glycemic response defined as A1C $\leq$ 6.5% at Week 24 will be summarized by treatment group. The proportion will be compared between each of the dapagliflozin AM dosing treatment groups and the placebo group using a two-sided Fisher's exact test.

8.4.3.3 Other Analyses

The analysis of change from baseline at Week 1 in FPG, the change from baseline at Week 24 in A1C, FPG, total body weight, A1C in subjects with baseline A1C ≥ 9%, A1C in subjects with baseline BMI ≥ 27 kg/m2, A1C in subjects with baseline BMI ≥ 30 kg/m2, the proportion of subjects achieving a therapeutic glycemic response, defined as A1C ≤ 6.5% at Week 24, and the proportion of subjects achieving a therapeutic glycemic response, defined as A1C < 7.0 % at Week 24, to assess each dapagliflozin PM dosing treatment group versus placebo will be similar to the secondary analysis except that no p-values will be generated.

Other efficacy outcomes measured as continuous variables including change from baseline at Week 24 in beta-cell function, insulin resistance, BMI, waist circumference, serum uric acid, fasting C-peptide, hs-CRP, PAI-1 and fibrinogen will be analyzed using an ANCOVA model with treatment group as an effect and baseline value as a covariate. Point estimates and 95% confidence intervals for the mean change within each treatment group as well as for the differences in mean change between each of the dapagliflozin (AM doing and PM dosing) treatment groups and the placebo group will be calculated. No p-values will be generated.

The percent change from baseline at Week 24 in total body weight will be analyzed using an ANCOVA model with treatment group as an effect and baseline value as a covariate. Point estimates and 95% confidence intervals for the mean change within each treatment group as well as for the differences in mean change between each of the dapagliflozin (AM doing and PM dosing) treatment groups and the placebo group will be calculated. No p-values will be generated.

The change from baseline at Week 24 in seated systolic blood pressure and seated diastolic blood pressure in subjects with baseline seated systolic blood pressure > 140 mmHg will be analyzed using an ANCOVA model with treatment group as an effect and baseline value as a covariate. Point estimates and 95% confidence intervals for the mean change within each treatment group as well as for the differences in mean change between each of the dapagliflozin (AM doing and PM dosing) treatment groups and the placebo group will be calculated.

A subgroup analysis of change from baseline at Week 24 in A1C will be carried out for the following subgroups: subjects with baseline A1C < 8%, subjects with baseline A1C ≥ 8% and < 9%, and subjects with baseline A1C ≥ 9%. The analysis will be performed using an ANOVA model with terms for treatment, baseline A1C category, and interaction between treatment and baseline A1C category. Point estimates and 95% confidence intervals for the differences in mean changes between each of the dapagliflozin (AM and PM dosing) treatment groups and the placebo group will be calculated for each of the above subgroups.

The proportion of subjects achieving a glycemic response at Week 24 within each dapagliflozin (AM and PM dosing) group and the placebo group will be summarized. Glycemic response is defined by each of the subgroups below:

- A1C decrease from baseline ≥ 0.5%,
- FPG <110 mg/dL (6.1 mmol/L)
- FPG < 126 mg/dL (7.0 mmol/L

Point estimates and 95% exact confidence intervals for the proportion in each treatment group and the difference in proportion between each of the dapagliflozin (AM and PM dosing) treatment groups and the placebo group will be calculated.

Fasting lipids (Total-C, LDL-C, HDL-C and TG) and FFA measurements will be log transformed, because the log transformed data is more likely to satisfy normal distributional assumptions. Percent changes from baseline at Week 24 in fasting lipids (Total-C, LDL-C, HDL-C and TG) and FFA, will be analyzed using ANCOVA of the logarithms of the post-treatment to baseline ratios with treatment group as an effect and log of baseline value as a covariate. Point estimates and 95% confidence intervals will be constructed for the relative difference of each of the dapagliflozin (AM and PM dosing) treatment groups versus the placebo group. No p-values will be generated.

The proportion of subjects discontinued or rescued for failing to achieve pre-specified glycemic targets at Weeks 4, 8, 12, 16, 20, and 24, will be summarized by treatment group. Point estimates and 95% exact confidence intervals for the differences in proportion between each of the dapagliflozin (AM and PM dosing) group and the placebo

group will be calculated. Kaplan-Meier plots of the time to discontinuation or to the start of rescue medication for failing to achieve pre-specified glycemic targets will be generated by treatment group.

The change from baseline at Week 24 in seated systolic blood pressure and seated diastolic blood pressure in subjects with baseline seated blood pressure > 140 mmHg will be analyzed using an ANCOVA model with treatment group as an effect and baseline value as a covariate. Point estimates and 95% confidence intervals for the mean change within each treatment group, as well as for the differences in mean change between each of the dapagliflozin treatment groups and the placebo group, will be calculated.

8.4.3.4 Analysis for subjects with enrollment AIC ≥ 10.1 and ≤ 12.0 %

Change from baseline in A1C, fasting plasma glucose, total body weight, beta cell function, insulin resistance, BMI, waist circumference, serum uric acid, fasting C-peptide, hs-CRP, PAI-1, fibrinogen, and percent change from baseline in total body weight, fasting lipids (Total-C, LDL-C,HDL-C and TG) and FFA at each scheduled measurement time point will be summarized by treatment group, along with 95% confidence intervals. In addition, the number and proportion of subjects discontinued or rescued for failing to achieve pre-specified glycemic targets at Weeks 4,8,12,16,20, and 24 will be summarized by treatment group, along with 95% exact confidence intervals.

8.4.4 Pharmacokinetic Analyses

The dapagliflozin plasma concentrations obtained by sampling of individual subjects will be used to build a population pharmacokinetic model to estimate pharmacokinetic parameters (e.g. CL/F, Vd/F, and ka). Possible covariate effects on PK parameters (e.g.gender effect on CL/F) may be identified and quantified. The estimated pharmacokinetic parameters will be used to compute individual exposure measures (e.g. AUC, Cmin).Relationships between these exposure measures and efficacy endpoints (e.g. changes from baseline in A1C, FPG) will be explored. Similar exploratory analyses may be performed for other efficacy and safety measures. The pharmacokinetic data and efficacy endpoint responses derived from this study may also be pooled with similar data from other studies to refine the modeled exposure-response relationship. Listings and

summary statistics will be reported for pharmacokinetic parameters and exposure measures. The pharmacokinetic analysis will be described in a separate report.

8.5 Interim Analyses

No interim analysis is being planned for this study.

9 ADMINISTRATIVE SECTION

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. Any significant deviation must be documented in the CRF.

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 enrollment.

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, study documentation, informed consent, and enrollment of WOCBP.

For sites using the BMS electronic data capture tool, each individual making entries and/or corrections on 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.

For electronic CRFs, corrections are made through the BMS electronic data capture tool that generates an automated audit trail including date and timestamp, full name of the person making the correction and original entry. The system also prompts the user to document reason for change that is also maintained in the audit trail.

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.

9.2 Records Retention

The investigator must retain investigational product disposition records, copies of CRFs (or electronic files), 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.

9.2.1 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 Pregnancy Surveillance Form. Paper CRFs must be completed legibly in ink. Subjects are to be identified by birth date and subject number, if applicable. All requested information must be entered on the CRF in the spaces provided. If an item is not available or is not applicable, it must be documented as such; do not leave a space blank.Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by the sponsor. Electronic data transfer is acceptable.

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.

For paper CRFs, a correction must be made by striking through the incorrect entry with a single line and entering the correct information adjacent to the incorrect entry. The correction must be dated, initialed and explained (if necessary) by the person making the correction and must not obscure the original entry.

The completed CRF, including any paper 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.

9.2.2 Investigational Product Records

It is the responsibility of the investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. 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 and use date or expiry date
- dates and initials of person responsible for each investigational product inventory entry/movement
- 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, broken)
- amount returned to the sponsor

- amount destroyed at study site, if applicable
- retain samples sent to third party for bioavailability/bioequivalence, if applicable

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

9.3 Return and Destruction of Investigational Product

9.3.1 Return of Investigational Product

Upon completion or termination of the study, all unused and/or partially used investigational product must be returned to BMS, if not authorized by BMS to be destroyed at the site.

All investigational product 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 investigational product(s) should be arranged by the responsible Study Monitor.

9.3.2 Destruction of Investigational Product

If investigational products are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted by BMS, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused investigational products can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor.

9.4 Publications

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 Event	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 adverse event 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 Reaction	An adverse event that is considered by either the investigator or the sponsor as certainly, probably, or possibly to the investigational product.
Expedited Safety Report	Rapid notification to investigators of all SAEs that are suspected (certainly, probably, or possibly related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure), or that could be associated with the study procedures.
Serious Adverse Event	Serious adverse event defined as any untoward medical occurrence that at any dose: results in death; is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), requires inpatient hospitalization or causes prolongation of existing hospitalization; results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect; is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do

Term	Definition
	not result in hospitalization.). For reporting purposes only, BMS also considers the occurrence of pregnancy, overdose (regardless of association with an AE), and cancer as important medical events.
SUSAR	Suspected, Unexpected, Serious Adverse Reaction as termed by the European Clinical Trial Directive (2001/20/EC).
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

Term	Definition
A1C	Glycosylated hemoglobin
ADA	American Diabetes Association
AE(s)	Adverse event(s)
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase
AM or am	Morning (ante meridian)
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BMS	Bristol-Myers Squibb
BP	Blood pressure
BUN	Blood urea nitrogen
CDC	Center for Disease Control
CHF	Congestive heart failure
CK	Creatine Kinase
Cm	Centimeter
CRF(s)	Case Report Form(s)
DBP	Diastolic Blood Pressure
dL	Deciliter
DM	Diabetes Mellitus
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
e.g.	exempli gratia (for example)
FDA	Food and Drug Administration
FFA	Free fatty acids
FPG	Fasting plasma glucose
FSH	Follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice(s)

HCG	Human Chorionic Gonadotropin
HDL-C	High-density lipoprotein cholesterol
HOMA	Homeostasis model assessment
HR	Heart Rate
hr(s)	Hour(s)
HRT	Hormone replacement therapy
ICH	International Council on Harmonization
i.e.	id est (that is)
IEC(s)	Independent ethics committee(s)
IP	Investigational Product
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
mg	Milligram
ml	Milliliter
mmHg	Millimeters of mercury
mmol	Millimole
N/A	Not Applicable
HCTZ	Hydrochlorothiazide
NHANES	National Health and Nutrition Examination Survey
hs-CRP	High Sensitivity C-Reactive Protein
nmol	Nanomole
NOAEL	No-Observed-Adverse-Effect Level
NYHA	New York Heart Association
OGTT	Oral glucose tolerance test
OL	Open-Label

PAI-1	Plasminogen Activator Inhibitor 1
pH	Symbol for the negative logarithm of the H+ ion concentration
PK	Pharmacokinetics
PM or pm	Afternoon (post meridian)
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTH	Parathyroid hormone
QD	Once a day
SAE(s)	Serious adverse event(s)
SBP	Systolic Blood Pressure
SD	Standard Deviation
SMBG	Self -monitoring of blood glucose
S_{cr}	Serum Creatinine
SGLT(s)	Sodium glucose transporter(s)
SGLT1	Sodium-dependent glucose transporter 1
SGLT2	Sodium-dependent glucose transporter 2
T½	Mean Terminal Half-Life
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
ULN	Upper limit normal
µmol	Micromole
US	United States
WK	Week
WOCBP	Women of childbearing potential
XR	Extended Release

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APPENDIX 1 ADDITIONAL ETHICAL CONSIDERATIONS

1 INFORMED CONSENT PROCEDURES

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. If the investigator makes changes to the informed consent form sample, BMS will ensure all required elements and local regulatory and legal requirements are met.

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

The investigator must provide the subject, or, in those situations where consent cannot be given by subjects, their legally acceptable representative with a copy of the consent form and written information about the study in the language in which the subject is most proficient. The language must be non-technical and easily understood. The investigator should allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study, then informed consent must be signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion. The subject or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study subjects prior to subject's participation in the study.

1.1 Subjects Unable to Give Written Informed Consent

1.1.1 Minors

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the informed consent form approved for the study prior to clinical study participation. (In the event that

the parents or legal guardians are unable to read, then an impartial witness should be present during the entire informed consent discussion). Whenever feasible, minors who are judged to be of an age of reason must also give their written assent by signing and dating the completed informed consent. All local laws, rules and regulations regarding informed consent of minors must be followed.

1.1.2 Subjects Experiencing Acute Events or Emergencies

A legally acceptable representative or legal guardian must provide informed consent when consent of the subject is not possible prior to clinical study participation, eg, for subjects experiencing an acute medical event such as myocardial infarction or stroke. Informed consent of the subject must additionally be obtained if they become capable of making and communicating their informed consent during the clinical study. All local laws, rules and regulations regarding informed consent of adult subjects incapable of giving informed consent must be followed.

1.1.3 Mentally Impaired or Incapacitated Subjects

Investigators (or whoever required by local regulations) should determine whether or not a mentally impaired or incapacitated subject is capable of giving informed consent and should sign a statement to that effect. If the subject is deemed mentally competent to give informed consent, the investigator should follow standard procedures. If the subject is deemed not to be mentally competent to give informed consent, a fully informed legal guardian or legally acceptable representative can be asked to give consent for, or on behalf of, the subject. All local laws, rules and regulations regarding informed consent of mentally impaired or incapacitated subjects must be followed.

Patients who are involuntarily hospitalized because of mental illness must not be enrolled in clinical studies

1.1.4 Other Circumstances

Subjects who are imprisoned or involuntarily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness must not be enrolled in clinical studies.

In circumstances where a subject's only access to treatment is through enrollment in a clinical study, eg, for subjects in developing countries with limited resources or for subjects with no marketed treatment options, the investigator must take special care to explain the potential risks and benefits associated with the study and ensure that the subject is giving informed consent.

When a subject may be in a dependent relationship with the investigator, a well-informed physician who is not engaged in the clinical study and is completely independent of the relationship between the subject and investigator should obtain the subject's informed consent.

1.1.5 Illiterate Subjects

If the subject, or, in those situations where consent cannot be given by the subject, their legally acceptable representative is unable to read, a reliable and independent witness should be present during the entire informed consent discussion. The choice of the witness must not breach the subject's rights to confidentiality. A reliable independent witness is defined as one not affiliated with the institution or engaged in the investigation. A family member or acquaintance is an appropriate independent witness. After the subject or legally acceptable representative orally consents and has signed, if capable, the witness should sign and personally date the consent form attesting that the information is accurate and that the subject, or, in those situations where consent cannot be given by subjects, their legally acceptable representative has fully understood the content of the informed consent agreement and is giving true informed consent.

1.2 Update of Informed Consent

The informed consent and any other information provided to subjects, or, in those situations where consent cannot be given by subjects, the subject's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the subject's consent, and should receive IRB/IEC approval/favorable opinion prior to use. The investigator, or a person designated by the investigator should fully inform the subject or the subject's legally acceptable representative 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.

During a subject's participation in the study, any updates to the consent form and any updates to the written information will be provided to the subject.

APPENDIX 2 SAE NOTIFICATION INFORMATION FOR SITES LOCATED OUTSIDE THE US

All SAEs must be immediately reported by confirmed facsimile transmission (fax). **The original SAE page must be mailed in the envelopes pre-addressed to the SAE central mailbox detailed in the Protocol (see Section 7.3.1). For those sites identified, the forms will be mailed to the local business address listed in the table below.**

Mexico **SAE Facsimile Number:** [redacted]

[redacted]

Russia **SAE Facsimile Number:** [redacted]

[redacted]

Canada **SAE Facsimile Number:** [redacted]

Contact the Medical Monitor assigned to this study. Please see protocol cover page and Section 7.3.1

APPENDIX 3 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 4 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 short-term treatment periods (in non-rescued subjects), the A1C values will be blinded to the Investigator and to the Sponsor. These values will be provided to the Investigator after the study has been completed or after completion of the rescue visit in subjects who require the initiation of rescue medication.

During the lead-in, short-term and long-term treatment periods, the urinary glucose values, including the urinary glucose:creatinine ratio, will be blinded to the Investigator and to the Sponsor. The urinary glucose 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:

- A1C (%)
- 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)
    - *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)
- Free Fatty Acid (FFA) (mg/dL, mmol/L)
- Metabolic Surrogate Markers
  - hs-CRP (mg/L)
  - PAI-1 (IU/mL, U/L)
  - Fibrinogen (mg/dL, g/L)
- Serum Markers of Bone Metabolism
  - Parathyroid Hormone (PTH) (pg/mL, ng/L)
  - Osteocalcin (ng/mL, μg/L)
  - Total Procollagen Type 1 N-Terminal Propectide (P1NP) (ng/mL, μg/L)
  - C-telopeptide of Type 1 Collagen (CTx) (μg/L or μg/mmol)
  - N-telopeptide of Type 1 Collagen (NTx) ((μg/L or μg/mmol)
  - 25-hydroxy vitamin D
- Cystatin-C (mg/L)

Enrollment-Specific Safety Panel

- Hepatitis Screen Panel:
  - Anti-hepatitis C virus antibody
    - *Reflex Testing: If positive, a reflex RIBA HCV will be obtained*
  - Hepatitis B surface antigen
- TSH (uIU/mL, mIU/L)

– *Reflex Testing: Abnormal TSH value at enrollment will be further evaluated by free T4 (ng/dL, pmol/L).*

Standard Safety Laboratory Panels:

Table Appendix 4A: Standard Blood Safety Laboratory Panels

Hematology

- Hemoglobin (g/dL, g/L)
- Hematocrit (%, V/V)
- Red blood cell (RBC) (x10E6/UL, x10E12/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 (x10E9/L)

Serum Chemistry

- AST (IU/L)
- ALT (IU/L)
- ALK-P (IU/L)
- CK/CPK (IU/L). *Reflex Testing: CKMB and Troponin I will be ordered if CK > 400 IU/L).*
- Total Bilirubin (mg/dL, μmol/L)
- Blood Urea Nitrogen (mg/dL, mmol/L)
- Bicarbonate (mEq/L, mmol/L)
- Serum Creatinine (mg/dL, μmol/L). **Glomerular Filtration Rate will be calculated by the Central Laboratory using the Modification in Diet and Renal disease (MDRD) formula and results will be reported to the sites and the Sponsor.** *(Levey AS, Coresh J, Balk E, Kausz AT, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification and stratification. Ann Int Med 2003; 139 (2): 137-47. Levey AS, Bosch JP, Breyer J, et al. A more accurate method to estimate glomerular filtration rate from serum Creatinine: A new Prediction Equation. Ann Int Med 1999;130 (6):461-470).*
- 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)

Table Appendix 4A: Standard Blood Safety Laboratory Panels

- Albumin (g/dL, g/L)
- Uric acid (mg/dL, μmol/L)

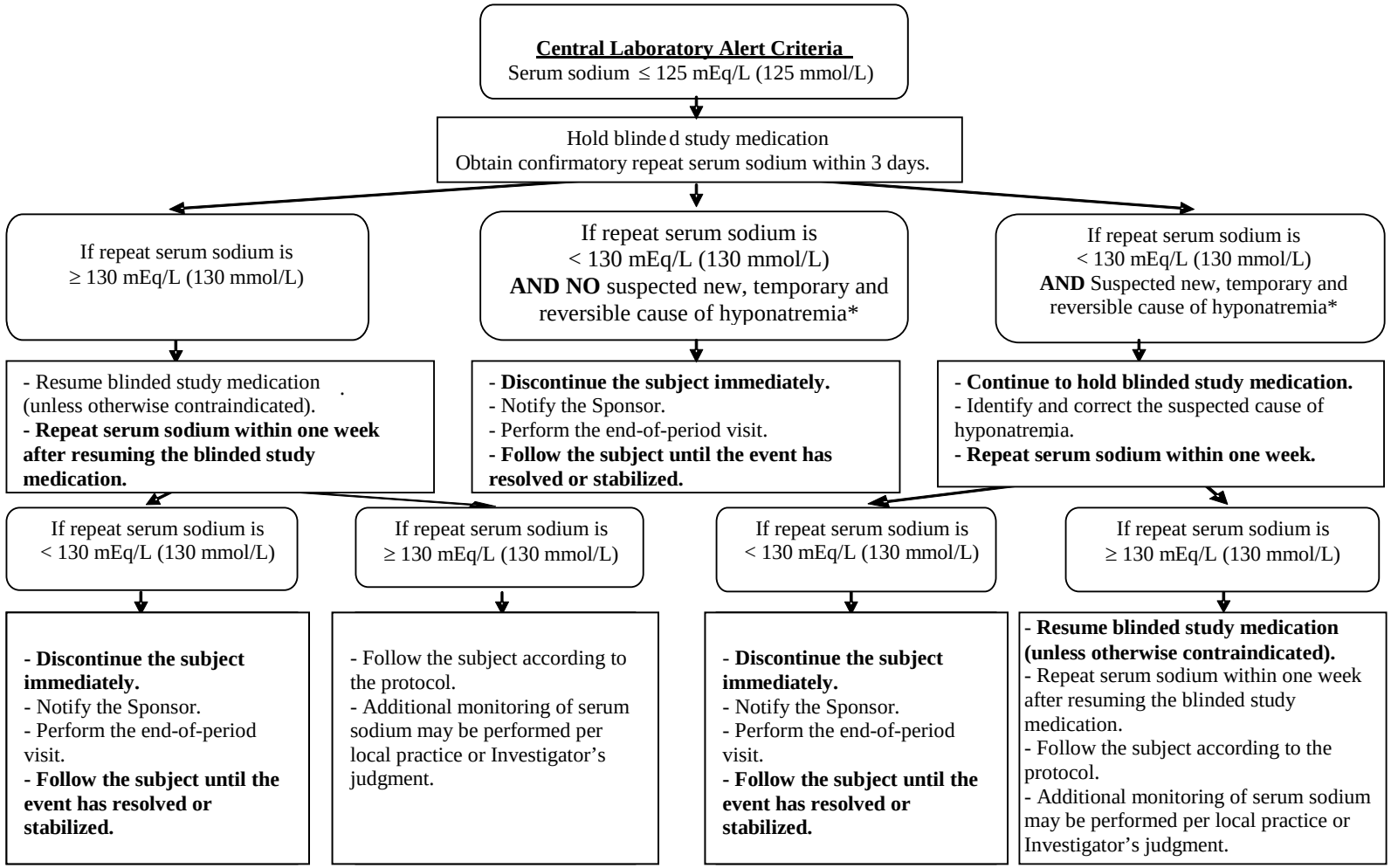
Urine Analyses

- Blood (dipstick). *Microscopy will be ordered if dipstick is positive for blood.*
- Albumin
- Creatinine
- Calculated Urinary albumin:creatinine ratio (UACR)
- Urine HCG pregnancy test for WOCBP (HCG minimum sensitivity of 25 IU/L; performed at site). *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, entry into lead-in Day -14, Day 1, Week 24, Week 50 and Week 102 visits will include the following assessments (spot urine):

- Glucose
- Urinary glucose:creatinine ratio

APPENDIX 5 HYPONATREMIA FLOW CHART



* Based on clinical assessment (other than the administration of blinded study medication)

For subjects whose serum sodium is between 126 and 129 mEq/L (126 and 129 mmol/L), the Investigator's clinical judgment should apply concerning whether such subjects should be followed according to this algorithm.