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Clinical Protocol MB102072

A Randomized, Double-Blind, Placebo-controlled, Parallel Group, Phase 2 Pilot Study to Explore the Safety, Pharmacokinetics and Pharmacodynamics of Dapagliflozin as an Add-on to Insulin Therapy in Subjects with Type 1 Diabetes Mellitus

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DOCUMENT HISTORY

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

SYNOPSIS

Clinical Protocol MB102072

Title of Study: Protocol MB102072: A Randomized, Double-Blind, Placebo-controlled, Parallel Group, Phase 2 Pilot Study to Explore the Safety, Pharmacokinetics and Pharmacodynamics of Dapagliflozin as an Add-on to Insulin Therapy in Subjects with Type 1 Diabetes Mellitus

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

Subjects on insulin monotherapy who meet criteria will be eligible for randomization in a 1:1:1:1:1 ratio into one of the following five blinded treatment arms:

- Dapagliflozin 1 mg QD for 14 days
- Dapagliflozin 2.5 mg QD for 14 days
- Dapagliflozin 5 mg QD for 14 days
- Dapagliflozin 10 mg QD for 14 days
- Matching placebo for 14 days

Study Phase: 2a

Research Hypothesis: There is no formal research hypothesis for this study to be statistically tested. The purpose of the study is to evaluate the safety profile and tolerability, particularly with regard to hypoglycemia, following once daily oral dose of 1, 2.5, 5 and 10 mg of dapagliflozin administered in subjects with type 1 diabetes mellitus (T1DM) for 14 days as well as pharmacokinetics (PK) and pharmacodynamics (PD) after 7 days of treatment.

Primary Objective: To assess the safety and tolerability of each dose of dapagliflozin (1 mg, 2.5 mg, 5 mg and 10 mg per day) plus insulin after up to 14 days of oral administration of double-blind treatment, as measured by numbers of subjects with SAEs, deaths or discontinuations due to AEs, events of hypoglycemia, AEs of genitourinary infection, or potentially clinically significant changes in vital signs.

Study Design:

The MB102072 is a randomized, double-blind, 5-arm, parallel-group, placebo-controlled exploratory Phase 2a trial to evaluate the safety, tolerability, PK and PD of dapagliflozin in subjects with type 1 diabetes who have inadequate glycemic control despite insulin use. Subjects on insulin monotherapy with central laboratory enrollment A1C $\geq$ 7.0% and $\leq$ 10.0% will be eligible for randomization in a 1:1:1:1:1 ratio into one of five blinded treatment arms noted above

Subjects will receive dapagliflozin or matching placebo for a total of 14 days and will be in-patient from Day -3 to Day 7. Subjects will receive standardized diets and be provided guidance for adjustment of insulin dosing during the inpatient stay. Subjects will be monitored closely with regard to safety parameters, including vital signs, safety laboratory tests and adverse events.

In addition to the routine safety laboratory tests, the following parameters will be closely monitored:

— Urinary ketones by urine dipstick, daily

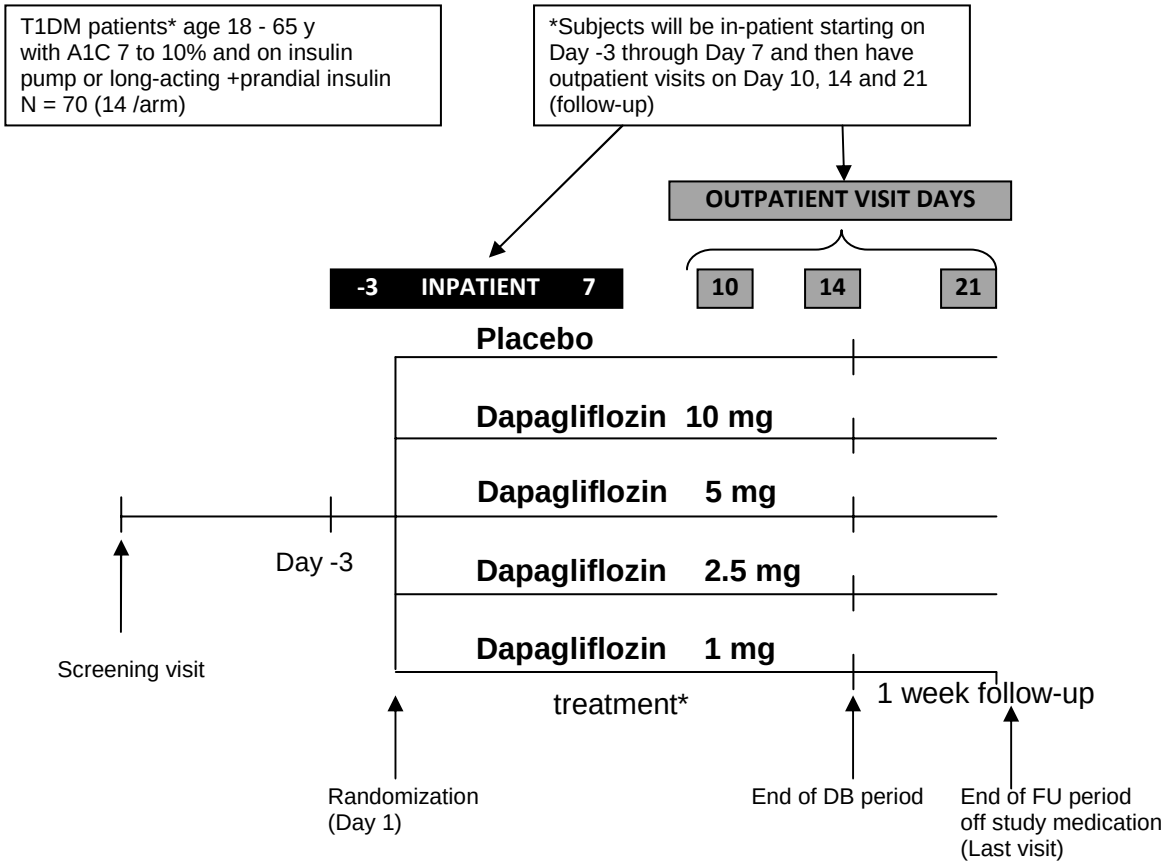
— Fluid intake and output, daily (during inpatient portion of the study only)

Date: [redacted]

— Serum β-hydroxybutyrate at baseline Day -2, Day 1, Day 7, Day 14 and Day 21

— Body weight- at screening, daily during inpatient portion of the study (starting day -2) and at each outpatient visit

Figure 1: Study Design



* Subjects will be inpatient from Day -3 to day 7 and then have outpatient visits on Day 10 (± 1 day), Day 14 (no window-relative to day 1/first dose) and a discharge visit on Day 21 (± 2 days).

Study Population: Men and women with type 1 diabetes, ages 18 to 65 years, inclusive, who have been receiving either multiple doses (at least 2X/day) of insulin consisting of long-acting (glargine or detemir) plus short-acting prandial insulin or on insulin pump (continuous subcutaneous insulin infusion, CSII). Subjects must have been on insulin therapy for at least 12 months prior to enrollment, and their method of insulin administration (multiple daily injections or CSII) must have been stable for at least 3 months prior to enrollment. The dose of basal insulin must have remained stable (within 20% variance of the total daily dose) for the 2 weeks preceding enrollment (per subject report). Subjects must have inadequate glycemic control, as defined as central laboratory A1C ≥ 7.0% and ≤ 10.0%, obtained at the enrollment visit (a single re-test is allowed). Randomization will be stratified by body mass index (BMI) categorization (≤ 23 kg/m2 vs. > 23 kg/m2) and method of insulin administration (pump or daily injections) to ensure equal representation across all treatment groups.

Date: [redacted]

Study Assessments and Primary Endpoints:

Primary Endpoints:

1) Number of subjects that experience during the 14 days of dapagliflozin exposure:
   a) Events of hypoglycemia
   b) Serious adverse events
   c) Deaths
   d) Adverse events leading to discontinuation of study therapy
   e) Adverse events of interest of genitourinary infection

2) Number of subjects with potentially clinically significant changes in vital signs during the 14 days of dapagliflozin exposure, defined as:

Marked Abnormality Criteria for Vital Signs

- Heart Rate (bpm): HR > 100 bpm and > 30 bpm above baseline, or HR < 55 bpm and > 15 bpm below baseline
- Systolic BP (mmHg): SBP > 140 mmHg and > 20 mmHg above baseline or SBP < 90 mmHg and > 20 mmHg below baseline
- Diastolic BP (mmHg): DBP > 90 mmHg and > 10 mmHg above baseline or DBP < 55 mmHg and > 10 mmHg below baseline

Orthostatic Change

- Heart Rate (bpm): Standing HR- Supine HR > 30 bpm
- Systolic BP (mmHg): Standing SBP- Supine SBP < -25 mmHg
- Diastolic BP (mmHg): Standing DBP - Supine DBP < -10 mmHg

Statistical Methods:

The purpose of the study is to evaluate the safety profile and tolerability of once daily oral dose of 1, 2.5, 5 and 10 mg of dapagliflozin in subjects with type I diabetes after 14 days of double-blind treatment as opposed to placebo.

No formal statistical hypothesis testing is planned for this study. Therefore, the sample size for this study is not based on any formal power considerations. The sample size target is 14 subjects per study arm, i.e. a total of 70 subjects to be randomized to dapagliflozin 1, 2.5, 5, 10 mg and placebo in 1:1:1:1:1 ratio.

Analysis will include the estimation of frequencies (for categorical endpoints) or summary statistics such as mean and 95% confidence intervals (for continuous endpoints) for each treatment arm. All adverse events that are serious or that result in discontinuation of study therapy will be described in depth.

Date: [redacted]

TABLE OF CONTENTS

Date: [redacted]

Date: [redacted]

1 INTRODUCTION AND STUDY RATIONALE

1.1 Study Rationale

Patients with T1DM require lifelong insulin therapy due to the inability to produce endogenous insulin. Insulin requirements in these subjects vary widely and depend on several factors such as body weight, activity level, food intake, etc. Insulin administration is often associated with weight gain and many patients with T1DM develop insulin resistance (inability to efficiently utilize insulin) and thus require high doses of insulin to maintain euglycemia. Insulin dosing that is mismatched to the insulin need often leads to excessive food intake related to increased appetite and the desire to avoid hypoglycemia. This situation can drive weight gain and set off a vicious cycle leading to increasing insulin requirements and worsening of their glycemic control. Dapagliflozin has a unique mechanism of action that does not directly affect either insulin resistance or insulin secretion, but rather improves glycemia by reduction of glucose reabsorption from proximal renal tubules. Dapagliflozin is expected to reduce mean daily glucose, improve glycemic control and reduce overall insulin requirements. Improved glycemic control with reduced variability may also lead to reduced frequency of hypoglycemia.

This study will be the first study of dapagliflozin in patients with T1DM and will include dosing with dapagliflozin for 14 days, with the first seven days in an in-patient setting to evaluate safety and also to more closely monitor insulin requirements. An initial evaluation of 7 days as an inpatient will provide optimal monitoring of subject safety and assessment of the effects of dapagliflozin in a structured setting, while the outpatient experience will allow for a more 'real-life' assessment of the safety of dapagliflozin and its potential effects on glycemic control. A steady state assessment of pharmacokinetics of dapagliflozin and its major inactive metabolite dapagliflozin 3-O-glucuronide is also planned to characterize the pharmacokinetics in this patient population for the first time. The 14-day total exposure would give adequate time to observe clinically relevant safety, pharmacokinetic and pharmacodynamic measures. Doses of 1 mg, 2.5 mg, 5 mg and 10 mg were all studied in the phase 3 program for T2DM and demonstrated efficacy. All four doses will be evaluated in the current study to provide an assessment of the safety and pharmacodynamic activity across the dose range and will help inform dose selection and insulin dose adjustment requirements for future T1DM studies.

1.2 Research Hypothesis

There is no formal research hypothesis for this study to be statistically tested. The purpose of the study is to evaluate the safety profile and tolerability, particularly with regard to hypoglycemia, following once daily oral dose of 1, 2.5, 5 and 10 mg of dapagliflozin administered in subjects with T1DM for 14 days as well as pharmacokinetics (PK) and pharmacodynamics (PD) after 7 days of treatment.

1.3 Objectives

Primary Objective:

To assess the safety and tolerability of each dose of dapagliflozin (1 mg, 2.5 mg, 5 mg and 10 mg per day) plus insulin after up to 14 days of oral administration of double-blind treatment, as measured by numbers of subjects with SAEs, deaths or discontinuations due to AEs, events of hypoglycemia, AEs of genitourinary infection, or potentially clinically significant changes in vital signs.

Secondary Objectives:

1) To assess the change from baseline in mean glucose based on 7-point central laboratory glucose monitoring achieved with dapagliflozin (1 mg, 2.5 mg, 5 mg and 10 mg per day) plus insulin versus placebo plus insulin after 7 days of oral administration of double-blind treatment.
2) To assess the pharmacokinetics of dapagliflozin and its major inactive metabolite, dapagliflozin 3-O-glucuronide, on Day 7.

Other/Exploratory Objectives:

1) To assess the change from baseline (Day -1) in the percent of 24-hour glucose readings obtained from continuous glucose monitoring system (CGMS) during the inpatient stay after 7 days of double-blind treatment with dapagliflozin plus insulin versus placebo plus insulin that fall within the following ranges:
   a) $\leq$ 50 mg/dL
   b) $\leq$ 70 mg/dL
   c) 71 - 180 mg/dL
   d) > 180 mg/dL
2) To assess change from baseline (Day -1) in glucose variability estimated from CGMS with dapagliflozin plus insulin versus placebo plus insulin after 7 days of oral administration of double-blind treatment

Date: [redacted]

3) To assess the percent change from baseline (Day -1) during the inpatient stay in total daily insulin dose with dapagliflozin plus insulin versus placebo plus insulin after 7 days of oral administration of double-blind treatment
4) To assess the change from baseline achieved with dapagliflozin (1 mg, 2.5 mg, 5 mg and 10 mg per day) plus insulin versus placebo plus insulin after 7 days of oral administration of double-blind treatment, for Fasting Plasma Glucose (FPG)
5) To assess the effect of dapagliflozin dose on 24 h urinary glucose excretion and the percent inhibition of renal glucose reabsorption after 7 days of oral administration of double-blind treatment.
6) To assess the change from baseline in systolic blood pressure (SBP) achieved with dapagliflozin (1 mg, 2.5 mg, 5 mg and 10 mg per day) plus insulin versus placebo plus insulin after 7 and 14 days of oral administration of double-blind treatment.
7) To assess other safety and tolerability parameters including: proportion of subjects with adverse events (not included in the primary objective) and marked abnormalities in clinical laboratory tests, as well as the change from baseline at each post-baseline time point of selected safety clinical laboratory parameters, physical measurements, vital signs and electrocardiogram data after 14 days of oral administration of double-blind treatment.

1.4 Product Development Background

Dapagliflozin has been designed as a potent and selective inhibitor of the renal sodium-glucose transporter, SGLT2. Multiple phase 2 and phase 3 studies, where dapagliflozin was used as a monotherapy or in combination with other oral hypoglycemic agents or insulin in subjects with type 2 diabetes mellitus (T2DM), have shown that there is a dose-dependent decrease in fasting plasma glucose (FPG) from baseline to week 12 (phase 2 studies) and week 24 (phase 3 studies) with dapagliflozin treatment. Dapagliflozin is also associated with a significant reduction of glycosylated hemoglobin (A1C) from baseline compared to placebo (0.4 - 0.56% and 0.54 - 0.68% for 5 and 10 mg doses, respectively).

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

In completed clinical studies, dapagliflozin was generally safe and well-tolerated. No clinically relevant changes from baseline were seen in either renal functions or serum

electrolytes in subjects treated with dapagliflozin. In Phase 2/3 studies, the frequency of overall adverse events (AEs) was similar to placebo. The majority of AEs were of mild intensity and did not require discontinuation. Overall, the frequency of genital infections was higher in subjects treated with dapagliflozin. The frequency of urinary tract infections (UTIs) was varied with a generally higher frequency observed in subjects treated with dapagliflozin. Infections were seen in both male and female subjects.

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

To date, dapagliflozin has not been studied in patients with T1DM and this will be the first study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of dapagliflozin in this population.

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. Dapagliflozin has been effective at lowering glucose and A1C in subjects with T2DM, when studied as monotherapy as well as in combination with insulin or oral anti-diabetic medications. Dapagliflozin has not previously been studied in subjects with type 1 diabetes. Because subjects with T1DM are absolutely insulin deficient, insulin treatment is required for survival and dapagliflozin would not be a replacement for insulin therapy. However, dapagliflozin reduces glucose by an insulin-independent mechanism (reduction of glucose reabsorption by the kidney, leading to glucose loss in the urine) and potentially may be effective in improving glycemic control in subjects with T1DM when used in combination with insulin.

As noted above, dapagliflozin was generally safe and well-tolerated in completed clinical studies in subjects with T2DM. Overall, the frequency of genital and urinary tract infections was higher in subjects treated with dapagliflozin and a small dose-dependent increase in hematocrit was observed in dapagliflozin treated subjects without any associated clinically relevant events.

In this pilot study in T1DM, the doses of dapagliflozin have been chosen to span the range of doses studied in the Phase 3 program in subjects with T2DM. It is expected that the safety and efficacy profile in subjects with T1DM will be similar to that observed in

subjects with T2DM. However, improvement in glucose control may result in an increased risk of hypoglycemia from concomitant insulin treatment. Therefore, dapagliflozin will be started in an inpatient setting to allow for careful insulin adjustment and to optimize safety monitoring.

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

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

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

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

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

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

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided

Date: [redacted]

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

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

2.3 Informed Consent

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

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

Investigators must:

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

Date: [redacted]

representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

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

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

The MB102072 is a randomized, double-blind, 5-arm, parallel-group, placebo-controlled exploratory Phase 2a pilot study to evaluate the safety, tolerability, PK and PD of dapagliflozin in subjects with type 1 diabetes who have inadequate glycemic control despite insulin use. Approximately 70 subjects on insulin monotherapy with central laboratory enrollment A1C $\geq$ 7.0% and $\leq$ 10.0% will be eligible for randomization in a 1:1:1:1:1 ratio into one of the following five blinded treatment arms:

- Dapagliflozin 1 mg QD
- Dapagliflozin 2.5 mg QD
- Dapagliflozin 5 mg QD
- Dapagliflozin 10 mg QD
- Matching placebo

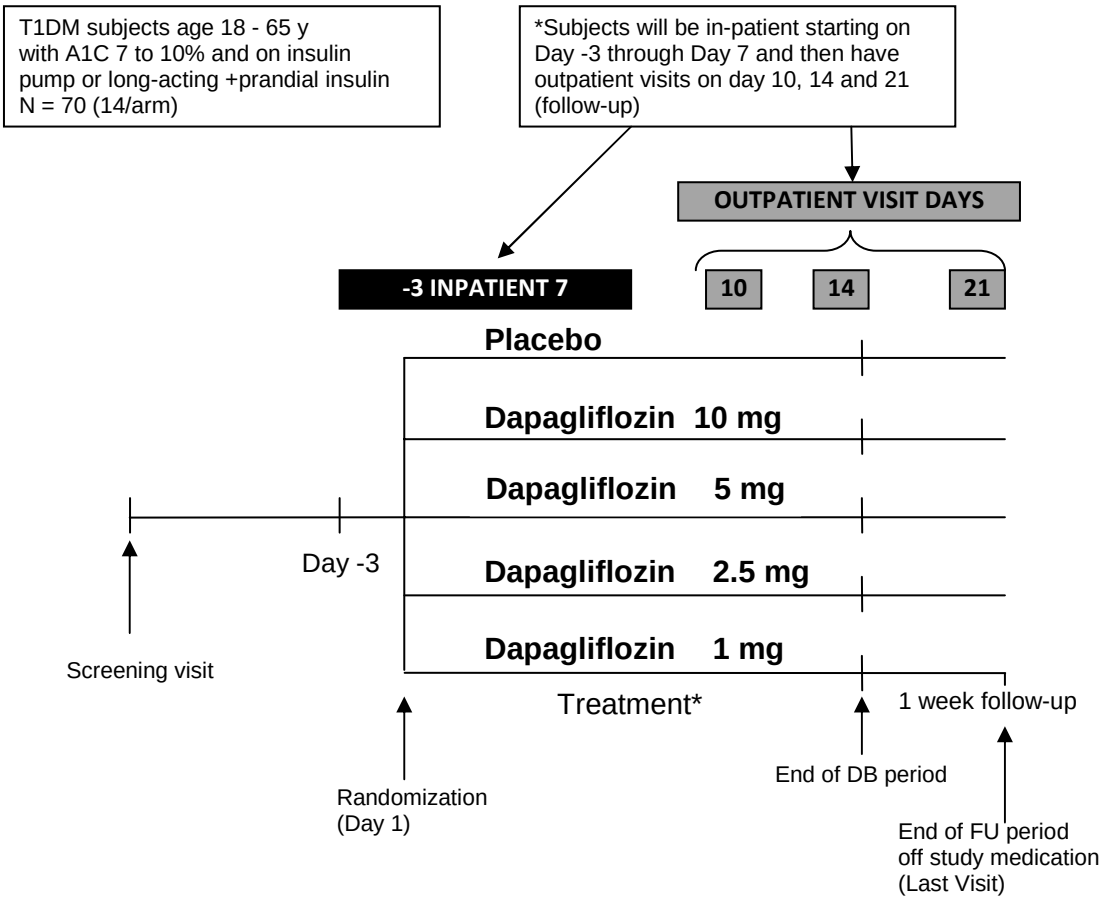
Subjects will receive dapagliflozin or matching placebo for a total of 14 days and will be in-patient from Day -3 to Day 7. Randomization will be stratified by body mass index (BMI) categorization ($\leq$ 23 kg/m^2 vs. > 23 kg/m^2) and method of insulin administration (pump or daily injections) to ensure equal representation across all treatment groups. Subjects will receive standardized diets and provided guidance for adjustment of insulin dosing during the inpatient stay. Subjects will be monitored closely with regard to safety parameters, including vital signs, safety laboratory tests and adverse events.

Date: [redacted]

In addition to the routine safety laboratory tests, the following parameters will be closely monitored:

- Urinary ketones by urine dipstick, daily
- Fluid intake and output, daily (during inpatient portion of the study only)
- Serum β-hydroxybutyrate at baseline Day -2, Day 1, day 7, Day 14 and Day 21
- Body weight - at screening, daily during inpatient portion of the study (starting day -2) and at each outpatient visit

Figure 3.1: Study Design Schematic



* Subjects will be inpatient from Day -3 to Day 7 and then have outpatient visits on Day 10 (± 1 day), Day 14 and a discharge visit on Day 21 (± 2 days).

Date: [redacted]

3.2 Post Study Access to Therapy

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

3.3 Study Population

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

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent

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

2) Target Population

a) Subject must have type 1 diabetes with inadequate glycemic control, defined as central laboratory A1C $\geq$ 7.0% and $\leq$ 10.0%, obtained at the screening 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 10.2% who are otherwise eligible, as determined by the Investigator.)

b) Insulin use, either multiple doses (at least 2x/day) of insulin consisting of long-acting (glargine or detemir) plus short-acting prandial insulin or on insulin pump (continuous subcutaneous insulin infusion, CSII), for at least 12 months and initiation of insulin immediately after diagnosis of diabetes. [Method of insulin administration (multiple daily injections or CSII) must have been stable for at least 3 months prior to Day -3. In addition, the dose of basal insulin must have remained stable (within 20% variance of the total daily dose) for the 2 weeks preceding Day -3 (per subject report)]

c) Central laboratory C-peptide value of < 0.7 ng/mL at screening

d) BMI 18.5 to 35.0 kg/m^2, inclusive at screening.

3) Age and Reproductive Status

a) Men and women, ages 18 to 65 years old.

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

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

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

d) Women must not be breastfeeding

3.3.2 Exclusion Criteria

1) Target Disease Exclusions

a) History of T2DM, maturity onset diabetes of young (MODY), pancreatic surgery or chronic pancreatitis.

b) Any use of oral hypoglycemic agents within 12 months prior to the Day -3 visit.

c) History of diabetes ketoacidosis (DKA) within 24 weeks prior to the Day -3 visit.

d) History of diabetes insipidus.

e) History of hospital admission for glycemic control (either hyperglycemia or hypoglycemia) within 6 months prior to the Day -3 visit

f) Frequent episodes of hypoglycemia as defined by more than one episode requiring assistance, emergency care (paramedics or emergency room care) or glucagon therapy, or more than 2 unexplained episodes of symptomatic hypoglycemia within 3 months prior to Day -3. An unexplained event is defined as an event that cannot be explained by circumstances such as dietary (e.g. missed meal), strenuous exercise, error in insulin dosing, etc.

g) Hypoglycemic unawareness.

h) History of Addison's disease or chronic adrenal insufficiency.

2) Medical History and Concurrent Diseases

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

a) Myocardial infarction

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

c) Unstable angina

d) Unstable congestive heart failure (CHF)

Date: [redacted]

e) CHF New York Heart Association (NYHA) Class III or IV (see Appendix 1)

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

g) Unstable or previously undiagnosed arrhythmia

3) Physical and Laboratory Test Findings

a) Aspartate aminotransferase (AST) > 2X Upper limit of normal (ULN)

b) Alanine aminotransferase (ALT) > 2X ULN

c) Serum total bilirubin > 2X ULN

d) Estimated GFR (eGFR) by the Modification of Diet in Renal Disease (MDRD) formula ≤ 60 mL/min/1.73m2. The renal function, eGFR will be estimated by the abbreviated MDRD, using laboratory measurements of serum creatinine collected at screening [eGFR (mL/min/1.73m2) = 175 x (standardized Scr)-1.154 x (Age)-0.203 x (0.742 if female) x (1.212 if Black)].

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

f) Creatine kinase (CK) > 3X ULN

g) Positive for hepatitis B surface antigen or anti-hepatitis C virus antibody.

h) Abnormal Free T4

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

4) Allergies and Adverse Drug Reaction

a) Allergies or contraindication to the contents of dapagliflozin tablets or insulin.

5) Renal, Hepatic, Hemotological/Oncological Diseases/Conditions

a) History of unstable or rapidly progressing renal disease.

b) Conditions of congenital renal glucosuria

c) Renal allograft

Date: [redacted]

d) Significant hepatic disease, including but not limited to, chronic active hepatitis and/or severe hepatic insufficiency.

e) Documented history of hepatotoxicity with any medication

f) Documented history of severe hepatobiliary disease

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

h) 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.

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

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

6) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

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

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

NOTE: Topical or inhaled corticosteroids are allowed.

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

e) 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.

f) 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.

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

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

Date: [redacted]

i) Previous participation in a clinical trial with dapagliflozin (BMS-512148) and/or with any other SGLT2 inhibitors.

j) Administration of any other investigational drug within 30 days of planned enrollment to this study.

k) No clinical conditions or clinically significant abnormalities, in any laboratory value(s) collected after screening and prior to randomization which, in the Investigator's judgment, should preclude entry into the treatment period

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

3.3.3 Women of Childbearing Potential

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

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

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

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

3.4.1.1 Prohibited Treatments

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

- Any injectable anti-diabetic medications other than insulin (including GLP-1 agonists and pramlintide)
- Any oral anti-diabetic medications.
- Acetaminophen-containing medications (contraindicated for the DexCom SEVEN PLUS System so subjects should not use medications that contain acetaminophen while wearing the Dexcom CGM device).
- Any diuretic therapy (e.g. loop diuretics, thiazide diuretics, aldosterone antagonists).
- Treatment with any systemic corticosteroid therapy.
- Administration of phentermine, benzphetamine, diethylpropion, methamphetamine, orlistat, and/or phendimetrazine.

3.4.1.2 Restricted Treatments

The following can be administered provided the dose was stable prior to screening 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™,DiaVite™, GlucoCare™, Gluotize™, GlycoNase™, SugarMax™ or Sugar Loss™.

3.4.2 Allowable Treatments and/or Therapies

Subjects may continue on stable doses (as defined by at least 3 months on therapy prior to Day -3, with at least one month on the same dose, per subject report) of angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARBs), selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, norepinephrine-dopamine reuptake inhibitors, HMG-CoA reductase inhibitors, ezetimibe, or fenofibrate.

3.4.3 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 5.3.7) and to the protocol visit schedule (see Section 5.1.1).
- 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 6.4).

3.5 Discontinuation of Subjects from Treatment

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

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness

Date: [redacted]

- Protocol-defined major hypoglycemia episode or recurrent non-major hypoglycemia episodes (see Section 3.5.1)
- Sustained elevated S_{Cr} (see Section 3.5.2)
- Sustained elevated liver safety abnormalities (see Section 3.5.3)
- Sustained hyponatremia (see Section 3.5.4).
- Sustained elevated CK (see Section 3.5.5)

All subjects who discontinue should comply with protocol specified follow-up procedures for Day 14/ET visit as outlined in Section 5.1. 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.

3.5.1 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 double-blind study medication), and/or other contributing factors (eg, excessive physical activity) have been evaluated and corrected. NOTE: Dose titration of double-blind study medication is not permitted at any time during the treatment period.

- 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 < 54 mg/dL (< 3 mmol/L) 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.

Date: [redacted]

Section 5.3.1 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.

3.5.2 Discontinuation Guidelines due to sustained elevated Serum Creatinine

Subjects will have double blind study medication withheld and a confirmatory, repeat S_{Cr} drawn within one week, if the following criterion is met:

- Male or female subjects: $S_{Cr} \geq 2.0$ mg/dL (176 μmol/L)

The following actions should be taken upon receipt of the central laboratory repeat SCr result:

- If the repeat S_{Cr} is < 2.0 mg/dL (176 μmol/L), double-blind study medication may be resumed unless otherwise contraindicated.
- If the repeat S_{Cr} is ≥ 2.0 mg/dL (176 μmol/L), the subject must be immediately discontinued from the study, the Sponsor notified, and the Day 14 visit performed. **The Investigator will follow the subject until the event has resolved or stabilized.**

3.5.3 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 total bilirubin (TB) (see Appendix 4 for algorithm flow chart). Subjects with central laboratory ALT and/or AST > 3 X ULN will be scheduled for a follow-up visit within 3 days following receipt of the initial laboratory results, to obtain repeat central laboratory ALT, AST, TB and Alkaline Phosphatase (ALK-P). In the event that the repeat laboratory assessments cannot be obtained within 3 days, the Investigator is encouraged to discuss possible alternatives with the Sponsor. Subjects should remain on study medication until confirmatory results are obtained, unless otherwise contraindicated.

Date: [redacted]

- If the repeat ALT and AST are ≤ 3X ULN, subject should continue in the double blind treatment period according to their original visit schedule unless otherwise contraindicated.
- If the repeat ALT and/or AST are > 3X ULN but ≤ 8X ULN and TB ≤ 1.5X ULN, the subject's medical history, including details of risk factors for liver diseases, should be evaluated for potential underlying etiologies. In addition, specialized blood sampling will be performed to evaluate liver function as well as identify potential causes of laboratory elevation(s). The Investigator should continue to monitor the subject's liver tests every 3 days following receipt of the prior laboratory results until the ALT and AST are ≤ 2X ULN or until ALT and AST are at or below baseline levels. The frequency of retesting can decrease to once a week or less if abnormalities stabilize and the subject is asymptomatic. Subjects should remain on study medication unless confirmatory results indicate that a criterion for discontinuation has been met or continuing study medication would be otherwise contraindicated.

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

- ALT and/or AST are > 3X ULN and TB > 1.5X ULN
- ALT and/or AST are > 5X ULN for ≥ 14 consecutive days, at any time after initial confirmatory results
- ALT and/or AST are > 8X ULN

In each of these situations, study medication will be discontinued, the Sponsor notified and the Day 14 visit performed within 3 days of the confirmed laboratory results. At the Day 14 visit, medical history including details of risk factors for liver diseases (if not previously assessed) will be requested and additional blood sampling performed (see Section 5.3.3 and Appendix 2). A referral consultation to a hepatologist or gastroenterologist (specializing in liver abnormalities) should be obtained.

Following the Day 14 visit, the Investigator should continue to monitor the subject's liver tests every 3 days following receipt of the prior laboratory results until the ALT and AST are ≤ 2X ULN or until ALT and AST are at or below baseline levels. The frequency of retesting can decrease to once a week or less if abnormalities stabilize and the subject is asymptomatic (see Appendix 4).

Date: [redacted]

3.5.4 Discontinuation Guidelines due to Hyponatremia

Subjects with a serum sodium ≤ 125 mEq/L (125 mmol/L) will have double-blind study medication withheld and a confirmatory, repeat serum sodium, drawn within 3 days following receipt of the initial laboratory result.

- If the repeat serum sodium is ≥ 130 mEq/L (130 mmol/L):
  - Double-blind study medication may be resumed unless otherwise contraindicated.
  - Serum sodium should be re-tested within one week after resuming the double blind study medication.
    - If the repeat of serum sodium, obtained within one week after resuming double-blind study medication, is < 130 mEq/L (130 mmol/L), the subject must be immediately discontinued from the study, the Sponsor notified and the Day 14/ET visit performed. **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 double-blind 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 double-blind study medication), the subject must be immediately discontinued from the study, the Sponsor notified and the Day 14/ET visit performed. **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 double-blind study medication):
  - Double-blind 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 Day 14/ET visit performed. **The Investigator will follow the subject until the event has resolved or stabilized.**

Date: [redacted]

- If the repeat of serum sodium, obtained within one week after the first repeat, is ≥ 130 mEq/L (130 mmol/L):
  - Double-blind study medication may be resumed unless otherwise contraindicated.
  - Serum sodium should be re-tested within one week after resuming double-blind 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 3 for algorithm flow chart).

3.5.5 Discontinuation Guidelines due to Elevated Creatine Kinase

Subjects with a CK > 10X ULN will have double-blind 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, double-blind study medication may be resumed unless otherwise contraindicated
- If the repeat CK is > 10X ULN, the subject must be immediately discontinued from the study, the Sponsor notified and the Day 14 visit performed. **The Investigator will follow the subject until the event has resolved or stabilized.**

4 TREATMENTS

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

4.1 Study Treatments

Table 4.1: Product Description: Double Blind Treatment Period (14 days)

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Placebo Matching Dapagliflozin 1 mg Tablet	0 mg	Bottle of 20 tablets / Blinded	Patient kit with 3 bottles (A,B,C)/ Blinded	Yellow, plain, round, film coated tablet	Store at 15 - 25 DEG C (59 - 77 DEG F). Store in tightly closed container
Placebo Matching Dapagliflozin 2.5/5 mg Tablets	0 mg	Bottle of 20 tablets / Blinded	Patient kit with 3 bottles (A,B,C)/ Blinded	Green, plain, diamond shaped, film coated tablet	Store at 15 - 25 DEG C (59 - 77 DEG F). Store in tightly closed container
Placebo Matching Dapagliflozin 10 mg Tablets	0 mg	Bottle of 20 tablets / Blinded	Patient kit with 3 bottles (A,B,C)/ Blinded	Green, plain, diamond shaped, film coated tablet	Store at 15 - 25 DEG C (59 - 77 DEG F). Store in tightly closed container
Dapagliflozin Tablet	1 mg	Bottle of 20 tablets / Blinded	Patient kit with 3 bottles (A,B,C)/ Blinded	Yellow, plain, round, film coated tablet	Store at 15 - 25 DEG C (59 - 77 DEG F). Store in tightly closed container
Dapagliflozin Tablet	2.5 mg	Bottle of 20 tablets / Blinded	Patient kit with 3 bottles (A,B,C)/ Blinded	Green, plain, diamond shaped, film coated tablet	Store at 15 - 25 DEG C (59 - 77 DEG F). Store in tightly closed container

Table 4.1: Product Description: Double Blind Treatment Period (14 days)

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Dapagliflozin Tablet	5 mg	Bottle of 20 tablets / Blinded	Patient kit with 3 bottles (A,B,C)/ Blinded	Green, plain, diamond shaped, film coated tablet	Store at 15 - 25 DEG C (59 - 77 DEG F). Store in tightly closed container
Dapagliflozin Tablet	10 mg	Bottle of 20 tablets / Blinded	Patient kit with 3 bottles (A,B,C)/ Blinded	Green, plain, diamond shaped, film coated tablet	Store at 15 - 25 DEG C (59 - 77 DEG F). Store in tightly closed container

4.1.1 Investigational Product

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

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

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

In this protocol, investigational products (also described above in Table 4.1) are:

- Dapagliflozin 1 mg tablets
- Dapagliflozin 2.5 mg tablets
- Dapagliflozin 5 mg tablets
- Dapagliflozin 10 mg tablets
- Placebo matching Dapagliflozin 1 mg tablets
- Placebo matching Dapagliflozin 2.5/5 mg tablets
- Placebo matching Dapagliflozin 10 mg tablets

4.1.2 Noninvestigational Product

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

In this protocol, noninvestigational product is insulin.

All Insulin medication will be commercially available and will not be provided by the Sponsor and must continue to be taken at a stable effective therapeutic dose in accordance with the protocol, as applicable.

Date: [redacted]

4.1.3 Handling and Dispensing

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

4.2 Method of Assigning Subject Identification

At the screening 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.

Subjects who meet the criteria will be randomly assigned by the IVRS to one of the following 5 double-blind treatment groups in a 1:1:1:1:1 ratio into one of the following five blinded treatment arms:

- Dapagliflozin 1 mg QD
- Dapagliflozin 2.5 mg QD
- Dapagliflozin 5 mg QD
- Dapagliflozin 10 mg QD
- Matching placebo

Subjects will receive dapagliflozin or matching placebo for a total of 14 days and will be in-patient from Day -3 to Day 7. Randomization will be stratified by body mass index (BMI) categorization ($\leq$ 23 kg/m^2 vs. > 23 kg/m^2) and method of insulin administration (pump or daily injections) to ensure equal representation across all treatment groups.

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

At all study visits when study medication is dispensed, each subject will be assigned a kit number by the IVRS. Kit numbers will be assigned randomly and will correspond to the numbers printed on the packages and kits containing study drug. Note: The kit assigned to each subject on Day 1 for inpatient dosing will be the same kit each subject takes home with them on Day 8 for outpatient dosing (site personnel will be dispensing one tablet

from each bottle during the inpatient period and the subject will be taking one tablet from each bottle during the outpatient period).

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

4.3 Selection and Timing of Dose for Each Subject

Upon entry into the double-blind treatment period (day 1), after **ALL** randomization visit procedures have been completed, each subject will be provided 1 kit of blinded study medication containing 3 bottles (each containing 20 tablets, corresponding to the dapagliflozin/matching placebo tablets as per Table 4.1) and will take 1 tablet from each bottle every day with the morning meal, for the duration of the treatment period.

Dose titration of double-blind study medication is not permitted at any time during the study.

Guidance for insulin is provided in section 5.

4.4 Blinding/Unblinding

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

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

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

4.5 Treatment Compliance

Each time blinded study medication is dispensed, compliance will be reinforced. When blinded study medication is returned, compliance will be assessed based upon subject’s interview, review of subject’s log/ePRO device and a count of the tablets returned.

Date: [redacted]

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 ePRO device and eCRF.

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (e.g. cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, i.e. incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

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

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to

applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.6.2 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible BMS Study Monitor.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

5.1.1 Flow Chart/Time and Events Schedule

Table 5.1.1: Flow Chart/Time and Events Schedule

Procedure	Screen-ing*	Inpatient						Outpatient			
		Baseline			Double-Blind Treatment					Follow-Up	Notes
		Day -3	Day -2	Day -1	Day 1	Day 2 to 6	Day 7	Day 8	Day 10[a]	Day 14/ET[b]	Day 21[c]	*Day -3 should occur within 30 days of screening visit.
ELIGIBILITY ASSESSMENT												
Subject Reports to Site	X	X							X	X	X	
Obtain Informed consent	X											
Review Medical History	X				X							
Review Selection Criteria	X	X			X							

Table 5.1.1: Flow Chart/Time and Events Schedule

Procedure	Screen-ing*	Inpatient						Outpatient				
		Baseline			Double-Blind Treatment						Follow-Up	Notes
		Day -3	Day -2	Day -1	Day 1	Day 2 to 6	Day 7	Day 8	Day 10[a]	Day 14/ET[b]	Day 21[c]	*Day -3 should occur within 30 days of screening visit.
Review Randomization Criteria					X							
Furlough from Clinic								X				
GENERAL PROCEDURES												
Brief Physical Examination	X						X			X	X	
Complete Physical Examination		X			X							
Seated Blood Pressure and Heart Rate	X		X	X	X	X	X	X	X	X	X	
Orthostatic Blood Pressure and Heart Rate				X	X		X			X		
ECG	X									X		
Height	X											

Date: [redacted]

Table 5.1.1: Flow Chart/Time and Events Schedule

Procedure	Screen-ing*	Inpatient						Outpatient				
		Baseline			Double-Blind Treatment						Follow-Up	Notes
		Day -3	Day -2	Day -1	Day 1	Day 2 to 6	Day 7	Day 8	Day 10[a]	Day 14/ET[b]	Day 21[c]	*Day -3 should occur within 30 days of screening visit.
Body Weight	X		X	X	X	X	X	X	X	X	X	Collect weight at screening, daily during the inpatient portion (starting day -2) and at every outpatient visit
Body Mass Index (BMI)	X											
Review concomitant medications/procedures	X	X	X	X	X	X	X	X	X	X	X	
Contact IVR system	X				X					X		
Provide Dietary/exercise Counseling		X					X		X	X		

Date: [redacted]

Table 5.1.1: Flow Chart/Time and Events Schedule

Procedure	Screen-ing*	Inpatient						Outpatient				
		Baseline			Double-Blind Treatment						Follow-Up	Notes
		Day -3	Day -2	Day -1	Day 1	Day 2 to 6	Day 7	Day 8	Day 10[a]	Day 14/ET[b]	Day 21[c]	*Day -3 should occur within 30 days of screening visit.
Dispense ePRO device (for insulin dosing and diary data) and glucose meters/supplies and provide instruction for use		X										
Review Insulin/diary data			X	X	X	X	X	X	X	X	X	
Adjustment of Insulin, as needed		X	X	X	X	X	X	X	X	X	X	
SAFETY ASSESSMENT												
Assess Adverse Events		X	X	X	X	X	X	X	X	X	X	
Assess Hypoglycemia episodes		X	X	X	X	X	X	X	X	X	X	

Date: [redacted]

Table 5.1.1: Flow Chart/Time and Events Schedule

Procedure	Screen-ing*	Inpatient						Outpatient				
		Baseline			Double-Blind Treatment						Follow-Up	Notes
		Day -3	Day -2	Day -1	Day 1	Day 2 to 6	Day 7	Day 8	Day 10[a]	Day 14/ET[b]	Day 21[c]	*Day -3 should occur within 30 days of screening visit.
Dispense Urine Ketone Dipstick & Training (as needed)		X						X	X			
Subject Performs Urine Ketones (dipstick) daily (record in diary)		X	X	X	X	X	X	X	X	X		This will begin on day -2 if entry in afternoon or evening
Review Urine Ketone Dipstick Results		X	X	X	X	X	X	X	X	X	X	
Record daily fluid intake and output		X	X	X	X	X	X					This will begin on day -2 if entry in afternoon or evening
Insert/calibrate CGMS		X				X (Day 4)		X		X		Data upload should occur at the time of the sensor change

Date: [redacted]

Table 5.1.1: Flow Chart/Time and Events Schedule

Procedure	Screen-ing*	Inpatient						Outpatient				
		Baseline			Double-Blind Treatment						Follow-Up	Notes
		Day -3	Day -2	Day -1	Day 1	Day 2 to 6	Day 7	Day 8	Day 10[a]	Day 14/ET[b]	Day 21[c]	*Day -3 should occur within 30 days of screening visit.
CGMS data collection for PD assessments				X	X		X			X (day 13)	X	Subjects will wear the device for the duration of the study and all data will be captured. Days marked indicate periods used for analysis by BMS.
SMBG -fingersticks- at least 4 x per day -before breakfast, lunch, dinner and bedtime (and as needed) including during outpatient period		X	X	X	X	X	X	X	X	X	X	Subjects should enter all valid SMBG values into the CGMS

Date: [redacted]

Table 5.1.1: Flow Chart/Time and Events Schedule

Procedure	Screen-ing*	Inpatient						Outpatient				
		Baseline			Double-Blind Treatment						Follow-Up	Notes
		Day -3	Day -2	Day -1	Day 1	Day 2 to 6	Day 7	Day 8	Day 10[a]	Day 14/ET[b]	Day 21[c]	*Day -3 should occur within 30 days of screening visit.
CENTRAL LABORATORY												
Pregnancy test (urine) WOCBP only	X		X	X					X	X	X	
Blood Standard Safety Laboratory Panel	X		X		X		X			X	X	
Urine Standard Safety Laboratory Panel	X		X		X		X			X	X	
24-h urine collection for Glucose, Sodium, Uric Acid and Creatinine				X	X		X					
7-point central laboratory glucose monitoring (before and 2-hr after each meal [breakfast, lunch, dinner] as well as bedtime[~11 pm])				X	X		X					

Date: [redacted]

Table 5.1.1: Flow Chart/Time and Events Schedule

Procedure	Screen-ing*	Inpatient						Outpatient				
		Baseline			Double-Blind Treatment						Follow-Up	Notes
		Day -3	Day -2	Day -1	Day 1	Day 2 to 6	Day 7	Day 8	Day 10[a]	Day 14/ET[b]	Day 21[c]	*Day -3 should occur within 30 days of screening visit.
FPG	X			X	X		X			X		
Fasting C-peptide	X											
Serum Insulin							X					Day 7 Pre-dose, after lunch and after dinner
A1C	X											
Hepatitis Screen Panel/TSH	X											
Fasting Serum Lipids	X						X			X		
FFA	X				X		X			X		
Serum β-hydroxybutyrate			X		X		X			X	X	

Date: [redacted]

Table 5.1.1: Flow Chart/Time and Events Schedule

Procedure	Screen-ing*	Inpatient						Outpatient				
		Baseline			Double-Blind Treatment						Follow-Up	Notes
		Day -3	Day -2	Day -1	Day 1	Day 2 to 6	Day 7	Day 8	Day 10[a]	Day 14/ET[b]	Day 21[c]	*Day -3 should occur within 30 days of screening visit.
PK sample collection at 0 h 0.5,1,2,3,4,6,8,12, and 24 h post-dose							X	X				24 h post-dose PK sample occurs Day 8 for dose administered on Day 7.
DRUG DISPENSING												
Dispense Study Medication					X	X	X	X	X			The kit assigned to each subject on Day 1 for inpatient dosing will be the same kit each subject takes home on Day 8 for outpatient dosing.

Date: [redacted]

Table 5.1.1: Flow Chart/Time and Events Schedule

Procedure	Screen-ing*	Inpatient						Outpatient				
		Baseline			Double-Blind Treatment						Follow-Up	Notes
		Day -3	Day -2	Day -1	Day 1	Day 2 to 6	Day 7	Day 8	Day 10[a]	Day 14/ET[b]	Day 21[c]	*Day -3 should occur within 30 days of screening visit.
Review Study Medication Compliance						X	X	X	X	X		Subjects will be instructed to take 1 tablet from each of 3 bottles every day of the 14-day treatment period (including days 9 and 11-14).

[a] Visit may be scheduled ± 1 day to allow flexibility of scheduling.

[b] All subjects who discontinue should have day 14/early termination (ET) procedures as indicated here.IVRS should be called to record status (ie discontinuation).The Day 14/ET e CRF will need to be completed.The investigator should arrange appropriate follow-up care, as applicable. It is important for Day 14 to occur 14 days relative to/from first dose

[c] Visit may be scheduled ± 2 days to allow flexibility of scheduling.

Date: [redacted]

5.2 Study Materials

BMS will supply the sites with the following materials:

- Blood glucose meters. One (1) meter will be provided to each study subject at enrollment and 1 meter will be provided to each investigative site.
- Glucose test strips
- Lancets
- Glucose control solutions
- CGMS devices and software to download data
- Electronic Case Report Forms (CRFs) [Serious Adverse Events Forms, Pregnancy Surveillance Forms, Events of Special Interest]
- Subject Alert Cards
- Subject education and site support materials (e.g. CGMS and ePRO instruction manuals)
- Study Drug inventory control forms
- Site File
- Subject Diary/ePRO devices to record insulin dose, study medication compliance, urine ketone testing, and hypoglycemia episodes (and for transfer of glucose meter data)
- Any other materials as locally required or agreed

The central laboratory will provide all laboratory-related materials (including urine ketone testing strips) to the study sites.

5.3 Safety Assessments

5.3.1 Self monitored blood glucose (SMBG) and reporting of hypoglycemia

Glucose meters will be supplied to each study site. At the Day -3 visit, subjects will receive a glucose meter, supplies and instruction on their use. Supplies will be provided to allow for assessments 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.

Date: [redacted]

Subjects should self-monitor their blood glucose at least 4 times per day (generally before breakfast, lunch, dinner and bedtime) and in the occurrence of hypoglycemic symptoms, and contact the Investigator in the event of an unusually high or low blood glucose value. The Investigator may require more frequent readings based on local clinical practice. In addition, study subjects should comply with 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.

Subjects should enter all valid SMBG values into the CGMS.

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

Guidance on Management and Reporting of Hypoglycemia Episodes

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

Study subjects must be properly instructed on the recognition and management of hypoglycemia. Subjects should record on their ePRO device 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, subjects should carry with them easily ingestible forms of carbohydrate at all times in order to treat an event of hypoglycemia should it occur.

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

Hypoglycemia eCRF pages will be used to document all reported episodes of hypoglycemia. The Investigator is responsible for questioning the subject about all symptoms reported on the hypoglycemia portion of the ePRO device and for determining if they meet the clinical definition of hypoglycemia. Only symptoms and/or blood glucose values deemed by the Investigator to meet the definition of hypoglycemia should be reported on the hypoglycemia eCRF pages. Signs and symptoms of hypoglycemia, hypoglycemia episode or discontinuation due to hypoglycemia should not be reported on the AE eCRF page, unless the event fulfills protocol criteria for a Serious Adverse Event (see Section 6.1), in which case an SAE form must be completed in addition to the hypoglycemia eCRF pages for hypoglycemia.

5.3.2 Daily Basal, Daily Bolus, and Total Daily Dose of Insulin (TDDI)

Subjects must demonstrate the ability to correctly self-administer subcutaneous insulin injections and to report their insulin doses in their ePRO device. The ePRO devices will be maintained by each study subject for documentation of insulin dosing, SMBG values and hypoglycemia episodes. For the purposes of the calculation of the daily basal insulin dose, daily bolus insulin dose and the TDDI, each day will begin at 12:00 am (midnight) and end at 11:59 pm.

Subjects should record the dose (in units) of all insulin taken (both basal and bolus regimen) throughout the day in the insulin dose portion of the ePRO device. This collection will begin starting at the Day -3 visit. The insulin dose will be reviewed by the site to identify any unusually high or low values. The subject should be questioned to obtain a possible explanation for unusual high or low values.

Subjects who have not recorded all of their insulin doses should be assessed by the study staff for their ability to comply with the protocol. The ePRO diaries are to be maintained to ensure subject safety and must be completed by the subject throughout the study. Compliance with prescribed insulin administration and ePRO diary completion should be assessed and re-enforced at every visit.

5.3.3 Central Laboratory Assessments

Blood/Urine Standard Safety Panel and Urine pregnancy tests- Refer to Appendix 2 for details.

Protocol Specific Tests:

- 7-point central lab glucose monitoring will be performed before and 2-hr after each meal [breakfast, lunch, dinner] as well as bedtime[~11 pm])- see central lab manual for details
- 24 hour urinary glucose and percent inhibition of renal glucose reabsorption- see Appendix 2 for formula
- FPG
- Fasting C-Peptide
- Serum insulin
- A1C
- Hepatitis Screen Panel/TSH
- Fasting Serum Lipids
- FFA
- Serum β-hydroxybutyrate
- 24 -hour urine collection - Urine will be collected over a 24-hour period on days -1, 1 and 7 for assessment of glucose, sodium, uric acid and creatinine. In the morning, on the day that the 24-h urine collection is started, the first morning void is not included in the 24-h collection. The date and time of the first urine should be recorded on the urine collection log as the start of the 24-h urine collection. All subsequent urinations throughout the entire day and night, and into the following day should be collected. The first voided urine of the subsequent day should be included in the 24-hr urine collection. The urine collection ends after 24 hrs and the stop time should equal the start time of the previous day. The stop date and time should be recorded on the urine collection log.

5.3.4 Urine ketone testing

The site will use Ketostix® ([redacted]) for urine ketone testing during the inpatient component of the study, and provide each subject with sufficient supplies of Ketostix® for urine ketone testing during the outpatient component of the study. Urine ketone testing will be performed according to the manufacturer's specifications and the subject should be trained in the procedure during the initial inpatient period. Urine ketone testing will be performed daily in the morning (shortly after arising, and fasted) and anytime the subject has symptoms suggestive of ketoacidosis or a fingerstick blood glucose in excess of 250 mg/dL. Results should be recorded in the subject diary/ePRO device. Results read from the color chart are 'Negative', 'Trace' (5 mg/dL), 'Small' (15 mg/dL), 'Moderate'

Date: [redacted]

(40 mg/dL), and 'Large' (80 - 160 mg/dL). The subject should contact the site for assistance with diabetes management in the event that a result of 'Moderate' or 'Large' is obtained.

5.3.5 Fluid intake/output

Fluid intake/output (24 hour) will be collected during the inpatient stay as indicated and captured on the eCRF.

5.3.6 Insulin Dosing Assessment and Adjustment Guidelines

Adjustment of a subject's pre-existing insulin dosing regimen may be required during the conduct of this study, due to changes in diet, activity, emotional stress during the study as well as potential effects of dapagliflozin to reduce blood glucose and thereby insulin requirements. Because this is a short-term study, the primary goal for insulin adjustment is to avoid significant hyperglycemia or hypoglycemia, rather than strict glycemic control. Insulin adjustment should not be performed to 'fine tune' glycemic control, but rather to ensure patient safety in the event that there is a significant change in insulin requirements. Maintaining the majority of blood glucose readings between 70 - 220 mg/dL is considered adequate glycemic control for subjects during the course of this study. In general, the goal would be to maintain fasting blood glucose between 70 - 140 mg/dL and postprandial blood glucose below 220 mg/dL, although these goals may be individualized based upon a specific subject's personal targets and stability of glycemic control at baseline.

The two main scenarios in which insulin adjustment is appropriate are unexpected events of either hypoglycemia or hyperglycemia. An unexpected event is defined as an event that cannot be explained by circumstances such as dietary (missed or unusually high carbohydrate meal), strenuous exercise, error in insulin dosing, etc. In subjects with one or more unexpected events of hypoglycemia or hyperglycemia, insulin dosing should be adjusted.

In the event insulin dose adjustment is deemed necessary, the investigator should guide insulin dose changes, based upon review of the insulin and glucose logs, as well as potential circumstances that may have contributed to erratic glucose control (e.g. insulin dosing errors, missed meals, unusual physical activity, etc). In addition, consultation with the subject and/or appropriate representatives of the subject's diabetes management team

is strongly recommended. The BMS Medical Monitor is also available to assist with insulin dose adjustment. Subjects should be instructed to contact the site for insulin dose adjustment instructions in the event they are experiencing poor glycemic control or have unexpected events of hypoglycemia or hyperglycemia.

As dapagliflozin has not been studied previously in T1DM, it is difficult to predict the impact upon glycemic control and insulin requirements in this population. Given the half-life of dapagliflozin of approximately 12 hours and the duration of pharmacodynamic activity of approximately 24 hours, basal insulin requirements may be reduced. In addition, the amount of glucose excreted in response to dapagliflozin is dependent upon the filtered glucose load, which reflects the plasma glucose concentration (and glomerular filtration rate). Therefore, reductions in bolus insulin may also be required. A reduction in both basal and bolus insulin commensurate with the proportion of each insulin a subject receives may be an appropriate first approach, with individualization for each subject based upon the results of glucose monitoring.

5.3.7 Diet/Exercise

Starting at Day -3 visit and for the duration of the study, subjects will be instructed on a diet and exercise program in accordance with the ADA (or similar local guidelines).

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.

The meals provided during the inpatient portion of the study should provide appropriate caloric intake for a weight-maintaining diet. During the inpatient period, the subjects should not be allowed foods from outside the clinic or additional snacks, except for the treatment of hypoglycemia.

5.3.8 Physical Examination (PE), ECG, Blood Pressure, Heart Rate

PE

A brief physical examination should include cardiovascular, lungs, abdomen, and extremities, and any organ systems pertinent to the subject's signs, symptoms, or adverse events

A complete physical examination should include general appearance, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdomen, lymph nodes, extremities, neurological, skin, genitourinary, and musculoskeletal.

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

ECG

ECGs will be performed at Screening and Day 14/ET visits.

The Investigator should review and assess all ECGs for any clinically significant abnormalities, and initial and date the report. The screening ECG must be assessed, and initialed and dated by the Investigator prior to randomizing the subject.

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

Date: [redacted]

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

Blood Pressure (BP) and Heart Rate (HR)

BP and HR measurements must be taken consistently as indicated throughout the study. Blood pressure measurements using a calibrated mercury sphygmomanometer throughout the study are preferred. If possible, blood pressure measurements should be taken by the same person, with the same device, throughout the study.

All measurements should occur at least 10 hours after the last ingestion of caffeine, alcohol, or nicotine. Only use either the right or the left arm when measuring these parameters. **At the randomization visit, it is crucial that the blood pressure measurement and heart rate be obtained prior to the first dose of blinded study medication.**

Seated BP

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 supported and feet flat on the floor.

Seated BP and HR will be determined from three replicate measurements obtained at least 1 minute apart. The average BP and HR will be determined from these 3 replicate measurements and reported in the eCRF.

Orthostatic BP

Orthostatic measurements should be obtained following completion of seated BP and heart rate and prior to administration of study medication. 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 3 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 3 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.

5.3.9 Guidance on Assessment of Urinary and Genital Infections

The following is presented to assist in the classification and management of urinary tract and genital infections. 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. Asymptomatic bacteriuria is prevalent among diabetic women, and is associated with pyuria in 70% of cases.[1] 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.[1, 2] 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 **must** 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 (eg pyelonephritis) or presumed urosepsis until the course of treatment of the infection has been completed and clinical recovery has occurred.

It is recommended that a follow-up urine culture be obtained within 7 days of clinical recovery from all urinary tract infections. Whether or not additional therapy is prescribed because of culture results should be determined by Investigator judgment, after consultation with the Medical Monitor.

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.

Guidance on Assessment of Hematuria

In the event that hematuria is observed during a subject's participation, the Sponsor recommends standard of care in diagnosing the cause of the hematuria.

It is the investigator's responsibility to report, as applicable based on Investigator's judgment and subject's medical history, related adverse events as defined in Section 6.0. 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.

5.3.10 Guidance on Assessment of Cardiovascular Events

A Clinical Event Committee (CEC) blinded to the treatment of the subjects, will independently adjudicate certain cardiovascular adverse events, and they will operate in accordance with a dedicated *Clinical Event Committee Charter/Manual of Operations: Dapagliflozin Program.*

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

- Death, including:
  - Cardiovascular Death
  - Non-cardiovascular Death

- Myocardial Infarction (MI), including:
  - ECG and/or cardiac enzymes confirmed MI
  - Sudden death
  - Percutaneous Coronary Intervention (PCI)-related MI
  - Coronary Artery Bypass Graft (CABG)-related MI

  - MI diagnosed via pathologic criteria
  - Silent MI

- Fatal and Non-fatal Stroke, including:
  - Ischemic Stroke
  - Hemorrhagic stroke

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

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

5.3.11 Guidance on Assessment of Hepatic Laboratory Abnormalities

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

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

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

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

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

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

- Specialized Liver Laboratory Panel (see Appendix 2)

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

For subjects who are discontinued from the study as a result of sustained elevated liver safety abnormalities as described in Section 3.5.3, additional blood sampling must be done within 3 days of the confirmed laboratory results (see Appendix 2), in conjunction with a Day 14 visit, in addition to the procedures noted above. A referral consultation to a hepatologist or gastroenterologist (specializing in liver abnormalities) should be obtained. Any additional tests and/or examinations should be carried out at the discretion of the Investigator. **Any further investigations and laboratory results for subjects with abnormal laboratory values at the follow-up visit should be made available to the Sponsor upon request.**

5.3.12 Guidance on Assessment of Cancer Cases

A cancer adjudication committee, blinded to the treatment of the subjects, will independently adjudicate certain cancer cases, and they will operate in accordance with a dedicated *Charter/Manual of Operations.* The committee will review certain cases to assess/determine diagnosis (cancer, non-cancer, not accessible). The committee creates and maintains the Charter, and completes adjudication forms on which it summarizes its assessment of cancer-related cases.

5.3.13 Survey of Subject Vital Status

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

5.4 Efficacy Assessments

Not Applicable

5.5 Pharmacokinetic Assessments

5.5.1 Pharmacokinetics: Collection and Processing

Table 5.5.1 lists the sampling schedule to be followed for the assessment of pharmacokinetics. Blood samples will be collected from an indwelling catheter or by direct venipuncture.

Further details of blood collection and processing will be provided to the site in a separate manual.

Table 5.5.1: Pharmacokinetic Sampling

Sample Collection Time		**Time (Relative To Dosing) Hours:Min**	**Blood Sample for PK Analysis**
Study Day	Time Event (hours)		
7	0.0 (pre-dose)	0:0 (pre-dose)	X
	0.5	0:30	X
	1.0	1:00	X
	2.0	2:00	X
	3.0	3:00	X
	4.0	4:00	X

Date: [redacted]

Table 5.5.1: Pharmacokinetic Sampling			
Sample Collection Time		**Time (Relative To Dosing) Hours:Min**	**Blood Sample for PK Analysis**
Study Day	Time Event (hours)		
	6.0	6:00	X
	8.0	8:00	X
	12.0	12:00	X
8	0.0	24:00	X
Total Number of Samples at each assessment			10

5.5.2 Pharmacokinetic Sample Analyses

The plasma samples will be analyzed for dapagliflozin and its metabolite, dapagliflozin 3 -O-glucuronide, by a validated LC/MS/MS assay.

5.5.3 Labeling and Shipping of Biological Samples

The samples should be shipped by overnight air express using insulated containers with enough dry ice to maintain the samples in a frozen state until they are received at the analytical site. Refer to the procedure manual for more detailed instructions. The arrangements for shipping are to be made by the investigative site. The site should contact the addressee by telephone and/or fax at least 1 day prior to the sample shipment to ensure proper receipt. Do not ship to arrive over weekends or holidays.

Detailed instructions for the pharmacokinetic blood collection, labeling, processing, storage and shipping will be provided to the site in the procedure manual.

5.6 Pharmacodynamics Assessments

Pharmacodynamic assessments will include the following:

7-point central laboratory glucose monitoring - will be performed before and 2-hr after each meal [breakfast, lunch, dinner] as well as bedtime [~11 pm])- see central lab manual for details

Date: [redacted]

24-hour urinary glucose excretion and percent inhibition of renal glucose reabsorption - see central lab manual for details

FPG- see central lab manual for details

Change in total daily insulin dose will be analyzed.Insulin may be adjusted as indicated in section 5.3.6 and the subjects' ePRO devices will capture basal, bolus, and total daily dose of insulin.

CGMS-

CGMS measures the subject's interstitial glucose level using electrodes that measure an electric signal produced by glucose oxidase reaction. The system records data approximately every 5 minutes. The data will remain blinded to the subject during the recording and will be downloaded into a data file. A CGMS sensor will be inserted subcutaneously at the site on Day -3, Day 4, Day 8, and 14 to allow monitoring from Day -3 through Day 21 as indicated in Table 5.1. Insertion on alternate days is permitted in the event that the sensor needs to be replaced. Detailed procedures (including calibration) will be described in an operations manual and site staff will be fully trained on the use of the CGMS. Subjects will be instructed on use of the meter and calibration according to manufacturer's instructions. Subjects will wear the sensor and perform calibration according to manufacturer's instructions.

Should a subject be using a CGMS device prior to entry into the study, they may continue to use the device during the study in accordance with their usual diabetes management care. Such a subject will be required to also use the blinded CGMS device according to protocol procedures.

5.7 Pharmacogenomic/Pharmacogenetic Assessments

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

5.8 Outcomes Research Assessments

Not applicable.

5.9 Other Assessments

- 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. Subject's weight will obtained at screening, daily during inpatient portion of the study and at each outpatient visit and will be recorded in the eCRF.
- Measurement of **height** should be performed with the subject's shoes removed. The subject's knees should be straightened, head held erect, and eyes forward.
- **BMI** is used as an index of obesity and is a method of defining normal body weight and excess body fat. It correlates in a population with percent body fat.
- BMI is determined by weight (kg) divided by height (m) squared

Method of BMI Calculation:

- Use actual height and weight to calculate BMI.
- To calculate BMI:
  - Convert pounds (lbs) to kilograms (kg = lb / 2.2)
  - Convert inches (in) to centimeters (cm=in x 2.54)
  - BMI = (weight in kg) / (height in cm/100)^2
  - Round to one decimal place (if .05 or greater, round up)

6 ADVERSE EVENTS

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

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

Date: [redacted]

6.1 Serious Adverse Events

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

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

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

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

NOTE:

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

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or event life threatening)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)

Date: [redacted]

- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

6.1.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

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

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms).When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: See Contact Information list.

SAE Facsimile Number: See Contact Information list.

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

Date: [redacted]

SAE Telephone Contact (required for SAE and pregnancy reporting): See Contact Information list.

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

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

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

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

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

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

6.3 Laboratory Test Abnormalities

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

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have study drug 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).

6.4 Pregnancy

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

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

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

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

6.5 Overdose

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

6.6 Potential Drug Induced Liver Injury (DILI)

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

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

AND

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

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Refer to Sections 5.3.10 - 12

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

Given that this study is designed for exploratory analysis, formal statistical hypothesis testing is not planned. Therefore, the sample size for this study is not based on any formal

power considerations. The sample size target is approximately 14 subjects per study arm, i.e. a total of approximately 70 subjects to be randomized to dapagliflozin 1, 2.5, 5, 10 mg and placebo in 1:1:1:1:1 ratio. Although the number of subjects is not based on statistical power considerations, 14 subjects per treatment group will provide 80% probability of observing at least one occurrence of any adverse event in a group assuming the incidence rate is 11 per hundred subjects in 14 days.

Analysis will include the estimation of frequencies (for categorical endpoints) or summary statistics such as mean and 95% confidence intervals (for continuous endpoints) for each treatment arm.

The primary objective of the study is to assess the safety and tolerability of each dose of dapagliflozin (1 mg, 2.5 mg, 5 mg and 10 mg per day) plus insulin after 14 days of oral administration of double-blind treatment. The number of subjects that experience events of major, minor and other hypoglycemia, serious adverse events, deaths, adverse events leading to discontinuation of study therapy, adverse events of interest of genitourinary infection and potentially clinically significant changes in vital signs during the 14 days of dapagliflozin exposure 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. No sample size determination or estimates of variations of incidence or summary statistics is calculated for safety and tolerability endpoints.

A secondary objective of the study is to assess the pharmacokinetics of dapagliflozin and its major inactive metabolite, dapagliflozin 3-O-gulcuronide, on Day 7. No sample size determination or estimates of variation are calculated for this objective, either.

An additional secondary endpoint, related to pharmacodynamics, is the change from baseline to Day 7 in mean glucose based on 7-point central laboratory glucose monitoring, which will be summarized for each study arm. Also, the difference between each dapagliflozin dose (1 mg, 2.5 mg, 5 mg and 10 mg per day) plus insulin versus placebo plus insulin will be summarized. Assuming a common standard deviation of 30 mg/dL in each treatment group, with 14 subjects per group, the half-width of the 95% confidence interval for the difference between any dapagliflozin + insulin treatment group and the placebo + insulin treatment group is estimated to be 22.22 mg/dL.

8.2 Populations for Analyses

- The pharmacodynamic dataset is the Randomized Subjects dataset which is defined as all randomized subjects who receive at least one dose of double-blind study medication. Whenever using the Randomized Subjects dataset, subjects will be presented in the treatment group to which they were randomized at the start of the double-blind treatment period (even if the treatment they received was different). 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 pharmacodynamic analysis of change or percent change from baseline. All efficacy analyses will be performed using the pharmacodynamic dataset.
- The safety data set is the Treated Subjects dataset which is defined as all treated subjects who received at least one dose of study medication. The Treated Subjects Data Set consists of all subjects who received at least one dose of double-blind study medication during the double-blind treatment period. The Treated Subjects Data Set would include any subject who accidentally received double-blind study medication but was not randomized in the study. All analyses using the Treated Subject Data Set will be presented by randomized treatment group, except in cases where information was available which indicated that a subject received a different treatment for the entire course of their participation in the study (or period).In this case, the safety data for those subjects will be presented by the treatment actually received. In case a subject never received the treatment as assigned by randomization, then the safety data for that subject will be presented by the first treatment received. All safety analyses will be performed using the safety data set.
- Pharmacokinetics data set consists of all available concentration-time data from subjects who receive dapagliflozin. All available derived pharmacokinetics parameter values will be included in the pharmacokinetics data set and reported. All pharmacokinetic analyses will be performed using the pharmacokinetics data set, but only subjects with adequate PK profiles will be included in the summary statistics and statistical analysis.

Randomization will be stratified by body mass index (BMI) categorization ($\leq$ 23 kg/m^2 vs. > 23 kg/m^2) and method of insulin administration (pump or daily injections) to ensure equal representation across all treatment groups.

8.3 Endpoint Definitions

The primary endpoints of the study are:

1. Number of subjects that experience during the 14 days of dapagliflozin exposure:
   a. Events of hypoglycemia
   b. Serious adverse events
   c. Deaths
   d. Adverse events leading to discontinuation of study therapy
   e. Adverse events of interest of genitourinary infection
2. Number of subjects with potentially clinically significant changes in vital signs during the 14 days of dapagliflozin exposure, defined as:

   Marked Abnormality Criteria for Vital Signs

   – Heart Rate (bpm): HR > 100 bpm and > 30 bpm above baseline, or HR < 55 bpm and > 15 bpm below baseline
   – Systolic BP (mmHg): SBP > 140 mmHg and > 20 mmHg above baseline or SBP < 90 mmHg and > 20 mmHg below baseline
   – Diastolic BP (mmHg): DBP > 90 mmHg and > 10 mmHg above baseline or DBP < 55 mmHg and > 10 mmHg below baseline

   Orthostatic Change

   – Heart Rate (bpm): Standing HR- Supine HR > 30 bpm
   – Systolic BP (mmHg): Standing SBP- Supine SBP < -25 mmHg
   – Diastolic BP (mmHg): Standing DBP - Supine DBP < -10 mmHg

The secondary endpoints of the study are:

1. Pharmacodynamic (PD) endpoint: change from baseline in mean glucose based on 7-point central laboratory glucose monitoring achieved with dapagliflozin (1 mg, 2.5 mg, 5 mg and 10 mg per day) plus insulin versus placebo plus insulin after 7 days of oral administration of double-blind treatment.
2. Pharmacokinetic endpoints: multiple-dose pharmacokinetic parameters of dapagliflozin and its major inactive metabolite, dapagliflozin 3-O-glucuronide, from the plasma concentration versus time data on Day 7:
   a. Cmax - Maximum observed plasma concentration
   b. Tmax - Time of maximum observed plasma concentration

c. AUC over a dosing interval [AUC(TAU) - area under the concentration-time curve in one dosing interval]
d. Ratio of metabolite to parent AUC (corrected for molecular weight)

Other pharmacodynamic endpoints of the study are:

1. Change from baseline (Day -1) after 7 days of administration of double-blind treatment in:
   a. The percent of 24-hour glucose readings obtained from continuous glucose monitoring system (CGMS) that fall within the ranges: ≤ 50 mg/dL, ≤ 70 mg/dL, 71-180 mg/dL and >180 mg/dL
   b. Fasting Plasma Glucose (FPG)
   c. 24-hr urinary glucose
   d. percent inhibition of renal glucose reabsorption
   e. Systolic blood pressure (SBP)
2. The percent change from baseline (Day -1) after 7 days of double-blind treatment in the following daily insulin dose quantities:
   a. daily basal insulin dose
   b. daily bolus insulin dose
   c. total daily dose of insulin

Other safety endpoints of the study are:

1. The proportion of subjects with adverse events (not included in the primary objective) and events and marked abnormalities in clinical laboratory tests after 14 days of administration of double-blind treatment.
2. The change from baseline at each post-baseline time point of selected safety clinical laboratory parameters, physical measurements, vital signs and electrocardiogram data after 14 days of administration of double-blind treatment

8.4 Analyses

Analyses of the data from the 14 days double-blind treatment period will be performed after all subjects have completed or have been discontinued from the study. In addition,

Date: [redacted]

all relevant queries must be resolved and the database must be locked for this 14 days period prior to the analyses.

8.4.1 Demographics and Baseline Characteristics

Frequency distributions and summary statistics for demographic and baseline variables summarized in pharmacodynamic 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 Efficacy Analyses

Not applicable

8.4.3 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 parameter of interest will be summarized by treatment group. The existence of a dose related trend pattern will be assessed for selected safety and tolerability endpoints.

8.4.4 Pharmacokinetic Analyses

Summary statistics will be tabulated for Cmax, Tmax, AUC (TAU), and Ratio of metabolite to parent AUC by arm and study day for both dapagliflozin and its major inactive metabolite, dapagliflozin 3-O-glucuronide.

Geometric means and coefficients of variation will be presented for Cmax, AUC (TAU), and Ratio of metabolite to parent AUC. Medians and ranges will be presented for Tmax.

8.4.5 Pharmacodynamic 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, ie, last observation carried forward (LOCF). For the endpoints in the inpatient period, only inpatient measures will be considered.

8.4.5.1 Analysis for Secondary Pharmacodynamic Endpoints

The secondary PD variable is the difference in the mean change from baseline to the end of the impatient period (i.e. day 7) in the average glucose based on 7-point central laboratory glucose monitoring. Summary statistics will be provided for each study arm. Also, the difference between each dapagliflozin (1 mg, 2.5 mg, 5 mg and 10 mg per day) plus insulin versus placebo plus insulin will be summarized. The existence of a dose related trend pattern will be assessed.

8.4.5.2 Analysis for Other Pharmacodynamic Endpoints

Other continuous variables listed below will be summarized at each time point of assessment. A point estimates and 95% confidence intervals for the mean change (percent change) from baseline will be provided within each treatment group. No p-values will be generated.

Change from baseline will be summarized for:

a) Fasting Plasma Glucose (FPG)
b) 24-hr urinary glucose
c) percent inhibition of renal glucose reabsorption
d) Systolic blood pressure (SBP)

Percent change from baseline will be summarized for:

a) 7 days of double-blind treatment in total daily insulin dose.

The percent of 24-hour glucose readings obtained from continuous glucose monitoring system (CGMS) that fall within the ranges: ≤ 50 mg/dL, ≤ 70 mg/dL, 71 - 180 mg/dL and > 180 mg/dL will also be summarized.

The variability of glucose measurements from CGMS will also be assessed

8.4.6 Pharmacogenomic Analyses

Not applicable

8.4.7 Outcomes Research Analyses

Not applicable

8.4.8 Other Analyses

Not applicable

8.5 Interim Analyses

Not applicable

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

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

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

- IRB/IEC for review and approval/favorable opinion
- Bristol-Myers Squibb
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to 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. Certain CRF pages and/or electronic files may serve as the source documents: CGM data, fingerstick (meter data) values, ePRO data including insulin dosing and urine ketones.

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 procedures, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

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

Date: [redacted]

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by the sponsor)is maintained at each study site where study drug is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

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

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

9.2.3 Case Report Forms

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

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

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

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

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by a qualified physician who is an investigator or subinvestigator. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

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

9.3 Clinical Study Report and Publications

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

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

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

The data collected during this study are confidential and proprietary to the sponsor. Any publications or abstracts arising from this study require approval by the sponsor prior to publication or presentation and must adhere to the sponsor's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including

abstracts or detailed summaries of any proposed presentations, must be submitted to the sponsor at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. Sponsor shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

Date: [redacted]

10 GLOSSARY OF TERMS

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

Date: [redacted]

11 LIST OF ABBREVIATIONS

Term	Definition
A1C	Glycosylated hemoglobin
ACEI	Angiotensin-Converting Enzyme Inhibitor
ADA	American Diabetes Association
AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
AM or am	Morning (ante meridian)
ANCOVA	Analysis of covariance
ARB	Angiotensin Receptor Blocker
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BMS	Bristol-Myers Squibb
BP	Blood Pressure
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CDC	Center for Disease Control
CGMS	Continuous glucose monitoring system
CHF	Congestive heart failure
CK	Creatine Kinase
Cm	Centimeter
Cmax	Concentration maximal
Cr	Creatinine
CRF(s)	Case Report Form(s)
DBP	Diastolic Blood Pressure
dL	Deciliter
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eg,	Exempli gratia (for example)
ET	Early termination
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
FSH	Follicle stimulating hormone
G or g	Gram

Date: [redacted]

Term	Definition
GCP	Good Clinical Practice(s)
GI	Gastrointestinal
HCG	Human Chorionic Gonadotropin
HDL-C	High-density lipoprotein cholesterol
HR	Heart Rate
hr(s) or h	Hour(s)
HRT	Hormone replacement therapy
ICH	International Council on Harmonization
ie,	id est (that is)
IEC(s)	Independent ethics committee(s)
IRB(s)	Institutional Review Board(s)
IU	International Units
IVRS	Interactive Voice Response System
Kg	Kilogram
L	Liter
Lb	Pound
Ln	Natural Logarithm
LOCF	Last observation carried forward
M or m	Meter
Max	Maximum
MBq	Megabecquerels
MCH	Mean cell hemoglobin
MCHC	Mean cell hemoglobin concentration
MCV	Mean cell volume
MDRD	Modification of Diet in Renal Disease
μCi	Microcuries
m	Meter
Min.	Minute
Mg	Milligram
Mg	Magnesium
mL	Milliliter
mmHg	Millimeters of mercury
mmol	Millimole
N/A	Not Applicable
Ng	Nanogram
nmol	Nanomole

Date: [redacted]

Term	Definition
NYHA	New York Heart Association
OAD	Oral Anti-Diabetic
OL	Open-Label
pH	Symbol for the negative logarithm of the H+ ion concentration
PK	Pharmacokinetics
PM or pm	Afternoon (or post meridian)
PTCA	Percutaneous Transluminal Coronary Angioplasty
QD	Daily dose
SA	Sickle cell trait
SAE(s)	Serious adverse event(s)
SBP	Systolic Blood Pressure
SD	Standard Deviation
SMBG	Self-monitored blood glucose
SCr	Serum Creatinine
SGLT(s)	Sodium glucose transporter(s)
SGLT1	Sodium-dependent glucose transporter 1
SGLT2	Sodium-dependent glucose transporter 2
T1/2	Mean Terminal Half-Life
TB	Total bilirubin
TG	Triglycerides
TIA	Transient Ischemic Attack
Tmax	Time to maximal concentration
TSH	Thyroid Stimulating Hormone
U	Units
UACR	Urine albumin creatinine ratio
ULN	Upper limit normal
μmol	Micromole
US	United States
WK	Week
WOCBP	Women of childbearing potential

Date: [redacted]

12 REFERENCES

1 Nicolle LE, Bradley S, Colgan R, et al. Infectious Diseases Society of American Guidelines for the Diagnosis and Treatment of Asymptomatic Bacteriuria in Adults. Clinical Infectious Diseases 2005; 40: 643-54.

2 U.S Preventive Services Task Force. Screening for Asymptomatic Bacteriuria. February 2004, http://www.ahrq.gov/clinic/uspstf/uspsbact.htm#related.

Date: [redacted]

APPENDIX 1 NEW YORK HEART ASSOCIATION FUNCTIONAL CLASS

I. Patients without limitation of physical activity. Ordinary activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II. Patients with slight limitation of physical activity who are comfortable at rest. Ordinary activity results in palpitation, dyspnea, or fatigue.
III. Patients with marked limitation of physical activity. Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.
IV. Patients with inability to carry on any physical activity without discomfort. Symptoms may be present at rest.

Date: [redacted]

APPENDIX 2 CENTRAL LABORATORY ASSESSMENTS

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

During the lead-in, double-blind treatment periods, the urinary glucose values, including the urinary glucose:creatinine ratio, will be masked/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:

- 7-point central lab glucose monitoring
- percent inhibition of renal glucose reabsorption (using formula noted below):

%IRR Percent inhibition of renal glucose reabsorption, calculated as

$$\%IRR = \frac{RCL}{GFR} * 100$$

where GFR is the glomerular filtration rate

- FPG (mg/dL)
- Serum insulin
- Fasting C-Peptide (ng/mL)
- A1C (%)
- Hepatitis Screen Panel/TSH
- Fasting Serum Lipids

Date: [redacted]

  - 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)

- FFA
- Serum β-hydroxybutyrate
- 24 -hour urine collection - Urine will be collected over a 24-hour period on days -1, 1 and 7 for assessment of glucose, sodium, uric acid and creatinine. In the morning, on the day that the 24-h urine collection is started, the first morning void is not included in the 24-h collection. The date and time of the first urine should be recorded on the urine collection log as the start of the 24-h urine collection. All subsequent urinations throughout the entire day and night, and into the following day should be collected. The first voided urine of the subsequent day should be included in the 24-hr urine collection. The urine collection ends after 24 hrs and the stop time should equal the start time of the previous day. The stop date and time should be recorded on the urine collection log.

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).*

Specialized Liver Panel

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

Date: [redacted]

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

Liver Discontinuation Panel

For subjects who are discontinued from the study as a result of sustained elevated liver safety abnormalities, additional central laboratory tests will be performed at the time of Early Termination (Day 14/ET) visit. Similar to the Specialized Liver Panel, these laboratory tests will study the possible causes of the increased ALT and/or AST and/or TB, and may include, but are not limited to, the following tests:

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

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

Standard Safety Laboratory Panels:

Appendix 2A Table: 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) *Reflex testing of Direct (Conjugated) and Indirect (Unconjugated) Bilirubin if TB > 1.5X ULN.*
- 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 re-expressed abbreviated (four-variable) Modification of Diet and Renal disease (MDRD) formula and results will be reported to the sites and the Sponsor.** (*Levey AS, Coresh J, Greene T, et al. Expressing the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate with Standardized Serum Creatinine Values. Clinical Chemistry 2007; 53:766-72*).
- Sodium (mEq/L, mmol/L)
- Potassium (mEq/L, mmol/L)
- Chloride (mEq/L, mmol/L)
- Calcium (mg/dL, mmol/L)
- Magnesium (mEq/L, mmol/L)
- Phosphorus (mg/dL, mmol/L)
- Total Protein (g/dL, g/L)
- Albumin (g/dL, g/L)
- Uric acid (mg/dL, µmol/L)

Date: [redacted]

Appendix 2A Table: Standard Blood Safety Laboratory Panels

Urine Analyses (Standard Urine Safety Panel)

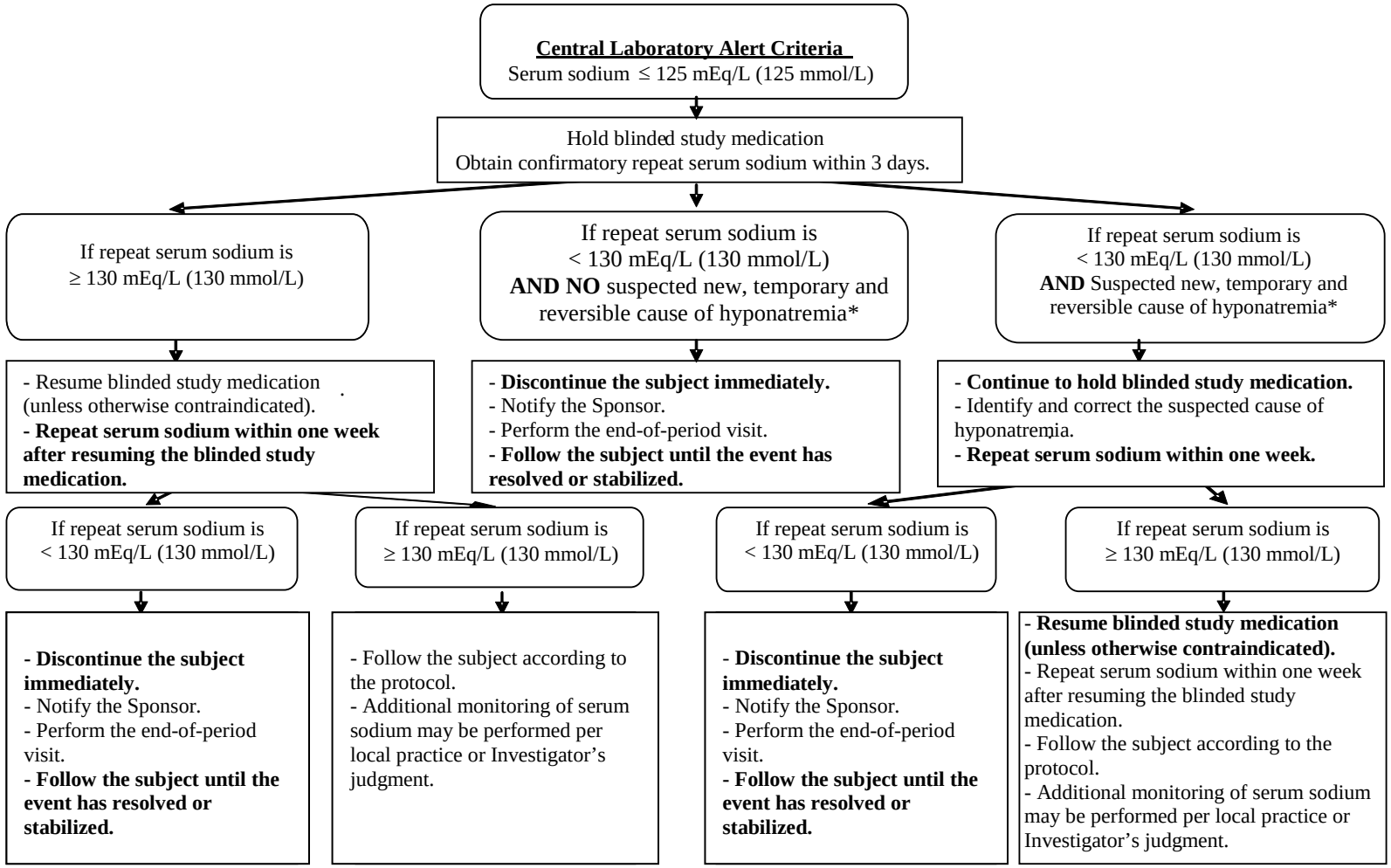
- Blood (dipstick). *Microscopy will be ordered if dipstick is positive for blood.*
- Albumin
- Creatinine
- Calculated Urinary albumin:creatinine ratio (UACR)
- Urine HCG pregnancy test for WOCBP (HCG minimum sensitivity of 25 IU/L; performed at site). *If a urine HCG test is positive, a blood specimen 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 -28, Day 1, Week 4, Week 8, Week 12, and Week 13 visits will include the following assessments (spot urine):

- Uric Acid
- Microalbumin
- Glucose
- Urinary glucose:creatinine ratio

Date: [redacted]

APPENDIX 3 HYPONATREMIA FLOW CHART



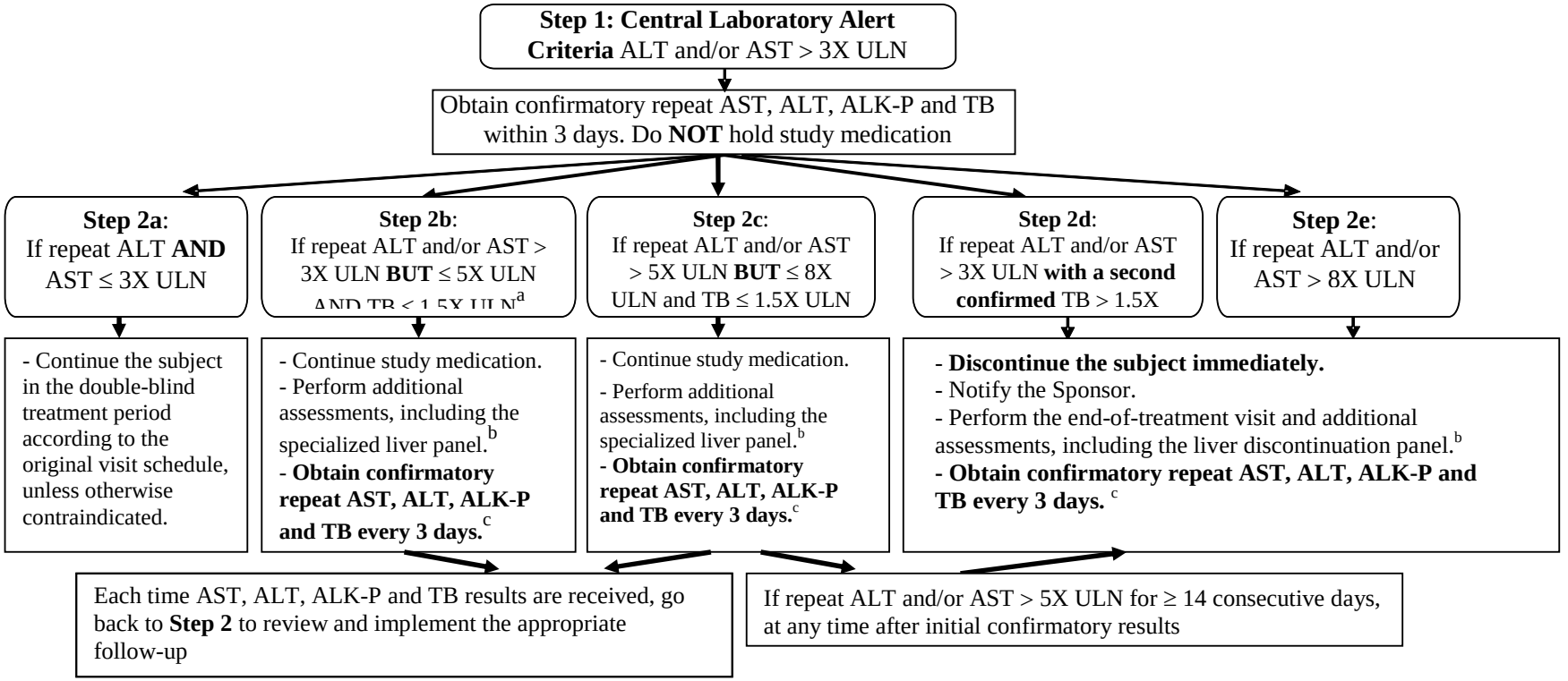
Date: [redacted]

* 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.

Date: [redacted]

APPENDIX 4 SUSTAINED ELEVATED LIVER SAFETY ABNORMALITIES FLOW CHART



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

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

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

Date: [redacted]