Protocol Number: MB102229
IND Number: 68,652
Ex-US Non-IND
EUDRACT Number 2013-004674-97
Date:
Revised Date:

Clinical Protocol MB102229

A Multicenter, Randomized, Double-Blind, Placebo-controlled, Parallel Group, Phase 3 Study to Evaluate the Efficacy and Safety of Dapagliflozin as an Add-on to Insulin Therapy in Subjects with Type 1 Diabetes Mellitus

Revised Protocol No.: 02
Incorporates Amendment 05

Study Director/Medical Monitor

Telephone (office):
Fax:

24-hr Emergency Telephone Number
Emergency Telephone Number
USA:
International:

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

Bristol-Myers Squibb Research and Development

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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 02		Incorporates Amendment 05
Amendment 05		The primary purpose of this amendment is to increase the randomization target by 55 to maintain the power for the primary endpoint as the first 55 randomized subjects will be excluded from the primary efficacy analysis due to an IVRS randomization system error but will be included in the safety analysis in the 'as treated' treatment groups . Additional statistically related changes in this amendment include: • Adding the ITT estimand analysis and sensitivity analyses for the primary efficacy endpoint. • Replacing the single-step Dunnett procedure with the Dunnett and Tamhane step-up procedure for improved power and greater emphasis on primary endpoint. • Replacing "Randomized subjects dataset" with "Full analysis dataset". • Replacing the Zhang et al method with a general logistic regression model for implementation considerations. • Adding statistical method to model the added exploratory endpoint, number of number of non-severe hypoglycemic events per subject in those achieving a HbA1c reduction of ≥0.5% Additional changes in this amendment include: • Adding an exploratory endpoint to compare the number of non-severe hypoglycemic events per subject in those achieving a HbA1c reduction of >0.5% on dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin from baseline to Week 24 visit. • Updating the guidance on DKA assessments and reporting to include the following: – Reductions in insulin doses of more than 20% are not recommended regardless of glucose values. If blood glucose is repeatedly low and a 20% reduction in total daily insulin dose cannot be avoided the daily dietary carbohydrate intake should be increased, as well as during and/or after elevated physical activity. – Investigators are recommended to advise subjects to take extra insulin and extra carbohydrates if elevated ketones are registered and to continue to measure blood ketones. Study medication should be interrupted during sick days if necessary – For subjects who report elevated ketones/ketosis or a DKA, it is recommended that the investigator consider reeducation concerning DKA at the next scheduled visit, at an un-scheduled visit or by telephone contact • Clarifying that the daily insulin dose reduction should be by up to 20% for both basal and bolus insulins after the first dose of study drug to minimize the risk of hypoglycemia • Adding that if total daily insulin dose is reduced upon initiation of study medication, attempts must be made to titrate insulin back to baseline total daily insulin dose. It is not recommended to reduce total daily insulin dose by more than 20% compared

Document	Date of Issue	Summary of Change
		to baseline at any time during the study unless medically indicated and close attention should be paid, especially in these subjects, to symptoms of, and risk factors for developing DKA. • Indicating that Tubal Ligation in this protocol is not considered surgical sterilization • Confirming that subjects are to record day and time of CGM sensor insertion if performed at home at week 11 and week 23 • Reinforcing that all results recorded in subject diary are to be reviewed by site staff during each study visit and that determination of a DKA event must be assessed and documented by the Principal Investigator or by a qualified sub-investigator • Adding guidance on recording blood ketone and glucose values associated with events that are deemed not to be a DKA event • Including local injections such as intramuscular or intra-articular in the systemic corticosteroid therapy exclusion criteria as well as adding drops to the topical corticosteroids that are allowed in the study • Clarifying that the Data Monitoring Committee will periodically evaluate the incidence of hypoglycemia and DKA events, as well as AEs, laboratory measurements, and safety assessments to ensure the ongoing safety of study subjects. • Adding multiple updates, confirmations and additions in the Study Flowchart
Revised Protocol 01		Incorporates Amendment 03
Amendment 03		The primary purpose of this amendment is to modify the Inclusion and Exclusion Criteria, based on feedback from the European Medicines Agency (EMA). Specifically, the EMA has endorsed removing the requirement that HbA1c may not drop more than 0.5% during the lead-in phase (between Screening and Week -1). Additional changes in this amendment include: • Adding guidance around requirements for performing the continuous glucose monitoring (CGM) assessments, recording meal information, and performing the 6-point self monitoring blood glucose (SMBG) for subjects who are lead-in failures or who discontinue study medication • Harmonizing the criteria for monitoring and discontinuing subjects with elevated liver function tests with the hepatic adjudication criteria • Providing guidance on allowing subjects to rescreen if they did not fail any of the screening or lead-in criteria and were not subsequently randomized within the applicable study visit windows (e.g. due to a planned medical procedure, vacation plans, or employment commitments) • Allowing a one-time repeat A1C test for subjects at week -1 if the test result is within ± 0.2% of the cut off values and adding a 7 day window to the current Lead-in Period window of 56 + 5 days for subjects who have a one-time A1C retest at Week -1 • Clarifying that a misdiagnosis of T2DM will be eligible if there is positive autoantibodies for GAD65, phosphatase IA-2/IA2β,

Document	Date of Issue	Summary of Change
		or zinc transporter 8 (ZnT8) (i.e. autoimmune diabetes) or a fasting c-peptide value below the lower limit of detection performed by a local or central laboratory • Adding the use of any GLP-1 receptor agonist has been added as long as it is within 1 month for once or twice daily administration or 2 months for once weekly administration prior to the screening visit: • Continuing to exclude metformin and/or thiazolidinediones if taken within 2 months prior to the screening visit however, the criteria has been broadened to include the use of insulin-sensitizing agents which would capture more agents than just those previously listed. • Changing the parameter for Serum Total Bilirubin (TB) to > 2X ULN unless exclusively caused by Gilbert's Syndrome • Providing guidance on monitoring renal function
Original Protocol		Not applicable

SYNOPSIS

Clinical Protocol MB102229

Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-controlled, Parallel Group, Phase 3 Study to Evaluate the Efficacy and Safety 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):

- Blinded dapagliflozin tablets 5 mg, and 10 mg administered orally for the 24-week double-blind short-term treatment period, and the 28-week subject and site blinded long-term treatment period of the study
- Matching placebo administered orally for the 24-week double-blind short-term treatment period, and the 28-week subject and site blinded long-term treatment period of the study

Study Phase: 3

Research Hypothesis: After 24 weeks of oral administration of double-blind treatment, the change from baseline in A1C (HbA1c) level with dapagliflozin plus adjustable insulin is greater than placebo plus adjustable insulin in subjects with type 1 diabetes who have inadequate glycemic control. In this study, adjustments of insulin dose can be made as deemed appropriate to be consistent with good medical practice.

Objectives:

Primary Objective

The primary objective of this study is to compare the change from baseline in HbA1c after 24 weeks of double-blinded treatment with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin.

Secondary Objectives:

Efficacy

Six secondary efficacy objectives are identified for special consideration in this study, in addition to the primary objective:

Compare the percent change from baseline in total daily insulin dose with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment

Compare the percent change from baseline in body weight with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment

Compare the change from baseline in the mean value of 24-hour glucose readings obtained from continuous glucose monitoring (CGM) with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment

Compare the change from baseline in mean amplitude of glucose excursion (MAGE) of 24-hour glucose readings obtained from CGM with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment

Compare the change from baseline in the percent of 24-hour glucose readings obtained from CGM that falls within the target range of > 70 mg/dL and ≤ 180 mg/dL with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment

Compare dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin for the proportion of subjects achieving an HbA1c reduction from baseline to Week 24 visit ≥ 0.5% without severe hypoglycemia events

Safety

- To assess the proportion of subjects with hypoglycemia events and the frequency and severity of the hypoglycemia events with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin
- To evaluate the safety and tolerability by assessment of adverse events (AE), vital signs, diabetic ketoacidosis (DKA) events, physical examination findings, ECGs, and laboratory values.

Other/Exploratory Objectives:

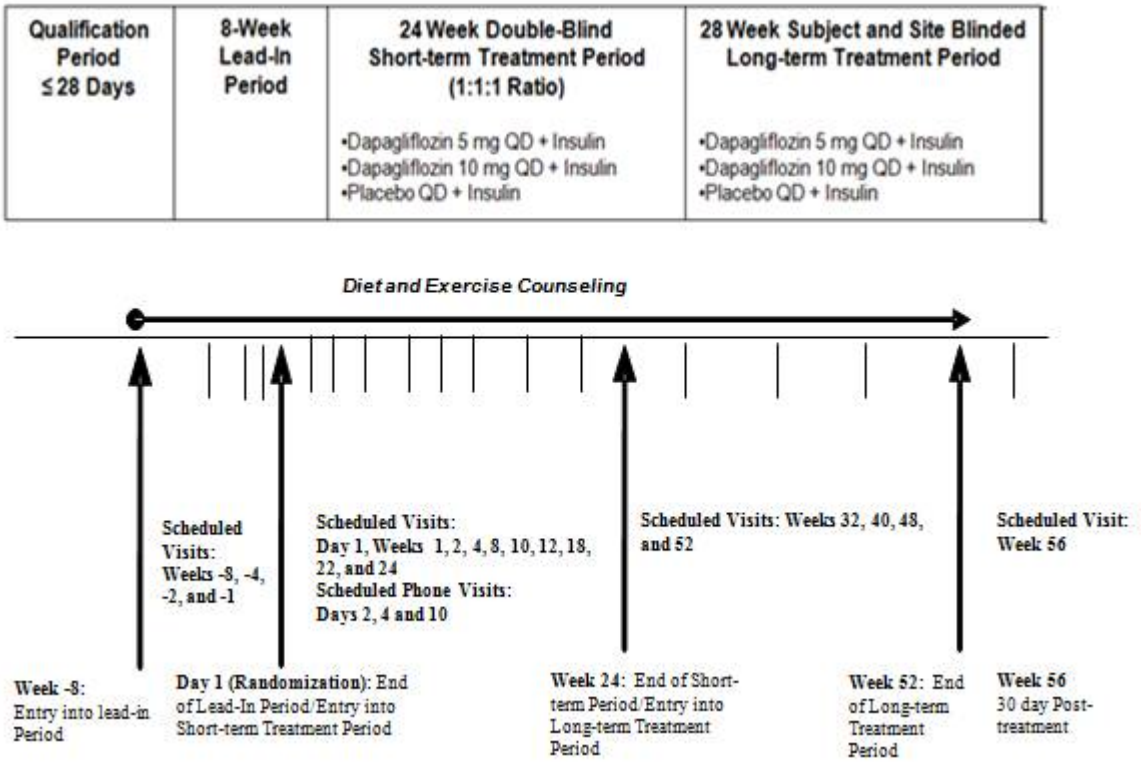
1) Assess the proportion of subjects with HbA1c reduction of at least 0.5% (≥ 0.5%) from baseline with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
2) Assess the proportion of subjects with HbA1c < 7.0% with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
3) Assess the change from baseline in fasting plasma glucose (FPG) with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
4) Assess the change from baseline in the percent of 24-hour glucose readings obtained from CGM that is within the hypoglycemic range of ≤ 70 mg/dL with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
5) Assess the change from baseline in seated systolic blood pressure with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment among subjects with hypertension at baseline, defined as seated SBP ≥ 140 mmHg and/or seated DBP ≥ 90 mmHg.
6) Assess the change from baseline in average glucose values measured by 6-point self monitor blood glucose (SMBG) with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
7) Assess the change from baseline in postprandial glucose values measured by 6-point SMBG with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
8) Assess the change from baseline in postprandial glucose values measured by CGM with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
9) Assess the change from baseline in standard deviation of 24-hour glucose readings obtained from CGM with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
10) Assess the change from baseline to Week 24 in health status, as measured by the EQ-5D-3L questionnaire, between dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment.
11) Assess the changes from baseline to Week 24 in the summary score for treatment satisfaction and scores for perceived frequency of hyperglycemia and perceived frequency of hypoglycemia, respectively, as measured by the Diabetes Treatment Satisfaction Questionnaire status (DTSQs) between the dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
12) To explore the relationship between observed and/or model estimated pharmacokinetic measures of exposure (eg, AUCss, Cmax, Cmin) and efficacy and/or safety endpoints by using model-based approaches. This analysis will be provided in a separate report.
13) Compare the number of non-severe hypoglycemic events per subject in those achieving an HbA1c reduction of ≥0.5% on dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin from baseline to Week 24 visit.

Study Design: This trial is a randomized, double-blinded, three-arm, parallel-group, placebo-controlled, multicenter trial to evaluate the efficacy and safety of dapagliflozin, when added to ongoing insulin therapy, in subjects with T1DM and inadequate glycemic control.

Potential subjects will be assessed for eligibility criteria at the screening visit. Eligible subjects will enter an 8-week lead-in period in order to optimize their diabetes management based on individual subject challenge to glycemic control (including hyperglycemia, hypoglycemia, erratic meal/exercise patterns, as defined by the investigator) and to assess the variability in blood glucose profiles and frequency of hypoglycemic episodes at baseline. No placebo or study medication will be provided during the lead-in period. On the Day 1 visit, subjects who meet all the protocol-specific enrollment and randomization criteria will be randomized into one of the three blinded treatment arms (dapagliflozin 5 mg QD, dapagliflozin 10 mg QD, or placebo QD) in a 1:1:1 ratio. Randomization will be stratified by the following factors to ensure equal representation across all treatment groups: 1) current use of CGM (this refers to an unblinded/personal device which may already be in use before using the blinded device as part of the study) categorized as yes vs. no; 2) method of insulin administration at baseline (multiple daily injections (MDI) three or more injections per day vs. continuous subcutaneous insulin infusion - CSII); and 3) baseline A1C $\geq$ 7.5% and < 9.0% vs. $\geq$ 9.0% and $\leq$ 10.5%.

Subjects will receive dapagliflozin 5 mg QD, 10 mg QD, or placebo QD for 24 weeks, followed by a 28-week subject and site blinded long-term treatment period. Besides study medications, subjects will be treated with MDI injections (three or more injections per day of basal and prandial insulin) or CSII. It is recommended that subjects reduce their daily insulin dose by up to 20% for both basal and bolus insulins after first dose of study drug on Day 1 following randomization to reduce risk of hypoglycemia although in some cases it may be necessary to reduce insulin (particularly basal insulin) in advance of study drug administration. It is at the discretion of the investigator to determine the extent to which to reduce the insulin doses. Throughout the study (from the beginning of the lead-in period to the end of the long-term treatment period), insulin dose may be adjusted as deemed appropriate to be consistent with good medical practice according to SMBG readings, local guidance and individual circumstances. Subjects will be monitored closely with regard to safety parameters, including vital signs, safety laboratory tests, ECGs, and adverse events.

Figure -1: Study Schematic



Notes:

Eligible subjects should have the Day 1 randomization visit within 56 ± 5 days of the Week -8 entry into lead-in period visit.

Subjects will receive the last dose of study medications on Week 52 visit and they will have the last follow-up visit on Week 56 visit (30 days after Week 52 visit).

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

Study Drug for MB102229		
Medication	**Potency**	**IP/Non-IP**
Dapagliflozin Film Coated Tablets	5mg	IP
Background Insulin	Varies	Non-IP

Study Population:

Key Inclusion Criteria:

- Diagnosis of T1DM. In addition, the following criteria also needs to be met;
  a) Central laboratory test of C-peptide < 0.7 ng/ml (or < 0.23 nmol/L)
- Ages 18 to 75 years, inclusive
- Insulin use for at least 12 months prior to screening per subject reported or medical records and
  a) Method of insulin administration (MDI or CSII) must have been unchanged for at least 3 months prior to the screening visit per subject reported or medical records. Subjects must be on a total insulin dose of ≥ 0.3 U/kg/day for at least 3 months prior to the screening visit.
  b) If on MDI insulin administration, the subject must be on ≥ 3 injections per day.
- A1C eligibility criteria include:
  a) Screening Visit: Central laboratory A1C ≥ 7.7% and ≤ 11.0%

  Note: a one-time repeat HbA1c test for subjects in screening is allowed if their initial test result is within □ 0.2% of the cut off values
  b) Week -1 Visit: Central laboratory A1C ≥ 7.5% and ≤ 10.5%

  Note: a one-time repeat A1C test for subjects in lead-in is allowed if their test result was within ± 0.2% of the cut off values
- BMI ≥ 18.5 kg/m^2
- Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of investigational product.
- WOCBP must agree to follow instructions for method(s) of contraception as outlined in the study.
- Women must not be breastfeeding

Key Exclusion Criteria:

- Target Disease Exceptions
  a) History of T2DM or maturity onset diabetes of young (MODY), pancreatic surgery, or chronic pancreatitis or other pancreatic disorders that could result in decreased β-cell capacity (eg, pancreatogenous diabetes)

Note: subjects with a previous misdiagnosis of T2DM in their medical history must have one of the following in order to be eligible for this trial:

- Positive autoantibodies for GAD65, phosphatase IA-2/IA2β, or zinc transporter 8 (ZnT8) (ie, autoimmune diabetes)

  Note: If additional time is needed to confirm positive autoantibodies, it can be granted by the Sponsor.

- Fasting c-peptide value below the lower limit of detection performed by local or central laboratory

b) Previous use of dapagliflozin and/or any other SGLT-2 inhibitors

c) Not applicable per Protocol Amendment 03

d) Any non-insulin, any antihyperglycemic agent use within 1 month prior to the screening visit

e) History of diabetes ketoacidosis (DKA) requiring medical intervention (eg, emergency room visit and/or hospitalization) within 1 month prior to the screening visit

f) History of hospital admission for glycemic control (either hyperglycemia or hypoglycemia) within 1 month prior to the screening visit

g) Frequent episodes of severe hypoglycemia as defined by more than one episode requiring medical assistance, emergency care (paramedics or emergency room care), and/or glucagon therapy administered by a third-party individual within 1 month prior to the screening visit

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

i) History of Addison's disease or chronic adrenal insufficiency

j) History of diabetes insipidus

k) Use of any GLP-1 receptor agonist within the following timeframe prior to the screening visit:

   i) 1 month for once or twice daily administration (eg. liraglutide)

   ii) 2 months for once weekly administration

l) Use of insulin-sensitizing agents, such as metformin and/or thiazolidinediones, within 2 months prior to the screening visit

- Medical History and Concurrent Diseases

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

  - Myocardial infarction
  - Cardiac surgery or revascularization (coronary artery bypass surgery [CABG]/percutaneous transluminal coronary angioplasty [PTCA])
  - Unstable angina
  - Unstable congestive heart failure (CHF)
  - CHF New York Heart Association (NYHA) Class III or IV
  - Transient ischemic attack (TIA) or significant cerebrovascular disease
  - Unstable or previously undiagnosed arrhythmia

b) Renal Disease:

  - History of unstable or rapidly progressing renal disease
  - Conditions of congenital renal glucosuria
  - Renal allograft

c) Hepatic Diseases:

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

d) Hematological and Oncological Disease/Conditions:

- History of hemoglobinopathy, with the exception of sickle cell trait (SA) or thalassemia minor; or chronic or recurrent hemolysis
- Known immunocompromised status, including but not limited to, individuals who have undergone organ transplantation or who are positive for the human immunodeficiency virus.
- 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 8 weeks prior to the screening visit.
- Malignancy within 5 years of the screening visit (with the exception of treated basal cell or treated squamous cell carcinoma)
- History of bladder cancer
- History of radiation therapy to the lower abdomen or pelvis at any time

- Physical and Laboratory Test Findings
  a) Aspartate Aminotransferase (AST) > 3X Upper limit of normal (ULN)
  b) Alanine aminotransferase (ALT) > 3X ULN
  c) Serum Total Bilirubin > 2X ULN unless exclusively caused by Gilbert's Syndrome
  d) Calculated Creatinine Clearance (CrCl) < 60 ml/min. The renal function, creatinine clearance will be estimated by the Cockcroft-Gault formula, using laboratory measurements of serum creatinine collected at the screening visit [Creatinine Clearance = [[140 - age(yr)]*weight(kg)/[72*serum Cr(mg/dl)] (multiply by 0.85 for women)].
  e) Hemoglobin ≤ 11.0 g/dL (110 g/L) for men; hemoglobin ≤ 10.0 g/dL (100 g/L) for women.
  f) Positive for hepatitis B surface antigen or anti-hepatitis C virus antibody
  g) 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 enrollment procedures and laboratory assessments performed as part of this re-test, and all of these must meet enrollment eligibility criteria. The subject's number will however remain the same as initially assigned.
- Allergies and Adverse Drug Reaction
  a) Allergies or contraindication to the contents of dapagliflozin tablets or insulin.
- Sex and Reproductive Status
  a) Women who are pregnant or breastfeeding
- Other Exclusion Criteria
  a) Prisoners or subjects who are involuntarily incarcerated
  b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness
  c) Subjects on a commercial weight loss program with ongoing weight loss, or on an intensive exercise program
  d) History of bariatric surgery or lap-band procedure within 12 months prior to screening
  e) Replacement or chronic systemic corticosteroid therapy (including local injections such as intramuscular or intra-articular,etc.), defined as any dose of systemic corticosteroid taken for > 4 weeks within 3 months prior to the Day 1 visit

NOTE: Topical (including drops) or inhaled corticosteroids are allowed

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

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

h) Subject is, in the judgment of the investigator, unlikely to comply with the protocol or is unable to correctly self-administer subcutaneous insulin injections and/or manage their insulin pump, or has any severe concurrent medical or psychological condition that may affect the interpretation of efficacy or safety data (including during the lead-in period)

i) Subject with any condition which, in the judgment of the investigator, may render the subject unable to complete the study or which may pose a significant risk to the subject

j) Subject is currently abusing alcohol or other drugs or has done so within the last 6 months prior to the Day 1 visit

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

l) Employee of BMS, AstraZeneca (AZ), or their relatives.

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

n) 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

Discontinuation of Subjects from Treatment:

Subjects MUST discontinue study treatment for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any AE clinical, 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 the Sponsor
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Creatinine Clearance (CrCl) < 30 ml/min
  - If at any time the subject´s CrCl (based on Cockroft-Gault) falls below 30 ml/min calculated at the central laboratory and confirmed at a repeated central laboratory measurement (to be obtained within 4 days, whenever possible) the subject should be discontinued from study medication
  - If at any time the subject´s CrCl (based on Cockroft-Gault) falls below 30 ml/min calculated at local laboratory, a central laboratory CrCl should be obtained promptly. If the CrCl is confirmed by the central laboratory and persists at a repeated central laboratory measurement (to be obtained within 4 days, whenever possible) the subject should be discontinued from study medication.
- Subjects experience at least one protocol-defined hypoglycemia episode that leads to a loss of consciousness and/or seizure as determined by investigator
- Change of insulin administration method (eg, switch from MDI to CSII, or vice versa)
  - ♦ Subjects are not allowed to change their insulin administration methods (eg, from MDI to CSII or vice versa) throughout the study. Under certain situations (eg, the replacement of an insulin pump), the subjects who are on CSII may be on temporary use of MDI. They should restart CSII administration as early as feasible. The period of time when a subject on temporary use of MDI should not be more than two weeks.
- Subjects with a central laboratory ALT and/or AST > 3xULN will be scheduled for a follow-up visit within 3 days following the receipt of the results. Subjects should be discontinued from study if the initial and repeat laboratory tests meet any of the following criteria:

- ♦ ALT and/or AST are > 3x ULN and total bilirubin (TB) > 2x ULN
- ♦ ALT and/or AST are > 5x ULN for ≥ 14 consecutive days, at any time after initial confirmatory results
- ♦ ALT and/or AST are > 10x ULN

Study Assessments:

Primary Assessment:

- Change from baseline in A1C (HbA1c)

Secondary Assessments:

- Percent change from baseline to the Week 24 in total daily insulin dose.
- Percent change from baseline to the Week 24 visit in body weight
- Change from baseline to the Week 24 visit in the mean value of 24-hour glucose readings obtained from CGM
- Change from baseline to the Week 24 visit in mean amplitude of glucose excursion of 24-hour glucose readings obtained from CGM
- Change from baseline to the Week 24 visit in the percent of 24-hour glucose readings obtained from CGM that falls within the range of > 70 mg/dL and ≤ 180 mg/dL
- Proportion of subjects achieving an HbA1c reduction from baseline to Week 24 visit ≥ 0.5% without severe hypoglycemia events

Safety Assessments: Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, ECGs, physical examinations, and clinical laboratory tests. The incidence of observed adverse events will be tabulated and reviewed for potential significance and clinical importance. Both hypoglycemia and diabetic ketoacidosis during the 24-week double-blinded short-term treatment period and the 28-week subject and site blinded long-term treatment period (the sponsor will be unblinded during the long-term treatment period) will be assessed.

Subjects will receive a combined blood glucose and ketone meter, supplies and instructions on their use. Subjects should self-monitor their blood glucose consistent with local treatment guidelines (typically four times daily or when experiencing symptoms suggestive of hypoglycemia) 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. The glucose values should be reviewed by the site to identify any unusual high or low values, and to confirm that the values are obtained from the subject.

Subjects will be advised to measure their blood ketones using a combined blood glucose and ketone meter provided by the sponsor when they have potential symptoms/signs of DKA (eg, excessive thirst, nausea and vomiting, frequent urination, weakness or fatigue, fruity-scented breath, confusion, and/or consistently elevated blood glucose) and/or during acute illness. Subjects should be instructed to measure their ketones if symptoms occur, regardless of plasma glucose values. Subjects should contact the site for assistance with diabetes management in the event that the blood ketone reading is 0.6 mmol/L or above in accordance with the ketone meter user guide provided.

Subjects must also be instructed that if attempts to contact the site are unsuccessful or if they are in urgent need of medical attention, that they should seek medical attention. They should provide information to the health care provider on their participation in a placebo controlled clinical study evaluating the effects of the SGLT2i dapagliflozin in addition to their insulin treatment.

Exploratory Assessments:

Subjects will be instructed to perform 6-point SMBG profiles according to the schedule presented in Study Flow Charts. 6-point SMBG profiles will be taken on any 3 days within one week before the scheduled visits, with 3 glucose measurements obtained preprandially (within 15 minutes prior to meal) and 3 glucose measurements

obtained postprandially (1.5- 2 hours after start of the meal) for the 3 main meals of the day. Subjects will be provided with a diary to record their SMBG measurements and mealtimes.

CGM will be used periodically to measure the subject's interstitial glucose level according to the schedule presented in Study Flow Charts. A CGM sensor will be inserted subcutaneously at the site on Week -2 visit, Week -1 visit, Week 10 visit and Week 22 visit to allow monitoring for two weeks Example: (Week -2 visit to Day 1 visit [as baseline]; Week 10 visit (the Week 10 office visit) until the Week 12 office visit, and Week 22 visit (the Week 22 office visit) until the Week 24 office visit. The data will remain blinded to the subject, the investigator and to the sponsor during the recording and will be downloaded into a data file. Detailed procedures (including calibration) will be described in an operations manual and site staff will be fully trained on the use of CGM. Subjects will wear the sensor and perform calibration according to manufacturer's instructions. If a subject uses a CGM device prior to entry into the study, he/she 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 CGM device according to protocol procedures.

Outcomes Research Assessments:

Patient reported outcomes (PROs) will be assessed at the Day 1 visit (prior to the first dose), the Week 24 visit, and the Week 52 visit by EQ-5D-3L for generic health status and DTSQs for treatment satisfaction. The instruments/questions will be self-administered using paper and pencil questionnaires. The EQ-5D-3L is a generic, preference-based utility questionnaire and consists of two parts, the EQ visual analogue scale (VAS) and the EQ-5D-3L index. The EQ VAS is a visual analogue scale ranging from 0 = worst possible health to 100 = best possible health. The EQ-5D-3L index is a five dimension questionnaire. The dimensions consist of mobility, self-care, usual activity, pain/discomfort and anxiety/depression. Each item has three levels: no problems, some problems and severe problems. The DTSQ has been developed to assess subject´s satisfaction with treatment and perception of change in hyper- and hypoglycaemia. The DTSQ status version (DTSQs) has 8 items.

Data Monitoring Committees:

An external data monitoring committee (DMC) with multidisciplinary representation will be established to evaluate on a periodic basis the incidence of hypoglycemia and DKA events, as well as AEs, laboratory measurements, and safety assessments to ensure the ongoing safety of study subjects. An independent reporting statistician not involved in the conduct of the study will be designated by BMS to provide the DMC with essential safety data during the study. The DMC responsibilities, authorities, and procedures will be documented in a DMC charter.

Statistical Considerations:

Sample Size:

The primary endpoint is the change from baseline in HbA1c to Week 24 visit.

With 243 subjects per treatment group with both baseline and at least one post baseline measurement, there is approximately 90% power to detect a difference in means of 0.35% between each dapagliflozin treatment group and placebo at the two-sided 0.0262 significance level (based on Dunnett and Tamhane step-up procedure), assuming a standard deviation (SD) of 1.1%. Assuming that 5% of subjects do not have a post-baseline assessment, a total of 768 subjects (256 subjects per treatment arm) need to be randomized to each dapagliflozin or placebo group in 1:1:1 ratio. In light of a randomization system error that affected the first 55 randomized subjects, the randomization target was increased by 55 in order to maintain the power for the primary endpoint as these 55 subjects will be excluded from the primary efficacy analysis. Thus, the total number of subjects to be randomized in the study will be 823.

A mean reduction in the primary endpoint of change from baseline in HbA1c of 0.35% was used to determine sample size as this represents a clinically meaningful improvement in glycemic control under the current study design with adjustable background insulin dose. A lesser degree of reduction in HbA1c in combination with other beneficial outcomes in secondary endpoints may also be clinically important.

Statistical Approach / Assumptions:

Unless otherwise specified, efficacy analyses will be performed using the full analysis dataset, which excludes the first 55 randomized subjects who were affected by the randomization system error

The primary endpoint is the change in A1C (HbA1c) from baseline to Week 24. The primary estimand for the primary endpoint is *treatment difference at Week 24 if subjects did not discontinue randomized treatment*. In order to maintain an overall Type I error rate of 5% for the endpoint, a Dunnett and Tamhane step-up procedure will be used, which allows for the correlation of 0.5 between the standard normal deviate for each comparison (Dunnett and Tamhane 1992). Applying the Dunnett and Tamhane procedure, statistical significance will be declared for both doses at the two-sided 5% level if the two-sided p-values from both pairwise comparisons are smaller than 5%. If the larger p-value among the two pairwise comparisons is greater than 5% and the smaller p-value is below 2.62%, then statistical significance will be declared for the latter comparison. The primary analysis of the change in HbA1c from baseline to Week 24 will be based on a longitudinal repeated measures analysis using 'direct likelihood'. The analysis will be based on the full analysis dataset who have a baseline assessment and any post-baseline double-blind treatment period assessment. The analysis will include all available data up to Week 24 or until premature discontinuation of randomized treatment, whichever occurs first. The analysis will be conducted regardless of insulin up-titration. The model is based on a missing at random (MAR) assumption with respect to missing data.

The SAS procedure PROC MIXED will be used. The preferred model will include the fixed categorical effects of treatment, week, randomization stratification factor (i.e. one term for each combination of all stratification factors) and treatment-by-week interaction, as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction. An unstructured matrix for the within-subject error variance-covariance will be used. The denominator degrees of freedom will be calculated according to the Kenward-Roger method. A number of back-up models will be defined in the statistical analysis plan in case of non-convergence of the preferred model or other issues. Point estimates and 95% confidence intervals for the mean change within each treatment group, as well as the difference in mean change between the dapagliflozin treatment group and placebo will be calculated. P-values for the difference in week 24 estimates between each dapagliflozin group and placebo will be calculated

The ITT estimand, i.e., *treatment difference at Week 24 regardless of treatment discontinuation,* will be evaluated as the secondary estimand of the primary endpoint. The analysis of the ITT estimand will include all available data up to Week 24, regardless of insulin up-titration and regardless of premature discontinuation of randomized treatment.

Sensitivity analyses will be conducted for the primary efficacy endpoint to assess the robustness of the primary efficacy results, including sensitivity analysis with respect to the ITT estimand, sensitivity analyses based on missing-not-at-random (MNAR) assumptions with respect to missing data, and sensitivity analysis with respect to insulin up-titration.

Statistical tests for secondary efficacy endpoints will be only conducted if there is a statistically significant difference in the primary endpoint for both pairwise comparisons, i.e., dapagliflozin 5mg vs. placebo and dapagliflozin 10mg vs. placebo. The same Dunnett and Tamhane step-up procedure will be applied to each secondary efficacy endpoint. Secondary efficacy endpoints will be tested in the order that they appear in the objectives section of the protocol and protocol synopsis. Statistical tests will be only performed for a given secondary endpoint if both comparisons for a proceeding secondary endpoint are significant. Otherwise, the testing procedure will stop at the secondary endpoint that does not reach statistical significance.

The percent change (using logarithmic transformation for the endpoint in the model) from baseline at Week 24 in total daily insulin dose and total body weight, the change from baseline at Week 24 in the mean value of 24-hour glucose readings obtained from CGM, mean amplitude of glucose excursion of 24-hour glucose readings obtained from CGM, and the percent of 24-hour glucose readings obtained from CGM that fall within the range of > 70 mg/dL and ≤ 180 mg/dL will be analyzed using a longitudinal repeated measures analysis, similarly to the model used for the primary efficacy analysis. The proportion of subjects achieving an HbA1c reduction from baseline to Week 24 $\geq 0.5\%$ without severe hypoglycemia events will be analyzed using a logistic regression model with adjustment for baseline values. In addition to point estimates and 2-sided 95% confidence intervals, p-values will be calculated for all endpoints. Nominal p-values will be presented for endpoints where type 1 error is not controlled. All secondary efficacy analyses will use subjects in the primary efficacy dataset (ie, full analysis dataset) who have a baseline assessment and any post-baseline double-blind treatment period assessment.

Analysis and Reporting:

There will be one study report at the end of short-term period and a second study report at the end of short-term plus long-term period.

The PK analysis may be provided in a separate report.

TABLE OF CONTENTS

1. INTRODUCTION AND STUDY RATIONALE

1.1 Study Rationale

1.1.1 Unmet Medical Need in Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) is a serious chronic disorder that results in the destruction of insulin-producing pancreatic β-cells. T1DM accounts for approximately 5-10% of all cases of diabetes worldwide, and its incidence continues to increase.[1] Patients with T1DM require lifelong insulin therapy due to their inability to produce endogenous insulin. Insulin requirements in these subjects vary widely and depend on several factors including body weight, activity level, and food intake.

People with T1DM must balance the goal of long-term glycemic control and reduction of complications of the disease with the day-to-day challenges of insulin therapy. The major limiting factor for restoring euglycemia is insulin-related hypoglycemia.[2] Unfortunately, recent data suggest hypoglycaemia remains a common event, with 11.8% of subjects in a clinic registry study experiencing at least one episode of severe hypoglycemia resulting in seizure or loss of consciousness within the past 12 months.[3] The occurrence of severe hypoglycemia did not appear to be related to HbA1c. However, the risk of multiple hypoglycemia episodes in T1DM can be related to the degree of glycemic variability[4], which suggests that reducing the swings in glucose may be of importance in this population.

Intensive insulin therapy is also associated with weight gain and insulin resistance, as evidenced in the Diabetes Control and Complications Trial[5,6]where subjects in the intensive treatment arm gained an average of 4.6 kg more than the control group over the 5 year study. It has been postulated that the weight gain associated with intensive insulin treatment is related to reductions in urinary glucose excretion, increased appetite and the ingestion of excess calories to manage or avoid hypoglycemia. Weight gain and insulin resistance may have a significant deleterious impact upon cardiovascular risk factors[7] at least in some people with T1DM, and has recently contributed to the concept of 'double diabetes'.[8]

Average HbA1c values greater than 8% have been reported in several large studies in people with T1DM [9,10], suggesting a large proportion of the population are unable to achieve recommended glycemic levels with insulin alone because of the challenges associated with insulin therapy. Novel therapies used as an adjunct to insulin that improve glycemic control and provide important secondary benefits such as reduction in insulin dose, attenuation of the weight gain, hypoglycemia and glycemic variability address important unmet needs for people with T1DM.

1.1.2 Introduction of Dapagliflozin and Study Rationale

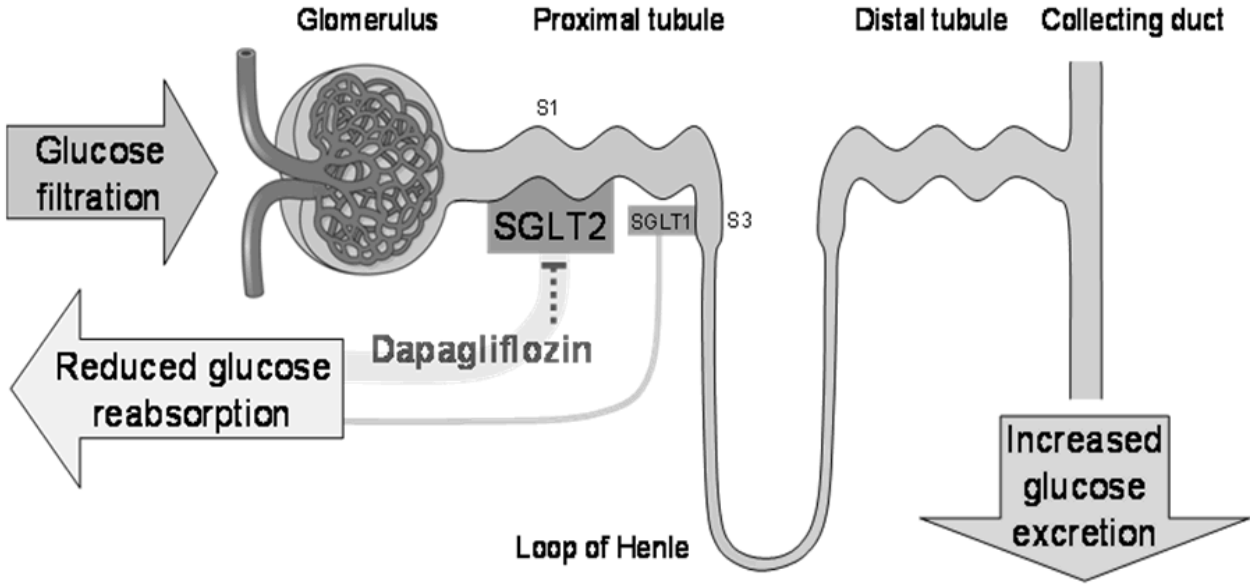
This study is a Phase 3 study, designed to evaluate the efficacy and safety of dapagliflozin 5 mg and 10 mg as an add-on to insulin therapy when used in subjects with type 1 diabetes mellitus with inadequate glycemic control.

Dapagliflozin is a stable, competitive, reversible, highly selective, and orally active inhibitor of SGLT-2, the major transporter responsible for renal glucose reabsorption. Dapagliflozin has been under investigation for use in the treatment of type 2 diabetes mellitus (T2DM). Dapagliflozin has been recently approved for marketing in 40 countries/regions including the European Union (EU; 5 or 10 mg dapagliflozin), United States (5 or 10 mg dapagliflozin), and Australia (10 mg dapagliflozin only), and is under investigation for marketing in numerous countries around the world.

Dapagliflozin's MOA is different from and complementary to the mechanisms of existing medications in other drug classes for T2DM, resulting in the direct, and insulin-independent, elimination of glucose by the kidney. Further, as SGLT-2 is almost exclusively expressed in the kidney, the highly selective nature of dapagliflozin minimizes the risk of off-target (ie, non-kidney) effects. Therefore, no effects are observed on glucose and/or other carbohydrate transport or absorption in any other organs, including the gut, and no other transporters are affected. As such, dapagliflozin offers an important additional strategy for improving glycemic control as an add-on to insulin in patients with T1DM.

Urinary glucose excretion induced by dapagliflozin depends upon the amount of glucose filtered by the kidney (Figure 1.1.2-1). This filtered load is the product of the plasma glucose concentration and the glomerular filtration rate (GFR). Therefore, the action of dapagliflozin is dependent upon the patient's plasma glucose and renal function, and is independent of the patient's beta cell function or insulin sensitivity, which translates into a relatively low risk of hypoglycemia. Furthermore, because the mechanism reduces hyperglycemia independently of insulin secretion or action, this approach to antidiabetic therapy provides an opportunity to achieve clinically important glycemic efficacy as an add-on to insulin in patients with T1DM.

Figure 1.1.2-1: How Dapagliflozin Works (Mechanism of Action)



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 hemoglobin A1C (HbA1c) from baseline compared to placebo (0.4 - 0.56% and 0.54 - 0.68% for 5 and 10 mg doses, respectively[11]).

In addition, dapagliflozin as add on therapy to insulin is now being investigated as a potential treatment for patients with T1DM with inadequate glycemic control (defined as HbA1c ≥ 7.5%). Dapagliflozin may be a clinically relevant adjunctive therapy for patients with T1DM given its insulin-independent MOA. Because patients with T1DM are insulin deficient, insulin treatment is required for preventing ketoacidosis and ultimately for survival. Thus, dapagliflozin would not be a replacement for insulin therapy in the setting of T1DM. However, dapagliflozin reduces blood glucose levels by an insulin-independent mechanism and may be effective in improving glycemic control in patients with T1DM when used in combination with insulin. In the T1DM population, the inhibition of urinary glucose reabsorption via SGLT-2 inhibition is expected to produce a glucose lowering similar to that observed in the T2DM population, as well as the modest reductions in blood pressure and body weight previously described. Furthermore, the amount of urinary glucose excreted following treatment with dapagliflozin is dependent upon the plasma glucose concentration[12], which may serve to blunt the excursions of glucose values over the course of the day (reduce glycemic variability).

The potential of dapagliflozin as a treatment option for the T1DM population was explored in a Phase 2a pilot study (MB102072). The MB102072 study was a randomized, double-blind, 5-arm, parallel-group, placebo-controlled exploratory Phase 2a trial to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of dapagliflozin in subjects with type 1 diabetes who had inadequate glycemic control despite insulin use. Subjects on insulin monotherapy with central laboratory enrollment HBA1C ≥ 7.0% and ≤ 10.0% were eligible for randomization in a 1:1:1:1:1 ratio into one of five blinded treatment arms noted above. Subjects received dapagliflozin or matching placebo for a total of 14 days and remained in-patient from Day -3 to Day 7 and then had outpatient visits on Day 10, Day 14, and a discharge visit on Day 21. In this pilot study, dapagliflozin was generally well tolerated at doses of 1, 2.5, 5 and 10 mg QD in subjects with T1DM. Hypoglycemia events were frequent in this population during study treatment. Events were relatively balanced across treatment groups. Consistent with the known mechanism of action of dapagliflozin, dose-related increases in 24 hour urinary glucose were observed. Based upon the similar PK characteristics in subjects with T1D compared to T2D or healthy subjects, the exposure response relationship in terms of urinary glucose excretion appear to be virtually identical in this T1D population to that previously described in T2D subjects, correcting for baseline differences in glycemic control and eGFR between the studies. Because dapagliflozin 5 mg was established as the minimally effective dose in T2D and the marked similarities in the PK and PD response that drives efficacy, it is expected that dapagliflozin 5 mg will also be the minimally effective dose in subjects with T1D. Evaluation of

exploratory endpoints suggests a potential for dapagliflozin to improve glycemic control in subjects with T1DM as evidenced by:

- Dose-related trends toward reduction in FPG at Day 7.
- Dose-related trends toward reduction in average daily glucose at Day 7 from continuous glucose monitoring (CGM).
- Trends to reduce glycemic variability over the day as evidenced by reduction in the standard deviation of 24 hour glucose values and reduction in the mean amplitude of glucose excursion determined from CGM at Day 7.
- Trends towards increased percentage of CGM readings at Day 7 in the target range (70 to 180 mg/dl).
- Trend towards reduction in total daily insulin dose with all dapagliflozin treatment.

In completed clinical studies in subjects with both T2DM and T1DM, 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 in subjects with T2DM, the frequency of overall adverse events (AEs) was similar to placebo. In the Phase 2 study in subjects with T1DM (MB102072), the frequency of overall adverse events (AEs) was similar to placebo. Compared to subjects with T2DM, hypoglycemia is more frequent in subjects with T1DM, but the frequency of hypoglycemia is relatively balanced across dapagliflozin treatment and placebo groups. Urine ketone tests revealed frequent positive urine ketone in this study, with a possibly slight increase in subjects receiving dapagliflozin 10 mg. No diabetic ketoacidosis was observed during the study period (from the start of study drugs to the end of follow-up).

It is expected that dapagliflozin will exhibit an efficacy and safety profile in subjects with T1DM that will be similar to that observed in T2DM. In fact, as a potentially novel therapy for T1DM, dapagliflozin as an adjunct to insulin may reduce HbA1c and insulin dose plus provide important secondary benefits such as attenuation of the weight gain, hypoglycemia and glycemic variability to address important unmet needs for people with T1DM.

1.2 Research Hypothesis

In subjects with type 1 diabetes that have inadequate glycemic control with insulin alone, the addition of dapagliflozin to adjustable insulin will result in a greater mean reduction in HbA1c after 24 weeks of double-blind treatment as opposed to placebo plus adjustable insulin. In this study, adjustments of insulin dose can be made as deemed appropriate to be consistent with good medical practice.

1.3 Objectives(s)

1.3.1 Primary Objectives

The primary objective of this study is:

- To compare dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin for the change from baseline in A1C (HbA1c) after 24 weeks of double-blinded treatment

1.3.2 Secondary Objectives

1.3.2.1 Efficacy

Six secondary efficacy objectives are identified for special consideration in this study, in addition to the primary objective:

1) Compare the percent change from baseline in total daily insulin dose with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
2) Compare the percent change from baseline in body weight with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
3) Compare the change from baseline in the mean value of 24-hour glucose readings obtained from CGMS with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
4) Compare the change from baseline in mean amplitude of glucose excursion of 24-hour glucose readings obtained from CGM with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
5) Compare the change from baseline in the percent of 24-hour glucose readings obtained from CGMS that falls within the target range of > 70 mg/dL and ≤ 180 mg/dL with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
6) Compare dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin for the proportion of subjects achieving an HbA1c reduction from baseline to Week 24 visit ≥ 0.5% without severe hypoglycemia events

1.3.2.2 Safety

- To assess the proportion of subjects with hypoglycemia events and the frequency and severity of the hypoglycemia events with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin
- To evaluate the safety and tolerability by assessment of adverse events (AE), vital signs, diabetic ketoacidosis events, physical examination findings, ECGs, and laboratory values.

1.3.3 Other/Exploratory Objectives

1) Assess the proportion of subjects with HbA1c reduction of at least 0.5% (≥ 0.5%) from baseline with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
2) Assess the proportion of subjects with HbA1c < 7.0% with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
3) Assess the change from baseline in fasting plasma glucose with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
4) Assess the change from baseline in the percent of 24-hour glucose readings obtained from CGM that is within the hypoglycemic range of ≤ 70 mg/dL with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
5) Assess the change from baseline in seated systolic blood pressure with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment among subjects with hypertension at baseline, defined as seated SBP ≥ 140 mmHg and/or seated DBP ≥ 90 mmHg
6) Assess the change from baseline in average glucose values measured by 6-point self monitored blood glucose (SMBG) with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
7) Assess the change from baseline in postprandial glucose values measured by 6-point self monitored blood glucose (SMBG) with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
8) Assess the change from baseline in postprandial glucose values measured by CGM with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
9) Assess the change from baseline in standard deviation of 24-hour glucose readings obtained from CGM with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
10) Assess the change from baseline to Week 24 in health status, as measured by the EQ-5D-3L questionnaire, between dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment.
11) Assess the changes from baseline at week 24 visit in the summary score for treatment satisfaction and scores for perceived frequency of hyperglycemia and perceived frequency of hypoglycemia, respectively, as measured by the Diabetes Treatment Satisfaction Questionnaire status (DTSQs) between the dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment
12) To explore the relationship between observed and/or model estimated pharmacokinetic measures of exposure (eg, AUCss, Cmax, Cmin) and efficacy and/or safety endpoints by using model-based approaches. This analysis will be provided in a separate report.

13) Compare the number of non-severe hypoglycemic events per subject in those achieving an HbA1c reduction of ≥ 0.5% on dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin from baseline to Week 24 visit.

1.4 Product Development Background

Dapagliflozin has been designed as a potent and selective inhibitor of the renal sodium-glucose transporter, SGLT-2. Multiple phase 2 and phase 3 studies, where dapagliflozin was used as monotherapy or in combination with other oral hypoglycemic agents or insulin in subjects with type 2 diabetes mellitus (T2DM), have shown that dapagliflozin is 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 the MB102009 and D1690C00006 studies, where dapagliflozin was added in subjects with T2DM receiving high doses of insulin, confirmed that dapagliflozin was effective in lowering HbA1c when combined with insulin in this population (HbA1c reduction of 0.6% relative to placebo).

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

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

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

1.5 Overall Risk/Benefit Assessment

Dapagliflozin is being developed as a potential new therapy for hyperglycemia in subjects with type 1 diabetes. Considering dapagliflozin's mechanism of action, this study's design features (including the inclusion, exclusion, and discontinuation criteria), and the planned safety procedures, participation in this study presents a minimal risk.

As noted above, dapagliflozin has been effective at lowering glucose and HbA1c in subjects with T2DM, when studied as monotherapy as well as in combination with insulin or oral anti-diabetic medications. In a recently concluded Phase 2a study, the combination therapy of dapagliflozin with insulin was assessed in subjects with type 1 diabetes mellitus with inadequate glycemic control. In that study, dapagliflozin was found generally safe and well-tolerated. Results from the

study also suggested that treatment with dapagliflozin as add-on to insulin may have potential to reduce glucose levels, decrease glycemic variability based on continuous glucose monitoring (CGM), and reduce total insulin dose.

Potential risks

The potential risks associated with dapagliflozin have been identified based upon the mechanism of action, the preclinical results, and the extensive clinical experience to date, including a study combining it with insulin when used in subjects with type 1 diabetes. The benefits and risks associated with the investigational drug and insulin, are well established and presented in their approved investigator brochure and prescribing information respectively. No study procedure will put subjects at a risk beyond those ordinarily encountered during the performance of routine medical examinations or tests.

Protection against risks

The present study has been designed with appropriate measures in place so as to monitor and minimize any of the potential health risks to participating subjects. In order to ensure the safety of all subjects participating in this study, the Sponsor will conduct a real-time review of all safety information from all ongoing clinical dapagliflozin studies as they become available. Safety signal detection will include the integration of all available sources of safety information, including clinical study data, adverse event reports, pre-clinical data, epidemiological studies and literature reports, to identify and characterize unrecognized safety risks or changes in those which are currently expected Adverse Drug Reactions. Any information that may affect the benefit-risk profile of dapagliflozin will be immediately communicated to relevant health authorities and appropriate actions will be taken regarding the clinical program as needed.

Given the potential increased risk of hypoglycemia when dapagliflozin is added on to insulin, it is recommended that subjects reduce their daily insulin doses by up to 20% for both basal and bolus insulins after the first dose of study drug on Day 1 visit following randomization to reduce the risk of hypoglycemia although in some cases it may be necessary to reduce insulin (particularly basal insulin) in advance of study drug administration. During the study, insulin dose may be adjusted as deemed appropriate to be consistent with good medical practice according to SMBG readings, local guidance and individual circumstances.

In addition, an external data monitoring committee (DMC) with multidisciplinary representation will be established to periodically evaluate the incidence of AEs (especially events of hypoglycemia and diabetic ketoacidosis), laboratory measurements, and safety assessments to ensure the ongoing safety of study subjects. An independent reporting statistician not involved in the conduct of the study will be designated by BMS to provide the DMC with essential safety data during the study. The DMC responsibilities, authorities, and procedures will be documented in a DMC charter.

All studies which include dapagliflozin are subject to a carefully designed patient risk management plan. Investigators are also provided guidance on appropriate management of potential risks such as hypoglycemia, urinary tract infections and decreased renal function

mentioned in the plan. In addition, for this trial, investigators are provided guidance on appropriate managements and potential risks associated with DKA.

Potential benefits to patients

As noted above, dapagliflozin added to background insulin therapy was well-tolerated in the Phase 2 study in subjects with T1DM (MB102072) and had a pharmacokinetic profile similar to the healthy and T2DM populations studied previously. Therefore, it is expected that the efficacy and safety profile of dapagliflozin in subjects with T1DM will be similar to that observed in T2DM subjects. Furthermore, because its mechanism is independent of insulin, dapagliflozin provides an opportunity to achieve clinically important glycemic efficacy in subjects with T1DM. In addition, all subjects will keep receiving insulin (dose can be adjusted) as active background therapy.

Subjects are also expected to receive some benefit in the form of increased medical care/attention when participating in study procedures, which includes multiple clinic visits and physical examinations over the 52 week study. Subjects will also receive counseling on diet and exercise. It is commonly observed that even subjects receiving placebo in diabetes studies show some improvement in glycemic control, likely due to their increased compliance to dietary and exercise counseling while they are participating in a clinical study.

2. ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

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

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

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

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

2.2 Institutional Review Board/Independent Ethics Committee

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

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

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

2.3 Informed Consent

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

In situations where consent cannot be given to subjects, their legally acceptable representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers 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 his or her informed consent during the study, consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

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

This trial is a randomized, double-blinded, three-arm, parallel-group, placebo-controlled, multicenter trial to evaluate the efficacy and safety of dapagliflozin, when added to ongoing insulin therapy, in subjects with T1DM and inadequate glycemic control.

Potential subjects will be assessed for eligibility criteria at the screening visit. Eligible subjects will enter an 8-week lead-in period in order to optimize their diabetes management based on individual subject challenge to glycemic control (including hyperglycemia, hypoglycemia, erratic meal/exercise patterns), as defined by Investigator and to assess the variability in blood glucose profiles and frequency of hypoglycemic episodes at baseline. No placebo or study medication will be provided during the lead-in period. On the Day 1 visit, subjects who meet all the protocol-specific enrollment and randomization inclusion criteria and meet none of the exclusion criteria will be randomized into one of the three blinded treatment arms (dapagliflozin 5 mg QD, dapagliflozin 10 mg QD, or placebo QD) in a 1:1:1 ratio. Randomization will be stratified by the following factors to ensure equal representation across all treatment groups;

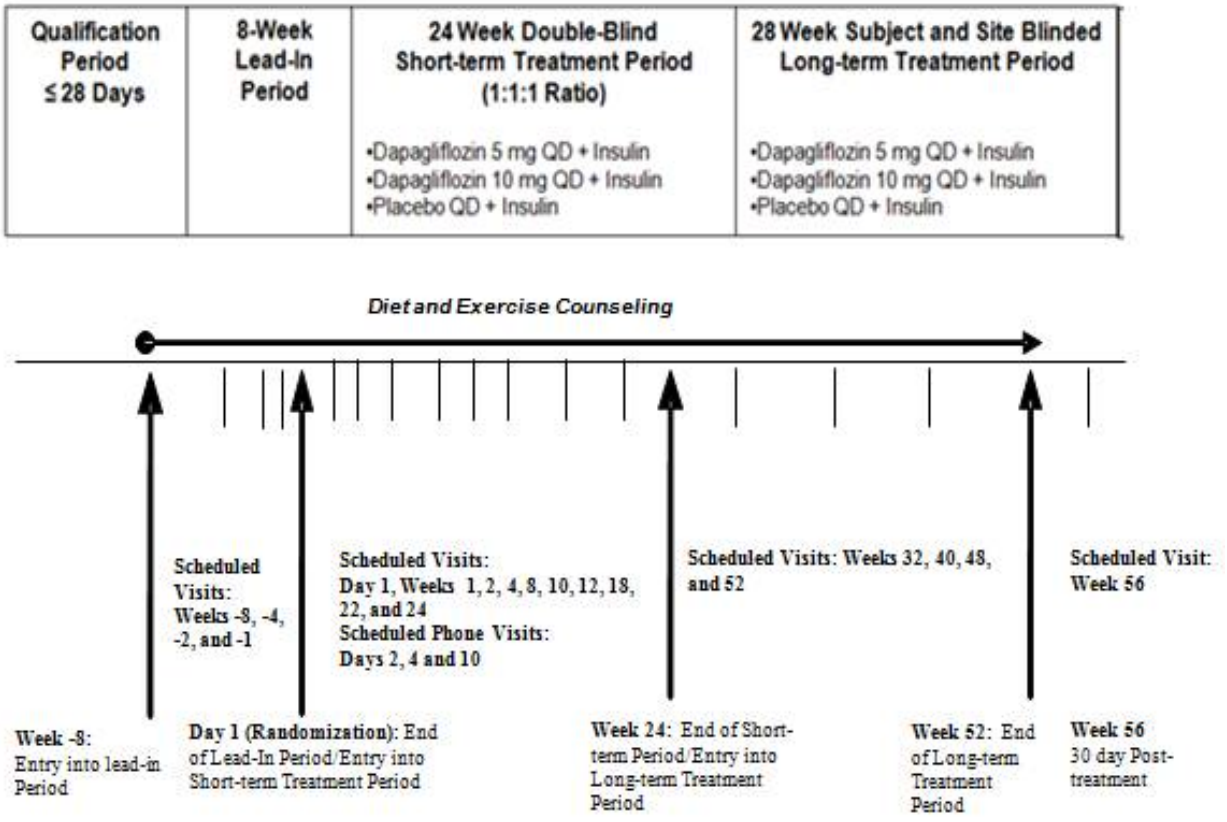
- Current (this refers to an unblinded/personal device already being used, in addition to the CGM device being introduced as part of the study) use of continuous glucose monitoring system (yes vs. no)
- Method of insulin administration at baseline (multiple daily injections (MDI) defined as three or more injections per day vs. continuous subcutaneous insulin infusion - CSII)
- Week -1 Visit (Baseline) A1C $\geq$ 7.5% and < 9.0% vs. $\geq$ 9.0% and $\leq$ 10.5%

Subjects will receive dapagliflozin 5 mg QD, 10 mg QD, or placebo QD for 24 weeks, followed by a 28-week subject and site blinded long-term treatment period. Besides study medications, subjects will be treated with MDI injection (three or more injections per day of basal and prandial insulin) or CSII. It will be recommended that subjects reduce their daily insulin dose by up to 20% for both basal and bolus insulins, similar to what was observed in study MB102-072, after the first dose of study drug to minimize the risk of hypoglycemia. In some cases, it may be necessary to reduce insulin (particular basal insulin) in advance of study drug administration. It is at the discretion of the investigator to determine the extent to which to reduce the insulin dose. Throughout the study (from the beginning of the lead-in period to the end of the long-term treatment period), insulin dose may be adjusted as deemed appropriate to be consistent with good

medical practice according to SMBG readings, local guidance and individual circumstances. Subjects will be monitored closely with regard to safety parameters, including vital signs, safety laboratory tests, ECGs, and adverse events.

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

Figure 3.1-1: Study Design Schematic



Notes:

Eligible subjects should have the Day 1 randomization visit within 56 ± 5 days of the Week -8 entry into lead-in period visit.

Subjects will receive the last dose of study medications at Week 52 Visit and they will have the follow-up visit at Week 56 Visit (30 days after Week 52 visit).

3.2 Post Study Access to Therapy

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

3.3 Study Population

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

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent
   a) Subjects or their legally responsible representatives must be willing and able to give < signed and dated written informed consent.
2) Target Population
   a) Diagnosis of T1DM. In addition, the following criteria also needs to be met;
      1. Central laboratory test of C-peptide < 0.7 ng/ml (or < 0.23 nmol/L)
   b) Not applicable per Protocol Amendment 03
   c) Subject Re-enrollment: This study does not permit the re-enrollment of a subject who has discontinued the study as a screen or lead-in failure. However any subject previously excluded for any of the criteria changed in Amendment 03 will be allowed to be rescreened.

      Subjects who did not fail any of the screening or lead-in criteria and are not subsequently randomized within the applicable study visit windows (eg, due to a planned medical procedure, vacation plans, or employment commitments) may rescreen after discussion and approval by the Sponsor.
3) Insulin use for at least 12 months per subject report or medical records and
   a) Method of insulin administration (MDI or CSII) must have been unchanged for at least 3 months prior to the screening visit per subject reported or medical records. Subjects must be on a total insulin dose of ≥ 0.3 U/kg/day for at least 3 months prior to the screening visit.
   b) If on MDI insulin administration subject must be on ≥ 3 injections per day.
4) A1C eligibility criteria include:
   a) Screening Visit: Central laboratory A1C ≥ 7.7% and ≤ 11.0%
      Note: a one-time repeat A1C test for subjects in screening is allowed if their initial test result was an A1C ± 0.2% of the cut off values
   b) Week -1 Visit: Central laboratory A1C ≥ 7.5% and ≤ 10.5%
      Note: a one-time repeat A1C test for subjects at week -1 is allowed if their test result is within ± 0.2% of the cut off values
      To ensure adequate time is given to complete the repeat week -1 A1C, a 7 day window (added to the current lead-in period window of 56 ± 5 days) will be allowed
5) Body Mass Index (BMI) ≥ 18.5 kg/m²
6) Age and Reproductive Status
   a) Men and women, ages 18 to 75 years, inclusive
   b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of investigational product.
   c) Women must not be breastfeeding.

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with dapagliflozin plus 4 days (> 5 half-lives of dapagliflozin) plus 30 days (duration of ovulatory cycle) for a total of 34 days post-treatment completion

e) Males who are sexually active with WOCBP must agree to the following instructions for the duration of treatment with dapagliflozin plus 4 days (>5 half-lives of dapagliflozin) plus 90 days (duration of sperm turnover) for a total of 94 days post-treatment completion.

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

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

- Male condoms with spermicide[13]
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- Non hormonal IUDs, such as ParaGard®
- Tubal ligation (not considered surgically sterile, see section 3.3.3)
- Vasectomy
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

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

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) History of T2DM or maturity onset diabetes of young (MODY), pancreatic surgery, or chronic pancreatitis or other pancreatic disorders that could result in decreased β-cell capacity (eg, pancreatogenous diabetes)

Note: subjects with a previous misdiagnosis of T2DM in their medical history must have one of the following in order to be eligible for this trial:

- Positive autoantibodies for GAD65, phosphatase IA-2/IA2β, or zinc transporter 8 (ZnT8) (ie, autoimmune diabetes)

  Note: If additional time is needed to confirm positive autoantibodies, it can be granted by the Sponsor.
- Fasting c-peptide value below the lower limit of detection performed by local or central laboratory

b) Previous use of dapagliflozin and/or any other SGLT-2 inhibitors

c) Not applicable per Protocol Amendment 03

d) Any non-insulin, antihyperglycemic agent, within 1 month prior to the screening visit

e) History of diabetes ketoacidosis (DKA) requiring medical intervention (eg, emergency room visit and/or hospitalization) within 1 month prior to the screening visit

f) History of hospital admission for glycemic control (either hyperglycemia or hypoglycemia) within 1 month prior to the screening visit

g) Frequent episodes of severe hypoglycemia as defined by more than one episode requiring medical assistance, emergency care (paramedics or emergency room care), and/or glucagon therapy administered by a third-party individual within 1 month prior to the screening visit

h) Symptoms of poorly controlled diabetes that would preclude participation in this trial including but not limited to marked polyuria and polydipsia with greater than 10% weight loss during the three months prior to Screening visit, or other signs and symptoms of poor glycemic control.

i) History of Addison's disease or chronic adrenal insufficiency

j) History of diabetes insipidus

k) Use of any GLP-1 receptor agonist within the following timeframe prior to the screening visit:

   i. 1 month for once or twice daily administration (eg. liraglutide)

   ii. 2 months for once weekly administration

l) Use of insulin-sensitizing agents, such as metformin and/or thiazolidinediones, within 2 months prior to the screening visit

2) Medical History and Concurrent Diseases

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

   1) Myocardial infarction
   2) Cardiac surgery or revascularization (coronary artery bypass surgery [CABG]/percutaneous transluminal coronary angioplasty [PTCA])
   3) Unstable angina
   4) Unstable congestive heart failure (CHF)
   5) New York Heart Association (NYHA) CHF Class III or IV
   6) Transient ischemic attack (TIA) or significant cerebrovascular disease
   7) Unstable or previously undiagnosed arrhythmia

b) Renal Disease:

   1) History of unstable or rapidly progressing renal disease
   2) Conditions of congenital renal glucosuria

3) Renal allograft

c) Hepatic Diseases:
   1. Significant hepatic disease, including, but not limited to, chronic active hepatitis and/or severe hepatic insufficiency

d) Hematological and Oncological Disease/Conditions:
   1. History of hemoglobinopathy, with the exception of sickle cell trait (SA) or thalassemia minor; or chronic or recurrent hemolysis
   2. Known immunocompromised status, including but not limited to, individuals who have undergone organ transplantation or who are positive for the human immunodeficiency virus
   3. 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 8 weeks prior to the screening visit
   4. Malignancy within 5 years of the screening visit (with the exception of treated basal cell or treated squamous cell carcinoma)
   5. History of bladder cancer
   6. History of radiation therapy to the lower abdomen or pelvis at any time

3) Physical and Laboratory Test Findings
   a) Aspartate Aminotransferase (AST) > 3X Upper limit of normal (ULN)
   b) Alanine aminotransferase (ALT) > 3X ULN
   c) Serum Total Bilirubin (TB) > 2X ULN unless exclusively caused by Gilbert's Syndrome
   d) Calculated Creatinine Clearance < 60 ml/min. The renal function, creatinine clearance will be estimated by the Cockcroft-Gault formula, using laboratory measurements of serum creatinine collected at the screening visit [Creatinine Clearance = [[140 - age (yr)]*weight (kg) / [72*serum Cr(mg/dl)] (multiply by 0.85 for women)].
   e) Hemoglobin ≤ 11.0 g/dL (110 g/L) for men; hemoglobin ≤ 10.0 g/dL (100 g/L) for women.
   f) Positive for hepatitis B surface antigen or anti-hepatitis C virus antibody
   g) 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 subjects who have had a prior diagnosis of a thyroid disorder and who are currently receiving thyroid replacement therapy. Such cases should be discussed with the Sponsor prior to re-testing. The subject must have all enrollment procedures and laboratory assessments performed as part of this re-test, and all of these must meet enrollment eligibility criteria. The subject's number will however remain the same as initially assigned.

4) Allergies and Adverse Drug Reaction
   a) Allergies or contraindication to the contents of dapagliflozin tablets or insulin.

5) Sex and Reproductive Status
   a) Women who are pregnant or breastfeeding

6) Other Exclusion Criteria
   a) Prisoners or subjects who are involuntarily incarcerate
   b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness
   c) Subjects on a commercial weight loss program with ongoing weight loss, or on an intensive exercise program.
   d) History of bariatric surgery or lap-band procedure within 12 months prior to screening.
   e) Replacement or chronic systemic corticosteroid therapy, defined as any dose of systemic corticosteroid (including local injections such as intramuscular or intra-articular,etc.) taken for > 4 weeks within 3 months prior to the Day 1 visit

      NOTE: Topical (including drops) or inhaled corticosteroids are allowed
   f) Any unstable endocrine, psychiatric or rheumatic disorders as judged by the Investigator
   g) Volume depleted subjects. Subjects at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics who cannot carefully monitor their volume status should be excluded from the study.
   h) Subject is, in the judgment of the Investigator, unlikely to comply with the protocol, or is unable to correctly self administer subcutaneous insulin injections and/or manage their insulin pump, or has any severe concurrent medical or psychological condition that may affect the interpretation of efficacy or safety data (including during the lead-in period).
   i) Subject with any condition which, in the judgment of the Investigator, may render the subject unable to complete the study or which may pose a significant risk to the subject.
   j) Subject is currently abusing alcohol or other drugs or has done so within the last 6 months prior to the Day 1 visit
   k) Subject is a participating investigator, study coordinator, employee of an investigator or immediate family member of any of the aforementioned.
   l) Employee of BMS, AstraZeneca (AZ), or their relatives.
   m) Administration of any other investigational drug within 30 days of the screening visit
   n) 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 that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

A woman of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes.

In addition, women under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.*

*Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. Below are suggested guidelines for the duration of the washout period. Investigators should use their judgment in checking serum FSH levels. If washout period exceeds 4 weeks, the subject must have all enrollment procedures and laboratory assessments repeated and all of these must meet enrollment eligibility criteria. The subject's number will however remain the same as initially assigned. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

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

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

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

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

- Antihyperglycemic medication (other than protocol required medication)
- Weight loss medication
- Newly initiated treatment with any systemic corticosteroid therapy (including local injections such as intramuscular or intra-articular,etc.) that will involve ≥ 5 days of therapy is not permitted (inhaled and topical, including drops, are allowed). The BMS Medical Monitor should be consulted prior to beginning therapy with corticosteroids for subjects who require systemic corticosteroid treatment.
- Acetaminophen (paracetamol) containing medications (such as Tylenol) while using the Dexcom CGM device and 24 hours prior to insertion.

3.4.2 Other Restrictions and Precautions

- Subjects must comply with their prescribed dosing regimen to preserve study integrity and ensure subject safety.
- Subjects should be cautioned that any new prescription medication, over-the-counter or herbal/nutritional therapies should be discussed thoroughly with the Investigator as concomitant use could result in alterations to their glycemic control and may place them at risk for significant hypoglycemic episodes.
- Subjects must make every attempt to adhere to the diet and exercise counseling (see Section 5.9.3) and to the study flow chart/time and event schedule (see Section 5.1)

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

3.5 Discontinuation of Subjects from Treatment

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

- Subject's request to stop study treatment
- 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
- Unblinding a subject for any reason (emergency or non-emergency)
- Pregnancy
- Termination of the study by the Sponsor
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Creatinine Clearance < 30 ml/min
  - ♦ If at any time the subject´s CrCl (based on Cockroft-Gault) falls below 30 ml/min calculated at the *central* laboratory and confirmed at a repeated central laboratory measurement (to be obtained within 4 days, whenever possible), the subject should be discontinued from study medication.
  - ♦ If at any time the subject´s CrCl (based on Cockroft-Gault) falls below 30 ml/min calculated at *local* laboratory, a *central* laboratory CrCl should be obtained promptly. If the CrCl is confirmed by the central laboratory and persists at a repeated central laboratory measurement (to be obtained within 4 days, whenever possible), the subject should be discontinued from study medication.
- Subjects experience at least one protocol-defined hypoglycemia episode that leads to a loss of consciousness and/or seizure as determined by the investigator (see Section 3.5.1)
- Change of insulin administration method (eg, switch from MDI to CSII or vice versa)
  - Note: Subjects are not allowed to change their insulin administration methods (MDI or CSII) throughout the study. Under certain situations (eg, the replacement of an insulin pump), the subjects who are on CSII may be on temporary use of MDI. They should restart CSII administration as early as feasible. The period of time when a subject is on temporary use of MDI should not be more than two weeks.
- Subjects with a central laboratory ALT and/or AST > 3xULN will be scheduled for a follow-up visit within 3 days following the receipt of the result (see Appendix 3 for further guidance). Subjects should be discontinued from study if the initial and repeat laboratory tests meet any of the following criteria:
  - ♦ ALT and/or AST are > 3x ULN and total bilirubin (TB) >2x ULN
  - ♦ ALT and/or AST are > 5x ULN for ≥ 14 consecutive days, at any time after initial confirmatory results

- ALT and/or AST are > 10x ULN

All subjects who discontinue investigational product in the 24 week double-blinded short term treatment period or in the 28 week subject and site blinded long-term treatment period are expected to continue and to comply with protocol specified follow-up procedures as outlined in Section 5 with the exception of the study drug and PK procedures.

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

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

3.5.1 Discontinuation Guidelines due to Protocol-Defined Hypoglycemia Episode or Recurrent Hypoglycemia Episodes

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

Subjects should be discontinued from study drug if they meet any of the following criteria;

- At least one hypoglycemia episode that leads to loss of consciousness and/or seizure
- Severe/recurrent hypoglycemia episodes where the possibility of down titration of contributing concomitant medication(s) (other than double-blind study medication), and/or contributing factors (eg, excessive physical activity) have been evaluated and corrected.

NOTE: Dose titration of double-blind study drug is not permitted at any time during the short-term and long-term treatment period.

Section 5.3.2.2 provides additional guidance on management and reporting of hypoglycemia.

3.6 Post Study Drug Study Follow up

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

Therefore as such, all subjects who discontinue investigational product in the 24 week double-blinded short term treatment period or in the subject and site blinded long-term treatment period should be asked to continue study participation for each scheduled visit for the remaining length of the study and complete all procedures as outlined in Section 5 study flowchart with the exception of study drug management and PK sampling. If continued study participation according to the protocol schedule is not possible, the investigator should contact the subject to discuss alternatives (eg, return to the clinic 30 days after discontinuation of study drug to perform the week 56 visit post treatment follow-up procedures as outlined in Section 5 study flowchart or be contacted by telephone 30 days after discontinuation of study drug to evaluate the following safety assessments: Adverse Events, Hypoglycemia events, and DKA episodes. Please note that after the discontinuation of study drug, management of subject's diabetes would be under the care and direction of the investigator and/or subject's healthcare providers.

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

Please utilize the Off Treatment Short Term and Off Treatment Long Term eCRF pages for this data completion.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

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

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a

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

4. STUDY DRUG

Study drugs include both non-investigational (NIMP) and investigational medicinal products (IMP) and can consist of the following:

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

Table 4-1:	**Study Drug for MB102229 - Product Description - Double-blinded Short-term Treatment and Subject and Site Blinded Long-term Treatment Period**				
Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Dapagliflozin Film Coated Tablet [a]	5 mg	IP	Blinded	Green, plain, diamond shaped, film coated tablet Reference footnote below for packaging	Store at 15-25 Degrees Celsius (59-77 Degrees Fahrenheit); Store in tightly closed container
Placebo for Dapagliflozin Film Coated Tablets [b]	0 mg	IP	Blinded	Green, plain, diamond shaped, film coated tablet Reference footnote below for packaging	Store at 15-25 Degrees Celsius (59-77 Degrees Fahrenheit); Store in tightly closed container
Insulin	Varies	Non-IMP	Open Label	Based on manufactured product specifications	Based on manufactured product specifications

[a] Blinded dapagliflozin 10 mg kit contains two (2) bottles of dapagliflozin 5 mg film coated tablets (35 count)
Blinded dapagliflozin 5 mg kit contains one (1) bottle of dapagliflozin 5 mg film coated tablets (35 count) and one (1) bottle of placebo for dapagliflozin film coated tablets (35 count)

[b] Blinded placebo kit contains two (2) bottles of placebo for dapagliflozin film coated tablets (35 count)

4.1 Investigational Product

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

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

In this protocol, investigational products are: (also described in Table 4-1) dapagliflozin 5 mg and matching placebo tablets; insulin will not be provided by the Sponsor since it is part of the subject's standard of care.

- Blinded dapagliflozin 5 mg and 10 mg dose administered orally for the 24-week double-blinded short-term treatment period, and the 28-week subject and site blinded long-term treatment period of the study
- Matching placebo dose administered orally for the 24-week double-blinded short-term treatment period, and the 28-week subject and site blinded long-term treatment period of the study

4.2 Non-investigational Product

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

In this protocol, non-investigational product(s) is: insulin

4.3 Storage and Dispensing

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

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

For non-investigational product, if marketed product is utilized, it should be stored in accordance with the package insert, summary of product characteristics (SmPC), or similar.

4.4 Method of Assigning Subject Identification

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

Subjects entering the 24-week double-blinded short-term treatment period

Following completion of the lead-in period, subjects who meet the criteria will be randomly assigned by the IVRS at the Day 1 Randomization visit, to one of the following three (3) double-blind treatment arms in a 1:1:1 ratio using a centralized blocked randomization schedule:

1) Blinded dapagliflozin 5 mg
2) Blinded dapagliflozin 10 mg
3) Blinded placebo

Randomization will be stratified by:

- Current use of continuous glucose monitoring system (yes or no)
  (this refers to an unblinded/personal device already being used/in addition to the CGM device being introduced as part of the study)
- Method of insulin administration at baseline
  (multiple daily injections (MDI) defined as three or more injections per day vs. continuous subcutaneous insulin infusion - CSII)
- Week -1 Visit (Baseline) A1C $\geq$ 7.5% and < 9.0% vs. $\geq$ 9.0% and $\leq$ 10.5%

Randomization schedules for both subject treatment and kits will be generated and kept by Bristol-Myers Squibb.

Subjects entering the 28-week long-term subject and site blinded treatment period

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

4.5 Selection and Timing of Dose for Each Subject

Dapagliflozin 5 mg, 10 mg, or placebo administered orally once daily for the 24-week double-blinded short-term treatment period and the 28-week subject and site blinded long-term treatment period.

4.6 Blinding/Unblinding

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

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

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

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

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

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

4.7 Treatment Compliance

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

4.8 Destruction and Return of Study Drug

4.8.1 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 (eg, cytotoxics or biologics).

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

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures (SOPs) and a copy provided to 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, (ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

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

It is the investigator's responsibility to arrange for disposal of all empty and partially full containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.9 Return of Study Drug

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

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.10 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

5. STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Flow chart for Protocol MB102229 - Qualification and Lead-in Period

Procedure	Qualification Period Screening Visit[a]	Lead-in Period (8 Weeks)				Notes
		Week -8[b]	Week -4[b]	Week -2[b]	Week -1[c]	
Eligibility Assessments						
Subject Reports to Site	X	X	X	X	X	
Obtain Informed Consent	X					
Review Inclusion/Exclusion Criteria	X					
Review Medical History	X					
General Procedures						
Complete Physical Examination	X					
Brief Physical Examination		X			X	
Body Weight	X	X			X	Refer to Section 5.9.1
Blood Pressure and Heart Rate	X	X			X	Refer to Section 5.3.9
Height	X					
ECG	X					
Body Mass Index (BMI)	X					
Review concomitant medications/procedures	X	X	X	X	X	
Contact IVR system	X	X				

Table 5.1-1: Flow chart for Protocol MB102229 - Qualification and Lead-in Period

Procedure	Qualification Period Screening Visit[a]	Lead-in Period (8 Weeks)				Notes
		Week -8[b]	Week -4[b]	Week -2[b]	Week -1[c]	
Provide Dietary and Exercise Counseling		X	X	X	X	
Dispense subject diaries and provide instructions		X	X	X	X	
Review subject diaries			X	X	X	
Adjust Insulin Dose, as needed		X	X	X	X	
Dispense Glucose and Ketone Meter and Strips and Provide Training		X				
Dispense Glucose and Ketone Strips			X			
Insert/calibrate CGM				X		If a lead-in subject fails lead-in prior to the Day 1 visit, the CGM will not be required to be completed between the week-2 visit and the Day 1 visit (Please refer to Section 5.9.4.3)
Replace CGM sensor, download data to review compliance, and provide training					X	
Record Meals for 7 days - Second week of CGM.					X	If a lead-in subject fails lead-in prior to the Day 1 visit, the meal recording for 7 days will not be required between the week -1 visit and the Day 1 visit (Please refer to Section 5.9.4.3)
SMBG profiles			X			If a lead-in subject fails prior to the Day 1 visit, the 6-point SMBG profile will not be required between the week -1 visit and the Day 1 visit Please refer to Section 5.9.4.2 in protocol

Table 5.1-1: Flow chart for Protocol MB102229 - Qualification and Lead-in Period						
Procedure	Qualification Period Screening Visit[a]	Lead-in Period (8 Weeks)				Notes
		Week -8[b]	Week -4[b]	Week -2[b]	Week -1[c]	
Safety Assessments[d]						
Assess Adverse Events		X	X	X	X	
Assess Hypoglycemia Episodes		X	X	X	X	
Assess DKA		X	X	X	X	
Laboratory Assessments						
Blood Standard Safety Laboratory Panel	X					
Urine Standard Safety Panel	X			X		
Pregnancy test (serum) WOCBP only	X					
Pregnancy test (urine) WOCBP only		X	X			
Spot Urine for glucose, albumin and creatinine quantification and determination of Glucose: Creatinine and Albumin:Creatinine ratios	X					
Fasting plasma glucose	X					
Fasting C-peptide	X					
A1C	X				X	
Hepatitis Screen Panel	X					
TSH	X					

Table 5.1-1: Flow chart for Protocol MB102229 - Qualification and Lead-in Period						
Procedure	Qualification Period Screening Visit[a]	Lead-in Period (8 Weeks)				Notes
		Week -8[b]	Week -4[b]	Week -2[b]	Week -1[c]	
Fasting Serum Lipids	X					
FFA	X					

[a] Screening visit may consist of two days. Second day is to collect lab work. The length of the Qualification period is ≤ 28 days.

[b] Week -8 visit, needs to be within 28 days of screening visit. Week -4 visit, and Week -2 visit may be scheduled ± 3 days to allow flexibility of scheduling.

[c] Week -1 visit should be scheduled at least 7 days but not longer than 10 days after Week -2 visit to accommodate for CGM data collection.

[d] These safety assessments; review of Adverse Events, Hypoglycemia events, and DKA episodes to be performed throughout the study according to the visit schedule as noted via "X".

Table 5.1-2: Flow chart for Protocol MB102229 - 24-week Double-blinded Short-term Treatment Period

Procedure	24-week Double-blinded Short-term Treatment Period													Notes
	Day 1[a]	Day 2 (Phone Visit)	Day 4 (Phone Visit)[b]	Week 1[b]	Day 10 (Phone Visit)[b]	Week 2[c]	Week 4[c]	Week 8[c]	Week 10[c]	Week 12[d]	Week 18[c]	Week 22[c]	Week 24/Early Termination Visit for Short Term[e]	
Eligibility Assessments														
Subject Reports to Site	X			X		X	X	X	X	X	X	X	X	
Review Inclusion/Exclusion Criteria	X													
Review Medical History	X													
General Procedures														
Brief Physical Examination				X						X				
Complete Physical Examination	X												X	
Body Weight	X			X		X	X	X		X	X		X	Refer to Section 5.9.1
Blood Pressure and Heart Rate	X			X		X	X	X		X	X		X	Refer to Section 5.3.9
ECG	X												X	
Review concomitant medications/procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 5.1-2: Flow chart for Protocol MB102229 - 24-week Double-blinded Short-term Treatment Period

Procedure	24-week Double-blinded Short-term Treatment Period													Notes
	Day 1[a]	Day 2 (Phone Visit)	Day 4 (Phone Visit)[b]	Week 1[b]	Day 10 (Phone Visit)[b]	Week 2[c]	Week 4[c]	Week 8[c]	Week 10[c]	Week 12[d]	Week 18[c]	Week 22[c]	Week 24/Early Termination Visit for Short Term[e]	
Insert/calibrate CGM									X[f]			X[f]		Please refer to Section 5.9.4.3
CGM Data Collection, data upload, and review	X									X[f]			X[f]	Please refer to Section 5.9.4.3
Record Meals for7 days - Second week of CGM.										X[f]			X[f]	Please refer to Section 5.9.4.3
6-point SMBG profiles	X									X[f]			X[f]	Please refer to Section 5.9.4.2 in protocol
Provide Dietary and Exercise Counseling	X			X		X	X	X		X	X		X	
Dispense subject diaries and - provide instructions	X			X		X	X	X	X	X	X	X	X	At Day 1, collect Lead-In Period diaries and dispense the first diaries in the Short Term Treatment Period.

Table 5.1-2: Flow chart for Protocol MB102229 - 24-week Double-blinded Short-term Treatment Period

Procedure	24-week Double-blinded Short-term Treatment Period													Notes
	Day 1[a]	Day 2 (Phone Visit)	Day 4 (Phone Visit)[b]	Week 1[b]	Day 10 (Phone Visit)[b]	Week 2[c]	Week 4[c]	Week 8[c]	Week 10[c]	Week 12[d]	Week 18[c]	Week 22[c]	Week 24/Early Termination Visit for Short Term[e]	
Re-dispense Blood Glucose and Ketone Strips & provide retraining as needed	X						X	X		X	X		X	
Review subject diaries	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adjust Insulin Dose, as needed	X[g]	X	X	X	X	X	X	X	X	X	X	X	X	
Collection of Double-blinded short-treatment period diaries. Dispense long-term treatment period diaries.													X	
Administer EQ-5D-3L and DTSQs	X												X	Completed prior to any other procedure. For Day 1 visit assessment to be completed prior to first dose
Safety Assessments[h]														
Assess Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 5.1-2: Flow chart for Protocol MB102229 - 24-week Double-blinded Short-term Treatment Period

Procedure	24-week Double-blinded Short-term Treatment Period													Notes
	Day 1[a]	Day 2 (Phone Visit)	Day 4 (Phone Visit)[b]	Week 1[b]	Day 10 (Phone Visit)[b]	Week 2[c]	Week 4[c]	Week 8[c]	Week 10[c]	Week 12[d]	Week 18[c]	Week 22[c]	Week 24/Early Termination Visit for Short Term[e]	
Assess Hypoglycemia Episodes	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assess DKA	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Assessments														
Pregnancy test (urine) WOCBP only	X						X	X		X	X	X	X	Home pregnancy test kits sent to home with WOCBP subjects to perform monthly pregnancy tests between visits and record results
Blood Standard Safety Laboratory Panel	X						X	X		X	X		X	
Urine Standard Safety Panel	X						X	X			X			

Table 5.1-2: Flow chart for Protocol MB102229 - 24-week Double-blinded Short-term Treatment Period

Procedure	24-week Double-blinded Short-term Treatment Period													Notes
	Day 1[a]	Day 2 (Phone Visit)	Day 4 (Phone Visit)[b]	Week 1[b]	Day 10 (Phone Visit)[b]	Week 2[c]	Week 4[c]	Week 8[c]	Week 10[c]	Week 12[d]	Week 18[c]	Week 22[c]	Week 24/Early Termination Visit for Short Term[e]	
Spot Urine for glucose, albumin and creatinine quantification and determination of Glucose: Creatinine and Albumin:Creatinine ratios	X									X	X		X	
FPG	X			X						X			X	
FFA	X												X	
A1C							X	X		X	X		X	
Fasting Serum Lipids	X									X			X	
Pharmacokinetic sampling	X									X	X		X[i]	Refer to Section 5.5
Pharmacogenetics (DNA) blood sample	X													Details are provided in Amendment #1. This amendment will need separate regulatory approval and informed consent. Refer to Section 5.6

Table 5.1-2: Flow chart for Protocol MB102229 - 24-week Double-blinded Short-term Treatment Period

Procedure	24-week Double-blinded Short-term Treatment Period													Notes
	Day 1[a]	Day 2 (Phone Visit)	Day 4 (Phone Visit)[b]	Week 1[b]	Day 10 (Phone Visit)[b]	Week 2[c]	Week 4[c]	Week 8[c]	Week 10[c]	Week 12[d]	Week 18[c]	Week 22[c]	Week 24/Early Termination Visit for Short Term[e]	
Clinical Drug Supply														
Randomize	X													
Dispense Study Drug	X						X	X		X			X	
Contact IVR system	X						X[j]	X[j]		X[j]			X[j]*	*Also, call if subject is having an early termination visit
Review Study Medication Compliance	X			X		X	X	X		X	X		X	
Review study drug dosing		X	X		X									

[a] Day 1 visit should be within 56 days +/- 5 days of the Week -8 visit. If a retest of A1C is done at week -1, a 7 day window (added to the current lead-in period window of 56 ± 5 days) will be allowed.

[b] Visits may be scheduled ± 1 day to allow flexibility of scheduling

[c] Visits may be scheduled ± 3 days to allow flexibility of scheduling.

[d] Week 12 visit should be scheduled at least 14 days after Week 10 visit in order to collect a full 14-day CGM data, but not longer than 17 days. Sensors need to be changed 7 days after insertion. Subjects will be trained at week-1 visit to change sensor. An ad-hoc visit may be performed if assistance is needed. If subject performs sensor change on their own, site should call to remind subject to change sensor 7 days after insertion

[e] Week 24 visit should be scheduled at least 14 days after Week 22 visit in order to collect a full 14-day CGM data, but not longer than 17 days. Sensors need to be changed 7 days after insertion. Subjects will be trained at week-1visit to change sensor. An ad-hoc visit may be performed if assistance is needed. If subject performs sensor change on their own, site should call to remind subject to change sensor 7 days after insertion.

[f] If a randomized subject terminates the study any time prior to the week 24 visit, the CGM, Recording Meals, and 6-point SMBG will not be required for the early termination visit. However, CGM, Recording Meals, and 6-point SMBG are expected to be performed at week 12 and week 24 off treatment visits, if the subject decides to continue with the study procedures

[g] For Day 1 visit - it will be recommended that subjects reduce their daily insulin dose by up to 20% for both basal and bolus insulins after first dose of study drug although in some cases it may be necessary to reduce insulin (particular basal insulin) in advance of study drug administration

[h] These safety assessments; review of Adverse Events, Hypoglycemia events, and DKA episodes to be performed throughout the study according to the visit schedule as noted via "X".

[i] The pharmacokinetic sample should be collected if the visit is being used as an early termination visit or if it is the subject's regularly scheduled week 24 visit and the subject is currently on study medication. In the event the subject discontinued study medication but is continuing in the study, any PK samples required at visits should not be done

[j] If visit is during the "off-treatment" or the Post Study Drug Study Follow-up phase (Section 3.6), the IVRS does not have to be contacted

Table 5.1-3: Flow chart for Protocol MB102229 - 28-week Subject and Site Blinded Long-term Treatment Period						
Procedure	28-week Subject and Site blinded Long-term Treatment Period					Notes
	Week 32[a]	Week 40[a]	Week 48[a]	Week 52[a]/Early termination visit for long term	Week 56[a]/ Post treatment follow-up (for both and short term and long term period)	
Eligibility Assessments						
Subject Reports to Site	X	X	X	X	X	
General Procedures						
Brief Physical Examination		X			X	
Complete Physical Examination				X		
Body Weight	X	X	X	X	X	Refer to Section 5.9.1
Blood Pressure and Heart Rate	X	X	X	X	X	Refer to Section 5.3.9
ECG				X		
Review concomitant medications/procedures	X	X	X	X	X	
Provide Dietary and Exercise Counseling	X	X	X	X		
Dispense study diaries and provide instructions	X	X	X	X		
Re-dispense Blood Glucose and Ketone Strips & provide retraining as needed	X	X	X	X		
Review subject diaries	X	X	X	X	X	
Adjust Insulin Dose, as needed	X	X	X	X		
Collection of Long-term treatment period diaries					X	

Table 5.1-3: Flow chart for Protocol MB102229 - 28-week Subject and Site Blinded Long-term Treatment Period						
Procedure	28-week Subject and Site blinded Long-term Treatment Period					Notes
	Week 32[a]	Week 40[a]	Week 48[a]	Week 52[a]/Early termination visit for long term	Week 56[a]/ Post treatment follow-up (for both and short term and long term period)	
Administer EQ-5D-3L and DTSQs				X		Complete prior to any other procedures
Safety Assessment[b]						
Assess Adverse Events	X	X	X	X	X	
Assess Hypoglycemia Episodes	X	X	X	X	X	
Assess DKA	X	X	X	X	X	
Laboratory Assessments						
Pregnancy test (urine) WOCBP only	X	X	X	X	X	Home pregnancy test kits and pregnancy logs sent home with WOCBP subjects to perform monthly pregnancy tests between visits and record results in log book.
Blood Standard Safety Laboratory Panel		X		X	X	
Urine Standard Safety		X		X	X	
Spot Urine for glucose, albumin and creatinine quantification and determination of Glucose: Creatinine and Albumin:Creatinine ratios				X	X	
FPG				X	X	

Table 5.1-3: Flow chart for Protocol MB102229 - 28-week Subject and Site Blinded Long-term Treatment Period

Procedure	28-week Subject and Site blinded Long-term Treatment Period					Notes
	Week 32[a]	Week 40[a]	Week 48[a]	Week 52[a]/Early termination visit for long term	Week 56[a]/ Post treatment follow-up (for both and short term and long term period)	
A1C	X	X	X	X	X	
Clinical Drug Supply						
Dispense Study Drug	X	X				
Contact IVR system	X[c]	X[c]		X[c]*		*Also, call if subject is having an early termination visit
Review Study Medication Compliance	X	X	X	X		

[a] Visits may be scheduled ± 5 days to allow flexibility of scheduling with the exception of Week 56 visit. Week 56 visit cannot be scheduled earlier than 30 days of week 52 visit or last dose of study drug but can have a longer window of 5 days.

[b] These safety assessments; review of Adverse Events, Hypoglycemia events, and DKA episodes, to be performed throughout the study according to the visit schedule as noted via "X".

[c] If visit is during the "off-treatment" or the Post Study Drug Study Follow-up phase (Section 3.6), the IVRS does not have to be contacted

5.1.1 Retesting During Screening or Lead-in Period

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

Any new result will override the previous result (ie, the most current result prior to Randomization) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

Retesting is limited to A1C and free T4 as described in Section 3.3.

5.2 Study Materials

BMS will supply the sites with the following materials:

- Blood glucose/ketone meters. One (1) meter will be provided to each study subject at lead-in and one (1) meter will be provided to each investigative site.
- Glucose and ketone test strips
- Lancets
- Glucose control solutions
- CGMS devices and software to download data
- Subject education and site support materials (eg, CGMS instruction manuals)
- Electronic Case Report Forms (eCRFs) [Serious Adverse Events Forms, Pregnancy Surveillance Forms, Events of Special Interest]
- Subject Alert Cards
- Study drug inventory control forms
- Site File
- Subject Diary:
  - Full Diary review by site staff is required for this study during each visit.
  - Use of subject diaries are mandatory for the study and will be maintained by each study subject for documentation of 6-point SMBG results and SMBGs from Day 1 visit to Week 2 visit, insulin doses, meal times during specific weeks of CGM monitoring, day/time of CGM sensor insertion if performed at home at Weeks 11 and 23, study medication dosing, ketone testing, DKA symptoms, hypoglycemia episodes, and if applicable WOCBP urine pregnancy results.
    - 6-point SMBG profiles:
      Subject will be instructed to perform and record in their diaries the results for their 6-point SMBG profiles taken on any 3 days within a week before Week -4 visit, Day 1 visit, Week 12 visit, and the Week 24 visit. The 6-points consist of the following; 3 glucose measurements obtained preprandially (within 15 minutes prior to meal) and 3 glucose measurements obtained postprandially (1.5 - 2 hours after the start of the meal) for the 3 main meals of the day. eCRF pages will be provided via electronic data capture (EDC) system to the sites so they can record the data obtained from the diaries into the study database.
    - SMBG:
      Subject will be instructed to perform and record in their diaries the results for at least 4-time self monitored glucose values (before breakfast, lunch, dinner, and bedtime)

every day during the first two weeks after randomization (Day 1 visit to Week 2 visit).

- Subjects are to be instructed to document their insulin dose in their study diaries during the protocol defined time period as outlined in Section 5.3.4. eCRF pages will be provided to the sites so they can record the data obtained from the diaries into the study database.
  - 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 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 diary completion should be assessed and re-enforced at every visit.
- Subjects are to record their meal times in their diary during the following time periods;
  - Week -1 to Day 1 prior to randomization
  - Week 11 to Week 12
  - Week 23 to Week 24
- Subjects are to record day and time of CGM sensor insertion if performed at home at week 11 and week 23
- The dates, time, and number of tablets of study medication taken by the subject are to be recorded in the study diary. eCRF pages will be provided to the sites so they can record the data obtained from the diaries into the study database
- Subjects are to record any hypoglycemic symptoms they may experience and SMBG values if they conducted the test when they have symptoms in their diaries. All events recorded in subject diary to be reviewed by site staff according to Section 5.3.2
- Any ketone testing performed by the subject. Symptoms potentially associated with diabetic ketoacidosis (DKA), and relevant events (Section 5.3.3) are to be recorded in the diary. All results recorded in subject diary to be reviewed by site staff during each study visit. Determination of a DKA event must be assessed and documented by the Principal Investigator or by a qualified sub-investigator.

- Any other materials as locally required or agreed upon.

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

5.3 Safety Assessments

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

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

5.3.1 Imaging Assessment for the Study

Not applicable.

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

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

5.3.2.1 Self Monitored Blood Glucose (SMBG)

Combination glucose and ketone meters will be supplied to each study site. At the entry into the lead-in period, subjects will receive a glucose and ketone meter, supplies and instruction on their use. Testing supplies will be provided to allow for blood glucose and ketone testing for the duration of the study. Subjects should bring their glucose meter with them to each study visit to ensure that it is functioning properly and for review of SMBG results. Subjects may keep the glucose meters at the end of the study. It is strongly preferred that subjects use the meter provided by the Sponsor. If a subject uses another meter to perform this test, these results will be captured on the eCRF page.

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 to contact the Investigator in the event of an unusually high or low blood glucose value. In addition, study subjects should comply with site's instructions with regard to self-monitoring of blood glucose and insulin adjustments accordingly and should report to the site blood glucose values and/or signs and symptoms suggestive of a hypoglycemia episode.

Subjects should attempt to enter all valid SMBG values into the CGM in order for the calibration of the system.

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

5.3.2.2 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 any hypoglycemic symptoms in their diaries. They should be encouraged to measure, when possible, their blood glucose values when they have symptoms of hypoglycemia. Subjects should carry 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 diary and for determining if they meet the clinical definition of hypoglycemia. Only symptoms and/or blood glucose values deemed by the Investigator to meet the definition of hypoglycemia should be reported on the hypoglycemia eCRF pages. Signs and symptoms of hypoglycemia, hypoglycemia episode or discontinuation due to hypoglycemia should not be reported on the AE eCRF page, unless the event fulfills protocol criteria for a Serious Adverse Event (see Section 6.1.1) in which case an SAE form must be completed in addition to the hypoglycemia eCRF pages for hypoglycemia.

5.3.3 Self-Monitored Blood Ketone Testing and Guidance on Management and Reporting of Diabetic Ketoacidosis Episodes

DKA is an expected event in subjects with type 1 diabetes. Subjects and their family members must be aware of the possibility that DKA may occur and the dangers associated with DKA.

Dapagliflozin reduces blood glucose by urinary excretion of glucose, thus representing a daily removal of a substantial amount of carbohydrate from the body. We estimate (from insulin:carbohydrate ratios) that the amount of glucose excreted in the urine in subjects on dapagliflozin may correspond to the glycemic effect achieved from as much as 20% of a subject's total daily insulin dose and, therefore, insulin dose reductions will have opposite glycemic effects compared to those of dapagliflozin. Furthermore, since DKA is caused by gross insulin deficiency and is mechanistically unrelated to glucose levels per se (as can be seen in euglycemic DKA), reductions in insulin doses of more than 20% are not recommended regardless of glucose values. If subjects have repeatedly low blood glucose and could otherwise not avoid a 20% reduction in total daily insulin dose, they are recommended to increase their daily dietary carbohydrate intake. Similarly, subjects should be reminded that during/after elevated physical activity/exercise, dapagliflozin continues to remove glucose in addition to what is being consumed by the physical activity. Therefore, additional (re-) fueling with carbohydrates is important and should generally be preferred over higher than usual reductions in subjects' insulin doses.

As noted above, subjects will receive a combined glucose and ketone meter and sufficient supplies at the entry into the lead-in period. Subjects will also be trained in the procedure of conducting blood ketone testing according to the manufacture's specifications. Subjects will be advised to measure their blood ketones using the glucose and ketone meter provided by the sponsor when they have potential symptoms/signs of DKA, including but not limited to; excessive thirst, nausea and vomiting, frequent urination, weakness or fatigue, fever, fruity-scented breath, confusion, and/or consistently elevated blood glucose), and/or during acute

illness. Subjects should be instructed to measure their ketones if symptoms occur, regardless of plasma glucose values. Blood ketone test results, symptoms potentially associated with DKA and relevant risk factors (eg, missed insulin injection, insulin pump malfunction, infection, heart attack, etc) should be recorded in the subject diary.

Study subjects must be properly instructed on the recognition and management of DKA. Subjects should contact the site for assistance with diabetes management in the event that they develop such symptoms or when the blood ketone reading is 0.6 mmol/l or above according to the glucose/ketone meter user guide, even if their blood glucose levels are not elevated. The investigator is recommended to advise the subject to take extra insulin and extra carbohydrates if elevated ketones are registered and continue to measure blood ketones. If deemed necessary, dosing of study medication should be interrupted during sick days.The action, follow-up and monitoring plan will be at the discretion of the investigator and will depend on his/her judgment of severity based on signs/symptoms of DKA, risk factors, relevant contributing factors, and blood glucose (with the caveat that the blood glucose may be lower than would be otherwise expected given elevated ketone levels). It is recommended that for subjects who report elevated ketones/ketosis, the investigator considers re-education concerning DKA at the next scheduled visit, at an un-scheduled visit or by telephone contact, as appropriate.

Subjects must also be instructed that if attempts to contact the site are unsuccessful or if they are in urgent need of medical attention, that they should seek medical attention. They should provide information to the health care provider on their participation in a placebo controlled clinical study evaluating the effects of the SGLT2i dapagliflozin in addition to their insulin treatment.

The blood ketone values should be reviewed by the site to identify any unusual high values, and to confirm that the values (from the glucose and ketone meter's memory and/or from the subject's diary) were obtained from the subject. If fingerstick blood ketone values are discordant from glycemic control assessed by the central laboratory or with clinical symptoms, the subject's glucose and ketone meter should be tested and the procedure for using it reviewed with the subject. Investigators will examine if any of the elevated ketone values from the subject's diary are associated with a DKA event. If yes, investigators will document all DKA related symptoms, relevant risk factors, and available laboratory test results (including blood ketone values and blood glucose values measured by the glucose/ketone meter) on the DKA eCRF pages and report this event to the Sponsor. Blood ketone and glucose values associated with events deemed not to be a DKA event should be recorded on the non-DKA eCRF log page.

In addition, the Sponsor will utilize Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) based on a list of pre-defined terms in MedDRA to identify potential DKA events. The list of these terms are included in the Data Monitoring Committee (DMC) Charter. Investigators will further evaluate these cases and if the event is determined to be DKA, the investigator will complete the DKA eCRF.

Regarding the reporting of DKA events, it is important to distinguish ketosis from DKA. Low levels of ketosis, in which blood or urine ketone values are elevated, can occur in individuals who follow a low-carbohydrate, high-fat diet (eg, dietary ketosis) or after prolonged periods of

fasting. However, ketosis is a benign condition if symptoms are absent and the blood pH remains buffered within normal limits (eg, no acidosis). In contrast, DKA episode may be confirmed when subjects have potential symptoms/signs of DKA (polyuria, polydipsia, weight loss, vomiting, abdominal pain, signs of volume depletion on physical examination), marked hyperglycemia, [although DKA has been reported in individuals with normal or mildly elevated plasma glucose levels as well] elevated blood/urine ketone values, and a metabolic acidosis characterized by low arterial blood pH values, decreased serum bicarbonate, and an increased anion gap. The combination of specific symptoms/signs of DKA and elevated blood/urine ketone values may be suggestive of DKA, recognizing that some subjects may not have lab test results (eg, blood gas measurement) to confirm acidosis.

During clinical trials, subjects frequently report symptoms of DKA when asked, even when treated with placebo or medications not otherwise associated with DKA. The Investigator is responsible for questioning the subject about all DKA related symptoms reported on the subject diary and for determining if they meet the clinical definition of DKA. Only the episodes deemed by the Investigator to meet the definition of DKA should be reported on the DKA eCRF pages. Signs and symptoms of DKA, DKA episode or discontinuation due to DKA should not be reported on the AE eCRF page, unless the event fulfills protocol criteria for a Serious Adverse Event (see Section 6.1.1), in which case an SAE form must be completed in addition to the DKA eCRF pages. If a DKA episode occurs in a subject that fails screening, the DKA eCRF pages do not need to be completed. However, if the event meets the protocol criteria for an SAE, the SAE form must be completed. For subjects who experience a DKA it is recommended that the investigator schedules a telephone or site visit for re-education in prevention of ketosis and DKA.

A DKA Adjudication Committee, blinded to the treatment of the subjects, will independently adjudicate all the DKA events reported by the Investigators during the study period. A separate Adjudication Manual will define and describe the procedure for the handling, reporting, and classification of these cases.

The key goals of treating DKA include correcting dehydration, hyperglycemia, and electrolyte imbalance, and identifying and appropriately treating comorbid precipitating events. Subjects with DKA should be carefully monitored until significant improvement in the symptoms, normalization of blood acidity (eg, pH> 7.3), and improvement/absence of ketones in blood or urine.

5.3.4 Insulin Dosing Adjustment and Data Collection 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.

During the lead-in period, subjects will be advised to self-monitor their blood glucose consistent with local treatment guidelines. The method of documentation for glucose results to be based on local clinic practice. Glucose control will be reviewed by the investigator at each visit. Insulin

dose may be adjusted as deemed appropriate to be consistent with good medical practice according to SMBG readings, local guidance and individual circumstances.

It is recommended that subjects reduce their daily insulin dose by up to 20% for both basal and bolus insulins after the first dose of study drug to minimize the risk of hypoglycemia. It is at the discretion of the investigator to determine the extent to which to reduce the insulin doses. In some cases, it may be necessary to reduce insulin (particular basal insulin) in advance of study drug administration. If total daily insulin dose is reduced upon initiation of study medication, attempts must be made to titrate insulin back to baseline total daily insulin dose. It is not recommended to reduce total daily insulin dose by more than 20% compared to baseline at any time during the study unless medically indicated and close attention should be paid, especially in these subjects, to symptoms of, and risk factors for developing DKA (See also Section 5.3.3). Subjects are to be instructed to document their daily individual insulin doses and self-monitor glucose values at least 4-times every day (before breakfast, lunch, dinner, and bedtime) during the first two weeks. This information will be used to facilitate appropriate insulin dose adjustment and ensure subject safety. For the rest of the study period (both short-term and long-term), subjects will be advised to continue self-monitoring their blood glucose as per local guidelines. Glucose control will be reviewed by the investigator at each visit. Insulin dose may be adjusted as deemed appropriate to be consistent with good medical practice according to SMBG readings, local guidance, and individual circumstances. The glycemic control goals may be individualized based upon a subject's personal target and stability of glycemic control at baseline.

Subjects are not allowed to change their insulin administration methods (MDI or CSII) throughout the study unless a subject using an insulin pump needs to replace the pump. Under this situation, the subject may be on temporary use of MDI and should restart CSII administration as early as feasible. The period of time a subject is on temporary use of MDI should not be more than two weeks.

Insulin Dosing Recording

At the following time periods the subjects will be instructed to record all their individual doses of (basal and bolus) insulin in their study diary.

- Week -2 visit to Day 1 visit prior to randomization
- Day 1 visit after randomization to Week 2 visit
- Week 10 visit to Week 12 visit
- Week 22 visit to Week 24 visit

The site will review these diary entries and record the total basal, total bolus, and total pre-mix (if applicable), daily dose of insulin the subject received on the eCRF. For statistical analysis purposes the total daily dose is defined as the sum of all these individual doses of insulin (both basal and bolus) during a 24-hour period.

Subject's daily individual insulin doses and self monitored glucose values collected from Day 1 visit (after randomization) to Week 2 visit will be used to facilitate appropriate insulin dose adjustment and ensure patient safety.

At the following time periods subjects will be instructed to record the basal and bolus insulin dose range taken for each week in their study diary.

- Week -8 visit to Week -2 visit
- Week 2 visit to Week 10 visit
- Week 12 visit to Week 22 visit
- Week 24 visit to Week 56 visit

The site will review these diary entries and record the weekly ranges subject received of insulin on the eCRF.

5.3.5 Guidance on Assessment of Urinary Infections & Hematuria

5.3.5.1 Guidance on Assessment of Urinary Infections

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

Study drug should be withheld in subjects with clinical evidence of upper tract UTI 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 by local laboratory within 7 days of clinical recovery from all treated urinary tract infections. Whether or not additional therapy is prescribed because of culture results should be determined by investigator judgment, after consultation with the Medical Monitor.

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

Asymptomatic Bacteriuria

During enrollment, treatment and follow up of subjects in this trial, the investigator may discover a subject with asymptomatic bacteriuria. Asymptomatic bacteriuria is defined as the presence of ≥ 105 colony forming units/mL of bacteria, in a properly collected voided urine specimen, without signs or symptoms typically attributed to urinary tract infection. Asymptomatic bacteriuria is prevalent among diabetic women, and is associated with pyuria in 70% of cases. Neither guidelines from the US[14,15] nor Europe[16] recommend screening for, or treatment of, asymptomatic bacteriuria in non-pregnant diabetic patients. In this study, the central laboratory will report urinary dipstick test results for hemoglobin but will not routinely report the results of

urinary dipstick tests for leukocyte esterase as a screening test for pyuria in surveillance urine examinations.

5.3.5.2 Guidance on Assessment of Hematuria

During the course of the study, hematuria should be investigated according to local standards and best clinical practices for a possible cause.

If NO common cause is identified, subjects should be further investigated based on American Urological Association (AUA) guidelines or equivalent local standard of care and best practices which could include referral to an urologist and undergoing evaluation that may include abdominal computed tomography (CT), urine cytology, and NMP-22 urine test. The subject should continue to be randomized/receive investigational product treatment during these investigations (unless otherwise contraindicated).

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

5.3.6 Guidance on Assessment of Cardiovascular Events

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

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

Death, including:

- Cardiovascular Death
- Non-cardiovascular Death

Myocardial Infarction (MI), including:

- ECG and/or cardiac enzymes confirmed MI
- Sudden death
- Percutaneous Coronary Intervention (PCI)-related MI
- Coronary Artery Bypass Graft (CABG)-related MI
- MI diagnosed via pathologic criteria
- Silent MI

Fatal and Non-fatal Stroke, including:

- Ischemic Stroke
- Hemorrhagic stroke

Serious Adverse Events of the following:

- Heart failure
- Cardiac arrhythmia
- Unstable angina
- Unplanned arterial revascularization (coronary, carotid and peripheral)
- Cardiac arrest with successful resuscitation
- Deep vein Thrombosis and Pulmonary Emboli
- Systemic non-stroke 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 Adjudication Reference Manual for Primary Investigators and Study Staff.

5.3.7 Guidance on Assessment of Hepatic Laboratory Abnormalities

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

- AST and/or ALT > 3x ULN and TB > 2 ULN (within 14 days of the AST and/or ALT elevation)
- Hepatic events timely related to death (within 30 days before death)
- AST and/or ALT > 10x ULN

Hepatic disorders leading to discontinuation from study drug and/or death

Liver laboratory abnormalities such as elevated AST and/or ALT with or without TB Elevations

A separate Adjudication Charter 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 Investigator's clinical judgment. Subjects who experience ALT and/or AST values > 3X ULN confirmed with a repeated test will have the following performed within 3 days of the confirmed laboratory results:

- AE assessment
- Physical examination for jaundice and other signs of liver diseases
- Review of relevant risk factors and current history focusing on possible causes of the increased ALT and/or AST and/or 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) -
  - should only be done once for elevated liver enzymes per Appendix 3 Sustained Elevated Liver Safety Abnormalities Flow Chart unless liver discontinuation panel is required

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

For subjects who are discontinued from study medication as a result of sustained elevated liver safety abnormalities, as described in Section 3.5, additional blood sampling must be done within 3 days of the confirmed laboratory results (see Appendix 3), in conjunction with an Early Treatment Discontinuation (End-of-Treatment) visit, in addition to the procedures noted above. A referral consultation to a hepatologist or gastroenterologist (specializing in liver abnormalities) should be obtained. Any additional tests and/or examinations should be carried out at the discretion of the Investigator. Any further investigations and laboratory results for subjects with abnormal laboratory values at the follow-up visit should be made available to the Sponsor upon request.

5.3.8 Physical Examination

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

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

5.3.9 Blood Pressure and Heart Rate

Blood pressure (BP) and heart rate (HR) measurements must be taken consistently throughout the study. Use only either the right or the left arm when measuring these parameters. Document which arm was used along with the observer's initials; the same arm should be used at each visit. The subject should be in a seated position allowing at least 5 minutes of rest before measurement. BP should be measured with the subject's arm resting on a table, and with subject's back supported and feet flat on the floor.

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

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

5.3.10 Electrocardiograms

ECGs will be performed at Screening visit, Day 1 visit, Week 24/ET visit, and Week 52/ET visit. 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

One original ECG print-out should be kept in the medical chart and ensure a copy, assessed, initialed and dated by the investigator, is maintained in the source documents for the study.

5.3.11 Guidance on Volume Depletion

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

5.3.12 Guidance on Monitoring Renal Function

Creatinine clearance (CrCl, based on Cockroft-Gault) ≥ 45 ml/min and < 60 ml/min

- At all scheduled and unscheduled visits, patients should be asked for symptoms of volume depletion, as well as other AEs, and vital signs should be assessed (including blood pressure measurement).
- Renal function should be monitored by central lab at all scheduled and unscheduled visits.

Creatinine clearance (CrCl, based on Cockroft-Gault) ≥ 30 ml/min and < 45 ml/min

- If the creatinine clearance (CrCl,based on Cockroft-Gault) falls below 45 ml/min, the subject should be scheduled for a re-test with 4 days, whenever possible
  - If the re-test CrCl (based on Cockroft-Gault) is ≥ 45 ml/min the subject can resume the normal visit schedule.
  - If re-test CrCl is still < 45 ml/min, the investigator should consider re-testing CrCl within one to two weeks, whenever possible.
- In addition, the investigator should consider evaluating the subject for potentially reversible causes of renal dysfunction including: concurrent use of NSAIDS, antibiotics, or other medications known to affect creatinine clearance; volume depletion; urinary tract infection and obstructive uropathy. Further re-testing and evaluation should be done every second week until stabilization.

Creatinine clearance (CrCl, based on Cockroft-Gault) < 30 ml/min

See Section 3.5 for re-testing instructions and possible need for study medication discontinuation.

Any subject that is discontinued from study medication due to deterioration in renal functions should be monitored closely by the investigator until abnormalities stabilize and the subject is asymptomatic.

5.3.13 Supplemental Visits

5.3.13.1 Early Treatment Discontinuation Visit

Subjects discontinued from the double-blinded short-term treatment period

Any subject who discontinues study medication during the 24-week double-blinded short-term treatment period must have the Week 24/Early Termination (ET) visit completed. The Week24/ET visit eCRF will also need to be completed and a Week 24/ ET visit laboratory kit will need to be used to collect ET Visit blood and urine samples. The IVRS must be called to record the subject status (ie, discontinuation status).

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

Any subject who discontinues study medication during the 28-Week subject and site blinded long-term treatment period must have the Week 52/Early Termination (ET) visit completed. The IVRS must be called to record the subject status (ie, discontinuation status). The Week 52/ET visit eCRF will also need to be completed and a Week 52/ET visit laboratory kit will need to be used to collect ET Visit blood and urine samples.

5.3.13.2 Early Treatment Discontinuation Follow-up (Off Treatment Procedures)

As noted in Section 3.6, all subjects who discontinue investigational product in the 24 week double-blinded short term treatment period or in the subject and site blinded long-term treatment period are expected to continue study participation for each scheduled visit for the remaining length of the study and complete all procedures as outlined in Section 5 study flowchart with the

exception of study drug management and PK sampling. If continued study participation according to the protocol schedule is not possible, the investigator should contact the subject to discuss alternatives (eg, return to the clinic 4 weeks/at least 30 days after discontinuation of study drug to perform the week 56 post treatment follow-up procedures as outlined in Section 5 study flowchart or be contacted by telephone 30 days after discontinuation of study drug to evaluate the following safety assessments: Adverse Events, Hypoglycemia events, and DKA episodes. Please note that after the discontinuation of study drug, management of the subject's diabetes would be under the care and direction of the investigator and/or subject's healthcare providers.

Please utilize the post treatment follow up pages in the eCRF post treatment section for this data completion.

5.3.13.3 Other Supplemental (Unscheduled) Visits

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

5.4 Efficacy Assessments

The procedures described in the sections that follow will be completed to capture information for efficacy assessments.

5.5 Pharmacokinetic Assessments

Plasma samples for analysis of dapagliflozin will be obtained on Day 1 visit at 60, 90 and 180 minutes post-dose. Additionally, PK samples will be obtained prior to dosing at Week 12 visit, Week 18 visit and Week 24 visit.

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

5.6 Pharmacogenomic/Pharmacogenetic Assessments

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

5.7 Biomarker Assessments

Not applicable.

5.8 Outcomes Research Assessments

Patient reported outcomes (PROs) will be assessed at day 1 visit, (prior to first dose), week 24 visit, and week 52 visit by EQ-5D-3L for generic health status and DTSQs for treatment satisfaction. The instruments/questions will be self-administered using paper and pencil questionnaires. The EQ-5D-3L is a generic, preference-based utility questionnaire and consists of two parts, the EQ VAS and the EQ-5D-3L index. The EQ VAS is a visual analogue scale ranging from 0 = worst possible health to 100 = best possible health. The EQ-5D-3L index is a five dimension questionnaire. The dimensions consist of mobility, self-care, usual activity,

pain/discomfort and anxiety/depression. Each item has three levels: no problems, some problems and severe problems. The Diabetes Treatment Satisfaction Questionnaire (DTSQ) has been developed to assess patient´s satisfaction with treatment and perception of change in hyper- and hypoglycemia.[17] The DTSQ status version (DTSQs) has 8 items.

PROs will be filled out prior to any other site activities and encounters with physician. The subjects will be instructed to complete the PRO questionnaires independently. The site will have a designated quiet space for subjects to use when completing the assessments. Each center should allocate responsibility for PRO assessment to a specified individual (eg, a research nurse). The research nurse or appointed individual should stress the information is confidential.

It is important that the value and relevance of health related quality of life (HRQoL) data are explained carefully to participating subjects so that they are motivated to comply with data collection. The research nurse or appointed individual should also stress that the information is confidential. Therefore, if the subject has any medical problems s/he should discuss them with the doctor or research nurse separately from their PRO assessment.

The instructions for completion of questionnaires are:

- It should be completed before any investigations or discussions about the status of the subject's disease with the clinic staff.
- The subject should complete it her/himself without any intervention from family, friends, center staff etc.
- Only one answer to every question should be checked.
- Center personnel should not review the responses to the questionnaire with the subject or with any other center staff.

Following completion, the nurse or appointed individual may quickly scan the questionnaire visually for completeness and should confirm verbally with the subject that the questionnaire has been completed fully.

5.9 Other Assessments

5.9.1 Weight

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

5.9.2 Height and Body Mass Index (BMI)

- Measurement of height should be performed with the subject's shoes removed. The subject's knees should be straightened, head held erect and eyes forward
- BMI is used as an index of obesity and is a method of defining normal body weight and excess body fat. BMI is determined by weight (kg) divided by height (m) squared.

Method of BMI Calculation:

- Use actual height and weight
- To calculate BMI:
  - convert pounds (lbs) to kilograms (kg = lb / 2.2)
  - convert inches (in) to meters (in X 0.0254)
  - BMI = (weight in kg) / (height in meters) ^{2}

5.9.3 Diet and Exercise Counseling

Starting at entry into the lead-in period (Week -8 visit), subjects will be instructed on a diet and an exercise program in accordance with the ADA or similar local guidelines to be followed for the study duration.

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

5.9.4 Pharmacodynamic Assessments

5.9.4.1 Fasting Plasma Glucose

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

5.9.4.2 6-point SMBG profiles

Subjects will be instructed to perform 6-point SMBG profiles as described below. It is strongly preferred that subjects use the meter provided by the Sponsor. If a subject uses another meter to perform this test, the site must try to determine the medium that the meter reports in (ie, plasma glucose vs. whole blood glucose). This information and results will be captured on an eCRF page. If subjects do not use the meter provided by the Sponsor, they should be instructed to continue using the same meter for all subsequent visits to avoid increasing variability.

Profiles will be obtained on any 3 days within a week before the Week -4 visit, Day 1 visit, Week 12 visit, and Week 24 visit, according to the schedules presented in study flow chart/time and event schedule (see Section 5.1). Each separate 6-point SMBG profile encompasses 1 day within one week before the scheduled visits, with 3 glucose measurements obtained preprandially (within 15 minutes prior to meal) and 3 glucose measurements obtained postprandially (1.5 - 2 hours after the start of the meal) for the 3 main meals of the day. Subjects will be provided with a diary to record these SMBG measurements and mealtimes, and eCRFs will be available for the investigator sites to capture these results.

If a lead-in subject fails prior to the Day 1 visit, the 6-point SMBG profile will not be required between the week -1 visit and the Day 1 visit.

If a randomized subject terminates the study any time prior to the week 24 visit, the 6-point SMBG profile will not be required for the early termination visit However, 6-point SMBG is expected to be performed at week 12 and week 24 off treatment visits, if the subject decides to continue with the study procedures.

5.9.4.3 Continuous Glucose Monitoring (CGM)

CGM 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. CGM will be used periodically to measure the subject's interstitial glucose level according to the schedule presented in study flow chart/time and event schedule (see Section 5.1).

A CGM sensor will be inserted subcutaneously at the site on Week - 2 visit, at Week - 1 visit (and removed prior to first dose on Day 1 visit), at Week 10 visit, and at Week 22 visit to allow monitoring for a two week time period. Example: Week -2 visit to Day 1 visit (as baseline), Week 10 visit (the Week 10 office visit) until the Week 12 office visit, and Week 22 visit (the Week 22 office visit) until the Week 24 office visit. During the following periods (Week -1 visit to Day 1 visit, Week 11 visit to Week 12 visit, and Week 23 visit to Week 24 visit), subjects will document their three main meal times in the diary every day. Subjects should be trained to perform sensor replacement at Week-1 visit. In addition, at Week -1 visit, sites should upload the sensor data to check subject's compliance with wearing the device.

The sensor requires at least one SMBG value to be entered every 12 hours for calibration during use. At a minimum, a SMBG value obtained in the morning (eg, fasting or pre-breakfast measurement) should be entered, as well as a value in the evening (eg, pre- or post-dinner measurement). Subjects may be instructed to use results from the 4 daily SMBG measures to fulfill these criteria. Every seven (7) days the sensor needs to be replaced and subjects can return to the site for assistance on this if needed. If the subject needs assistance with sensor replacement, an ad-hoc visit should be performed, if this occurs a data upload is also recommended at this time. If subjects opt to perform sensor replacement at home sites should call subject 7 days after insertion as a reminder. Please refer to the Sweet Spot Manual for further instructions on data uploads during an ad hoc visit.

The data will remain blinded to the subject, the investigator, and to the Sponsor during the recording and will be downloaded into a data file. The downloaded file should be printed and reviewed by the site for review of monitoring compliance. **The subjects should make every attempt to be at ≥ 100% compliance with use of device.** If a subject is not compliant the reason should be discussed with the subject, documented in source notes, and the subject should be re-educated about importance of CGM compliance.

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

If a subject uses a CGM device prior to entry into the study, he/she 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 CGM device according to protocol procedures.

If a lead-in subject fails lead-in prior to the Day 1 visit, the CGM will not be required to be completed between the week-2 visit and the Day 1 visit. In addition, the meal recording for 7 days will not be required between the week -1 visit and the Day 1 visit.

If a randomized subject terminates the study any time prior to the week 24 visit, the CGM and meal recording for 7 days during the second week of CGM will not be required for the early termination visit. However, CGM and meal recording is expected to be performed at week 12 and week 24 off treatment visits, if the subject decides to continue with the study procedures after discontinuation of study drug.

5.10 Results of Central Laboratory Assessments

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

During the short-term double-blinded short-term treatment period, (Day 1 visit to Week 24 visit), the HbA1c values, continuous glucose monitoring values, and urinary glucose values, including spot urine for glucose, albumin and creatinine quantification, determination of glucose: creatinine and albumin:creatinine ratios, and urine glucose dipstick values, will be masked to the Sponsor and will not be available to the investigator.

During the subject and site blinded long-term treatment period, (after week 24 visit through week 56 visit), the above measurements will be unmasked to the Sponsor. These values will still not be available to the investigator, except for the HbA1c values, until after the study completion. HbA1c values will be provided to the investigator during the subject- and site-blinded long-term treatment period.

6. ADVERSE EVENTS

An *Adverse Event (AE)* is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation subject administered 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 (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

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

> Related: There is a reasonable causal relationship between study drug administration and the AE.

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

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

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

6.1 Serious Adverse Events

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

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

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

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for additional information on 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 an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)

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

6.1.1 Serious Adverse Event Collection and Reporting

Section 2.8.1 and Table 3 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing.

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

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

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

SAEs, whether related or not related to study drug, and pregnancies must be reported to AstraZeneca or it's designee within 24 hours. SAEs must be recorded on the SAE Report Form and 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: AEMailboxClinicalTrialTCS@astrazeneca.com

SAE Facsimile Number:

- (Sweden)
- (UK)
- (Germany)
- (US)

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

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

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

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to AstraZeneca 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 and for those present at the end of study drug 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.

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

6.3 Laboratory Test Result Abnormalities

The following laboratory test result 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 test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

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

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives (approximately 3 days) after product administration, the investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and

forward a Pregnancy Surveillance Form to AZ (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

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

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

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

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 BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

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

6.6 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

1) Aminotransferase (ALT or AST) elevation > 3 x upper limit of normal (ULN)
   AND
2) Total bilirubin (TB) > 2 x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
   AND

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

6.7 Other Safety Considerations

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

6.7.1 AEs of Special Interest

Event categories of special interest for this study may include, but are not limited to, hypoglycemia, fractures, hepatobiliary, genital infections, urinary tract infections, volume depletion, worsening renal function, hypersensitivity, and DKA.

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

Liver test abnormalities accompanied by jaundice or hyperbilirubinemia

This category of events include all AEs where hepatocellular damage (with elevations of ALT or AST > 3x ULN) is combined with hepatic dysfunction (with elevation of total bilirubin > 2x ULN) or jaundice. With respect to LFT abnormalities, both central-lab results and adverse events will be monitored.

For each non-serious event in this category, notify the Medical Monitor within 24 hours to discuss next steps in reporting.

7. DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

7.1 Cardiovascular Adjudication Committee

An Independent Adjudication Committee, blinded to the treatment of subjects, will classify cardiovascular adverse events, such as, but not limited to, death, myocardial infarction, and stroke reported in the study (see Section 5.3.6 for more details).

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

7.2 Hepatic Adjudication Committee

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

- AST and/or ALT > 3X ULN and TB > 2 X ULN (within 14 days of the AST and/or ALT elevation)
- Hepatic events timely related to death (within 30 days before death)
- AST and/or ALT > 10X ULN

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

7.3 DKA Adjudication Committee

A DKA Adjudication Committee, blinded to the treatment of the subjects, will independently adjudicate all the DKA events reported by the Investigators during the study period.

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

7.4 Data Monitoring Committee

An external data monitoring committee (DMC) with multidisciplinary representation will be established to evaluate on a periodic basis the incidence of hypoglycemia and DKA events, as well as AEs, laboratory measurements, and safety assessments to ensure the ongoing safety of study subjects. An independent reporting statistician not involved in the conduct of the study will be designated by BMS to provide the DMC with essential safety data during the study.

The DMC responsibilities, authorities, and procedures will be documented and followed according to the DMC charter.

8. STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The primary endpoint is the change from baseline in HbA1c to the Week 24 visit.

With 243 subjects per treatment group with both baseline and at least one post baseline measurement, there is approximately 90% power to detect a difference in means of 0.35% between each dapagliflozin treatment group and placebo at the two-sided 0.0262 significance level (based on Dunnett and Tamhane step-up procedure), assuming a standard deviation (SD) of 1.1%. Assuming that 5% of subjects do not have a post-baseline assessment, a total of 768 subjects (256 subjects per treatment arm) need to be randomized to each dapagliflozin or placebo group in 1:1:1 ratio. In light of a randomization system error that affected the first 55 randomized subjects, the randomization target was increased by 55 in order to maintain the power for the primary endpoint as these 55 subjects will be excluded from the primary efficacy analysis. Thus, the total number of subjects to be randomized in the study will be 823.

A reduction in the primary endpoint of change from baseline in HbA1c of 0.35% was used to determine the sample size, as this represents a clinically meaningful improvement in glycemic control under the current study design with adjustable background insulin dose. A lesser degree of reduction in HbA1c in combination with other beneficial outcomes in secondary endpoints may also be clinically important.

8.2 Populations for Analyses

8.2.1 Definition of Analysis Datasets

The following datasets will be used for analyses:

- **Enrolled subjects dataset**: The enrolled subjects dataset includes data collected from all subjects who signed informed consent.
- **Lead-in subjects dataset**: The lead-in subjects dataset includes data collected from all subjects who have at least one vital sign measurement during the lead-in period.
- **Full analysis dataset**: The full analysis dataset will consist of all randomized subjects who took at least one dose of double-blind study medication during the short-term double-blind period. The first 55 randomized subjects will be excluded from the full analysis dataset due

to the presence of a randomization system error. Whenever using the full analysis dataset, subjects will be presented in the treatment group to which they were randomized at the start of the short-term double-blind treatment period (even if the treatment they received was different).

- **Evaluable subjects dataset**: The evaluable subjects dataset will be a subset of the full analysis dataset through exclusion of subjects with important protocol deviations. Important protocol deviations are those that have the potential to impact the results of the primary analysis. Detailed exclusion criteria for the evaluable subjects dataset will be specified in the SAP. All decisions to exclude subjects from the full analysis dataset to form the evaluable subjects dataset will be made prior to the unblinding of the study
- **Treated subjects dataset**: The treated subjects dataset consists of all subjects who received at least one dose of double-blind study medication during the short-term double-blind treatment period. The treated subjects dataset would include any subject who accidentally received double-blind study medication but was not randomized in the study. These subjects will be included in analyses using the treated subject dataset in the treatment they received. For randomized subjects, all analyses using the treated subject dataset 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 the case where 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.
- **Short-term completers dataset**: The short-term completers dataset will consist of all subjects in the full analysis dataset who completed the short-term double-blind treatment period. Whenever using the short-term completers dataset, subjects will be presented in the treatment group to which they were randomized at the start of the short-term double-blind treatment period (even if the treatment they received in the short-term or long-term was different).

Efficacy analyses will be performed using the full analysis dataset, which is considered as the primary efficacy dataset. Primary efficacy analysis will be reanalyzed using the evaluable subjects' dataset if more than 10% of the subjects in any treatment group are found to significantly violate the terms and conditions of the protocol. Otherwise, efficacy analysis will be restricted to the primary efficacy dataset.

Safety analyses will be based on the treated subjects dataset which consists of all subjects who received at least one dose of double-blind study medication.

8.2.2 Randomization System Error

At the beginning of the trial, the IVRS randomization system failed to map the randomization schedule to the correct treatment groups. This randomization system error caused some of the first 55 randomized subjects to be assigned to and receive treatment that was different from the intended treatment as per the randomization schedule. The discovery of this error was triggered by the DMC's query concerning an apparent imbalance in treatment allocation. The investigation into this error was conducted by IVRS behind the firewall without compromising the blinding of

the trial. The error has since been corrected for the 56th and subsequent randomized subjects. The first 55 randomized subjects continue with study procedures and assessments without any interruptions and they continue to receive treatment as assigned by IVRS.

Based on a blinded assessment, the Sponsor determined that due to the systematic nature of this error and its large magnitude, inclusion of the first 55 randomized subjects in the efficacy analyses would potentially bias the treatment estimates, regardless if they were analyzed in the treatment groups as assigned by the IVRS or if they were analyzed in the treatment groups per the randomization schedule. As such, these 55 subjects will be excluded from the full analysis dataset, which is the primary efficacy dataset. These 55 subjects will be included in safety analysis in the 'as treated' treatment groups.

8.3 Endpoints

8.3.1 Primary Endpoint

The primary endpoint of this study is the change in HbA1c from baseline to the Week 24 visit.

8.3.2 Secondary Endpoints

The secondary efficacy endpoints are:

1. Percent change from baseline to the Week 24 visit in total daily insulin dose
2. Percent change from baseline to the Week 24 in body weight
3. Change from baseline to the Week 24 visit in the mean value of 24-hour glucose readings obtained from CGM
4. Change from baseline to the Week 24 visit in mean amplitude of glucose excursion (MAGE) of 24-hour glucose readings obtained from CGM
5. Change from baseline to the Week 24 visit in the percent of 24-hour glucose readings obtained from CGM that falls within the range of > 70 mg/dL and ≤ 180 mg/dL
6. Proportion of subjects achieving an HbA1c reduction from baseline to the Week 24 visit ≥ 0.5% and without severe hypoglycemia events

8.3.3 Safety

The safety endpoints include:

- The proportion of subjects with hypoglycemia events and the frequency and severity of the hypoglycemia events
- The proportion of subjects experiencing adverse events (AE), DKA events, and marked abnormalities in clinical laboratory tests and
- The change from baseline at each post-baseline time point of assessment of selected safety clinical laboratory parameters, physical measurements, vital signs, and electrocardiogram data.

8.3.4 Exploratory Endpoints

The efficacy exploratory endpoints of the study are:

1) Proportion of subjects with HbA1c reduction from baseline to the Week 24 visit of at least 0.5% (≥ 0.5%)
2) Proportion of subjects with HBA1C < 7.0% after 24 weeks of double-blinded treatment
3) Change from baseline to the week 24 visit in FPG
4) Change from baseline to the week 24 visit in the percent of 24-hour glucose readings obtained from CGM that falls within the hypoglycemic range of ≤ 70 mg/dL.
5) Change from baseline to the week 24 visit in seated systolic blood pressure among subjects with hypertension at baseline, defined as seated SBP ≥ 140 mmHg and/or seated DBP ≥ 90 mmHg.
6) Change from baseline to the week 24 visit in average glucose values measured by 6-point self monitored blood glucose (SMBG).
7) Change from baseline to the week 24 visit in postprandial glucose values measured by 6-point self monitored blood glucose (SMBG).
8) Change from baseline to the week 24 visit in postprandial glucose values measured by CGM
9) Change from baseline to the week 24 visit in the standard deviation of 24-hour glucose readings obtained from CGM.
10) Change from baseline to the week 24 visit in each of the 5 dimensions, as well as the health status index of the EQ-5D-3L questionnaire.
11) Changes from baseline to the week 24 visit in the summary score for treatment satisfaction and scores for perceived frequency of hyperglycemia and perceived frequency of hypoglycemia, respectively, as measured by the Diabetes Treatment Satisfaction Questionnaire status (DTSQs)
12) To explore the relationship between observed and/or model estimated pharmacokinetic measures of exposure (eg, AUCss, Cmax, Cmin) and efficacy and/or safety endpoints by using model-based approaches. This analysis will be provided in a separate report.
13) Number of non-severe hypoglycemic events per subject in those achieving a HbA1c reduction of ≥ 0.5%

8.4 Analyses

Analyses of the data from the short-term period will be conducted once all randomized subjects have either completed the short-term double-blind period or discontinued study medication from the short-term double-blind period. In addition all relevant queries must be resolved and the database must be locked for this period before the blind is broken for analyses.

Analyses of the data from both short-term double-blinded and long-term subject- and site-blinded treatment periods will be performed after all subjects have completed or have been discontinued from the study. In addition, all relevant queries must be resolved and the database must be locked for this study prior to analyses.

8.4.1 Demographics and Baseline Characteristics

Frequency distributions and summary statistics for demographic and baseline variables summarized in efficacy analyses will be computed by treatment group, as well as for all subjects

combined. No statistical test will be carried out for comparison of any baseline measurement among the treatment groups.

8.4.2 Efficacy Analyses

Unless otherwise specified, efficacy analyses will be performed using the full analysis dataset, which excludes the first 55 randomized subjects who were affected by the randomization system error.

8.4.2.1 Primary Efficacy Analyses

The primary endpoint is the change in HbA1c from baseline to the Week 24 visit. The primary estimand for the primary endpoint is *treatment difference at Week 24 if subjects did not discontinue randomized treatment*. In order to maintain an overall Type I error rate of 5% for the endpoint, a Dunnett and Tamhane step-up procedure will be used, which allows for the correlation of 0.5 between the standard normal deviate for each comparison (Dunnett and Tamhane 1992)[18]. Applying the Dunnett and Tamhane procedure, statistical significance will be declared for both doses at the two-sided 5% level if the two-sided p-values from both pairwise comparisons are smaller than 5%. If the larger p-value among the two pairwise comparisons is greater than 5% and the smaller p-value is below 2.62%, then statistical significance will be declared for the latter comparison.

The primary analysis of the change in HbA1c from baseline to the Week 24 visit will be based on a longitudinal repeated measures analysis using 'direct likelihood'. The analysis will be based on the full analysis dataset who have a baseline assessment and any post-baseline double-blind treatment period assessment. The analysis will include all available data up to Week 24 or until premature discontinuation of randomized treatment, whichever occurs first. The analysis will be conducted regardless of insulin up-titration. The model is based on a missing at random (MAR) assumption with respect to missing data

The SAS procedure PROC MIXED will be used. The preferred model will include the fixed categorical effects of treatment, week, randomization stratification factor (i.e. one term for each combination of all stratification factors) and treatment-by-week interaction, as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction. An unstructured matrix for the within-subject error variance-covariance will be used. The denominator degrees of freedom will be calculated according to the Kenward-Roger method. A number of back-up models will be defined in the statistical analysis plan in case of non-convergence of the preferred model or other issues. Point estimates and 95% confidence intervals for the mean change within each treatment group as well as the difference in mean change between the dapagliflozin treatment group and placebo will be calculated. P-value for the differences in the week 24 visit estimates between each dapagliflozin group and placebo will be calculated.

The ITT estimand, i.e., *treatment difference at Week 24 regardless of treatment discontinuation,* will be evaluated as the secondary estimand of the primary endpoint. The analysis of the ITT

estimand will include all available data up to Week 24, regardless of insulin up-titration and regardless of premature discontinuation of randomized treatment.

Sensitivity analyses will be conducted for the primary efficacy endpoint to assess the robustness of the primary efficacy results, including sensitivity analysis with respect to the ITT estimand, sensitivity analyses based on missing-not-at-random (MNAR) assumptions with respect to missing data, and sensitivity analysis with respect to insulin up-titration.

8.4.2.2 Secondary Efficacy Analyses

Statistical tests for secondary efficacy endpoints will be only conducted if there is a statistically significant difference in the primary endpoint for both pairwise comparisons, ie, dapagliflozin 5mg vs. placebo and dapagliflozin 10 mg vs. placebo. The same Dunnett and Tamhane step-up procedure will be applied to each secondary efficacy endpoint. Secondary efficacy endpoints will be tested in the order that they appear in the objectives section of the protocol and protocol synopsis. Statistical tests will be only performed for a given secondary endpoint if both comparisons for a proceeding secondary endpoint are significant. Otherwise, the testing procedure will stop at the secondary endpoint that does not reach statistical significance.

The percent change (using logarithmic transformation for the endpoint in the model) from baseline to the Week 24 visit in total daily insulin dose and total body weight, the change from baseline to the Week 24 visit in the mean value of 24-hour glucose readings obtained from CGM, mean amplitude of glucose excursions of 24-hour glucose readings obtained from CGM, and the percent of 24-hour glucose readings obtained from CGM that fall within the range of > 70 mg/dL and ≤ 180 mg/dL will be analyzed using a longitudinal repeated measures analysis, similarly to the model used for primary efficacy analysis. The proportion of subjects achieving an HbA1c reduction from baseline to Week 24 visit $\geq 0.5\%$ without severe hypoglycemia events will be analyzed using a logistic regression model with adjustment for baseline value. In addition to point estimates and 95% confidence intervals, p-values will be calculated for all endpoints. Nominal p-values will be presented for endpoints where type 1 error is not controlled. All secondary efficacy analyses will use subjects in the primary efficacy dataset (ie, full analysis dataset) who have a baseline assessment and any post-baseline double-blind treatment period assessment.

8.4.2.3 Exploratory Efficacy Analyses

The proportion of subjects with HbA1c reduction from baseline to the week 24 visit last observation carried forward (LOCF) of at least 0.5% ($\geq 0.5\%$) and the proportion of subjects with HbA1c to the Week 24 visit LOCF $< 7.0\%$ will be summarized for each treatment group. For these analyses, LOCF refers to the Week 24 value, or the last post-baseline measurement prior to Week 24 if no measurement is available at Week 24. Poisson regression will be used to model number of non-severe hypoglycemic events per subject in those achieving a HbA1c reduction of $\geq 0.5\%$. Point estimates and 2-sided 95% confidence intervals for the proportion in each treatment group and for the differences in proportions between each dapagliflozin treatment groups and the placebo treatment group will be calculated. No p-values will be generated.

The change from baseline to the week 24 visit in the following parameters will be analyzed using a longitudinal repeated measures model similar to the primary efficacy analysis:

- fasting plasma glucose
- percent of 24-hour glucose readings obtained from CGM that falls within the range of ≤ 70 mg/dL
- seated systolic blood pressure among subjects with hypertension at baseline, defined as seated SBP ≥ 140 mmHg and/or seated DBP ≥ 90 mmHg,
- average glucose values measured by 6-point SMBG
- postprandial glucose values measured by 6-point SMBG
- postprandial glucose values measured by CGM
- standard deviation of 24-hour glucose readings obtained from CGM

8.4.3 Safety Analyses

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

The proportion of subjects with at least one hypoglycemic episode will be summarized by treatment group and by the severity of the events. The frequency of the hypoglycemia will also be summarized. Subjects with adjudicated DKA events will also be summarized by treatment group.

All AEs 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 will be summarized by treatment group.

Changes from baseline at each of the scheduled time points in each selected safety clinical laboratory parameters, physical measurements, vital signs and electrocardiogram data will be summarized by treatment group.

8.4.4 Pharmacokinetic Analyses

The dapagliflozin plasma concentrations obtained by sampling of individual subjects will be used to build a population PK (PPK) model to estimate PK parameters (eg, oral clearance [CL/F], apparent volume of distribution [Vd/F], and absorption rate constant [ka]). Possible covariate effects on PK parameters may be identified and quantified. The estimated parameters will be used to derive individual exposure measures (eg, AUC, Cmin). Relationships between observed exposures, and/or these model based estimates of exposures, and efficacy/safety endpoints (eg, changes from baseline in HbA1C, average daily glucose concentration, hypoglycemia) will be explored. The PK data and efficacy endpoint responses derived from this study may also be pooled with similar data from other studies to refine the model-based exposure-response relationship. Listings and summary statistics will be reported for the sampled pharmacokinetic measurements. The PPK and exposure-response analyses will be described in a separate report.

8.4.5 Biomarker Analyses

Not applicable

8.4.6 Outcomes Research Analyses

The change from baseline to the week 24 visit LOCF (week 24 value or the last post-baseline measurement prior to week 24 if no measurement is available at week 24, [ie, last observation carried forward]) in each of the 5 dimensions of the EQ-5D-3L questionnaire will be analyzed with shift tables showing difference as to the respective classifications at baseline.

The change from baseline to the week 24 visit LOCF in the following will be analyzed as continuous variables: 1) health status index of the EQ-5D-3L questionnaire; 2) the summary score for treatment satisfaction and scores for perceived frequency of hyper- and perceived frequency of hypoglycemia, respectively, as measured by the Diabetes Treatment Satisfaction Questionnaire status (DTSQs). These will be analyzed using an ANCOVA model with treatment group as effect and baseline value and randomization stratification factor (ie, one term for each combination of all stratification factors) as covariates. Point estimates and 2-sided 95% confidence intervals for the mean change within each treatment group, as well as for the differences in the mean change between each dapagliflozin treatment group and the placebo treatment group will be calculated. No p-values will be generated.

All above mentioned analyses will use subjects in the primary efficacy dataset (ie, full analysis dataset) who have at least one baseline assessment and any post-baseline double-blind treatment period assessment.

8.4.7 Other Analyses

Not applicable

8.5 Interim Analyses

There are no planned interim analyses for this study.

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, the deviation or change will be submitted as soon as possible to:

- IRB/IEC for review and approval/favorable opinion
- BMS

- 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 done via 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 pages and/or electronic files may serve as the source documents, including but not limited to; CGM data, fingerstick blood glucose values recorded in the diary and meter data (SMBGs and ketones), insulin pump data, and the diary data as noted in Section 5.1.1

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: good clinical practice (GCP), AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

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

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

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

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by BMS) is maintained at each study site where study drug are 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 identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

9.2.3 Case Report Forms

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

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

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

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

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS 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 BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

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

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

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

The data collected during this study are confidential and proprietary to AZ. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTAg) governing {Study, site or Investigator} participation in the study. These requirements include, but are not limited to, submitting proposed publications to AZ at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTAg.

10. GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or BMS 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)
Serious Adverse Event	Serious adverse event defined as any untoward medical occurrence that at any dose: results in death; is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), requires inpatient hospitalization or causes prolongation of existing hospitalization; results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect; is an important medical event (defined as a medical event(s) that may not be immediately life threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.). For reporting purposes only, BMS also considers the occurrence of pregnancy, overdose (regardless of association with an AE), and cancer as important medical events.

11. LIST OF ABBREVIATIONS

Term	Definition
A1C	Glycosylated Hemoglobin
ADA	American Diabetes Association
AE	Adverse event
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUA	American Urological Association
AZ	AstraZeneca
BMI	Body mass index
BMS	Bristol-Myers Squibb
BP	Blood pressure
C	Celsius
CABG	Coronary artery bypass graft
CFR	Code of Federal Regulations
CEC	Clinical event committee
CGM	Continuous Glucose Monitoring
CHF	Congestive Heart Failure
CK	Creatine kinase
Cm	Centimeter
CPK	Creatine phosphokinase
CrCl	Creatinine Clearance
Cr	Creatinine
CRF	Case Report Form, paper or electronic
CSII	Continuous subcutaneous insulin infusion
CT	Computed Tomography
CTAg	Clinical Trial Agreement
CV	Cardiovascular
DBP	Diastolic blood pressure
DKA	Diabetic Ketoacidosis

Term	Definition
dL	Deciliter
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
DTSQs	Diabetes Treatment Satisfaction Questionnaire
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
Eg	exempli gratia (for example)
EQ-5D-3L	Euro Quality of life 5 dimensions 3 levels
ET	Early Termination
FDA	Food and Drug Administration
FFA	Free Fatty Acid
FPG	Fasting Plasma Glucose
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
g/L	Grams/liter
g/dl	Grams/decliter
GFR	glomerular filtration rate
HbA1c	Glycosylated Hemoglobin
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HCG	Human Chorionic Gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
HRQoL	Health related Quality of Life
HRT	Hormone replacement therapy
ICF	Informed Consent
ICH	International Conference on Harmonisation
Ie	id est (that is)

Term	Definition
IEC	Independent Ethics Committee
IMP	Investigational medicinal products
IRB	Institutional Review Board
IU	International Unit
IUD	Intrauterine Device
IVRS	Interactive Voice Response System
Kg	kilogram
Lb	Pound
LFT	Liver function test
LOCF	Last observation carried forward
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hemoglobin Concentration
MCV	Mean Cell Volume
M	Meter
MDI	Multiple daily injections
MDRD	Modification of diet in renal disease
Mg	milligram
mL	milliliter
MI	Myocardial infarction
Min	minute
Mmol	Millimole
MOA	Mechanism of Action
MODY	Maturity onset diabetes of young
NIMP	Non-investigational medicinal products
NSAID	Nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
PK	Pharmacokinetics
PPK	Population Pharmacokinetics
PRO	Patient reported outcomes
PT	Prothrombin time

Term	Definition
PCI	Percutaneous Coronary Intervention
PTCA	Percutaneous transluminal coronary angioplasty
PE	Pulmonary Embolism
QD, qd	quaque die, once daily
SA	Sickle cell trait
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SGLT-2	Sodium-dependent glucose transporter 2
SI	International System of Units
SMBG	Self monitored blood glucose
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA Queries
SOP	Standard Operating Procedures
TB	Total bilirubin
TG	Triglycerides
TIA	Transient Ischemic Attack
TSH	Thyroid Stimulating Hormone
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
ULN	Upper limit of normal
UTI	Urinary Tract Infection
VAS	Visual Analogue Scale
WOCBP	women of childbearing potential

12. REFERENCES

[1] Daneman D. Type 1 Diabetes. Lancet 2006;367:847-58.

[2] Cryer PE. Hypoglycaemia: The limiting factor in the glycaemic management of Type 1 and Type II Diabetes. Diabetologia 2002;45:937.948.

[3] Weinstock RS, Xing D, Maahs DM, Michels A, Rickels MR, Peters AL, et al. Severe hypoglycemia and diabetic ketoacidosis in adults with type 1 diabetes: results from the T1D Exchange clinic registry. J Clin Endocrinol Metab 2013;98(8):3411-9.

[4] Kilpatrick ES, Rigby AS, Goode K, Atkin SL. Relating mean blood glucose and glucose variability to the risk of multiple episodes of hypoglycaemia in type 1 diabetes.Diabetologia. 2007;50(12):2553-61

[5] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. N Engl J Med 1993;329:977–986.

[6] Kilpatrick ES, Rigby AS, Atkin SL. Insulin resistance, the metabolic syndrome, and complication risk in type 1 diabetes: "double diabetes" in the Diabetes Control and Complications Trial. Diabetes Care. 2007;30(3):707-12.

[7] Ferriss JB, Webb D, Chaturvedi N, Fuller JH, Idzior-Walus B; The EURODIAB Prospective Complications Group. Weight gain is associated with improved glycaemic control but with adverse changes in plasma lipids and blood pressure in Type 1 diabetes. Diabet Med 2006;23(5):557-64.

[8] Cleland SJ, Fisher BM, Colhoun HM, Sattar N, Petrie JR. Insulin resistance in type 1 diabetes: what is 'double diabetes' and what are the risks? Diabetologia. 2013;56(7):1462-70.

[9] Soedamah-Muthu SS, Chaturvedi N, Witte DR, Stevens LK, Porta M, Fuller JH for the EURODIAB Prospective Complications Study Group. Relationship between risk factors and mortality in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study (PCS). Diabetes Care 2008;31(7):1360-6.

[10] Beck RW, Tamborlane WV, Bergenstal RM, Miller KM, DuBose SN, Hall CA for the T1D Exchange Clinic Network. The T1D exchange clinic registry. J Clin Endocrinol Metab 2012;97(12):4383-9.

[11] Investigator Brochure Version 07: Dapagliflozin (BMS-512148). Bristol-Myers Squibb Research and Development and AstraZeneca AB, 22-Dec-2010, BMS Document Control Number 930005487.

[12] Defronzo RA, Hompesch M, Kasichayanula S, Liu X, Hong Y, Pfister M, Morrow LA, Leslie BR, Boulton DW, Ching A, Lacreta FP, Griffen SC. Characterization of renal glucose reabsorption in response to dapagliflozin in healthy subjects and subjects with type 2 diabetes. Diabetes Care 2013;36:3169-3176.

[13] Kestelman P. et. al., Efficacy of the Simultaneous Use of Condoms and Spermicides Family Planning Perspectives.Vol 23 (5); October 1991; Gabbay MB, Thomas J, Gibbs A, Hold P. A Randomized Crossover Trial of The Impact of Additional Spermicide on Condom Failure Rates. Sex Transm Dis 2008; 35: 862-8.

[14] Nicolle LE, Bradley S, Colgan R, Rice JC, Schaeffer A, Hooton TM. Infectious diseases society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria inadults. Clin Infect Dis 2005;40:643-54.

[15] US Preventative Services Taskforce. Recommendation Statement Screening orAsymptomatic Bacteriuria. Revised 2004. Available athttp://www.ahrq.gov/clinic/uspstf/uspsbact.htm

[16] European Association of Urology. Guidelines on the management of urinary and male genitaltract infections 2008. Available at http://www.uroweb.org/

[17] Bradley C (1994) The Diabetes Treatment Satisfaction Questionnaire: DTSQ. In Bradley C (ED) (1994) Handbook of Physchology and Dianetes: a guide to Psychological Measurement in diabetes research and practice. Chur, Switzerland: Harwood Academic Publishers.

[18] Dunnett CW and Tamhane AC. A step-up multiple test procedure. J of the American Statistical Association. 1992;87(417):162-170.

APPENDIX 1 NEW YORK HEART ASSOCIATION FUNCTIONAL CLASS

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

APPENDIX 2 CENTRAL LABORATORY ASSESSMENTS

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

During the double-blinded short-term treatment period, (Day 1 to Week 24), the HbA1c values will be masked to the Investigator, subjects, and to the Sponsor. These values will be provided to the Investigator after the study has been completed. During the subject and site blinded long-term treatment period, after the Week 24 visit (Week 32 to Week 56), the HbA1c values will be unmasked.

Spot Urine for glucose, albumin, and creatinine quantification and determination of glucose:creatinine and albumin:creatinine ratios, will be masked to the Investigator and Sponsor throughout the study, (short-term treatment period and long-term treatment period). These values will be provided to the Investigator after the study has been completed.

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

PROTOCOL-SPECIFIC CENTRAL LABORATORY ASSESSMENTS:

- A1C (%, mmol/mol)
- FPG (mg/dL, mmol/L)
- Fasting C-peptide (ng/mL, nmol/L)
- Fasting serum lipid profile:
  - Total-C (mg/dL, mmol/L)
  - Calculated LDL-C (mg/dL, mmol/L)
    - *Except screening period, reflex testing will occur for Direct LDL-C if TG > 400 mg/dL (4.52 mmol/L)*
  - HDL-C (mg/dL, mmol/L)
  - TG (mg/dL, mmol/L)
- Free Fatty Acids

Screening-Specific Safety Panel

- Thyroid stimulating hormone (TSH)
  - *Reflex Testing: abnormal TSH value at enrollment will be further evaluated by free T4.*
- Hepatitis Screen Panel:
  - Anti-hepatitis C virus antibody
    - *Reflex Testing: Low positive results require confirmation.*
- Hepatitis B surface antigen
- Serum Pregnancy test for women of childbearing potential

Specialized Liver Panel:

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

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

Liver Discontinuation Panel:

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

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

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

Standard Safety Laboratory Panels:

Table Appendix 2: Standard Safety Laboratory Panels

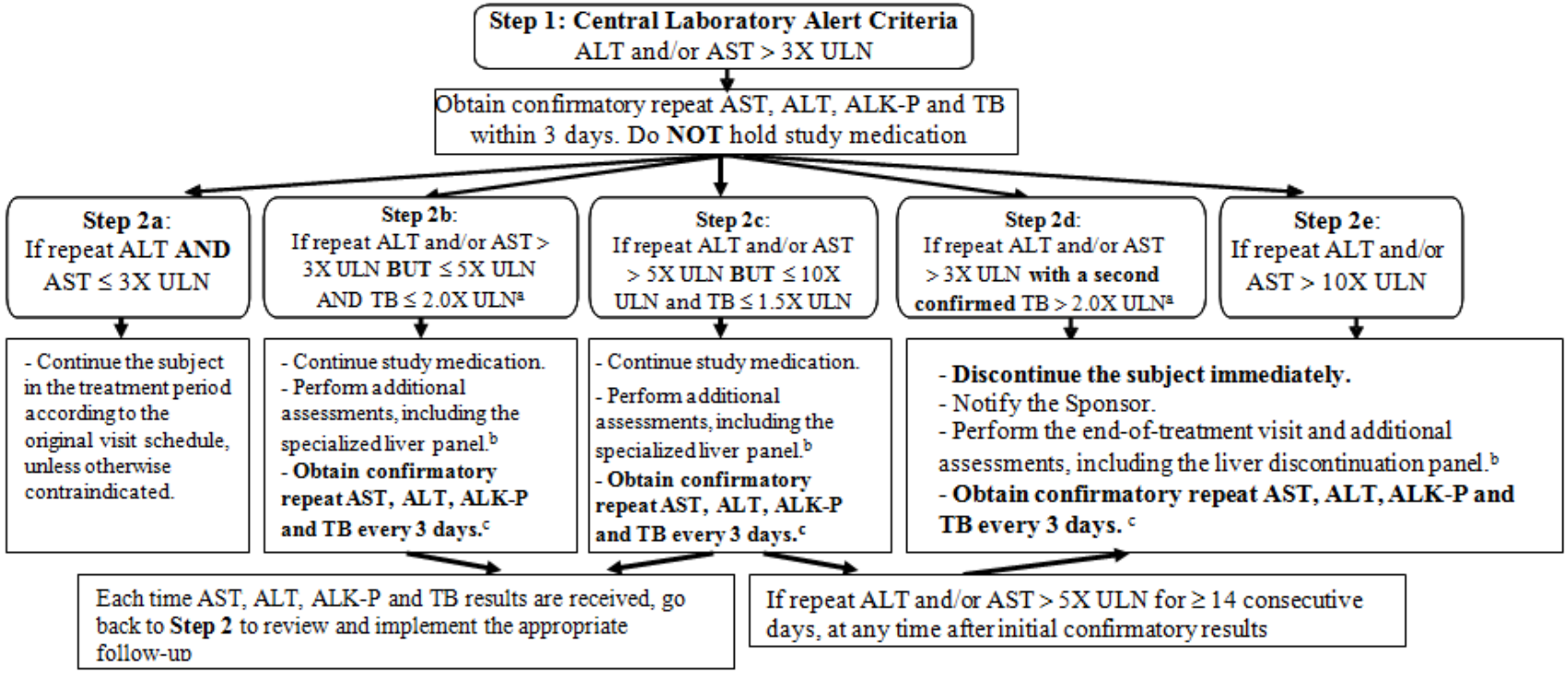
Hematology
• Hemoglobin (g/dL, g/L) • Hematocrit (%, V/V) • Red blood cell (RBC) ($x10^6$/UL, $x10^{12}$/L) *RBC count indices:* • Mean Cell Volume (MCV) (fL) • Mean Cell Hemoglobin (MCH) (pg/cell) • Mean Cell Hemoglobin Concentration (MCHC) (gHb/dL, gHb/L) • White blood cell Count and Differential •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

Serum Chemistry
• AST (IU/L) • ALT (IU/L) • ALK-P (IU/L) • CK/CPK (IU/L). *Reflex Testing: Troponin I will be ordered if CK > 400 IU/L).* • Total Bilirubin (mg/dL, μmol/L), Reflex test for direct bilirubin when TB is elevated >1.5ULN • Serum Creatinine (mg/dL, μmol/L). Creatinine Clearance will be calculated by the Central Laboratory using the Cockcroft-Gault formula and results will be reported to the sites and the Sponsor. • Blood Urea Nitrogen (mg/dL, mmol/L) • Albumin (g/dl, g/L) • Bicarbonate (mEq/L, mmol/L) • 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) • Uric acid (mg/dL, μmol/L)

Table Appendix 2: Standard Safety Laboratory Panels

Urine Analyses
Urine HCG pregnancy test for WOCBP (HCG minimum sensitivity of 25 IU/L; performed at site or at home). *If a urine HCG test is positive, a blood specimen will be obtained and a serum pregnancy test will be performed by the central laboratory for confirmation.*
Urinalysis standard safety panel (without microscopy) will be performed at the following visits; Screening Week -2, Day 1, Week 4, Week 8, Week 18, Week 40, Week 52, and Week 56 At the following visits; Screening, Day 1, Week 12, Week 18, Week 24, and Week 52 and Week 56, the following tests will also be performed; • Spot Urine for glucose, albumin, and creatinine quantification and determination of glucose:creatinine and albumin:creatinine ratios • Creatinine • Calculated Urinary albumin:creatinine ratio (UACR)

APPENDIX 3 SUSTAINED ELEVATED LIVER SAFETY ABNORMALITIES FLOW CHART



[a] In subjects with repeat ALT or AST > 3X ULN but ≤ 10X ULN, only subjects with TB ≤ 2.0X ULN at Step 1 should be followed according to Step 2b. Subjects with an initial TB and confirmatory repeat TB > 2.0X ULN should be followed according to Step 2d.

[b] Refer to section 5.3.7 for details on additional assessments to be performed (AE assessment, PE, review of current medical history including focused review of risk factors for liver diseases and collection of blood samples [specialized liver panel or liver discontinuation panel]).

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