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Clinical Protocol MB102077

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Subjects with Type 2 Diabetes with Inadequately Controlled Hypertension treated with an Angiotensin-Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB) and an Additional Antihypertensive Medication

Study Director / Central Medical Monitor

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This protocol contains information that is confidential and proprietary to Bristol-Myers Squibb

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Original Protocol	Not applicable	

SYNOPSIS

Clinical Protocol MB102077

Title of Study: Protocol MB102077: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Subjects with Type 2 Diabetes with inadequately controlled hypertension treated with an Angiotensin-Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB) and an additional Antihypertensive medication.

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

- Blinded dapagliflozin tablets 2.5 mg administered orally for the 12 week double-blind treatment period.
- Blinded dapagliflozin tablets 5 mg administered orally for the 12 week double-blind treatment period.
- Blinded dapagliflozin tablets 10 mg administered orally for the 12 week double-blind treatment period.
- Matching placebo for the dapagliflozin tablets 2.5 mg, 5 mg and 10 mg, administered orally for the 4 week lead-in period and the12 week double-blind treatment period.

Study Phase: 3

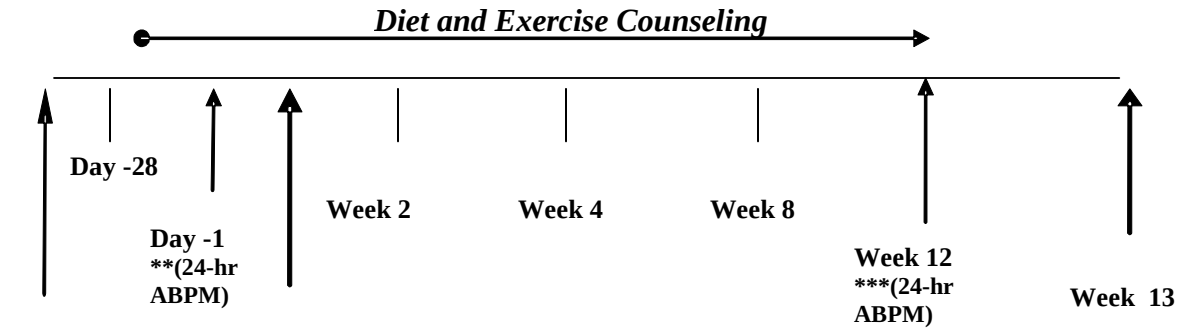
Research Hypothesis: After 12 weeks of oral daily administration, there will be a greater mean reduction from baseline in blood pressure and glycosylated hemoglobin (HbA1c) achieved with dapagliflozin plus ACEI or ARB and an additional antihypertensive medication compared to placebo plus ACEI or ARB and an additional antihypertensive medication in subjects with type 2 diabetes with inadequately controlled hypertension (Seated systolic blood pressure (SBP) ≥ 140 and < 165 mmHg, **AND** seated diastolic blood pressure (DBP) ≥ 85 and < 105 mmHg).

Primary Objective: To compare the change from baseline in seated systolic blood pressure after 12 weeks of double-blind treatment with each dose of dapagliflozin (2.5 mg, 5 mg and 10 mg) versus placebo and to compare the change from baseline in HbA1c after 12 weeks of double-blind treatment with each dose of dapagliflozin (2.5 mg, 5 mg and 10 mg) versus placebo.

Study Design: The MB102077 study is a randomized, double-blind, 4-arm, parallel-group, placebo-controlled Phase 3 trial. Subjects will be on a commercially available stable dose of an oral anti-diabetic (OAD) for at least 6 weeks, (12 weeks for a thiazolidinedione (TZD)) with central laboratory glycosylated hemoglobin (HbA1c) ≥ 7% and ≤ 10% at enrollment. Subjects will also be on a commercially available stable dose of an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) and an additional antihypertensive medication for at least 4 weeks with inadequately controlled hypertension (SBP ≥ 140 and < 165 mmHg, DBP ≥ 85 and < 105 mmHg). Subjects will be eligible for randomization into one of the four blinded treatment arms, either dapagliflozin 2.5 mg, dapagliflozin 5 mg QD, dapagliflozin 10 mg QD, or matching placebo QD, in a 1:1:1:1 ratio. Subjects will be randomized within strata according to their additional antihypertensive medication use (thiazide/thiazide-like diuretics vs calcium channel blockers, beta blockers or alpha adrenergic blockers). Subjects will be treated for 12 weeks with a 4 week placebo lead-in period and a 1 week follow-up period.

Figure 1 Study Schematic

Qualification Period ≤ 14 Days	4 - Week Single-Blind Placebo Lead-In Period	12 Week Double-Blind Treatment Period	1 - Week Follow - up Period (no blinded study medication)
		• *Dapagliflozin 2.5 mg QD • *Dapagliflozin 5 mg QD • *Dapagliflozin 10 mg QD • *Placebo QD	



Enrollment **Day 1: (Randomization):** End of Lead-In Period/Entry into Treatment Period, baseline measurements

End of Treatment Period/ Entry into Follow-Up Period

* **Subjects will also take their stable dose of commercially available OAD plus ACEI or ARB and an additional antihypertensive medication with their blinded medication.**

****24-hr Ambulatory Blood Pressure Monitoring (ABPM) during lead-in must be conducted between days -7 and -1, *prior* to randomization.**

*****24hr ABPM during Double-Blind period must be completed within 1 week prior to the Week 12/ET visit.**

Study Population: Men and women with type 2 diabetes, ages ≥ 18 to ≤ 89 years, who have type 2 diabetes with inadequately controlled hypertension. HbA1c must be between ≥ 7.0% and ≤ 10.0%, while on a stable dose (ie, no change in prescribed treatment regimen) of an oral anti-diabetic agent (OAD) for at least 6 weeks prior to the enrollment visit, 12 weeks for a thiazolidinedione (TZD).

Subjects must have inadequate BP control, defined as systolic BP (SBP) ≥ 140 and < 165 mmHg, **AND** diastolic BP (DBP) ≥ 85 and < 105 mmHg **at the enrollment and Day 1 visits** while on a stable dose of ACEI or ARB, and an additional antihypertensive medication (thiazide/thiazide-like diuretic or calcium channel blocker, beta blocker, alpha adrenergic blocker) for at least 4 weeks prior to the enrollment visit.

All OAD, ACEI or ARB and additional antihypertensive medications will be commercially available and will not be supplied by Bristol-Myers Squibb.

Subjects must also have a Body Mass Index (BMI) ≤ 45.0 kg/m^2 as well as a central laboratory enrollment C-peptide value of ≥ 0.8 ng/mL (0.30 nmol/L)

Key Exclusion Criteria Include:

- AST > 3X ULN
- ALT > 3X ULN
- Serum total bilirubin (TB) ≥ 1.5X ULN
- Serum Creatinine (S_{Cr}) ≥ 2.0 mg/dL unless subject is on metformin then the exclusionary limits will be S_{Cr} ≥ 1.50 mg/dL (133 mmol/L) for male subjects; S_{Cr} ≥ 1.40 mg/dL (124 mmol/L) for female subjects
- Estimated creatinine clearance (Crcl) of < 50ml/min

Study Assessments and Primary Endpoint: The co-primary endpoints are the change in seated systolic blood pressure from baseline at Week 12, or the last post-baseline measurement prior to Week 12 if no Week 12 assessment is available, and the change in HbA1c from baseline at Week 12, or the last post-baseline measurement prior to Week 12 if no Week 12 assessment is available.

Statistical Methods: The first primary objective is to compare the differences in mean change between each dapagliflozin (2.5 mg, 5 mg and 10 mg) treatment group and the placebo treatment group in seated systolic blood pressure. With 262 subjects per treatment group with post-baseline measurements, there is at least 90% power to detect a difference of 4.5 mmHg in mean change from baseline in seated systolic blood pressure between each (2.5 mg, 5 mg and 10 mg) dapagliflozin treatment group and placebo treatment group at significance level of 0.017, assuming a standard deviation (SD) of 14 mmHg. If the result for the first primary endpoint is significant then a test for the second primary endpoint will be conducted. With 262 subjects per treatment group with post-baseline measurements, there is at least 96% power to detect a difference of 0.4% in mean change from baseline in HbA1c between each dapagliflozin (2.5 mg, 5 mg and 10 mg) treatment group and the placebo treatment group at significance level of 0.017, assuming a SD of 1.1%. Overall, with 262 subjects per treatment group, there is at least 86% power to detect 1 dapagliflozin treatment group that meets both co-primary endpoints with overall Type I error controlled at the 0.05 significance level (using Bonferroni's adjustment).

The primary comparisons are between each of the dapagliflozin (2.5 mg, 5 mg and 10 mg) treatment groups and the placebo treatment group. Each comparison between the dapagliflozin treatment group and placebo treatment group will be performed at the two-sided 0.017 level, using Bonferroni's adjustment so the family-wise Type I error rate is controlled at the 0.05 significance level.

Assuming 5% of the subjects do not have a post-baseline assessment, a total of 1104 subjects (276 subjects for each dapagliflozin treatment group and placebo treatment group) need to be randomized.

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1 INTRODUCTION AND STUDY RATIONALE

1.1 Study Rationale

The current trial is designed to evaluate the effects of dapagliflozin on blood pressure when used in subjects with type 2 diabetes (T2DM) who have inadequate glycemic control and inadequately controlled hypertension while taking an Angiotensin-Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB) and an additional antihypertensive medication.

In dapagliflozin Phase 2 and 3 studies, dose-dependent reductions in blood pressure have been observed in doses between 1.0 mg to 10 mg in monotherapy studies as well as in add-on to other oral hypoglycemic agents or insulin studies. These blood pressure reductions are consistent with the known osmotic diuretic effect of dapagliflozin, which results from its inhibition of proximal renal tubular glucose and sodium re-absorption. Because of early concerns that this mechanism could also potentially be associated with an increased risk of certain adverse events, such as hypotension, orthostatic hypotension, hypovolemia, and electrolyte abnormalities, Phase 3 studies completed to date have been designed to evaluate blood pressure as a safety parameter rather than as an efficacy parameter.

Results from four Phase 3 studies have now demonstrated that dapagliflozin does not considerably increase the risk of these adverse events. Furthermore, the dose-dependent reductions in blood pressure observed in some of these studies, though modest, have been clinically meaningful (systolic -2.1 to -7.7 mmHg, diastolic -1 to -3.3 mmHg) and comparable to the reductions observed in other currently marketed antihypertensive medications.[1] (Of note, antihypertensive medications were not controlled during these clinical trials). A significant number of patients with type 2 diabetes have blood pressure that is above the target range, and modest lowering of blood pressure could be beneficial in reducing long-term complications.

Because previous Phase 3 studies were not designed to measure blood pressure as a primary or key secondary endpoint, this study will evaluate the safety and efficacy of adding 2.5 mg, 5 mg or 10 mg dapagliflozin compared with placebo for subjects with

inadequate glycemic control and inadequately controlled blood pressure currently taking a stable dose of an oral antidiabetic drug (OAD) for T2DM and an ACEI or ARB for hypertension plus an additional antihypertensive medication. Change from baseline in seated systolic blood pressure and glycosylated hemoglobin (HbA1c) will be the primary endpoints for this study to evaluate the effect of dapagliflozin on blood pressure in T2DM subjects with inadequate glycemic control. A substantial number of T2DM patients take either an ACEI or an ARB for hypertension, and those patients that are not adequately controlled with an ACEI or ARB alone are often treated with an additional antihypertensive medication including thiazide or thiazide-like diuretics, calcium channel blockers, beta blockers or alpha adrenergic blockers. In order to gain the most insight into the BP lowering effect of dapagliflozin, this study will employ both office BP measurements (seated, supine and standing) and 24-hr ambulatory BP monitoring (ABPM).

1.2 Research Hypothesis

After 12 weeks of oral daily administration, there will be a greater mean reduction from baseline in glycosylated hemoglobin (HbA1c) and blood pressure achieved with dapagliflozin plus ACEI or ARB and an additional antihypertensive medication compared to placebo plus ACEI or ARB and an additional antihypertensive medication in subjects with type 2 diabetes with inadequately controlled hypertension. (Seated systolic blood pressure (SBP) ≥ 140 and < 165 mmHg, **AND** seated diastolic blood pressure (DBP) ≥ 85 and < 105 mmHg).

1.3 Objectives

1.3.1 Primary Objectives

- To compare the change from baseline in **seated systolic blood pressure** after 12 weeks of double-blind treatment between each dapagliflozin (2.5 mg, 5 mg, and 10 mg) treatment group and the placebo treatment group.
- To compare the change from baseline in **HbA1c** after 12 weeks of double-blind treatment between each dapagliflozin (2.5 mg, 5 mg, and 10 mg) treatment group and the placebo treatment group.

1.3.2 Secondary Objectives

- To compare the change from baseline in **24 hour ambulatory systolic blood pressure** after 12 weeks of double-blind treatment between each dapagliflozin (2.5 mg, 5 mg, and 10 mg) treatment group and the placebo treatment group.
- To compare the change from baseline in **seated and 24 hour ambulatory diastolic blood pressure** after 12 weeks of double-blind treatment between each dapagliflozin (2.5 mg, 5 mg, and 10 mg) treatment group and the placebo treatment group.
- To compare the change from baseline in **serum uric acid** after 12 weeks of double-blind treatment between each dapagliflozin (2.5 mg, 5 mg, and 10 mg) treatment group and the placebo treatment group.

1.3.3 Exploratory Objectives

- To assess the **proportion of subjects achieving goal blood pressure**, defined as blood pressure < 130/80 mmHg, after 12 weeks of double-blind treatment between each dapagliflozin (2.5 mg, 5 mg, and 10 mg) treatment group and the placebo treatment group.
- To assess the **proportion of subjects achieving improved blood pressure control,** defined as a blood pressure of < 140/90 mmHg, after 12 weeks of double-blind treatment between each dapagliflozin (2.5 mg, 5 mg, and 10 mg) treatment group and the placebo treatment group.
- To assess the change from baseline in **fasting plasma glucose** after 12 weeks of double-blind treatment between each dapagliflozin (2.5 mg, 5 mg, and 10 mg) treatment group and the placebo treatment group.
- To assess the change from baseline in **ambulatory daytime (6am – 10pm) and nighttime (10pm – 6am) systolic and diastolic blood pressure** after 12 weeks of double-blind treatment between each dapagliflozin (2.5 mg, 5 mg, and 10 mg) treatment group and the placebo treatment group.
- To assess the change from baseline in **uric acid excretion** (by spot urine test) after 12 weeks of double-blind treatment between each dapagliflozin (2.5 mg, 5 mg, and 10 mg) treatment group and the placebo treatment group.

1.4 Product Development Background

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

Worldwide, there are an estimated 150 million people who have type 2 diabetes.[2] According to the Centers for Disease Control (CDC) in 2005, 7% of the United States (US) population has diabetes, of which approximately 15 million have been diagnosed.

The currently available therapies to treat type 2 diabetes augment the action or delivery of insulin to lower blood glucose. However, despite therapy, many patients do not achieve control of their type 2 diabetes. According to the National Health and Nutrition Examination Survey (NHANES) III, only 36% of subjects with type 2 diabetes achieve glycemic control defined as a HbA1c < 7.0% with current therapies.[3] In an effort to treat type 2 diabetes, aggressive therapy with multiple pharmacologic agents may be prescribed. However, despite this increased use of aggressive therapy, there has been a decline in glycemic control. Therefore, additional therapies are warranted.

Dapagliflozin is a potent and selective inhibitor of the renal sodium-glucose transporter, SGLT2. This compound is being developed as an orally active agent for the treatment of type 2 diabetes, and represents a novel therapeutic approach for the treatment of this disorder. Intestinal absorption and renal reabsorption of glucose are mediated through sodium glucose transporters (SGLT).[4] Two sodium-dependent glucose transporters, SGLT1 and SGLT2, have been identified as the major transporters of glucose in the human. [5, 6] SGLT1 is expressed in the gastrointestinal tract, heart, skeletal muscle, liver, lung, and kidney, while SGLT2 is expressed almost exclusively in the kidney. SGLT2 is present in the S1 segment of the proximal tubule, where > 90% of renal glucose reabsorption occurs.[7] SGLT1 is found in the S3 segment of the proximal tubule, where < 10% of filtered glucose is reabsorbed. Thus, SGLT2 appears to be the major transporter

responsible for renal glucose transport, mediating glucose re-uptake from the glomerular filtrate.

Dapagliflozin has undergone in vitro and in vivo evaluation in a variety of models; the results from these evaluations are detailed in the Investigator brochure.

1.4.1 Summary of Clinical Efficacy

1.4.1.1 MB102008

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

There was a statistically significant decrease in HbA1c in all dapagliflozin groups as compared with the placebo group. There was also a dose-dependent decrease in fasting plasma glucose (FPG) from baseline to Week 12 in all doses of dapagliflozin. There was a statistically significant difference in mean change from baseline in FPG in each of the 5 mg, 10 mg, 20 mg, and 50 mg dapagliflozin groups compared to placebo. Increased total urinary glucose excretion was observed at all dapagliflozin doses, consistent with the mechanism of action of this compound. The maximum increase in glucose excretion was observed at dapagliflozin doses ≥ 20 mg.

The proportion of dapagliflozin-treated subjects achieving a therapeutic glycemic response (defined as HbA1c < 7%) at Week 12 ranged from 40% to 59%. A statistically significant difference compared to placebo was attained only at the 50 mg dose of dapagliflozin. There were reductions in postprandial glucose (area under the curve) from baseline, compared with placebo, for all doses of dapagliflozin. Decreases in total body weight from baseline in all dapagliflozin groups were greater than placebo. The percent decreases from baseline were comparable for the 2.5 mg to 10 mg groups, and larger for the 20 mg and 50 mg doses, where they were likewise comparable.

1.4.1.2 MB102003

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

1.4.1.3 Phase 3 Studies

In the Phase 3 studies, MB102014, MB012013, and MB102033, 1429 subjects have been treated with dapagliflozin doses of up to 10 mg. The 24-week short-term periods have been concluded for MB102014, a study in which dapagliflozin was added on to metformin, MB102013, a dapagliflozin monotherapy study, and MB012033, a study in which dapagliflozin was added on to insulin. The results from the short-term periods of the studies confirmed clinically meaningful benefits of dapagliflozin 5 mg and 10 mg on HbA1c, as well FPG. A greater percentage of subjects treated with dapagliflozin achieved target glycemic goals including HbA1c levels < 7% compared to subjects treated with placebo. The dapagliflozin 10 mg groups generally achieved greater reductions from baseline in HbA1c than the dapagliflozin 2.5 and 5 mg groups. Dapagliflozin treatment consistently demonstrated a lowering of body weight and blood pressure in a dose dependent fashion between 2.5 mg to 10 mg in monotherapy as well as add-on to other oral hypoglycemic agents or insulin studies.

1.4.2 Summary of Clinical Safety

1.4.2.1 MB102008

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

Dapagliflozin increases urinary excretion of glucose, a potential substrate for urinary and vaginal pathogens. Table 1.4.2.1 summarizes the percentage of reports of AEs related to urinary and genital infections, according to their preferred terms, for all subjects receiving dapagliflozin, placebo, and metformin.

Table 1.4.2.1: Proportion of Subjects with Adverse Events of Urinary or Genital Tract Infection by Treatment Allocation In Study MB102008

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

Changes in mean serum creatine kinase (CK) compared with baseline were small and inconsistent in all treatment groups. The maximum increase in mean serum CK was 25 mEq/L, observed in the 10 mg dapagliflozin treatment group at two weeks. An AE of

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

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

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

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

Mean standing systolic BPs decreased from baseline by 4 to 5 mmHg in the 10 to 50 mg dapagliflozin treatment groups, and by 2 to 3 mmHg at the lower doses; the placebo group changed by +0.8 mmHg and the metformin group by -0.3 mmHg. Mean changes in standing diastolic BPs ranged from -2.5 mmHg to +0.8 mmHg, without relationship to dose; changes of +1.0 mmHg and 0 mmHg were seen in the placebo and metformin groups. Orthostatic hypotension was reported in one subject receiving dapagliflozin at the 50 mg dose (0.4% of all dapagliflozin-treated subjects), and in no subjects receiving

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

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

Disturbances in serum electrolyte concentrations were infrequent. Hypokalemia and hyponatremia were both reported in one subject receiving dapagliflozin, (0.4% each of all subjects receiving dapagliflozin), and hypokalemia was reported in one subject on placebo (1.9% of subjects receiving placebo). The marked abnormality of hypokalemia (serum potassium ≤ 2.5 mEq/L) was seen in 2 subjects receiving the 50 mg dose, and no subjects in any other study group. Mean serum phosphorus compared with baseline increased by 0.2 mg/dL at the 20 mg and 50 mg doses, 0.1 mg/dL at the 5 mg and 10 mg doses, and was unchanged at the 2.5 mg dose. The marked abnormality of hyperphosphatemia (≥ 5.6 mg/dL for ages 17-65 years; ≥ 5.1 mg/dL for ages ≥ 66 years) was observed in 1 subject treated with 5 mg dapagliflozin, 3 subjects treated with 20 mg dapagliflozin, and 1 subject treated with metformin. Mean serum magnesium (Mg) concentrations increased up to 0.2 mEq/L. Mean serum uric acid concentrations declined by approximately 1 mg/dL at all dapagliflozin doses. Neither urolithiasis nor acute gouty arthritis was reported in dapagliflozin treated subjects.

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

Markers of bone metabolism, urinary C-telopeptide and deoxypyridinolone excretions, and serum osteocalcin concentration, increased compared with baseline in subjects treated with dapagliflozin. There were small increases in mean serum parathyroid hormone (PTH) concentration without apparent relationship to dose. The clinical significance of these findings is unknown.

1.4.2.2 Clinical Pharmacology Studies

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

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

At least 150 subjects have received dapagliflozin in clinical pharmacology studies. One hundred sixteen healthy subjects and at least 39 subjects with type 2 diabetes have received at least 1 single oral dose (2.5 to 500 mg and 5 to 100 mg, respectively) of dapagliflozin. Multiple daily oral doses (2.5 to 100 mg) of dapagliflozin were administered to 30 healthy subjects for up to 14 days, and at least 38 subjects with type 2 diabetes received multiple oral daily doses (5 to 100 mg) for up to 14 days.

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

To date, AEs of clinical interest in clinical pharmacology studies include hypoglycemia episodes and urinary and genital infection. In subjects treated with dapagliflozin, symptoms suggestive of hypoglycemia were reported by 1 healthy volunteer (treated with 20 mg dapagliflozin) and 2 subjects with type 2 diabetes (1 treated with 5 mg dapagliflozin and metformin and 1 subject treated with 25 mg dapagliflozin and metformin). All cases of hypoglycemia in subjects who received dapagliflozin resolved within 25 minutes, were categorized to be of mild or moderate intensity, and considered possibly related to the study drug by the Investigator. Vulvovaginal mycotic infection was reported by 2 subjects, both with type 2 diabetes, who received dapagliflozin (1 treated with 100 mg dapagliflozin and metformin and 1 subject treated with 25 mg

dapagliflozin). The events were judged by the Investigator to be mild in intensity and unlikely related to study drug. Laboratory data indicated the amount of glucose excreted in the urine by these subjects was not substantially higher than the mean amount of glucose excreted by other subjects in the same randomization groups. Both subjects participated at the same clinical site.

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

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

1.4.3 Other Clinical Studies

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

MB102007 is an open-label, parallel, single-dose study designed to assess the single-dose PK of dapagliflozin in subjects with type 2 diabetes with mild, moderate, or severe renal impairment compared with subjects with type 2 diabetes and healthy subjects with normal renal function. Forty subjects received a single oral dose of 50 mg dapagliflozin. Overall, there was no clear relationship between the frequency of AEs and the severity of renal function impairment. The results of this study are detailed in the Investigator brochure.

MB102009 is a Phase 2b study in subjects with type 2 diabetes treated with insulin and oral hypoglycemic agents (metformin and/or a thiazolidinedione [TZD]). Seventy one (71) subjects were randomized to 1 of 2 daily doses of dapagliflozin (10 or 20 mg) or placebo for a 12-week treatment period. The results of this study are detailed in the Investigator brochure.

Additional, ongoing, Phase 3 clinical studies are summarized in Table 1.4.3 below. The results of these studies are detailed in the Investigator brochure.

Table 1.4.3: Summary of Ongoing, Randomized, Double-Blind Phase 2b and 3 Studies

Study	Subject population	Planned N per arm/ N treated with dapagliflozin/ Total	Duration	Treatment arms Background therapy	Primary efficacy assessment
MB102013 Monotherapy vs placebo	Drug-naïve subjects with HbA1c 7.0% - 10.0%	70/420/490[a]	24 weeks + 78 wks	7 arms: dapagliflozin 2.5mg, 5 mg, or 10 mg, in the morning or evening, vs placebo Background therapy: None	Superiority: change in HbA1c at 24 wks vs placebo
	Drug-naïve subjects with HbA1c > 10.0% - 12.0%	35/70/70[b]	24 wks + 78 wks	2 arms: dapagliflozin 5 mg or 10 mg in the morning Background therapy: None	
MB102014 Add-on to metformin vs placebo	Subjects on metformin ≥ 1500 mg/day with HbA1c 7.0% - 10.0%	136/408/544[c]	24 wks + 78 wks	4 arms: dapagliflozin 2.5 mg, 5 mg, or 10 mg or placebo Background therapy: Metformin ≥ 1500 mg/day	Superiority: change in HbA1c at 24 wks vs placebo
D1690C00005 Add-on to a sulfonylurea vs placebo	Subjects on a sulfonylurea with HbA1c 7.0% - 10.0%	136/408/544[d]	24 wks + 24 wks	4 arms: dapagliflozin 2.5 mg, 5 mg, or 10 mg or placebo Background therapy: Glimepiride 4 mg/day	Superiority: change in HbA1c at 24 wks vs placebo
MB102030 Add-on to a thiazolidinedione vs placebo	Subjects on pioglitazone with HbA1c 7.0% - 10.5%	139/278/417	24 wks + 24 wks	3 arms: dapagliflozin 5 mg or 10 mg or placebo Background therapy: Pioglitazone ≥30 mg	Superiority: change in HbA1c at 24 wks vs placebo

Table 1.4.3: Summary of Ongoing, Randomized, Double-Blind Phase 2b and 3 Studies

Study	Subject population	Planned N per arm/ N treated with dapagliflozin/ Total	Duration	Treatment arms Background therapy	Primary efficacy assessment
D1690C00006 Add-on to insulin vs placebo	Subjects on insulin ≥ 30 IU/day with HbA1c 7.5% - 10.5%	161/483/644[e]	24 wks + 24 wks + 52 wks	4 arms: dapagliflozin 2.5 mg, 5 mg, or 10 mg or placebo Background therapy: Insulin ≥ 30 IU/day	Superiority: change in HbA1c at 24 wks vs placebo
D1690C00004 Add-on to metformin vs active comparator	Subjects on metformin ≥ 1500 mg/day with HbA1c 6.5% - 10.0%	373/373/746[f]	52 wks + 52 wks + 104 wks	2 arms: dapagliflozin titrated dose of 2.5-5-10 mg or glipizide titrated dose of 5-10-20 mg Background therapy: Metformin ≥1500 mg	Non-inferiority: change in HbA1c at 52 wks vs glipizide
MB102021 Initial combination with metformin vs active comparator	Treatment-naïve subjects with HbA1c 7.5% - 12.0%	200/400/600[g]	24 wks	3 arms: dapagliflozin 5 mg + metformin XR, dapagliflozin 5 mg, or metformin XR up to 2000 mg Background therapy: None	Superiority: change in HbA1c at 24 wks vs metformin alone and vs dapagliflozin alone
MB102029 Diabetes and moderate renal impairment	Subjects with type 2 diabetes and moderate renal impairment (eGFR 30 - 59 mL/min/1.73m^2) and with HbA1c 7.0% - 11.0%	84/168/252	24 wks + 28 wks	3 arms: dapagliflozin 5 mg or 10 mg, vs placebo. Background therapy: Any	Superiority: change in HbA1c at 24 wks vs placebo

Table 1.4.3: Summary of Ongoing, Randomized, Double-Blind Phase 2b and 3 Studies

Study	Subject population	Planned N per arm/ N treated with dapagliflozin/ Total	Duration	Treatment arms Background therapy	Primary efficacy assessment
MB102032 Second monotherapy vs placebo	Drug-naive subjects with HbA1c 7.0% – 10.0%	70/210/280[h]	24 wks	4 arms: dapagliflozin 1 mg, 2.5mg, or 5 mg once daily, or placebo. Background therapy: None	Superiority: change in HbA1c at 24 wks vs placebo
D1690C00012 Dual energy X-ray absorptiometry (weight and bone) Add-on to metformin vs placebo	Subjects on metformin ≥ 1500 mg/day with HbA1c 6.5% - 8.5%	91/91/182	24 wks + 78 wks	2 arms: dapagliflozin 10 mg or placebo. Background therapy: Metformin ≥1500 mg	Non-inferiority: change in body weight at 24 wks vs placebo
MB102034 Initial combination with metformin vs active comparator	Treatment-naïve subjects with HbA1c 7.5% - 12.0%	200/400/600	24 wks	3 arms: dapagliflozin 10 mg + metformin XR, dapagliflozin 10 mg, or metformin XR up to 2000 mg Background therapy: None	Superiority: change in HbA1c at 24 wks vs metformin alone and vs dapagliflozin alone
MB102035 Exploratory glomerular filtration rate	Subjects on metformin and/or a sulfonylurea with HbA1c 6.6% - 9.5% and inadequate blood pressure control	25/25/75	12 wks	3 arms: dapagliflozin 10 mg or hydrochlorothiazide 25 mg or placebo. Background therapy: metformin and/or sulfonylurea	Exploratory: change in baseline GFR at 12 weeks vs hydrochlorothiazide vs placebo

Table 1.4.3: Summary of Ongoing, Randomized, Double-Blind Phase 2b and 3 Studies

Study	Subject population	Planned N per arm/ N treated with dapagliflozin/ Total	Duration	Treatment arms Background therapy	Primary efficacy assessment
MB102045 - Clamp study	Failure on Metformin with or without an insulin secretagogue	22/22/44	12 wks	2 arms: dapagliflozin 5 mg or placebo. Background therapy: Metformin ≥500 mg/day + insulin secretagogue (a sulfonylurea, a glinide or a DPP-IVi), if applicable	Superiority: Change in insulin secretion at 12 weeks vs placebo
D1690C00010 Add-on to DPP4i versus Placebo (+/- background metformin)	DPP4i failure with HbA1c 7.2%-10 %, subjects taking DPP4i at screen with HbA1c 7.7 %-10.5 %, subjects not taking DPP4i at screen	108/108/432	24 weeks + 48 weeks	4 arms: dapagliflozin 10 mg or placebo Background therapy: sitagliptin 100 mg and metformin 1500 mg/day	Superiority: Change in A1c at 24 weeks vs placebo
D1690C00018 Cardiovascular high-risk study	Subjects with Type 2 Diabetes, Cardiovascular Disease and HTN with HbA1c 7.0% - 10.0% on existing therapy	470/470/940	24 weeks + 28 weeks	2 arms: dapagliflozin 10 mg vs placebo	Superiority: change in HbA1c and proportion of subjects meeting 3 item benefit criteria (HbA1c, weight, and systolic BP) at week 24 vs placebo

[a] For MB102013 (HbA1c 7.0%-10.0%), the actual N treated with dapagliflozin is 410 subjects for an actual total of 485 randomized subjects

[b] For MB102013 (HbA1c 10.1%-12.0%), the actual N treated with dapagliflozin is 73 subjects for an actual total of 73 randomized subjects

[c] For MB102014, the actual N treated with dapagliflozin is 409 subjects for an actual total of 546 randomized subjects

[d] For D1690C00005, the actual N treated with dapagliflozin is 450 subjects for an actual total of 597 randomized subjects

[e] For D1690C00006, the actual N treated with dapagliflozin is 610 subjects for an actual total of 807 randomized subjects

[f] For D1690C00004, the actual N treated with dapagliflozin is 400 subjects for an actual total of 801 randomized subjects

[g] For MB102021, the actual N treated with dapagliflozin is 203 subjects for an actual total of 598 randomized subjects

[h] For MB102032, the actual N treated with dapagliflozin is 214 subjects for an actual total of 282 randomized subjects

1.5 Overall Risk/Benefit Assessment

This protocol includes an experimental compound, dapagliflozin, being developed as a potential new therapy for hyperglycemia in subjects with type 2 diabetes. Other conventional treatments are currently available for subjects with type 2 diabetes and include insulin therapy and oral medications. Each of these conventional therapies entails risks and side effects that will not be reviewed here. In this study, the doses of dapagliflozin have been chosen to provide efficacy in reducing hyperglycemia and blood pressure while mitigating the potential for fluid and electrolyte imbalance. Pre-specified criteria have been included in the study for discontinuation of subjects with significantly worsened hyperglycemia or hypertension.

In completed clinical studies, dapagliflozin was generally safe and well-tolerated. No clinically relevant changes from baseline were seen in either renal functions or serum electrolytes in subjects treated with dapagliflozin. In Phase 2/3 studies, the frequency of overall adverse events (AEs) was similar to placebo. The majority of AEs was of mild intensity and did not require discontinuation. Overall, the frequency of genital infections was higher in subjects treated with dapagliflozin. The frequency of urinary tract infections (UTIs) was varied with a generally higher frequency observed in subjects treated with dapagliflozin. Infections were seen in both male and female subjects. A small dose-dependent increase in hematocrit was observed in dapagliflozin treated subjects without any associated clinically relevant events. There was no increased frequency of hyponatremia or hypotension observed in subjects treated with dapagliflozin, and no increase in the proportion of subjects with orthostatic hypotension compared with placebo. There were no trends in elevation of blood pressure in any of the studies. Blood pressure generally declined in the Phase 2 and 3 studies. Additional clinical safety and efficacy information is available in the Investigator Brochure.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

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

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

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

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

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to subjects. The investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates.

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

2.3 Informed Consent

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

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

Investigators must:

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

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

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

MB102077 is a Phase 3 trial to evaluate the effect of dapagliflozin 2.5 mg, 5 mg and 10 mg in subjects with type 2 diabetes who have inadequate glycemic control and inadequately controlled hypertension, while on a stable dose of an oral anti-diabetic (OAD) for at least 6 weeks (12 weeks for a TZD). Subjects will also be on a stable dose of an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) plus an additional antihypertensive medication for at least 4 weeks prior to enrollment.

For the purpose of this protocol, inadequate glycemic control and inadequately controlled hypertension have been defined as follows:

- **Inadequate glycemic control**: HbA1c $\geq 7.0\%$ and $\leq 10.0\%$ evaluated at the enrollment visit by the central laboratory.
- **Inadequately controlled hypertension**: Seated systolic BP (SBP) ≥ 140 and < 165 mmHg, **AND** seated diastolic BP (DBP) ≥ 85 and < 105 mmHg, each representing the mean of three determinations, evaluated at the enrollment and Day 1 visits.

Approximately 1104 subjects will be randomized into one of four treatment arms dapagliflozin 2.5 mg, 5 mg, or 10 mg QD or matching placebo QD (276 dapagliflozin 2.5 mg, 276 dapagliflozin 5 mg, 276 dapagliflozin 10 mg, 276 placebo) in a 1:1:1:1 ratio. Subjects will be treated for 12 weeks with a 4-week placebo lead-in period and a 1 week follow-up period.

Subjects will be randomized globally within strata according to their additional antihypertensive medication use (thiazide or thiazide-like diuretics versus calcium channel blockers, beta blockers or alpha adrenergic blockers).

Allowing approximately 11 months for subject recruitment, this study will be conducted over 15 months. The end of treatment will be the date the last subject takes the last dose of study medication during the treatment period. The end of the study will be the date of the last visit of the last subject participating in the study (end of the 1 week follow up period, Week 13).

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

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

The study design includes the following four study periods:

1) Qualification Period: up to 14 days following enrollment central laboratory samples collection. The exception is for subjects for whom re-test(s) was/were done in accordance with section 3.3.1 (see inclusion criteria 2 and 4 and exclusion criterion 33). In these subjects, the duration of the qualification period may exceed 14 days following enrollment central laboratory samples collection, and should be completed as soon as possible following receipt of the retested result(s). ***Note: The single-blind lead-in study medication and all the enrollment visit central laboratory results must have been received at the site prior to entry into lead-in Day -28 visit.***
2) Lead-in Period: 4 weeks ± 5 days.

3) Double-Blind Treatment Period: 12 weeks ± 5 days.
4) Follow -Up Period: 1 week ± 3 days.

3.1.1 Qualification Period

Subjects with type 2 diabetes who are on a stable dose of an oral anti-diabetic (OAD) for at least 6 weeks (12 weeks for a TZD), on a stable dose of an ACEI or ARB plus one additional medication (either a thiazide or thiazide-like diuretic or a calcium channel blocker, beta blocker or alpha adrenergic blocker) for hypertension for at least 4 weeks, will be eligible for protocol-specific assessments during the qualification period. Signature of the protocol-specific informed consent form constitutes the first procedure of the qualification period, followed by the assignment of a unique subject number by the IVRS. Protocol-specific assessments and procedures may then be performed, as part of the enrollment visit, to evaluate the subject's eligibility. The enrollment visit procedures may be completed on one or more days during the qualification period.

During the qualification period, subjects will maintain their stable dose of a commercially available OAD plus their stable dose of a commercially available ACEI or ARB and a stable dose of an additional commercially available antihypertensive medication (thiazide/thiazide-like diuretic, calcium channel blocker, beta blocker or alpha adrenergic blocker).

When all inclusion and exclusion criteria have been evaluated and the requirements for entry into the lead-in period have been met, the end of the qualification period / entry into lead-in period Day -28 visit will be scheduled. The end of the qualification period is the same day as the entry into lead-in period. Day -28 visit should be scheduled **within** 14 days of the enrollment central laboratory samples collection. The exception is for subjects for whom re-test(s) was/were done in accordance with Section 3.3 (see inclusion criteria 2 and 4 and exclusion criterion 33). In these subjects, the lead-in Day -28 visit should take place as soon as possible following receipt of the retested result(s).

3.1.2 Lead-In Period

Eligible subjects who complete the qualification period will have Day -28 visit performed and will enter the lead-in period. During the lead-in period, subjects will continue to maintain their stable dose of commercially available OAD, ACEI or ARB and will also continue to maintain their stable dose of an additional commercially available antihypertensive medication.

The lead-in period is a 4-week period during which subjects will receive single-blind placebo. Subjects will be instructed to take all study medication as well as their stable dose of ACEI or ARB and additional hypertensive medication once a day between 6am and 11am, at a similar time each day throughout the study. All medication (including blinded study medication, antihypertensive medications and OAD) must be withheld on the morning of each study visit. Compliance will be assessed based upon subject's interview, review of subject's log and a count of the blinded tablets returned at each visit and its importance will be stressed. The visit must be re-scheduled within 3 days if the study medication was not withheld accordingly.

Subjects will also receive diet and exercise counseling consistent with the American Diabetes Association (ADA) recommendations (or similar local guidelines). A Registered Dietitian, Registered Nurse, Physician, Certified Diabetes Educator, Nutritionist, or other qualified member of the study team who has appropriate documented training will provide this counseling.

Upon entry in the lead-in period Day -28, subjects will also be given a blood glucose meter and instructed on its use by site personnel. Subjects should demonstrate the ability to correctly perform self-monitoring of blood glucose (SMBG) during the lead-in period, as required per protocol (see Section 5.3.1).

A scheduled visit will occur at Day -14 to assess fasting plasma glucose (FPG), seated blood pressure and study compliance. **If the subject has a FPG > 270 mg/dl at this visit, FPG will be repeated within one week. If the repeated FPG value is > 270 mg/dl, the subject will be discontinued.** If the subject's seated blood pressure, determined from the mean of 3 replicated measurements, is > 180/110 mmHg at this visit,

the subject will be discontinued from the study. No ABPM or randomization procedures will be performed on subjects discontinued from the study at the Day -14 visit.

The lead-in period will also include 24-hr ABPM between Day -7 and Day -1 prior to randomization. The 24-hr ABPM should be initiated upon completion of all other lead-in visit procedures including administration of the single-blind study medication and between 6am and 11am to ensure trough BP measurements are obtained. Subjects should be instructed to withhold all medication (including blinded study medication, antihypertensive medications and OAD) on the morning of the study visit and to bring their medication to the visit with them. Once the ABPM cuff is in place, the subject should be instructed to take all morning medication while in the office. Initiation of the 24-hour ABPM must be re-scheduled within 3 days if the study medication was not withheld accordingly.

Note: If subjects are taking an additional antihypertensive medication (a (thiazide or thiazide-like diuretic, calcium channel blocker, beta blocker or alpha adrenergic blocker) that is dosed BID, the subject should take their evening dose at their normal daily time while the ABPM cuff is in place (ie, 12 hours ± 3 hours after the morning medication taken in the office).

The subjects should be scheduled to return to the site following completion of the 24-hr ABPM recording and instructed to withhold all morning medication (including blinded study medication, all antihypertensive medications and OAD) until the ABPM cuff is removed. The 24-hr ABPM data will be downloaded and immediately reviewed and assessed upon transmission. In the event of inadequate data collection (see Section 5.4.2.1), the 24-hr ABPM must be repeated and confirmed as adequate prior to scheduling the randomization visit.

Single-blind placebo will be used to assess subject's compliance with treatment. Subjects should demonstrate good compliance with study medication (≥ 70% and ≤ 130%) during the lead-in period to be eligible for entry into the double-blind treatment period. **For subjects with a compliance between ≥ 70% AND < 80% or > 120% AND ≤ 130%, the Investigator should ensure that there is no systematic factor which may result in unacceptable compliance with study medication during the treatment period of the**

trial. Such cases should be discussed with the Medical Monitor prior to randomization.

The lead-in period should be completed in 4 weeks ± 5 days.

3.1.3 Double-Blind Treatment Period

Following completion of the lead-in period, eligible subjects will enter into the randomized, double-blind, treatment period. Subjects will continue to maintain their stable dose of commercially available OAD, ACEI or ARB and additional antihypertensive medication. Subjects should also continue to take single-blind lead-in study medication throughout any randomization procedures performed on days prior to Day 1 randomization.

Randomization Visit

The first dose of double-blind study medication should only be administered on Day 1 AFTER ALL randomization visit procedures have been completed.

On Day 1, following completion of ALL randomization visit procedures, the IVRS will randomly assign subjects in a 1:1:1:1 ratio to receive one of the following double-blind treatment regimens:

- Dapagliflozin 2.5 mg QD
- Dapagliflozin 5 mg QD
- Dapagliflozin 10 mg QD
- Placebo QD

Subjects will be randomized globally within strata according to their additional antihypertensive medication use (thiazide or thiazide-like diuretics versus calcium channel blockers, beta blockers or alpha adrenergic blockers).

Subjects will be instructed to take all study medication as well as their stable dose of ACEI or ARB and additional hypertensive medication once a day between 6am and 11am, at a similar time each day throughout the study. If subjects are taking an additional

antihypertensive medication that is dosed BID, the subject should continue to take the evening dose at the normal daily time throughout the study (ie, 12 hours ± 3 hours after the morning medication is taken).

All medication (including blinded study medication, all antihypertensive medications and OAD) must be withheld on the morning of each study visit. Compliance with the daily dosing schedule will be evaluated by subject interview at each visit and its importance will be stressed. The study visit must be re-scheduled within 3 days if the study medication as well as the stable dose of ACEI or ARB and additional antihypertensive medication was not taken between 6am and 11am on the day preceeding the study visit and withheld the morning of the study visit, as instructed.

Dose titration of double-blind study medication is not permitted at any time during the treatment period. In addition, the stable dose of a commercially available OAD, ACEI or ARB and additional antihypertensive medication should remain unchanged for the entire duration of the study.

Double-Blind Treatment Period Visits:

Following randomization, subjects will be followed for a total of 12 weeks on double-blind study medication. Scheduled visits will occur at Weeks 2, 4, 8, and Week 12/Early Termination (ET).

Subjects who discontinue prematurely from the double-blind treatment period will have all Week 12/ET procedures completed prior to discontinuation.

Similar to the randomization visit procedures, Week 12/ET visit procedures should preferably be completed on the same day when possible, or on consecutive days, or, in subjects unavailable on consecutive days, no more than 1 day apart. The Week 12/ET procedures will include 24-hr ABPM (to be conducted within 1 week prior to the Week 12/ET visit). Initiation of the 24-hr ABPM should begin between 6am and 11am to ensure trough BP measurements are obtained. Subjects should be instructed to withhold all medication (including blinded study medication, all antihypertensive medications and OAD) on the morning of the study visit and bring their medication to the visit with them. Once the ABPM cuff is in place, the subject should be instructed to take all medication

while in the office. Initiation of the 24-hour ABPM must be re-scheduled within 3 days if the study medication was not withheld accordingly.

The subjects should be scheduled to return to the site following completion of the 24-hr ABPM recording and to withhold morning medication (including blinded study medication, all antihypertensive medications and OAD) until the ABPM cuff is removed.

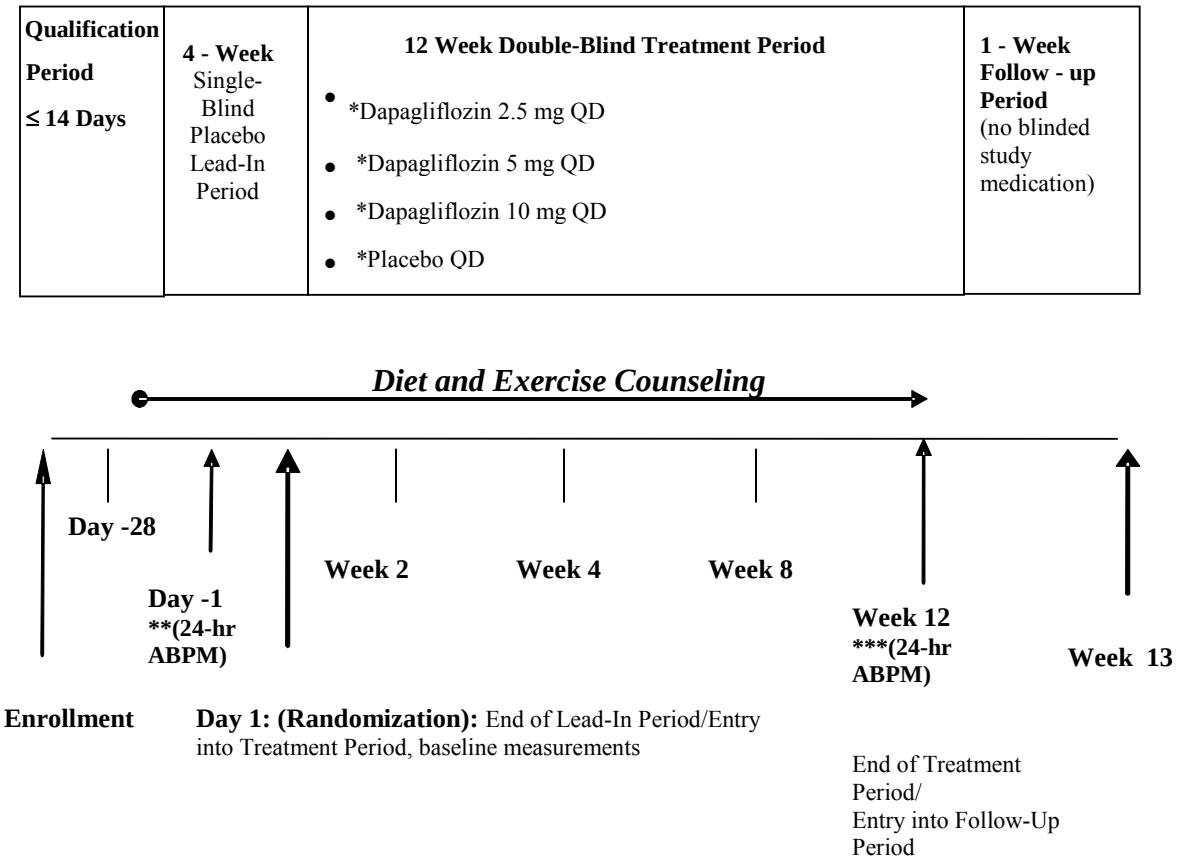
The 24-hr ABPM data will be downloaded and immediately reviewed and assessed upon transmission. In the event of inadequate data collection (see Section 5.4.2.1) the 24-hr ABPM must be repeated and confirmed as adequate prior to completing the Week 12/ET visit. Subjects must remain on study medication through the completion of the 24-hr ABPM and Week 12/ET procedures.

3.1.4 Follow-Up Visit

Following the 12 week double-blind treatment period subjects will be seen 1 week later for a scheduled Week 13 visit. This will be the conclusion of the study once all procedures are completed. During the follow-up period, subjects will not take any blinded study medication but will continue to maintain their stable dose of a commercially available OAD, ACEI or ARB and additional antihypertensive medication.

3.1.5 Study Schematic

Figure 3.1.5 Study Schematic



*** Subjects will also take their stable dose of commercially available OAD plus ACEI or ARB and an additional antihypertensive medication with their blinded medication.**
****24-hr Ambulatory Blood Pressure Monitoring (ABPM) during lead-in must be conducted between days -7 and -1, *prior* to randomization.**
*****24hr ABPM during Double-Blind period must be completed within 1 week prior to the Week 12/ET visit.**

3.2 Post Study Access to Therapy

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

3.3 Study Population

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

3.3.1 Inclusion Criteria

Signed Written Informed Consent

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

Target Population

2) Subjects must have type 2 diabetes with inadequate glycemic control, defined as central laboratory HbA1c ≥ 7.0% and ≤ 10.0% obtained at the enrollment visit.

   Note: A one-time central laboratory re-test of the HbA1c is allowed in subjects with an initial central laboratory HbA1c of 6.9% or 10.1% who are otherwise eligible, as determined by the Investigator.

3) Subjects must be on a stable dose of an OAD for at least 6 weeks (12 weeks for a TZD) prior to enrollment, stable doses of an ACEI or an ARB and one additional antihypertensive medication (either a thiazide or thiazide-like diuretic or a calcium channel blocker, beta blocker or alpha adrenergic blocker) for at least 4 weeks. Stable dose is defined as a dose that has remained the same for the specified number of weeks, as mentioned above, prior to the enrollment visit (ie, same prescribed total daily dose).

   Note: Subjects treated with more than one OAD (combination OAD medications) will be allowed as long as the doses of the combination OAD medications have been stable for the specified number of weeks.

   – Also refer to prohibited and/or restricted treatments section 3.4.1.

4) Subjects must have inadequately controlled hypertension, defined as seated SBP ≥ 140 and < 165 mmHg **AND** seated DBP ≥ 85 and < 105 mmHg, each representing the mean of three consecutive determinations, evaluated **at both the enrollment and Day -1 visits**.

   – ***Enrollment Visit Only: If the mean seated BP value obtained at enrollment visit does not meet the above definition, a one-time retest of seated BP within 3 days may be allowed, as determined by the Investigator, prior to the Day 1 visit.***

5) C-peptide ≥ 0.8 ng/mL (0.30 nmol/L).

6) BMI ≤ 45.0 kg/m^2 at the enrollment visit.

Age and Reproductive Status

7) Men and women ages must be ≥ 18 and ≤ 89 years old at the time of the enrollment visit. Men and women of childbearing potential (WOCBP) must be using an

acceptable method of contraception to avoid pregnancy throughout the study in such a manner that the risk of pregnancy is minimized. See Section 3.3.3 for the definition of WOCBP.

WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of investigational product. Women must not be breastfeeding

3.3.2 Exclusion Criteria

Target Disease Exceptions

1) History of diabetes insipidus
2) Symptoms of poorly controlled diabetes that would preclude participation in this trial including, but not limited to, marked polyuria and polydipsia with greater than 10% weight loss during the 3 months prior to enrollment, or other signs and symptoms.
3) History of diabetic ketoacidosis or hyperosmolar nonketotic coma.

Medical History and Concurrent Diseases

CV/Vascular Diseases:

4) History of malignant or accelerated hypertension.
5) Known or suspected secondary hypertension.

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

6) Myocardial infarction.
7) Cardiac surgery or revascularization (coronary artery bypass surgery [CABG]/ percutaneous transluminal coronary angioplasty [PTCA]).
8) Unstable angina.
9) Unstable congestive heart failure (CHF).
10) CHF New York Heart Association (NYHA) Class III or IV. (see Appendix 1)
11) Transient ischemic attack (TIA) or significant cerebrovascular disease.
12) Unstable or previously undiagnosed arrhythmia.

Metabolic Diseases

13) History of Gout

Renal Diseases

14) History of unstable or rapidly progressing renal disease.
15) Conditions of congenital renal glucosuria.
16) Renal allograft

Hepatic Diseases

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

Hematological and Oncological Diseases/Condition

20) History of hemoglobinopathy, with the exception of sickle cell trait (SA) or thalassemia minor; or chronic or recurrent hemolysis.
21) Donation of blood or blood products to a blood bank, blood transfusion, or participation in a clinical study requiring withdrawal of > 400 mL of blood during the 6 weeks prior to the enrollment visit.
22) Malignancy within 5 years of the enrollment visit (with the exception of treated basal cell or treated squamous cell carcinoma of the skin).
23) Known immunocompromised status, including but not limited to, individuals who have undergone organ transplantation or who are positive for the human immunodeficiency virus.

Central Laboratory Test Findings at Enrollment

24) Aspartate Aminotransferase (AST) > 3X Upper limit of normal (ULN).
25) Alanine aminotransferase (ALT) > 3X ULN.
26) Serum total bilirubin (TB) ≥ 1.5X ULN
27) Serum Creatinine (S_{Cr}) ≥ 2.0 mg/dL unless subject is on metformin then the exclusionary limits will be S_{Cr} ≥ 1.50 mg/dL (133 mmol/L) for male subjects; S_{Cr} ≥ 1.40 mg/dL (124 mmol/L) for female subjects
28) Estimated creatinine clearance (Crcl) of < 50ml/min
29) Hemoglobin ≤ 10.0 g/dL (100 g/L) for men; hemoglobin ≤ 9.0 g/dL (90 g/L) for women.
30) Creatine kinase (CK) > 3X ULN.
31) Positive for hepatitis B surface antigen.
32) Positive for anti-hepatitis C virus antibody.
33) Abnormal free T4 value.

Note: Abnormal thyroid stimulating hormone (TSH) value at enrollment will be further evaluated by 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.

Allergies and Adverse Drug Reaction

34) Allergies or contraindication to the contents of dapagliflozin tablets.

Other Exclusion Criteria

35) Obesity that would limit accurate blood pressure measurement
36) History of bariatric surgery or lap-band procedure.
37) Administration of sibutramine, phentermine, rimonabant, benzphetamine, diethylpropion, methamphetamine, orlistat, and/or phendimetrazine.
38) Prisoners or subjects who are involuntarily incarcerated
39) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness
40) Replacement or chronic systemic corticosteroid therapy, defined as any dose of systemic corticosteroid taken for > 4 weeks within 3 months prior to enrollment visit.

NOTE: Topical or inhaled corticosteroids are allowed.

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

Randomization Criteria:

Prior to randomization (first dose of double-blind study medication), the following criteria **MUST** be met:

- Subjects must have inadequately controlled hypertension, defined as SBP ≥ 140 and **<** 165 mmHg **AND** DBP ≥ 85 and < 105 mmHg, each representing the mean of three consecutive determinations, evaluated at both the enrollment and Day 1 visits.
- All non-central laboratory-related selection criteria evaluated at the enrollment visit have been met and have continued to be met throughout the lead-in period, and up to

the randomization visit. Central laboratory values that meet selection criteria at the enrollment visit are not required to meet the selection criteria at the entry into lead-in Day -28 visit. **However, in the event of new laboratory abnormalities noted at the entry into lead-in Day -28 visit, the Investigator should ensure that they do not represent new and significant comorbidity that would preclude safe participation in the protocol. Such cases should be discussed with the medical monitor.**

- No clinical conditions or clinically significant abnormalities, in any laboratory value(s) collected after enrollment and prior to randomization and/or ECG, which, in the Investigator's judgment, should preclude entry into the treatment period.
- Subjects should demonstrate good compliance with the administration of study medication (≥ 70% and ≤ 130%) during the lead-in period. **For subjects with a compliance between ≥ 70% AND < 80% or > 120% AND ≤ 130%, the Investigator should ensure that there are no systematic factors that may result in unacceptable compliance with study medication during the treatment period of the trial. Such cases should be discussed with the Medical Monitor prior to randomization.**
- Subjects should demonstrate the ability to perform SMBG as required per protocol (see Section 5.3.1).
- The total daily dose of commercially available OAD medication has remained stable since the enrollment visit.
- The total daily dose of commercially available ACEI or ARB and an additional antihypertensive medication has remained stable since the enrollment visit.

3.3.3 Women of Childbearing Potential

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

- Amenorrhea ≥ 12 consecutive months without another cause and a documented serum follicle stimulating hormone (FSH) level >35 mIU/mL
- Women with irregular menstrual periods and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL
- Women on hormone replacement therapy (HRT)

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

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

3.4.1.1 Prohibited Treatments

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

- Insulin
- Any injectable anti-diabetic medications (including GLP-1 agonists and amylin)
- Any additional oral anti-diabetic medications (other than the stable OAD medication (s) the subject is taking as described in inclusion criterion No.3).
- Antihypertensive medications other than **either** ACEI **or** ARB (as described in inclusion criterion No.3) unless the subject meets the criteria for severe or sustained hypertension (as described in section 3.5.1) and is eligible for antihypertensive rescue medication).
- Treatment with any systemic corticosteroid therapy that will involve ≥ 5 days of therapy (inhaled and topical are allowed). The medical monitor should be consulted prior to beginning therapy with corticosteroids for subjects who require systemic corticosteroid treatment.
- Administration of sibutramine, phentermine, rimonabant, benzphetamine, diethylpropion, methamphetamine, orlistat, and/or phendimetrazine.

3.4.1.2 Restricted Treatments

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

- Herbal/over-the-counter preparations:
  - St. John's Wort
  - Fenugreek
  - Flaxseed
  - Chromium
  - Ginseng
  - Natural agents marketed for lowering blood sugar such as Antibetic™, Alphabetic™, Diabetics™, DB-7™, Diabetica™, Diabetiks™, Dia-Comp™,DiaVite™, GlucoCare™, Gluotize™, GlycoNase™, SugarMax™ or Sugar Loss™.

3.4.2 Other Restrictions and Precautions

Subjects must comply with their prescribed dosing regimen to preserve study integrity and ensure subject safety.

Subjects should be cautioned that any new prescription, over-the-counter or herbal/nutritional therapies should be discussed thoroughly with the Investigator prior to initiation as concomitant use could result in alterations to their glycemic control and may place them at risk for significant hypoglycemic episodes.

- Subjects must make every attempt to adhere to the diet and exercise counseling (see Section 5.9.2) and to the protocol visit schedule (see Section 5.1.1).
- Women of child-bearing potential must immediately contact the Investigator if they suspect they might be pregnant and if they have changed or plan to change their birth control method (see Section 6.4).

3.5 Discontinuation of Subjects from Treatment

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

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy (see section 6.4)
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Clinical signs and symptoms of hypotension which, in the opinion of the investigator, indicate a need for less aggressive blood pressure treatment than specified in the protocol
- Protocol-defined lack of glycemic control (see Section 3.5.2)
- Sustained elevated S_{Cr} (see Section 3.5.3)
- Protocol-defined major hypoglycemia episode or recurrent non-major hypoglycemia episodes (see Section 3.5.4)
- Sustained elevated liver safety abnormalities (see Section 3.5.5)
- Sustained elevated CK (see Section 3.5.6)
- Sustained hyponatremia (see Section 3.5.7).

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

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

3.5.1 Guidelines for the addition of a supplemental antihypertensive medication to control Sustained or Severe Hypertension

Subjects will continue to receive their current stable dose of commercially available ACEI/ARB plus an additional anti-hypertensive medication throughout the study.

- **Criteria for Sustained Hypertension:**
  - If the subject's seated blood pressure, determined from the mean of 3 replicated measurements, is between 165-180 mmHg systolic and 105-110 mmHg diastolic at any visit following randomization, the subject should continue taking study drug and return for a repeat blood pressure check in 3 days. If the subject's blood pressure continues to be > 165/105 mmHg, the subject may be eligible to receive open-label antihypertensive rescue medication.
- **Criteria for Severe Hypertension:**
  - If the subject's seated blood pressure, determined from the mean of 3 replicated measurements, is > 180/110 mmHg at any visit following randomization, the subject may be eligible to receive open-label antihypertensive rescue medication.

Subjects that have sustained or severe hypertension (as defined above) at any post randomization visit during the double-blind treatment period may be eligible to receive open-label rescue medication. Rescue medication means the addition of an approved oral antihypertensive agent, used according to conventional standards of care, to treat hypertension which may therefore allow the subject to remain in the trial.

The rescue medication should be prescribed by the Investigator in accordance with the approved product label in the applicable country and will not be provided by the Sponsor.

All rescue decisions will be based on confirmed local measurements, and the Medical Monitor will be notified. BP rescue evaluations (seated, orthostatic and the 24 hour ABPM) will be performed, **prior to the first dose of rescue medication being administered.** A supplemental (unscheduled) visit eCRF will need to be completed to collect all BP rescue evaluations.

Note: If a subject needs rescue for hypertension, the ABPM done at time of rescue will be the last ABPM measurement for the study and will *not* be repeated 1 week prior to Week 12.

3.5.2 Discontinuation Guidelines Due to Protocol-Defined Lack of Glycemic Control

Subjects will continue to receive their current stable dose of commercially available OAD throughout the study. No new anti-diabetic therapy will be added during the study. At any

time following randomization, subjects with lack of glycemic control (defined at a FPG of > 270 mg/dl (central lab result) confirmed by a second central lab FPG > 270 mg/dl within one week) will be discontinued from the study for safety reasons. At this time, the Sponsor will be notified, and the Week 12/ET visit performed (see Section 5.3.8.1). Subjects will not receive rescue medication for lack of glycemic control at any time during the study.

3.5.3 Discontinuation Guidelines due to Sustained Elevated Serum Creatinine

In subjects taking commercially available metformin as their OAD

Subjects with a S_{cr} ≥ 1.50 mg/dL (133 μmol/L) but < 2.00 mg/dL (176 μmol/L) (males) or ≥ 1.40 mg/dL (124 μmol/L) but < 2.00 mg/dL (176 μmol/L) (females) **OR subjects (male or female) with an increase from baseline in S_{cr} of > 0.50 mg/dL (44.2 μmol/L), will have commercially available metformin withheld** and a confirmatory, repeat S_{cr} drawn within one week. Subjects with a S_{cr} ≥ 2.0 mg/dL (176 μmol/L) (males and females) **will have both double-blind medication and commercially available metformin** withheld and a confirmatory, repeat S_{cr} drawn within one week.

- If the repeat S_{cr} is < 1.50 mg/dL (133 μmol/L) (males) or < 1.40 mg/dL (124 μmol/L) (females), metformin may be resumed unless otherwise contraindicated.
- If the repeat S_{cr} is ≥ 1.50 mg/dL (133 μmol/L) (males) or ≥ 1.40 mg/dL (124 μmol/L) (females), the subject must be immediately discontinued from the study, the Sponsor notified, and the early termination visit performed (see section 5.3.8.1). **The Investigator will follow the subject until the event has resolved or stabilized.**

In subjects taking an OAD other than metformin

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

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

The following actions should be taken upon receipt of the central laboratory repeat S_{Cr} result:

- If the repeat S_{Cr} is < 2.0 mg/dL (176 μmol/L), double-blind study medication may be resumed unless otherwise contraindicated.
- If the repeat S_{Cr} is ≥ 2.0 mg/dL (176 μmol/L), the subject must be immediately discontinued from the study, the Sponsor notified, and the Week 12/ET visit performed (see Section 5.3.8.1). **The Investigator will follow the subject until the event has resolved or stabilized.**

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

Subjects will be discontinued from study medication if they experience severe and/or frequent hypoglycemia episodes, defined as ≥ 1 major episode or recurring non-major episodes in the event where the possibility of down-titration of contributing concomitant medication(s) (other than double-blind study medication), and/or other contributing factors (eg, excessive physical activity) have been evaluated and corrected. ***NOTE: Dose titration of double-blind study medication or commercially available metformin and/or TZD's is not permitted at any time during the treatment period. For subjects on an insulin secretagogue (such as sulphonureas, glinides, DPP IV inhibitors) as their commercially available OAD, the dose of the insulin secretagogue may be decreased.***

Major Episodes are defined as symptomatic episodes requiring external (3rd party) assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value < 54 mg/dL (< 3 mmol/L) and prompt recovery after glucose or glucagon administration

- Recurring Non-Major Episodes are defined as any recurrent hypoglycemia episodes, as determined by the Investigator, not meeting the definition of Major Episodes.

Section 5.3.1 provides additional guidance on management and reporting of hypoglycemia. **It is the Investigator's clinical assessment whether subjects who experience non-recurrent and non-major episodes of hypoglycemia should be discontinued from study medication.**

3.5.5 Discontinuation Guidelines due to Sustained Elevated Liver Safety Abnormalities

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

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

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

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

In each of these situations, study medication will be discontinued, the Sponsor notified and the Week 12/ET visit performed within 3 days of the confirmed laboratory results (see Section 5.3.8.1). At the Week 12/ET visit, medical history including details of risk

factors for liver diseases (if not previously assessed) will be requested and additional blood sampling performed (see Section 5.3.4 and Appendix 2). A referral consultation to a hepatologist or gastroenterologist (specializing in liver abnormalities) should be obtained.

Following the Week 12/ET visit, the Investigator should continue to monitor the subject's liver tests every 3 days following receipt of the prior laboratory results until the ALT and AST are ≤ 2X ULN or until ALT and AST are at or below baseline levels. The frequency of retesting can decrease to once a week or less if abnormalities stabilize and the subject is asymptomatic. (see Appendix 4).

3.5.6 Discontinuation Guidelines due to Sustained Elevated Creatine Kinase

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

- If the repeat CK is ≤ 10X ULN, double-blind study medication may be resumed unless otherwise contraindicated
- If the repeat CK is > 10X ULN, the subject must be immediately discontinued from the study, the Sponsor notified and the Week 12/ET visit performed (see Section5.3.8.1). **The Investigator will follow the subject until the event has resolved or stabilized.**

3.5.7 Discontinuation Guidelines due to Hyponatremia

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

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

- If the repeat of serum sodium, obtained within one week after resuming double-blind study medication, is < 130 mEq/L (130 mmol/L), the subject must be immediately discontinued from the study, the Sponsor notified and the Week 12/ET visit performed (see Section5.3.8.1). **The Investigator will follow the subject until the event has resolved or stabilized.**
- If the repeat of serum sodium, obtained within one week after resuming double-blind study medication, is ≥ 130 mEq/L (130 mmol/L), the subject may continue in the study and will be followed according to the protocol. Additional monitoring of serum sodium may be performed according to the local practice or Investigator's judgment.

- If the repeat serum sodium is < 130 mEq/L (130 mmol/L) **AND** there is no suspected new, temporary and reversible cause of hyponatremia based on clinical assessment (other than the administration of double-blind study medication), the subject must be immediately discontinued from the study, the Sponsor notified and the Week 12/ET visit performed (see Section5.3.8.1). **The Investigator will follow the subject until the event has resolved or stabilized.**
- If the repeat serum sodium is < 130 mEq/L (130 mmol/L) **AND** there is a suspected new, temporary and reversible cause of hyponatremia based on clinical assessment (other than the administration of double-blind study medication):
  - Double-blind study medication will continue to be withheld.
  - The suspected cause of hyponatremia should be identified and corrected.
  - Serum sodium should be re-tested within one week after the first repeat:
    - If the repeat of serum sodium, obtained within one week after the first repeat, is < 130 mEq/L (130 mmol/L):
      - The subject must be immediately discontinued from the study, the Sponsor notified and the Week 12/ET visit performed (see Section 5.3.8.1). **The Investigator will follow the subject until the event has resolved or stabilized.**
    - If the repeat of serum sodium, obtained within one week after the first repeat, is ≥ 130 mEq/L (130 mmol/L):
      - Double-blind study medication may be resumed unless otherwise contraindicated.
      - Serum sodium should be re-tested within one week after resuming double-blind study medication,
      - The subject may continue in the study and will be followed according to the protocol. Additional monitoring of serum sodium may be performed according to the local practice or Investigator's judgment.

For subjects whose serum sodium is between 126 and 129 mEq/L (126 and 129 mmol/L), the Investigator's clinical judgment should apply concerning whether such subjects should be followed according to the above algorithm (see Appendix 3 for algorithm flow chart).

4 TREATMENTS

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

4.1 Study Treatments

Table 4.1 A: Product Description: Single Blind Lead in Period (4 weeks)

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Placebo Matching Dapagliflozin 2.5/5mg Tablet	0mg	Bottle of 35 tablets/ Blinded	Patient Kit with 2 Bottles/ Blinded	Green, plain, diamond shaped, film coated tablet	Store at 15-25 DEG C (59-77 DEG F). Store in tightly closed container.
Placebo Matching Dapagliflozin 10mg Tablet	0mg	Bottle of 35 tablets/ Blinded	Patient Kit with 2 Bottles/ Blinded	Green, plain, diamond shaped, film coated tablet	Store at 15-25 DEG C (59-77 DEG F). Store in tightly closed container.

Table 4.1 B: Product Description: Double Blind Treatment Period (12 Weeks)

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Placebo Matching Dapagliflozin 2.5/5 mg Tablet	0mg	Bottle of 90 tablets/ Blinded	Patient Kit with 2 Bottles/ Blinded	Green, plain, diamond shaped, film coated tablet	Store at 15-25 DEG C (59-77 DEG F). Store in tightly closed container.
Placebo Matching Dapagliflozin 10mg Tablet	0mg	Bottle of 90 tablets/ Blinded	Patient Kit with 2 Bottles/ Blinded	Green, plain, diamond shaped, film coated tablet	Store at 15-25 DEG C (59-77 DEG F). Store in tightly closed container.
Dapagliflozin Tablet	2.5mg	Bottle of 90 tablets/ Blinded	Patient Kit with 2 Bottles/ Blinded	Green, plain, diamond shaped, film coated tablet	Store at 15-25 DEG C (59-77 DEG F). Store in tightly closed container.
Dapagliflozin Tablet	5mg	Bottle of 90 tablets/ Blinded	Patient Kit with 2 Bottles/ Blinded	Green, plain, diamond shaped, film coated tablet	Store at 15-25 DEG C (59-77 DEG F). Store in tightly closed container.
Dapagliflozin Tablet	10mg	Bottle of 90 tablets/ Blinded	Patient Kit with 2 Bottles/ Blinded	Green, plain, diamond shaped, film coated tablet	Store at 15-25 DEG C (59-77 DEG F). Store in tightly closed container.

4.1.1 Investigational Product

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

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

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

In this protocol, investigational product(s) is/are:

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

4.1.2 Noninvestigational Product

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

In this protocol, noninvestigational product(s) is/are:

- OAD
- ACEI or ARB
- An additional antihypertensive medication

All OAD, ACEI, ARB and additional antihypertensive medication will be commercially available and will <u>not</u> be provided by the Sponsor and must continue to be taken at a stable dose in accordance with the protocol, as applicable.

4.1.3 Handling and Dispensing

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

4.2 Method of Assigning Subject Identification

At the enrollment visit, each subject will be assigned a unique sequential subject number by the IVRS. The subject number will consist of five digits which are assigned sequentially (70001, 70002, 70003, etc,) by the IVRS. This number will be used for identification throughout the study and will not be used for any other participant.

At the time of entry into the lead-in period (Day -28 visit), the site will call IVRS in order for the single-blind lead-in medication to be assigned and dispensed.

Subjects who successfully complete the lead-in period and meet the criteria for entry into the treatment period (see Section 3.3), will be randomly assigned by the IVRS to one of the following 4 double-blind treatment groups in a 1:1:1:1 ratio:

- Dapagliflozin 2.5 mg QD
- Dapagliflozin 5 mg QD
- Dapagliflozin 10 mg QD
- Placebo QD

Randomization will be stratified based upon additional antihypertensive medication use. The two strata for randomization are defined as follows:

- Strata 1: thiazide or thiazide-like diuretics
- Strata 2: calcium channel blockers, beta blockers or alpha adrenergic blockers

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

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

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

4.3 Selection and Timing of Dose for Each Subject

Single-Blind Lead-In Period

Upon entry into the lead-in period (Day -28 visit), each subject will be provided a patient kit containing 2 bottles and will be instructed to take 1 tablet every day with the morning meal from each bottle, for the duration of the lead-in period. Subjects should also continue to take single-blind lead-in study medication throughout any randomization procedures performed on days prior to Day 1 randomization.

Double-Blind Treatment Period

Upon entry into the double-blind treatment period, after **ALL** randomization visit procedures have been completed, each subject will be provided 1 kit of blinded study medication containing Bottle A and Bottle B and will be instructed to take 1 tablet from each bottle every day with the morning meal, for the duration of the treatment period.

Follow-Up Period

No Blinded study medication will be taken during the follow-up visit.

Note: Throughout the study, subjects will also take their stable dose of commercially available OAD, ACEI or ARB and an additional antihypertensive medication.

4.3.1 Dose Modifications

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

In addition, the commercially available dose of OAD, ACEI or ARB and additional antihypertensive medication should remain unchanged for the entire duration of the study.

4.4 Blinding/Unblinding

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

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

4.5 Treatment Compliance

Each time blinded study medication is dispensed, compliance will be reinforced. When blinded study medication is returned, compliance will be assessed based upon subject’s interview, review of subject’s log 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.

The subject's compliance with OAD, ACEI or ARB and additional antihypertensive medication will be recorded in the designated eCRF pages. The dates of dosing, including interruptions, missed doses or overdose, must be recorded on the eCRF, based on subject's interview.

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

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

4.6.2 Return of Study Drug

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

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1A: Flow Chart for Protocol MB102077 - Qualification, Lead - in, Double Blind Treatment, and Follow - up Periods.

Procedure	Qualification Period	Lead-in Period			12 Week Double Blind Treatment Period					Follow -up	Notes
	Enrollment	Day -28	Day - 14	*Day -1	Day 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 13	*Day -1 visit may be performed between Day -7 and Day -1
Eligibility Assessments											
Obtain Informed consent	X										
Review Medical History	X				X						
Review Inclusion/Exclusion Criteria	X										
Review Randomization Criteria					X						
General Procedures											
Brief Physical Examination	X						X	X		X	See 5.3.5
Complete Physical Examination		X			X				X		See 5.3.5
Body Weight	X	X		X	X	X	X	X	X	X	

Table 5.1A: Flow Chart for Protocol MB102077 - Qualification, Lead - in, Double Blind Treatment, and Follow - up Periods.

Procedure	Qualification Period	Lead-in Period			12 Week Double Blind Treatment Period					Follow -up	Notes
	Enrollment	**Day -28**	**Day - 14**	***Day -1**	**Day 1**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 13**	*Day -1 visit may be performed between Day -7 and Day -1
Seated Blood Pressure/ Heart rate	X	X	X	X	X	X	X	X	X	X	Seated blood pressure must be taken in 3 replicate measurements. **See section 5.3.6**
Orthostatic BP and Heart Rate					X				X		Orthostatic B/P must be taken after seated B/P and must be supine and standing.

Table 5.1A: Flow Chart for Protocol MB102077 - Qualification, Lead - in, Double Blind Treatment, and Follow - up Periods.

Procedure	Qualification Period	Lead-in Period			12 Week Double Blind Treatment Period					Follow -up	Notes
	Enrollment	Day -28	Day - 14	*Day -1	Day 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 13	*Day -1 visit may be performed between Day -7 and Day -1
24-hr Ambulatory Blood Pressure Monitoring (ABPM)				X					X		Baseline 24-hr ABPM will be done between days -7 and -1. Week 12, 24-hr ABPM will be done within 1 week prior to the Week 12 visit. **Note: If a subject needs rescue for hypertension the ABPM must be done prior to administration of the first dose of rescue medication and will be the last ABPM measurement for the study.**
12-Lead ECG	X				X				X		
Height	X										
Body Mass Index (BMI)	X										

Table 5.1A: Flow Chart for Protocol MB102077 - Qualification, Lead - in, Double Blind Treatment, and Follow - up Periods.

Procedure	Qualification Period	Lead-in Period			12 Week Double Blind Treatment Period					Follow -up	Notes
	Enrollment	Day -28	Day - 14	*Day -1	Day 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 13	*Day -1 visit may be performed between Day -7 and Day -1
Review concomitant medications/procedures	X	X		X	X	X	X	X	X	X	
Contact IVR system	X	X			X				X		Call IVRS to register the enrollment, Day -28, and Day 1 visits as well as any change in subject status (ie, screening failure during the qualification period, discontinuation during the lead-in period, discontinuation from or completion of the double-blind treatment period).
Provide Diet and Exercise Counseling		X			X	X	X	X			
Dispense Glucose Meter and Supplies/ Provide Instructions		X			X		X				
Dispense Logs/Provide Instructions		X			X		X				

Table 5.1A: Flow Chart for Protocol MB102077 - Qualification, Lead - in, Double Blind Treatment, and Follow - up Periods.

Procedure	Qualification Period	Lead-in Period			12 Week Double Blind Treatment Period					Follow -up	Notes
	Enrollment	Day -28	Day - 14	*Day -1	Day 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 13	*Day -1 visit may be performed between Day -7 and Day -1
Review Study Logs				X	X	X	X	X	X		
Safety Assessments											
Assess Adverse Events		X	X	X	X	X	X	X	X	X	
Assess Genitourinary symptoms		X	X	X	X	X	X	X	X	X	
Assess Hypoglycemia episodes		X	X	X	X	X	X	X	X	X	
Assess Cardiovascular events		X	X	X	X	X	X	X	X	X	
Central Laboratory											
Pregnancy test (urine) WOCBP only	X				X	X	X	X	X		
Blood Standard Safety Laboratory Panel	X	X			X		X	X	X	X	
Urine Standard Safety Laboratory Panel	X	X			X		X	X	X	X	
Serum Uric acid		X			X		X	X	X	X	

Table 5.1A: Flow Chart for Protocol MB102077 - Qualification, Lead - in, Double Blind Treatment, and Follow - up Periods.

Procedure	Qualification Period	Lead-in Period			12 Week Double Blind Treatment Period					Follow -up	Notes
	Enrollment	Day -28	Day - 14	*Day -1	Day 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 13	*Day -1 visit may be performed between Day -7 and Day -1
Spot urine test for Uric Acid, Microalbumin, Glucose Quantification and Glucose: Creatinine Ratio		X			X		X	X	X	X	
HbA1c	X	X			X		X	X	X	X	
FPG	X	X	X		X		X	X	X	X	
Fasting C-peptide	X										
Fructosamine					X				X		
Fasting Serum Lipids (Total-C, LDL-C, HDL-C, TG)					X				X		
Hepatitis Screen Panel and TSH	X										The hepatitis screen panel includes hepatitis B surface antigen and anti-hepatitis C virus antibody.

Table 5.1A: Flow Chart for Protocol MB102077 - Qualification, Lead - in, Double Blind Treatment, and Follow - up Periods.

Procedure	Qualification Period	Lead-in Period			12 Week Double Blind Treatment Period					Follow -up	Notes
	Enrollment	**Day -28**	**Day - 14**	***Day -1**	**Day 1**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 13**	*Day -1 visit may be performed between Day -7 and Day -1
Drug Dispensing											
Dispense Study Medication		X			X						Those supplied by the sponsor or sourced by the investigator. The first dose of double-blind study medication should only be administered on **Day 1 AFTER ALL** randomization visit procedures have been completed.
Re-dispense Study Medication						X	X	X			
Review Study Medication Compliance			X	X	X	X	X	X	X		

5.1.1 Visit Scheduling and Visit Windows

Scheduled study visits will occur at:

- Qualification (corresponding to "screening" when calling into the IVRS)
- Lead-in Day -28 (corresponding to "enrollment" when calling into the IVRS)
  - Entry into lead-in Day -28 visit should be completed **up to 28 days** following enrollment central laboratory samples collection. The exception is for subjects for whom re-test(s) was/were done in accordance with Section 3.3 (see inclusion criteria 2 and 4 and exclusion criterion 33). In these subjects, the lead-in Day -28 visit should take place as soon as possible following receipt of the retested result(s). ***Note: The single-blind lead-in study medication and all enrollment visit central laboratory results must have been received at the site prior to entry into lead-in Day -28 visit.***
  - The lead-in period should be completed in 4 weeks ± 5 days.
- Randomization (corresponding to "randomization" when calling into the IVRS)
  - The randomization visit should occur 4 weeks ± 5 days after the Day -28 visit.
  - The IVRS should only be called upon completion of **ALL** randomization visit procedures.
- Weeks 2, 4, 8 and 12/ET of the double-blind treatment period
  - Throughout the double-blind treatment period, study visits should occur on the designated visit day ± 5 days (**based on randomization visit date**)

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

5.1.2 Subject Preparation

5.1.2.1 Regular Study Visits

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

- Subjects should arrive at the site between 6 AM and 10 AM.
- Subjects should be in a fasting state (at least 10 hrs).
- Subjects should refrain from tobacco, caffeine, and alcohol for 10 hours.

- Subjects should take blinded study medication, stable dose of commercially available OAD, ACEI or ARB, and additional hypertensive medication on the day preceding the study visit.
- Subjects should withhold their dose of blinded study medication, stable dose of OAD, ACEI or ARB and additional hypertensive medication on the visit date.

Note: The visit must be rescheduled within 3 days if the medication was not withheld accordingly.

5.2 Study Materials

BMS will supply the sites with the following materials:

- Blood glucose meters. One meter will be provided to each study subject at Day -28 visit and one additional meter will be provided to each investigative site
- Blood glucose test strips
- Lancets
- Glucose control solutions
- Subject logs for hypoglycemia episodes or events suggestive of hypoglycemia episodes reporting
- Paper Case Report Forms (CRFs) and/or Electronic Case Report Forms (eCRFs). [note: Paper CRF pages may be used for items such as Serious Adverse Events Forms, Pregnancy Surveillance Forms, Events of Special Interest] Sample source documentation worksheets
- Sample source documentation worksheets
- Patient education material and site support tools
- Study drug inventory control forms
- Pre-Screening Logs

The sites will have available a well-calibrated scale for body weight measurement, a 12-lead ECG machine, and a calibrated BP machine for vital signs assessment.

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

The central ABPM vendor will provide the ABPM devices and associated supplies, including the Manual of Instructions.

5.3 Safety Assessments

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

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

5.3.1 Self-Monitoring of Blood Glucose (SMBG)

Glucose meters will be supplied to each study site. At the entry into lead-in Day -28 visit, subjects will receive a glucose meter, supplies and instruction on their use. Supplies will be provided to allow for approximately 60 blood glucose assessments per month for the duration of the study. **The Investigator may require more frequent readings based on local clinical practice.** Subjects should bring their glucose meter with them to each study visit to ensure that it is functioning properly. Subjects may keep the glucose meters at the end of the study.

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

The memory of the glucose meter should be reviewed to compare with the subject's hypoglycemia episode log, as applicable. The glucose values should be reviewed by the site to identify any unusual high or low values, and to confirm that the values (from the glucose meter's memory and/or from the subject's hypoglycemia log) were obtained for the subject. If fingerstick glucose values are discordant from glycemic control assessed by the central laboratory or with clinical symptoms, the subject's glucose meter should be tested and the procedure for using it reviewed with the subject.

Guidance on Management and Reporting of Hypoglycemia Episodes

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

Study subjects must be properly instructed on the recognition and management of hypoglycemia. **Subjects should record in their personal log books any hypoglycemic symptoms.** They should be encouraged to measure, when possible, their blood glucose values when they have symptoms of hypoglycemia. In accordance with ADA standards of treatment[8], subjects should carry with them easily ingestible forms of carbohydrate at all times in order to treat an event of hypoglycemia should it occur.

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

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

5.3.2 Guidance on Assessment of Urinary and Genital Infections

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

Asymptomatic bacteriuria is defined as the presence of ≥ 10^5 colony forming units/mL of bacteria, in a properly collected voided urine specimen, without signs or symptoms typically attributed to urinary tract infection.[9] Asymptomatic bacteriuria is prevalent among diabetic women, and is associated with pyuria in 70% of cases.[9] Neither the Infectious Diseases Society of America nor the U.S. Preventive Services Task Force recommends screening for, or treatment of, asymptomatic bacteriuria in non-pregnant diabetic patients.[9,10] In this study, the central laboratory will not routinely report the results of urinary dipstick tests for leukocyte esterase as a screening test for pyuria in surveillance urine examinations.

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

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

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

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

other vaginal pathogens. A urine culture is not required for diagnosis of genital infections.

It is the investigator's responsibility to report, as applicable based on Investigator's judgment and subject's medical history, related adverse events as defined in Section 6.0. Additional information, including but not limited to completion of supplemental eCRFs may be requested for certain adverse events and/or laboratory abnormalities which are reported/identified during the course of the study.

5.3.3 Guidance on Assessment of Cardiovascular Events

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

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

- Death, including:
  - Cardiovascular Death
  - Non-cardiovascular Death
- Myocardial Infarction (MI), including:
  - ECG and/or cardiac enzymes confirmed MI
  - Sudden death
  - Percutaneous Coronary Intervention (PCI)-related MI
  - Coronary Artery Bypass Graft (CABG)-related MI
  - MI diagnosed via pathologic criteria
  - Silent MI
- Fatal and Non-fatal Stroke, including:
  - Ischemic Stroke
  - Hemorrhagic stroke
- Serious Adverse Events of the following:
  - Heart failure
  - Cardiac arrhythmia
  - Unstable angina

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

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

5.3.4 Guidance on Assessment of Hepatic Laboratory Abnormalities

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

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

- AE assessment
- Physical Examination for jaundice and other signs of liver diseases
- Review of relevant risk factors and current history focusing on possible causes of the increased ALT and/or AST and/or TB, including:
  - Use of suspect concomitant medication [including over-the-counter (ie, acetaminophen/paracetamol), herbal and vitamin preparations]
  - Recent alcohol consumption or recreational drug/narcotic use
  - Recent unaccustomed physical exertion
  - Occupational or environmental exposure to hepatotoxins
  - Other conditions which may cause liver diseases or which may cause abnormal test results
- Specialized Liver Laboratory Panel (see Appendix 2)

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

For subjects who are discontinued from the study as a result of sustained elevated liver safety abnormalities as described in Section 3.5.5, additional blood sampling must be done within 3 days of the confirmed laboratory results (see Appendix 2), in conjunction with a Week 12/ET visit, in addition to the procedures noted above. A referral consultation to a hepatologist or gastroenterologist (specializing in liver abnormalities) should be obtained. Any additional tests and/or examinations should be carried out at the discretion of the Investigator. **Any further investigations and laboratory results for subjects with abnormal laboratory values at the follow-up visit should be made available to the Sponsor upon request.**

5.3.5 Physical Examination

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

5.3.6 BP and Heart Rate

BP and heart rate (HR) measurements must be taken consistently throughout the study. Only use either the right or the left arm when measuring these parameters. Document which arm was used along with the observer's initials. The same arm should be used for each position and at each visit.

All measurements should occur at least 10 hours after the last ingestion of caffeine, alcohol, or nicotine.

At the randomization visit, it is crucial that the BP measurement and heart rate be obtained prior to the first dose of double-blind study medication.

5.3.6.1 Seated BP and Heart Rate

Seated blood pressure (BP) and heart rate (HR) will be measured at every visit. The subject should first rest for at least 10 minutes in the seated position. Seated blood BP will be determined from the mean of 3 replicated measurements obtained at least 1 minute apart. However, if the 3 consecutive seated BP readings are not within **8 mm Hg** of each other, an additional two BP readings should be obtained (total = 5) and incorporated into the calculated mean for systolic BP and diastolic BP to be reported in the eCRF. For the initial BP recording, BP should be measured in both arms. If the pressure is higher in one arm than the other, then this arm must be used for BP measurement. If there is no difference in the BP measurements between arms, use the subject's dominant arm for all future BP measurements. If possible, BP should be measured by the same person, with the same device at each visit.

Please follow the standardized steps outlined below for <u>seated</u> measurements:

- Situate the individual in a quiet environment with the feet flat on the floor, the back against the chair and with the arm resting on a table or other support so that the midpoint of the cuff is at the level to the heart.
- Use only a calibrated blood pressure monitor and/or manual sphygmomanometer.
- Select an appropriately sized cuff. Bladder width should be at least 40% of arm circumference; bladder length should be at least 80% circumference.
- Record the measurements with the date and time in the subject chart.
- Record the subject's position, the arm used for the measurement and the name of the person recording the measurement.
- Wait 1 minute before repeating the BP measurements in the same arm to permit the release of blood trapped in the arm veins.
- Calculate the mean BPs

5.3.6.2 Orthostatic BP and Heart Rate

At selected visits where orthostatic BP and heart rate are measured (including rescue for hypertension), measurements should be obtained following completion of seated BP and heart rate measurement and prior to administration of study medication.

The supine BP and HR must be measured prior to the standing BP. The subject should rest in the supine position for at least 5 minutes prior to measurement of BP and HR. Supine BP will be determined from three replicate measurements obtained at least 1 minute apart. The average BP and HR will be determined from these 3 replicate measurements and reported in the eCRF.

The subject will then stand for 2 to 3 minutes. After this time, measure the BP with the arm supported at the antecubital fossa at heart level. Standing BP and HR will be determined from 3 replicate measurements obtained at least 1 minute apart. The average BP and HR will be determined from these three replicate measurements and reported in the eCRF.

5.3.7 12-Lead Electrocardiogram (ECG)

ECGs will be performed at Enrollment, Day 1 and Week 12/ET visits.

The Investigator should review and assess all ECGs for any clinically significant abnormalities, and initial and date the report. The Day 1 visit 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

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

5.3.8 Early Termination Visits and Supplemental Visits

5.3.8.1 Early Termination Visit (Week 12/ET visit)

Any subject who is discontinued from the double-blind treatment period must have Week 12/ET visit procedures including 24-hr ABPM performed at the time of study discontinuation.

Subjects who discontinue between Randomization and Week 12 visits due to Sustained Elevated Liver Safety Abnormalities:

- Subjects who discontinue study medication during the double-blind treatment period due to sustained elevated liver safety abnormalities discontinuation criteria should also have additional blood samples collected at the time of discontinuation (see Appendix 2). A "Liver Discontinuation" visit laboratory kit will need to be used to collect recommended blood samples. Additionally, supplemental (unscheduled) visit eCRF pages as well as supplemental eCRFs will need to be completed to collect "Liver Discontinuation" information (see Section 5.3.4).

The IVRS must be called to record the subject status (ie, discontinuation status). The Week 12/ET eCRF will need to be completed. The Investigator will discharge the subject from the study and arrange appropriate follow-up care, if applicable.

5.3.8.2 Supplemental 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 page(s) of the eCRF must be completed.

5.4 Efficacy Assessments

5.4.1 Primary Efficacy Assessment

- The co-primary efficacy assessments are to compare the change from baseline in **seated systolic blood pressure** after 12 weeks of double-blind treatment between each dapagliflozin (2.5 mg, 5 mg, and 10 mg) treatment group and the placebo treatment group **AND** to compare the change from baseline in **HbA1c** after 12 weeks of double-blind treatment between each dapagliflozin (2.5 mg, 5 mg, and 10 mg) treatment group and the placebo treatment group.

5.4.2 Secondary Efficacy Assessments

The secondary efficacy assessments are:

- To compare the change from baseline in **24 hour ambulatory systolic blood pressure** after 12 weeks of double-blind treatment between each dapagliflozin (2.5 mg, 5 mg, and 10 mg) treatment group and the placebo treatment group.
- To compare the change from baseline in **seated and 24 hour ambulatory diastolic blood pressure** after 12 weeks of double-blind treatment between each dapagliflozin (2.5 mg, 5 mg, and 10 mg) treatment group and the placebo treatment group.
- To compare the change from baseline in **serum uric acid** after 12 weeks of double-blind treatment between each dapagliflozin (2.5 mg, 5 mg, and 10 mg) treatment group and the placebo treatment group.

5.4.2.1 24-hr Ambulatory Blood Pressure (ABPM)

Ambulatory blood pressure monitoring (ABPM) will be performed twice during the study, at baseline between Day-7 and Day -1 and at the end of study, within 1 week prior to Week 12/ET visits, for a duration of 24-hrs each time. If the subject meets criteria for rescue due to hypertension, the second ABPM will be performed prior to the first dose of rescue medication. Each site will receive training on the process, equipment, subject instruction and preparation, device placement, procedures for operating the ABPM equipment, data quality and procedures for transmitting the ABPM data to a central ABPM vendor.Each site will be provided with a training manual, which will include the details on the ABPM procedure.

The ABPM units will be calibrated, applied and used per the manufacturer's and the central ABPM vendor instructions. Following initiation of the 24-hr ABPM at the study site, the subject will return home with instructions to continue their normal daily activities. The subject will return the ABPM unit to the site following completion of the 24-hr recording, for data transfer to the central ABPM vendor.

The 24-hr ABPM data will be downloaded and immediately reviewed and assessed upon transmission. In the event of inadequate data collection, the 24-hr ABPM must be repeated and confirmed as adequate between Day -7 and Day -1 (prior to scheduling the randomization visit) or at end of study, 1 week prior to Week 12/ET visit ABPM.

Inadequate ABPM data collection may include, but is not limited to:

- Duration of ABPM < 24-hrs
- Less than 80% of successful readings
- Two or more consecutive hours of missing data

Timing of Administration of Blinded Study Medication and Commercially Available OAD, ACEI or ARB and additional antihypertensive medication

- Initiation of the 24-hr ABPM should begin between 6am and 11am to ensure trough BP measurements are obtained.
- Subjects should be instructed to withhold all medication (including blinded study medication, OAD, ACEI or ARB and additional hypertensive medication) on the morning of the study visit and to bring their medication to the visit with them.

Note: Initiation of the 24-hour ABPM must be re-scheduled within 3 days if the study medication was not withheld accordingly.

- Once the ABPM cuff is in place, the subject should be instructed to take all morning medication while in the office.
- If subjects are taking an additional antihypertensive medication (a thiazide or thiazide-like diuretic, calcium channel blocker, beta blocker or alpha adrenergic blocker) that is dosed BID, the subject should take their evening dose at their normal daily time while the ABPM cuff is in place (ie, 12 hours ± 3 hours after the morning medication taken in the office).
- The subjects should be scheduled to return to the site following completion of the 24-hr ABPM recording and to withhold medication (including blinded study medication, OAD, ACEI or ARB and additional hypertensive medication) until the ABPM cuff is removed.

5.4.2.2 Serum Uric Acid

Central laboratory serum uric acid levels will be determined at the Day -28, Day 1, Weeks 4, 8, 12 and Week 13 visits.

5.4.3 Other (Exploratory) Efficacy Assessments

The other (exploratory) efficacy assessments in this study are:

- To assess the **proportion of subjects achieving goal blood pressure**, defined as blood pressure < 130/80 mmHg, after 12 weeks of double-blind treatment between each dapagliflozin (2.5 mg, 5 mg, and 10 mg) treatment group and the placebo treatment group.
- To assess the **proportion of subjects achieving improved blood pressure control,** defined as a blood pressure of < 140/90 mmHg, after 12 weeks of double-blind treatment between each dapagliflozin (2.5 mg, 5 mg, and 10 mg) treatment group and the placebo treatment group.
- To assess the change from baseline in **fasting plasma glucose** after 12 weeks of double-blind treatment between each dapagliflozin (2.5 mg, 5 mg, and 10 mg) treatment group and the placebo treatment group.
- To assess the change from baseline in **ambulatory daytime (6am – 10pm) and nighttime (10pm – 6am) systolic and diastolic blood pressure** after 12 weeks of

double-blind treatment between each dapagliflozin (2.5 mg, 5 mg, and 10 mg) treatment group and the placebo treatment group.

- To assess the change from baseline in **uric acid excretion** (by spot urine test) after 12 weeks of double-blind treatment between each dapagliflozin (2.5 mg, 5 mg, and 10 mg) treatment group and the placebo treatment group.

5.5 Pharmacokinetic Assessments

Not Applicable

5.6 Pharmacodynamics Assessments

Not Applicable

5.7 Pharmacogenomic/Pharmacogenetic Assessments

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

5.8 Outcomes Research Assessments

Not Applicable

5.9 Other Assessments

5.9.1 Weight Measurement

Total body weight will be measured at every scheduled visit. Measurement of weight should be performed with the subject dressed in indoor clothing, shoes removed, and bladder empty. Subjects should be weighed on the same scale at all visits.

5.9.2 Diet and Exercise Counseling

Starting at entry into lead-in Day -28 visit and for the duration of the study, subjects will be instructed on a diet and an exercise program in accordance with the ADA (or similar local guidelines).

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

5.9.3 Height Measurement

Measurement of height should be performed at the enrollment visit with the subject's shoes removed. The subject's knees should be straightened, head held erect, and eyes forward.

5.9.4 Body Mass Index

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

- Use actual height (see Section5.9.3) and weight
- If the subject was not weighed in kg, convert pounds (lbs) to kilograms (kg = lb / 2.2).
- Similarly, convert inches (in) to centimeters (cm = in X 2.54).
- BMI = (weight in kg) / (height in cm/100)^2.
- Round to one decimal place (if 0.05 or greater, round up).

5.9.5 Survey of Subject Vital Status

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

6 ADVERSE EVENTS

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

disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

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

6.1 Serious Adverse Events

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

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

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

Although pregnancy, overdose and cancer are not always serious by regulatory definition, these events must be handled as SAEs for data transmission purposes (See Section 6.1.1 for reporting pregnancies).

NOTE:

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

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or event life threatening)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

6.1.1 Serious Adverse Event Collection and Reporting

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

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

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

SAEs must be recorded in the eCRF, pregnancies on a Pregnancy Surveillance Form. SAEs, whether related or not related to study drug, and pregnancies must be reported to ICON Clinical Research within 24 hours, by entering the SAE into the eCRF or Pregnancy Surveillance Form.

In the rare event that the Oracle Clinical Remote Data Capture (OC RDC) system is off-line and a patient experiences a Serious Adverse Event, the site will call the **ICON SAE hotline** numbers and complete the 2 part SAE form and fax to I**CON Medical Affairs within 24-hours** using the I**CON Medical Affairs and Drug Safety SAE Fax Number** provided in the **BMS Contact Information List.**

In the event that the ICON Medical Monitor/Contact cannot be reached, the alternate BMS contact is:

Bristol-Myers Squibb Medical Monitor:

Office:
Fax:

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.). All original paper SAE Forms (if used) and Pregnancy Surveillance Forms are to remain on site.

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE eCRF should be completed within 24 hours and reported to ICON using the same procedure used for transmitting the initial SAE.

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

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

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

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

6.3 Laboratory Test Abnormalities

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

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy.

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

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject or a female partner of a male study participant is pregnant or may have been

pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued for the female study participant in an appropriate manner (eg, dose tapering if necessary for subject safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

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

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

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

6.5 Overdose

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

6.6 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Refer to section 5.3.3

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The co-primary endpoints are the change in seated systolic blood pressure from baseline at Week 12 and the change in HbA1c at Week 12, or the last post-baseline measurement prior to Week 12, if no Week 12 assessment is available.

The first primary objective is to compare the differences in mean change between each dapagliflozin (2.5 mg, 5 mg and 10 mg) treatment group and the placebo treatment group in seated systolic blood pressure. With 262 subjects per treatment group with post-baseline measurements, there is at least 90% power to detect a difference of 4.5 mmHg in mean change from baseline in seated systolic blood pressure between each (2.5 mg, 5 mg and 10 mg) dapagliflozin treatment group and placebo treatment group at significance level of 0.017, assuming a standard deviation (SD) of 14 mmHg. If the result for the first primary endpoint is significant then a test for the second primary endpoint will be conducted. With 262 subjects per treatment group with post-baseline measurements, there is at least 96% power to detect a difference of 0.4% in mean change from baseline in HbA1c between each dapagliflozin (2.5 mg, 5 mg and 10 mg) treatment group and the placebo treatment group at significance level of 0.017, assuming a SD of 1.1%. Overall, with 262 subjects per treatment group, there is at least 86% power to detect 1 dapagliflozin treatment group that meets both co-primary endpoints with overall Type I error controlled at the 0.05 significance level (using Bonferroni's adjustment).

The primary comparisons are between each of the dapagliflozin (2.5 mg, 5 mg and 10 mg) treatment groups and the placebo treatment group. Each comparison between the dapagliflozin treatment group and placebo treatment group will be performed at the two-sided 0.017 level, using Bonferroni's adjustment so the family-wise Type I error rate is controlled at the 0.05 significance level.

Assuming 5% of the subjects do not have a post-baseline assessment, a total of 1104 subjects (276 subjects for each dapagliflozin treatment group and placebo treatment group) need to be randomized.

8.2 Populations for Analyses

Two efficacy data sets are specified for this study:

- The primary efficacy data set will consist of all randomized subjects who receive at least one dose of double-blind study medication. In addition, randomized subjects must have both a baseline and at least one post-baseline measurement for the time point under consideration to be included in the efficacy analysis of change from baseline.
- The secondary efficacy data set is a subset of the primary data set excluding primary efficacy variable data which may have been affected by protocol deviations as determined by the Medical Monitor. All decisions to exclude data from the primary data set will be made prior to the unblinding of the study.

The co-primary efficacy variables of change from baseline in seated systolic blood pressure and change from baseline in HbA1c will be reanalyzed using the secondary efficacy data set only if more than 10% of the subjects in any regimen are found to significantly violate the terms and conditions of the protocol. Otherwise, efficacy analysis will be restricted to the primary efficacy data set.

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

8.3 Endpoint Definitions

The co-primary endpoints are the change in seated systolic blood pressure and the change in HbA1c from baseline at Week 12, or the last post-baseline measurement prior to Week 12, if no Week 12 assessment is available. For subjects rescued for hypertension, measurements obtained after initiation of rescue medication will not be considered in calculating the co-primary endpoint of seated systolic blood pressure.

The secondary endpoints include the change in 24 hour ambulatory systolic blood pressure from baseline at Week 12, or the last post-baseline measurement prior to Week 12, if no Week 12 assessment is available, the change in seated and 24 hour ambulatory diastolic blood pressure from baseline at Week 12, or the last post-baseline measurement prior to Week 12, if no Week 12 assessment is available and the change in serum uric acid from baseline at Week 12, or the last post-baseline measurement prior to Week 12, if no Week 12 assessment is available. For subjects rescued for hypertension, measurements obtained after initiation of rescue medication will not be considered in calculating the secondary endpoints of 24 hour ambulatory systolic blood pressure and seated and 24 hour ambulatory diastolic blood pressure.

8.4 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, for all changes from baseline to a specific time point post-baseline, analyses will be based on measurements available at that time point or the last post-baseline measurement prior to that time point, if no measurement is available at that time point, ie, last observation carried forward (LOCF). For subjects who started anti-hypertensive rescue medication on the day of, or prior to, the specific time point, their last post-baseline measurement prior to the time and date of the first dose of rescue medication will be used for analyses of all blood pressure measurements.

8.4.2.1 Primary Analysis

The co-primary efficacy analysis will compare the change in seated systolic blood pressure from baseline at Week 12 and change in HbA1c from baseline at Week 12 for each dapagliflozin (2.5 mg, 5 mg and 10 mg) treatment group and the placebo treatment

group. The primary analysis will be conducted using a hierarchical testing procedure to maintain the overall 0.05 significance level.

The first primary analysis for the change in seated systolic blood pressure from baseline at Week 12 will be based on an analysis of covariance (ANCOVA) model with treatment group as the effect and baseline seated systolic blood pressure value and randomization strata as the covariates. Point estimates and 95% confidence intervals for the mean change within each treatment group as well as for the differences in mean change between each dapagliflozin (2.5 mg, 5 mg and 10 mg) treatment group and placebo treatment group will be estimated. P-values will be calculated to compare the treatment effect in each of the dapagliflozin (2.5 mg, 5 mg and 10 mg) treatment groups to that in the placebo treatment group. Each treatment group comparison will be performed at the two-sided 0.017 significance level, using Bonferroni's adjustment so the family-wise Type I error rate is controlled at the 0.05 significance level.

If the result for the first primary endpoint is significant then a test for the second primary endpoint will be conducted. The second primary analysis for the change in HbA1c from baseline at Week 12 will be based on an ANCOVA model with treatment group as the effect and baseline HbA1c value and randomization strata as the covariates. Point estimates and 95% confidence intervals for the mean change within each treatment group as well as for the differences in mean change between each dapagliflozin (2.5 mg, 5 mg and 10 mg) treatment group and placebo treatment group will be estimated. If the first primary endpoint for a treatment group was significant at the 0.017 significance level then p-values will be calculated to compare the treatment effect in that dapagliflozin treatment group to that in the placebo treatment group for the second primary endpoint. Each treatment group comparison will be performed at the two-sided 0.017 significance level, using Bonferroni's adjustment so the family-wise Type I error rate is controlled at the 0.05 significance level.

8.4.2.2 Secondary Analyses

The family-wise Type I error rate related to the primary and secondary efficacy endpoints will be controlled at the 2-sided 0.05 level within each treatment group by using a hierarchical closed testing procedure. In other words, the hierarchical closed testing procedure will handle each investigative treatment separately.

Specifically, if both co-primary comparisons (both change in seated systolic blood pressure and change in HbA1c) between a dapagliflozin treatment group and the placebo group are significant at the 0.017 level, then the secondary efficacy endpoints for that treatment group will be performed. In order to control the family-wise Type I error rate across the primary and key secondary endpoints, the interpretation of the statistical significance of treatment comparisons for each secondary efficacy endpoint will be done using a hierarchical closed testing procedure which will be defined in the statistical analysis plan, prior to unblinding of the treatment assignments.

The change from baseline in 24 hour ambulatory systolic blood pressure at Week 12, the change from baseline in seated diastolic blood pressure at Week 12, the change from baseline in 24 hour ambulatory diastolic blood pressure at Week 12, and the change from baseline in serum uric acid at Week 12 will be analyzed using an ANCOVA model with treatment group as an effect and baseline value and strata as covariates. Point estimates and 95% confidence intervals will be calculated to compare the treatment effect of each dapagliflozin (2.5 mg, 5 mg and 10 mg) treatment group to the placebo treatment group. If appropriate, a p-value will also be presented.

8.4.2.3 Exploratory Analyses

The proportion of subjects achieving goal blood pressure, defined as blood pressure < 130/80 mmHg and the subjects achieving improved blood pressure control, defined as blood pressure <140/90 mmHg at Week 12 will be summarized for each treatment group. Point estimates and 95% confidence intervals for the proportion in each treatment group and for the difference in proportion between each dapagliflozin (2.5 mg, 5 mg and 10 mg) treatment group and the placebo treatment group will be calculated. No p-values will be generated.

Other efficacy outcomes measured as continuous variables include change from baseline at Week 12 in fasting plasma glucose, 24 hour ambulatory daytime (6am – 10pm) systolic blood pressure, 24 hour ambulatory daytime (6am – 10pm) diastolic blood pressure, 24 hour ambulatory nighttime (10pm – 6am) systolic blood pressure, 24 hour ambulatory nighttime (10pm – 6am) diastolic blood pressure and uric acid excretion (by spot urine test) will be analyzed using an ANCOVA model with treatment group as effect and baseline value and randomization strata as covariates. Point estimates and 95%

confidence intervals for the mean change within each treatment group as well as for the differences in mean change between each dapagliflozin (2.5 mg and 10 mg) treatment group and the placebo treatment group will be calculated. No p-values will be generated.

8.4.3 Safety Analyses

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

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

8.4.4 Pharmacokinetic Analyses

Not Applicable

8.4.5 Pharmacodynamic Analyses

Not Applicable

8.4.6 Pharmacogenomic Analyses

Not Applicable

8.4.7 Outcomes Research Analyses

Not Applicable

8.4.8 Other Analyses

Not Applicable

8.5 Interim Analyses

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. Any significant deviation must be documented in the CRF.

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

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

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

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

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

9.1.2 Monitoring

Bristol-Myers Squibb will conduct the study in collaboration with ICON Clinical Research.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

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

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

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

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

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

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

9.2.2 Study Drug Records

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

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

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

9.2.3 Case Report Forms

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

All sites will be using an electronic data capture tool. Electronic CRFs will be prepared for all data collection fields except for fields for pregnancy, which will be reported on the Pregnancy Surveillance form. Spaces may be left blank only in those circumstances permitted by study-specific eCRF completion guidelines provided by the sponsor.

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

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

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

9.3 Publications

The data collected during this study are confidential and proprietary to the sponsor. Any publications or abstracts arising from this study require approval by the sponsor prior to publication or presentation and must adhere to the sponsor's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the sponsor at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. Sponsor shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

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

11 LIST OF ABBREVIATIONS

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

Term	Definition
GCP	Good Clinical Practice(s)
GI	Gastrointestinal
HbA1c	Glycosylated hemoglobin
HCG	Human Chorionic Gonadotropin
HCTZ	Hydrochlorothiazide
HDL-C	High-density lipoprotein cholesterol
HR	Heart Rate
hr(s) or h	Hour(s)
HRT	Hormone replacement therapy
ICH	International Council on Harmonization
ie,	id est (that is)
IEC(s)	Independent ethics committee(s)
INF	Infinity
IRB(s)	Institutional Review Board(s)
IU	International Units
IVRS	Interactive Voice Response System
Kg	Kilogram
L	Liter
Lb	Pound
Ln	Natural Logarithm
LOCF	Last observation carried forward
M or m	Meter
Max	Maximum
MBq	Megabecquerels
MCH	Mean cell hemoglobin
MCHC	Mean cell hemoglobin concentration
MCV	Mean cell volume
MDRD	Modification of Diet in Renal Disease
µCi	Microcuries
m	Meter
Min.	Minute
Mg	Milligram
Mg	Magnesium
mL	Milliliter
mmHg	Millimeters of mercury
mmol	Millimole

Term	Definition
N/A	Not Applicable
Ng	Nanogram
NHANES	National Health and Nutrition Examination Survey
nmol	Nanomole
NOAEL	No-Observed-Adverse-Effect Level
NYHA	New York Heart Association
OAD	Oral Antin-Diabetic
OL	Open-Label
pH	Symbol for the negative logarithm of the H+ ion concentration
PK	Pharmacokinetics
PM or pm	Afternoon (or post meridian)
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTH	Parathyroid hormone
PV	Plasma volume
QD	Daily dose
SA	Sickle cell trait
SAE(s)	Serious adverse event(s)
SBP	Systolic Blood Pressure
SD	Standard Deviation
SMBG	Self -monitoring of blood glucose
SCr	Serum Creatinine
SGLT(s)	Sodium glucose transporter(s)
SGLT1	Sodium-dependent glucose transporter 1
SGLT2	Sodium-dependent glucose transporter 2
SU	Sulfonylurea
T1/2	Mean Terminal Half-Life
TB	Total bilirubin
TG	Triglycerides
TIA	Transient Ischemic Attack
Tmax	Time to maximal concentration
TSH	Thyroid Stimulating Hormone
TZD	Thiazolidinedione
U	Units
UACR	Urine albumin creatinine ratio
ULN	Upper limit normal
μmol	Micromole

Term	Definition
US	United States
WK	Week
WOCBP	Women of childbearing potential

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APPENDIX 1 NEW YORK HEART ASSOCIATION FUNCTIONAL CLASS

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

APPENDIX 2 CENTRAL LABORATORY ASSESSMENTS

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

During the lead-in and double-blind treatment periods, the HbA1c values will be masked/blinded to the Investigator and to the Sponsor. These values will be provided to the Investigator after the study has been completed.

During the lead-in, double-blind treatment periods, the urinary glucose values, including the urinary glucose:creatinine ratio, will be masked/blinded to the Investigator and to the Sponsor. The urinary glucose values will be provided to the Investigator after the study has been completed.

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

PROTOCOL-SPECIFIC CENTRAL LABORATORY ASSESSMENTS:

- HbA1c (%)
- FPG (mg/dL, mmol/L)
- Fasting C-peptide (ng/mL, nmol/L)
- Fructosamine (μmol/L)
- Fasting serum lipid profile:
  - Total-C (mg/dL, mmol/L)
  - Calculated LDL-C (mg/dL, mmol/L)
    - *Reflex testing will occur for Direct LDL-C if TG > 400 mg/dL (4.52 mmol/L)*
  - HDL-C (mg/dL, mmol/L)
  - TG (mg/dL, mmol/L)

Enrollment-Specific Safety Panel

- Hepatitis Screen Panel:
  - Anti-hepatitis C virus antibody
    - *Reflex Testing: If positive, a reflex RIBA HCV will be obtained*
  - Hepatitis B surface antigen
- TSH (uIU/mL, mIU/L)
  - *Reflex Testing: Abnormal TSH value at enrollment will be further evaluated by free T4 (ng/dL, pmol/L).*

Specialized Liver Panel

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

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

Liver Discontinuation Panel

For subjects who are discontinued from the study as a result of sustained elevated liver safety abnormalities, additional central laboratory tests will be performed at the time of Early Termination (Week 12/ET) visit. Similar to the Specialized Liver Panel, these laboratory tests will study the possible causes of the increased ALT and/or AST and/or TB, and may include, but are not limited to, the following tests:

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

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

Standard Safety Laboratory Panels:

Appendix 2A Table: Standard Blood Safety Laboratory Panels

Hematology
• Hemoglobin (g/dL, g/L) • Hematocrit (%, V/V) • Red blood cell (RBC) (x10E6/UL, x10E12/L) *RBC count indices:* • Mean Cell Volume (MCV) (fL) • Mean Cell Hemoglobin (MCH) (pg/cell) • Mean Cell Hemoglobin Concentration (MCHC) (gHb/dL, gHb/L) • White blood cell Count and Differential • Platelet count (x10E9/L)
Serum Chemistry
• AST (IU/L) • ALT (IU/L) • ALK-P (IU/L)

Appendix 2A Table: Standard Blood Safety Laboratory Panels

- CK/CPK (IU/L). *Reflex Testing: CKMB and Troponin I will be ordered if CK > 400 IU/L).*
- Total Bilirubin (mg/dL, μmol/L) *Reflex testing of Direct (Conjugated) and Indirect (Unconjugated) Bilirubin if TB > 1.5X ULN.*
- Blood Urea Nitrogen (mg/dL, mmol/L)
- Bicarbonate (mEq/L, mmol/L)
- Serum Creatinine (mg/dL, μmol/L). **Glomerular Filtration Rate will be calculated by the Central Laboratory using the Modification in Diet and Renal disease (MDRD) formula and results will be reported to the sites and the Sponsor.** *(Levey AS, Coresh J, Balk E, Kausz AT, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification and stratification. Ann Int Med 2003; 139 (2): 137-47. Levey AS, Bosch JP, Breyer J, et al. A more accurate method to estimate glomerular filtration rate from serum Creatinine: A new Prediction Equation. Ann Int Med 1999;130 (6):461-470).*
- Sodium (mEq/L, mmol/L)
- Potassium (mEq/L, mmol/L)
- Chloride (mEq/L, mmol/L)
- Calcium (mg/dL, mmol/L)
- Magnesium (mEq/L, mmol/L)
- Phosphorus (mg/dL, mmol/L)
- Total Protein (g/dL, g/L)
- Albumin (g/dL, g/L)
- Uric acid (mg/dL, μmol/L)

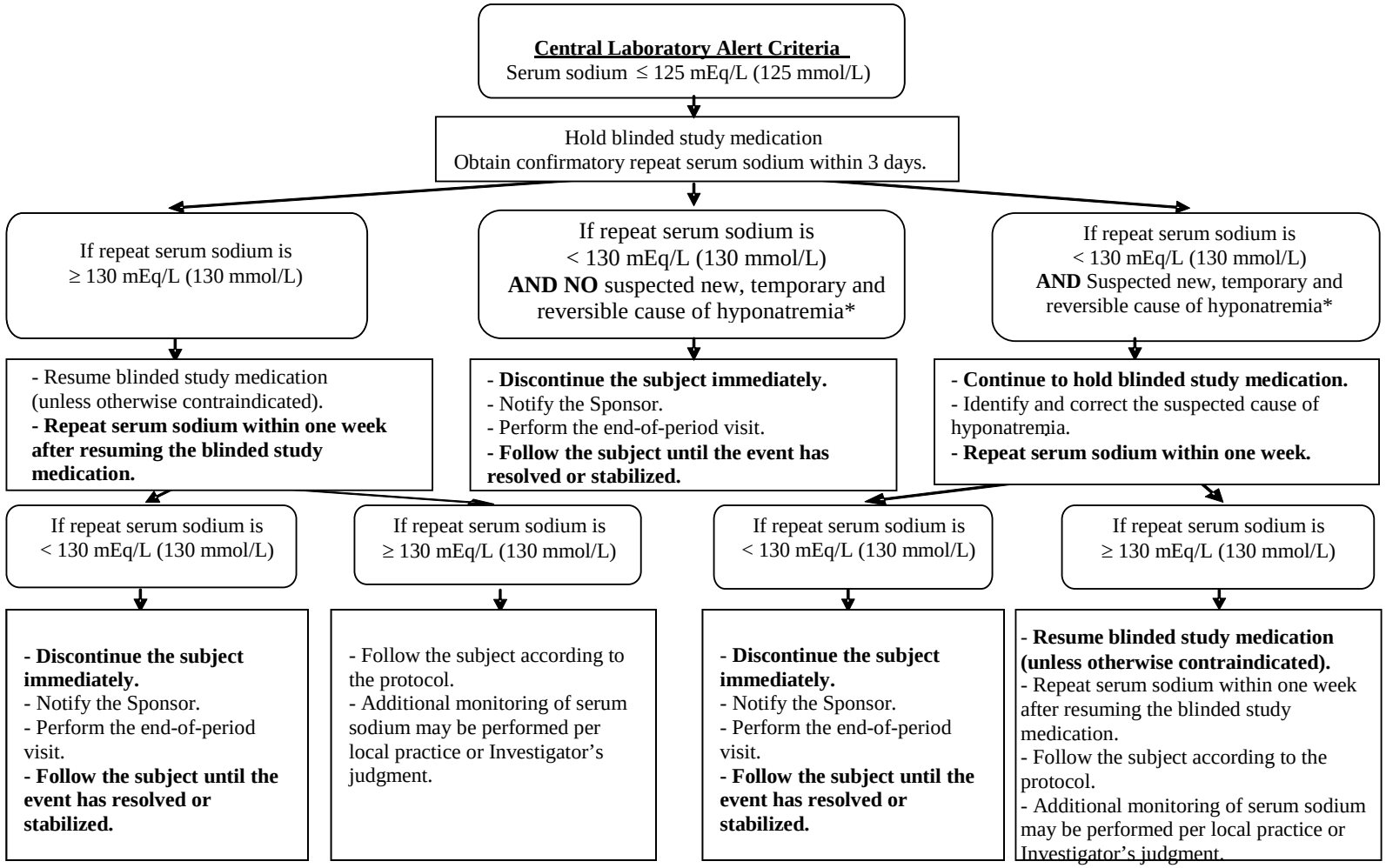
Urine Analyses (Standard Urine Safety Panel)

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

In addition to the above assessments, entry into lead-in Day -14, Day 1, Week 4, Week 8, Week 12 and Week 13 visits will include the following assessments (spot urine):

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

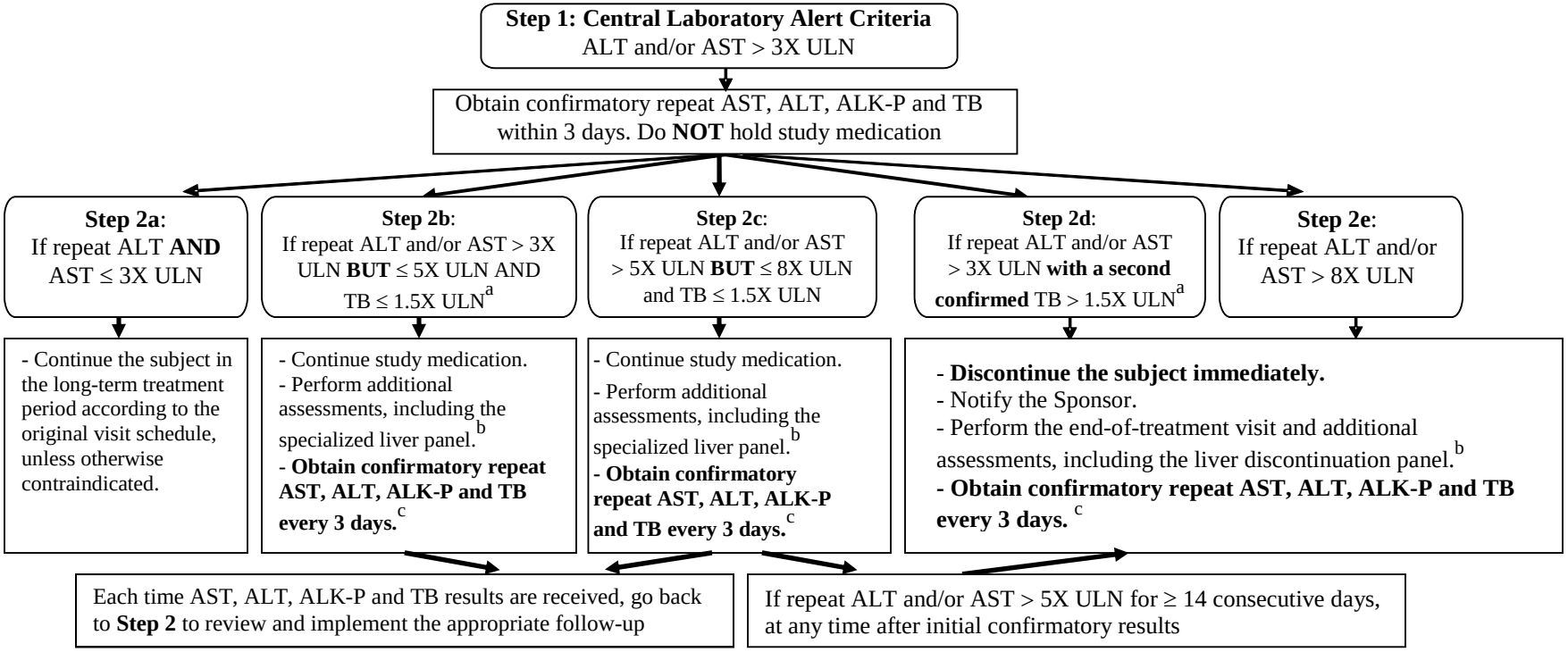
APPENDIX 3 HYPONATREMIA FLOW CHART



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

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

APPENDIX 4 SUSTAINED ELEVATED LIVER SAFETY ABNORMALITIES FLOW CHART



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

[b] Refer to section 6.3.4 for details on additional assessments to be performed (AE assessment, PE, review of current medical history including focused review of risk factors for liver diseases and collection of blood samples [specialized liver panel or liver discontinuation panel]).

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

Protocol Number: MB102077
Site Number: Site Specific
IND Number IND 68,652
EUDRACT Number 2010-019798-13
Date:

Protocol MB102077: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Subjects with Type 2 Diabetes with inadequately controlled hypertension treated with an Angiotensin-Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB) and an additional Antihypertensive medication.

Pharmacogenetics Blood Sample Amendment Number 01 - Site Specific

Medical Monitor:

Telephone (office):
Fax:

Protocol Manager:

Telephone (office):
Fax:

Study Director:

Telephone (office):
Fax:

24-hr Emergency Telephone Number:
USA:
International:

Bristol-Myers Squibb Research and Development

This amendment must be maintained with the referenced protocol.

TABLE OF CONTENTS

1 AMENDMENT RATIONALE

The information gained from Pharmacogenetic research studies is expected to result in safer and more effective therapies and to lead to the discovery of new diagnostics, prognostics and molecular targets and pathways. To learn more about the association between a subject's genetic makeup and drug response, subjects will be asked to voluntarily give a blood sample so that scientists can perform exploratory pharmacogenetic research.

This research will be limited to information recorded on the case report form or generated from the main clinical trial and results from the associated pharmacogenetic blood sample. Subjects will not be contacted in the future by the sponsor to provide any further information.

Pharmacogenetics can be defined as the study of how variations in genes influence drug response. Genetic factors are considered to play an important role in the observed inter-individual differences in the metabolism, toxicity, and pharmacological response of drugs. The ability to determine which genes and their variants are associated with toxicity and efficacy for a specific drug will improve drug therapy and subsequently be beneficial to patients.

2 OBJECTIVES

The objective of this Amendment is to permit the collection and storage of blood samples for use in future exploratory pharmacogenetic research. Bristol-Myers Squibb will use DNA obtained from the blood sample and health information collected from the main clinical trial, MB102077 to study the association between genetic variation and drug response. Bristol-Myers Squibb may also use the DNA to study the causes and further progression of Type 2 Diabetes and other Metabolic diseases. Samples from this study may also be used in conjunction with pharmacogenetic research results from other clinical studies to accomplish this objective.

3 STUDY SITES

Pharmacogenetic sample collection will be performed at sites that permit pharmacogenetic studies to be conducted in compliance with all applicable laws, rules, and regulations.

4 SUBJECT SELECTION CRITERIA

To participate in this Pharmacogenetic Sample Amendment, subjects must provide a signed Pharmacogenetic Blood DNA informed consent and must have consented to participate in the main clinical trial MB102077.

5 PROCEDURES

Subjects who have consented to participate in this study and who have voluntarily given written informed consent for pharmacogenetic sample collection will have a one-time blood sample collected at Week 4. If the pharmacogenetic blood sample is not collected at Week 4, it may be collected at any other subsequent scheduled sample collection. For each subject, approximately 10mL of blood (less than 2 teaspoons) will be collected. The sample will be stored at Bristol-Myers Squibb Sample Bank for pharmacogenetic research.

No pre-determined number of study subjects is required, as participation for pharmacogenetic analysis is strictly voluntary. Subjects will be asked to read, understand, and sign an informed consent form designed for the purpose of collecting a one time sample for pharmacogenetic research. **Subjects will be informed that they will not be excluded from the main clinical trial MB102077 if they do not wish to participate in the Pharmacogenetics Sample Amendment.**

6 PHARMACOGENETIC STATISTICAL ANALYSIS

Joint exploratory data analysis may be performed in the future by Statistical Genetics and Biomarkers in Global Biometric Sciences and the Department of Pharmacogenomics in Discovery Medicine at Bristol-Myers Squibb to investigate if genetic variants (genotypes)

are associated with clinical outcomes (phenotypes) such as, but not limited to, drug response, efficacy, safety, toxicity, and overall survival. The following potential analyses may be performed as appropriate:

- Examine demographic factors such as race/ethnicity, age and gender to determine appropriate stratification or adjustment for the analysis.
- Summarize allele and genotype frequencies from the sample with 95% confidence intervals.
- Explore the relationship among genetic variation, expression of genes and proteins and clinical outcomes using methods such as, but not limited to, chi-squared tests, linear models, generalized linear models, non-parametric models, survival models or clustering algorithms.

7 CONFIDENTIALITY

Bristol Myers Squibb will work to protect the confidentiality of research subjects who volunteer to participate in the pharmacogenetic analyses and ensure that the analyses are conducted in compliance with all applicable laws, rules and regulations.

All samples are stored in a de-identified fashion, meaning that they are labeled only with a randomly-generated bar code number. The link between this bar code number and the coded identification number assigned to the study subject is maintained in a secure Bristol-Myer Squibb database and is not shared with the laboratories or researchers that analyze the samples.

Bristol-Myers Squibb **does not** receive the subject's name, phone number, address or National ID Number (Such as an identity card number, passport number or US Social Security number) when collecting data from the clinical trial and as such cannot link the identity of the subject to the pharmacogenetic research analyses. Therefore, any data from the pharmacogenetic analyses that might be released into the public domain will be predominately aggregate data from analyses of many samples. For example, a scientific research publication or a presentation at a scientific meeting will not contain any information which would allow the person reading the article or attending the presentation to identify the individual participants. This will minimize the chance that the

genetic information will be used as a basis for discrimination (e.g., when the subject applies for life or medical insurance).

8 SUBJECT RIGHTS

Study subjects can withdraw their consent to participate in the Pharmacogenetic Sample Amendment even after the sample has been shipped to the Bristol-Myers Squibb Sample Bank. As long as the Investigator or Investigator's designee retains the clinical trial records, a study subject will be able to contact his/her Investigator or the Investigator's designee and ask for his/her sample to be withdrawn from the Sample Bank and destroyed.

8.1 Record Retention

The Investigator must retain essential documents for the maximum period required by applicable regulations and guidelines[1] or Institutional procedures, or for the period specified by the sponsor, whichever is longer. The Investigator must contact Bristol-Myers Squibb prior to destroying any records associated with the study.

Bristol-Myers Squibb will notify the Investigator when the trial records are no longer needed.

If the Investigator withdraws from the study (e.g. relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g. another Investigator, IRB). Notice of such a transfer will be given in writing to Bristol-Myers Squibb.

9 WITHDRAWAL OF SUBJECTS FROM PHARMACOGENETIC RESEARCH

Subjects have, at any time, the option to withdraw consent for participation from:

1) Only the Pharmacogenetic Sample Amendment independent of the main clinical trial (MB102077);

OR

2) Only the main clinical trial (MB102077) independent of the Pharmacogenetic Sample Amendment;

OR

3) Both the main clinical trial (MB102077) and Pharmacogenetic Sample Amendment.

Subjects who wish to withdraw their consent from the Pharmacogenetic Sample Amendment (i.e., have their sample in the Sample Bank destroyed) should contact the Investigator. The Investigator will submit a Sample Withdrawal Form to the Bristol-Myers Squibb Sample Bank (see Appendix 1).

It is possible that subjects may decide to withdraw consent from the main clinical trial (MB102077) but continue with their consent for the Pharmacogenetic Sample Amendment. In such cases the Investigator should inform subjects that their sample would remain stored at the Bristol-Myers Squibb Sample Bank and may be used for pharmacogenetic research.

If a subject requests to withdraw consent for the Pharmacogenetic Sample Amendment after the time the Investigator is legally required to maintain the records linking the subject's sample and coded health information to their identity, and the records have been destroyed, the sample will become anonymous and unable to be withdrawn.

10 DESTRUCTION OF BLOOD SAMPLE AND RELATED MATERIAL

In the case of subjects who have withdrawn their consent for participation in the Pharmacogenetic Sample Amendment the Investigator will send a Sample Withdrawal Form to the Bristol-Myers Squibb Sample Bank. Bristol-Myers Squibb Sample Bank, upon receipt of the Sample Withdrawal Form, will destroy any remaining blood sample and any material obtained from the sample in accordance with BMS procedure for Sample Destruction. A copy of the sample withdrawal form is provided in Appendix 1. After all samples have been destroyed Bristol-Myers Squibb Sample Bank will provide the Investigator with verification of the sample destruction. In the case of samples that have been partially analyzed, the remaining sample will be destroyed but Bristol-Myers

Squibb shall be entitled to retain and use any research results obtained prior to the withdrawal of consent.

11 FLOW CHART/TIME AND EVENTS SCHEDULE

Time and Events Schedule:

Procedure	Week 4 Visit
Pharmacogenetic Sample Informed Consent	X[a]
Pharmacogenetic Sample Collection	X[b]

[a] Informed consent for pharmacogenetic testing may be obtained at any time during the trial PRIOR to the collection of the pharmacogenetic sample.

[b] If the pharmacogenetic sample is not collected at Week 4 Visit, it may be collected at any other subsequent scheduled sample collection.

12 PHARMACOGENETIC SAMPLE COLLECTION AND PROCESSING

The whole blood pharmacogenetic sample will be shipped at room temperature to the designated central laboratory. The laboratory will divide each sample into two aliquots. The samples will then be labeled, frozen, and transferred to the Bristol-Myers Squibb Sample Bank for storage and future analysis. Details for collection, processing, storing and shipping these samples will be provided in a separate procedure manual.

13 INFORMED CONSENT

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representative are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from every subject or, in those situations where consent cannot be given by subjects, their legally acceptable representative, prior to study participation.

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

The following section contains Bristol-Myers Squibb procedures on obtaining informed consent from subjects or their legally acceptable representative prior to participating in a clinical trial. Procedures are described for all subjects including those who are unable to give informed consent. The relevant procedures must be used whenever they are applicable.

A separate informed consent will be obtained from study subjects who voluntarily agree to participate in the Pharmacogenetic Sample Amendment. The informed consent form for pharmacogenetic sample collection reflecting this Amendment will be submitted for review and approval to the IRB/Ethics Committee charged with this responsibility.

13.1 Informed Consent Procedures

Preparation of the consent form is the responsibility of the Investigator and must include all elements required by ICH, GCP and applicable regulatory requirements, and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form must also include a statement that Bristol-Myers Squibb and regulatory authorities have direct access to subject records. Prior to the beginning of the study, the Investigator must have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects.

The Investigator must provide the subject or legally acceptable representative with a copy of the informed consent form and written information about the study in the language in which the subject is most proficient. The language must be non-technical and easily understood. The Investigator should allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study, then informed consent must be signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion. The subject or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study subjects prior to subject's participation in the trial

14 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

This amendment, the informed consent form for pharmacogenetic sample collection and any advertisement for subject recruitment will be submitted for review and approval to the IRB/Ethics Committee charged with this responsibility. The investigator must have on file written and dated approval/favorable for this amendment from the IRB/Ethics Committee before this sample is collected.

15 REFERENCES

1. Code of Federal Regulations, CFR 312.57, and International Conference on Harmonisation, ICH Guidelines.

2. The Pharmacogenetic Working Group (2001). “Terminology for Sample Collection in Clinical Genetic Studies.” The Pharmacogenomics Journal 1: 101-103.

APPENDIX 1 SAMPLE WITHDRAWAL PROCEDURES

Bristol-Myers Squibb
Research & Development

FAX TRANSMITTAL SHEET

FAX THIS COMPLETED PAGE TO:
BRISTOL-MYERS SQUIBB SAMPLE BANK

Fax:

WITHDRAWAL OF PERMISSION FOR USE OF SPECIMENS IN FUTURE PHARMACOGENETIC RESEARCH

This section is to be completed by either the Investigator or the coordinator at the institution.

The study subject indicated below (Only identify the study subject using the study subject number; **DO NOT** provide any other identifying information such as the study subject's name or social security number) initially provided informed consent for his/her samples to be used for pharmacogenetic research by BMS. After discussion with a study staff member at our institution, he/she has now indicated that he/she wants to withdraw consent for future pharmacogenetic research by BMS and have his/her sample destroyed.

PROTOCOL NUMBER: _____ **SITE NUMBER:** _____

STUDY SUBJECT NUMBER: _____

INVESTIGATOR NAME: _____ **INVESTIGATOR FAX:** _____

INVESTIGATOR SIGNATURE: _____

DATE OF REQUEST: _____

This section is to be completed by the Bristol-Myers Squibb Sample Bank and faxed back to the Investigator.

CONFIRMATION OF SAMPLE DESTRUCTION

The pharmacogenetic sample and related material derived from the sample obtained from the study subject indicated above has been destroyed. Please notify the study subject that this has occurred.

VERIFIED BY: _____ **DATE:** _____

PRINT NAME: _____

AMENDMENT ACKNOWLEDGEMENT

I have read this Amendment and agree that it contains all necessary details for carrying out the changes described. I understand that it must be reviewed by the Institutional Review Board/Ethics Committee overseeing the conduct of the study and approved or given favorable opinion before implementation unless to eliminate an immediate hazard to subjects.

If this Amendment substantially alters the study design or increases potential risk to subjects, the consent form will be revised and submitted to the Institutional Review Board/Independent Ethics Committee for approval/positive opinion. I will use the new consent form for any new subjects prior to enrollment, and for subjects currently enrolled in the study if they are affected by the Amendment.

_____ _____

Investigator's printed name and signature *Date*

_____ _____

Medical Monitor/Study Director *Date*
(If required by applicable regulations and guidelines.)

Protocol Number: MB102077
Site Specific
Amendment Number: 01

Protocol Number: MB102077
IND Number: IND 68,652
EUDRACT Number 2010-019798-13
Date:

Protocol MB102077: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Subjects with Type 2 Diabetes with Inadequately Controlled Hypertension treated with an Angiotensin-Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB) and an Additional Antihypertensive Medication

Amendment Number 02
Site Number: All

Study Director / Central Medical Monitor

Telephone (office):
Fax:

24-hr Emergency Telephone Number:
USA:
International:

Bristol-Myers Squibb Research and Development
Metabolics Clinical Research and Development

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

This amendment must be maintained with the referenced protocol.

Amendment Rationale:

The purpose of this amendment is to modify the dapagliflozin treatment groups that will be included in the study. The 2.5 mg dapagliflozin treatment group has been removed based on emerging phase 3 data which indicates that 5 and 10 mg doses of dapagliflozin may have a better overall benefit-risk profile. This study will now be a 3-arm blinded treatment study, and all study objectives have been revised to evaluate the differences between each of the two dapagliflozin (5mg and 10 mg) treatment groups and the placebo treatment group. A total of 765 subjects (255 subjects for each treatment group) will be randomized in the study with a total of 726 subjects (242 subjects per treatment group) expected to have post-baseline assessments. There will be at least 90% power to detect a 4.5 mmHg difference in mean change from baseline in seated systolic blood pressure at a significance level of 0.025, assuming a standard deviation of 14 mmHg, and at least 95% power to detect a difference of 0.4% in mean change from baseline in HbA1c between each (5 mg and 10 mg) dapagliflozin treatment group and the placebo treatment group at a significance level of 0.025, assuming a standard deviation of 1.1%. The effects of the 2.5 mg dose on blood pressure will be evaluated in a separate currently ongoing study (MB102073).

This amendment also updates the hypertension inclusion criteria for subjects newly entering the study. Subjects must be on a stable minimally effective therapeutic dose of an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) for at least 4 weeks prior to study enrollment. By specifying minimally effective therapeutic doses for each available ACEi and ARB, each subject will enter the study with a seated blood pressure ≥ 140/85 mmHg on a background dose of an ACEi or ARB with potential therapeutic blood pressure lowering benefits. Subjects will also need to have a mean 24-hour ambulatory blood pressure ≥ 130/80 mmHg at randomization. Office blood pressure measurements tend to overestimate the average level of blood pressure. Including a minimum mean 24-hour ambulatory blood pressure in the randomization criteria for the study will provide additional evidence of baseline hypertension in the study population. This amendment also adds alpha adrenergic agonists to the list of acceptable additional antihypertensive medications that subjects must be taking along with a minimally effective therapeutic of an ACEi or ARB at enrollment and throughout the study.

In this amendment, standardization of the blood pressure monitoring devices that will be used for the study has been added. Measuring blood pressure by millimeters of mercury (mmHg) with a calibrated mercury sphygmomanometer is still considered to be the highest standard and will be the preferred method for office blood pressure measurements in this study. If a mercury sphygmomanometer is not available for office blood pressure measurements, a list of acceptable automated blood pressure monitoring devices has been included in Appendix 6. The acceptable devices have all met the criteria of the Association for the Advancement of Medical Instruments (AAMI) and the British Hypertension Society (BHS) blood pressure monitor validation protocols.

In addition, this amendment adds another ambulatory blood pressure exploratory endpoint which will evaluate mean trough systolic and diastolic blood pressure at hours 21 - 24 post-dosing of dapagliflozin. These evaluations will be conducted at baseline and Week 12 to add additional information to the office blood pressure measurements about the residual effect of dapagliflozin on blood pressure at the end of the dosing interval.

This amendment further expands the existing procedures for the ongoing review of hepatic laboratory tests and hepatic events. Additional hepatic laboratory monitoring was implemented across the program in 2009 using the Food and Drug Administration (FDA) *Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation* (July 2009) as a reference. This amendment now incorporates ongoing external blinded review of specific hepatic laboratory tests and hepatic events. Bristol-Myers Squibb (BMS) and AstraZeneca (AZ) will request the opinions of independent hepatologists to determine the probability that drug-induced liver injury (DILI) is the cause of liver-related abnormalities.

Changes to the Protocol:

1) Synopsis, Study Design, Study Population and Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s), Synopsis - Primary Objective, and Protocol Sections 1.3.1, 1.3.2, 1.3.3, 4.1.1, 5.4.1, 5.4.2, and 5.4.3: Deletion of the 2.5 dapagliflozin arm due to study design change. Also deletion of extra “mg” in the schematic, added “central” to alpha adrenergic agonist to synopsis and Protocol Section 1.1 Rationale, Section 3.1 Study Design, Section 3.1.1, Qualification Period, Section 3.1.2 Lead-In Period, Section 3.1.3, Double-Blind Treatment Period, Section 3.3.1 Inclusion Criteria #3, Section 4.1.2 Non Investigational Product and Section 3.5.1 Guidelines for the Addition of a Supplemental Antihypertensive Medication to Control Sustained or Severe

Hypertension. Added words "effective therapeutic" to dose of ACEI or ARB. Design changed from 4 arm to 3 arms. Updated randomized subjects to 765 (255 dapagliflozin 5 mg, 255 dapagliflozin 10 mg and 255 placebo). Updated recruitment period to 9 months and study conducted over 13 months.

2) Synopsis, Study Schematic and Protocol Section 3.1.5 Study Schematic. Added Day -14 to schematic. Deletion of 2.5 dapagliflozin dose arm.
3) Synopsis, Study Population and Protocol Section 3.1 Study Design and Section 3.1.2 Lead-In period, Section 3.3.1 Inclusion criteria #5, Section 3.3.2 Randomization criteria, Section 5.4.2.1 24-hr Ambulatory Blood Pressure (ABPM). Added randomization criteria: Subjects must have a mean 24-hour blood pressure ≥ 130/80 mmHg as measured by ambulatory blood pressure monitoring (ABPM) during lead in, measured between Day -7 and Day -1, within 1 week prior to the Day 1 randomization visit.
4) Synopsis Statistical Methods Updated, Protocol Body Section 8 Statistical Considerations section updated.
5) Protocol Section 1.1 Rationale, Protocol Section 3.1 Study Design, Protocol Section 3.1.1 Qualification Period, Protocol Section 3.1.2 Lead in Period, Protocol Section 3.1.3 Double-Blind Treatment Period, Protocol Section 3.3.1 Inclusion Criteria #3,Protocol Section 5.4.2.1 24-hr Ambulatory Blood Pressure Monitoring (ABPM), added "alpha adrenergic agonists" to list of additional antihypertensive medications.
6) Protocol Section 1.3.3 Exploratory Objective, Protocol Section 5.4.3 Other (Exploratory) Efficacy Assessments, Protocol Section 8.4.2.3 Exploratory Analysis, clarified objective to evaluate mean trough systolic and diastolic blood pressure for hours 21-24 post dosing with dapagliflozin,
7) Protocol Section Table 1.4.3 Summary of Phase 2B and 3 Studies, table updated to reflect current updated information to date.
8) Protocol Section 3.3.1 Inclusion Criteria #3- added the word "central" to alpha adrenergic agonist.
9) Protocol Section 3.1.2 Lead-In Period, Protocol Section 3.1.3 Double-Blind Treatment: Clarification that Antihypertensive medication and OAD should be taken as prescribed at a similar time each day. Morning medication should be withheld on the morning on the study visit.
10) Protocol Section 3.3.2 Exclusion Criteria, added additional program level exclusion criteria numbers 41-47.
11) Protocol Table 4.1B- The last row in this table showing Dapagliflozin 10 mg has been deleted because it was a duplication of the previous row and therefore not needed.
12) Protocol Section 4.2 Method of Assigning Subject Identification, removed dapagliflozin 2.5 mg changed treatment groups to 3 and added central alpha adrenergic agonist to Strata 2.

13) Protocol Table 5.1.A Flow Chart X's added to Week 2 for Safety Assessments. Also Serum Uric Acid row was deleted as this is part of the Standard Safety Panel drawn on the exact days/weeks.
14) Protocol Section 5.1.1 Visit Scheduling and Visit Windows, Clarification: entry into lead-in Day -28 visit should be completed **up to 14 days** following enrollment central laboratory samples collection.
15) Protocol Section 5.1.2.1 Regular Study Visits, Clarification: Subjects should arrive at the site between 6 AM and 11 AM. Subjects should be in a fasting state (at least 8 hrs).
16) Protocol Section 5.2 Study Materials, Protocol Section 5.3.6, Protocol Section 5.3.6.1 Seated Blood Pressure and Heart Rate, clarification of blood pressure equipment. The sites will have available a well-calibrated scale for body weight measurement, a 12-lead ECG machine, and a calibrated mercury sphygmomanometer blood pressure monitor or one of the validated automated blood pressure monitoring devices listed in Appendix 6 for seated, standing and supine blood pressure measurements. **Blood pressure measurements using a calibrated mercury sphygmomanometer throughout the study are preferred.**
17) Protocol Section 5.3.4 Guidance on Assessment of Hepatic Laboratory Abnormalities, further expanded section to include addition of an assessment of specific Hepatic disorders and Liver abnormalities by an independent Hepatic Adjudication Committee.
18) Protocol Section 5.4.2.1, clarified subjects should withhold morning medication (included blinded study medication, OAD and ACEI or ARB and additional hypertensive medication) until ABPM cuff is removed when subjects return from completion of 24-hr ABPM.
19) Protocol Section 5.4.2.2 Serum Uric Acid corrected visit to say Enrollment not Day -14.
20) Protocol Section 6.1.1 Serious Event Collection and Reporting, updated ICON contact information updated ICON contact information, fax numbers for regions.
21) Appendix 2, Central Laboratory Assessments, updated Urine Analysis spot urine section to include Day -28.
22) Appendix 4, Sustained Elevated Liver Safety Abnormalities Flow Chart corrected long term to double blind treatment for Step 2a.
23) Appendix 5 added, Eligible Doses of Angiotensin Converting Enzyme Inhibitors (ACE-I) and Angiotensin Receptor Blockers (ARB)
24) Appendix 6 added, Automated Blood Pressure Monitors Acceptable For Blood Pressure Measurements.

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.

AMENDMENT ACKNOWLEDGMENT

I have read this Amendment and agree that it contains all necessary details for carrying out the changes described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion before implementation unless to eliminate an immediate hazard to subjects.

If this Amendment substantially alters the study design or increases potential risk to subjects, the consent form will be revised and submitted to the Institutional Review Board/Independent Ethics Committee for approval/positive opinion. I will use the new consent form for any new subjects prior to enrollment, and for subjects currently enrolled in the study if they are affected by the Amendment.

_____ _____

Investigator's printed name and signature *Date*

_____ _____

Medical Monitor/Study Director *Date*
(If required by applicable regulations and guidelines.)

Protocol Number: MB102077
Site Number:
Amendment Number: 02

Protocol Number: MB102077
IND Number: IND 68,652
EUDRACT Number 2010-019798-13
Date:

Protocol MB102077: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Subjects with Type 2 Diabetes with Inadequately Controlled Hypertension on an Angiotensin-Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB) and an Additional Antihypertensive Medication

Amendment Number 07
Site Number: All

Study Director/Central Medical Monitor

Telephone (office):
Fax:

24-hr Emergency Telephone Number:
USA:
International:

Bristol-Myers Squibb Research and Development
Metabolics Clinical Research and Development

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

This amendment must be maintained with the referenced protocol.

Amendment Rationale:

The purpose of this amendment is to revise the definition of Post Menopause in regard to documented serum Follicle Stimulating Hormone (FSH) levels when determining whether female study participants meet the criteria for Women of Childbearing Potential (WOCBP). Female study participants ≥ 62 years old with amenorrhea of ≥ 1 year will not be required to have a documented serum FSH level > 35 mIU/mL in order to meet the definition of Post Menopause. This change is being implemented due to the older mean age of the subjects meeting the eligibility requirements for this trial.

Additionally this amendment will add guidance on assessment of hematuria observed during study participation.

This amendment also corrects a typographical error in the units of measure of Serum Creatinine (Scr).

This amendment has no impact on the analysis or study conduct. There is no urgency with the implementation of this amendment and it will apply to all subjects in all countries once approved.

Changes to the Protocol:

1) **Section Study Synopsis, Key Exclusion Criteria:** Fourth bullet, Fixed typo in unit of measure: Serum Creatinine (SCr) ≥ 2.0 mg/dL unless subject is on metformin then the exclusionary limits will be SCr ≥ 1.50 mg/dL (133 μmol/L) for male subjects; SCr ≥ 1.40 mg/dL (124 μmol/L) for female subjects
2) **Section 3.3.2 Exclusion Criteria-Central Laboratory Test Findings:** Fixed typo in unit of measure - At Enrollment Serum Creatinine (SCr) ≥ 2.0 mg/dL unless subject is on metformin then the exclusionary limits will be SCr ≥ 1.50 mg/dL (133 μmol/L) for male subjects; SCr ≥ 1.40 mg/dL (124 μmol/L) for female subjects
3) **Section 3.3.3 Women of Childbearing Potential:** Change: Added below notation

- Amenorrhea ≥ 12 consecutive months without another cause and a documented serum follicle stimulating hormone (FSH) level >35 mIU/mL or
- Women with irregular menstrual periods and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL or

NOTE: FSH level testing is not required for women ≥ 62 years old with amenorrhea of ≥ 1 year.

- Women on hormone replacement therapy (HRT)

4) **Section 5.3.2 Guidance on Assessment of Urinary and Genital Infections:** Add a section for *Guidance on Assessment of Hematuria*, after the Urinary Tract section and prior to the Genital Infection section - add text: **Guidance on Hematuria:** In the event that hematuria is observed during a subject's participation, the Sponsor recommends standard of care in diagnosing the cause of the hematuria.

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.

AMENDMENT ACKNOWLEDGMENT

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_____ _____

Investigator's printed name and signature *Date*

_____ _____

Medical Monitor/Study Director *Date*
(If required by applicable regulations and guidelines.)

Protocol Number: MB102077
Site Number:
Amendment Number: 07

Protocol Number: MB102077
IND Number: IND 68,652
EUDRACT Number 2010-019798-13
Date:

Protocol MB102077: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Subjects with Type 2 Diabetes with Inadequately Controlled Hypertension treated with an Angiotensin-Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB) and an Additional Antihypertensive Medication

Amendment Number 08
Site Number: All

Study Director/Central Medical Monitor

Telephone (office):
Fax:

24-hr Emergency Telephone Number:
USA:
International:

Bristol-Myers Squibb Research and Development
Metabolic Diseases Clinical Research and Development

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

This amendment must be maintained with the referenced protocol.

Amendment Rationale:

The purpose of this amendment is to discontinue enrolling additional subjects in the dapagliflozin 5 mg blinded study treatment arm. Subjects previously randomized to the double-blinded 5 mg study arm will complete the study with no dose modifications. The study will proceed with subjects randomized to only the dapagliflozin 10 mg or placebo blinded study treatment arms. The totality of data from the dapagliflozin development program has shown that the 10 mg dapagliflozin dose provides optimal efficacy and is safe and well tolerated for the general T2DM population. The primary and secondary study objectives will evaluate the effects of the 10 mg dose of dapagliflozin versus placebo. For subjects randomized according to the original study design, safety and efficacy parameters in the 5 mg arm will also be summarized.

Additionally, this amendment will increase the size of the 10 mg and placebo blinded study treatment arms. With 343 subjects per treatment group with post-baseline measurements, there is at least 80% power to detect a difference of 3 mmHg in mean change from baseline in seated systolic blood pressure between the dapagliflozin 10 mg treatment group and placebo treatment group at significance level of 0.05, assuming a standard deviation (SD) of 14 mmHg. Also with 343 subjects per treatment group with post-baseline measurements, there is at least 99% power to detect a difference of 0.4% in mean change from baseline in HbA1c between the dapagliflozin 10 mg treatment group and the placebo treatment group at significance level of 0.05, assuming a SD of 1.1%. Discontinuing enrollment in the 5 mg blinded study treatment arm and increasing the size of the 10 mg and placebo blinded study treatment arms will result in minimal changes to the overall number of subjects expected to be enrolled in the study.

This amendment will also revise several inclusion/exclusion criteria:

- The upper boundary of the HbA1c inclusion criterion at enrollment will be adjusted from 10% to 10.5%.
- The exclusion criterion for “history of gout” will be removed.
- The exclusion criterion for subjects taking insulin as an antidiabetic agent will be removed.

Recent data has shown that treatment with dapagliflozin 10 mg is safe and efficacious in these populations and exclusion from this study is not necessary. Allowing these populations to be included in the study will also provide information on the effects of the dapagliflozin 10 mg dose on blood pressure and HbA1c in a more inclusive diabetic population.

In addition, the exclusion criteria for estimated creatinine clearance will be changed from < 50 ml/min to < 60 ml/min to align with the most recent dapagliflozin development program guidance.

This amendment has no impact on the analysis or study conduct or subjects' safety. There is no urgency with the implementation of this amendment and it will apply to all subjects in all countries once approved.

Changes to the Protocol:

1) Synopsis: Investigational Product, Primary Objective, Study Design, Study Schematic: Removal of the 5.0 mg dapagliflozin dose arm.

2) Synopsis: Study Design and Schematic: Add inclusion of a stable dose of insulin as monotherapy or in combination with an Oral Antidiabetic agent (OAD). Also added insulin reduction instructions according to HbA1c values throughout the study period. Added randomizing globally within strata for insulin use at baseline.

3) Synopsis: Study population: changing HbA1c upper range to 10.5 % and added inclusion of insulin.

4) Synopsis: Key Exclusion criteria, change estimated creatinine clearance (Crcl) to < 60 ml/min.

5) Synopsis: Statistical methods: Removal of the 5.0 mg dapagliflozin dose arm and decreased number of randomized subjects from 765 to 722, reduced treatment arms from 4 to 2 and changed individual treatment arms to 361 subjects. Removed paragraph explaining use of Bonferroni's adjustment.

6) Protocol sections: Study Rationale 1.1, Objectives 1.3 (primary 1.3.1, secondary 1.3.2 and exploratory 1.3.3), Study Design and Duration 3.1, Qualification Period 3.1.1, Lead-In Period 3.1.2, Double Blind Treatment Period (Randomization Visit) 3.1.3, Study Schematic 3.1.5, Inclusion criteria 3.3.1, Study Treatments 4.1 and Table 4.1 B, Investigational Product 4.1.1, Method of Assigning Subject Identification 4.2, Dose Modifications 4.3.1, Efficacy Assessments 5.4 (Primary Efficacy Assessments 5.4.1, and Secondary Efficacy Assessments 5.4.2, Exploratory Efficacy Assessments 5.4.3.

a) removal of the dapagliflozin 5.0 mg dosing arm

b) change in upper limit of HbA1c to 10.5%

c) change in total number of randomized subjects

d) change in randomization scheme to 1:1

e) added global stratification for insulin use

f) added insulin inclusion and information regarding insulin adjustments during the study period.

g) changes to inclusion criteria 2, (increase upper limit of HbA1c to 10.5% and allow retest for HbA1c of 10.6 %) and criteria 3, allowing subjects who are on insulin.

h) add 1 exploratory objective

7) Table 1.4.3: Summary of Ongoing, Randomized, Double-blind Phase 2b and 3 Studies: updated table with current information.

8) Section 1.5, Overall Risk/Benefit Assessment: updated section with current information.

9) Added sub-section 3.1.3.1 entitled: Algorithm for Insulin dose reduction by 25% in subjects who are on insulin therapy and have an HbA1c measurement of 7.0 - 7.4% at enrollment.

10) Follow-Up Visit 3.1.4: statement added that if needed subjects can be treated as appropriate for their diabetes without any restrictions by the protocol.

11) Exclusion Criteria 3.3.2: Metabolic Diseases, Notation for History of Gout criteria #13 subjects can be entered into the study under revised protocol #4. Exclusion criteria # 28 change estimated creatinine clearance to < 60ml/min.

12) Prohibited Treatments 3.4.1.1: changed Insulin to Inhaled Insulin

13) Added subsection 3.5.2.1 Changes in Insulin Dose

14) Section 3.5.4 Discontinuation Guidelines due to Protocol-defined Major Hypoglycemia Episode or Recurrent Non-Major Hypoglycemic Episodes: added paragraph on Insulin Dose Reduction.

15) Selection and Timing of Dose for Each Subject 4.3: updated section based on removal of 5.0 mg dapagliflozin dosing arm.

16) Destruction and Return of Study Drug 4.6.1 and 4.6.2: updated language to reflect new language in protocol model document.

17) Table 5.1A: added an X to Visit 13 under study review logs.

18) Added Cancer adjudication new section directly after section 5.3.4 (new section is numbered 5.3.5).

19) All previous sections 5.3.5 - 5.3.8.2 have been renumbered.

20) Sample Size Determination 8.1, Analysis 8.4: added brief description of analysis. Primary Analysis 8.4.2.1, Secondary Analysis 8.4.2.2, Exploratory Analysis 8.4.2.3: Section updated to reflect removal of the 5.0 Dapagliflozin dosing arm and change to sample size.

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.

AMENDMENT ACKNOWLEDGMENT

I have read this Amendment and agree that it contains all necessary details for carrying out the changes described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion before implementation unless to eliminate an immediate hazard to subjects.

If this Amendment substantially alters the study design or increases potential risk to subjects, the consent form will be revised and submitted to the Institutional Review Board/Independent Ethics Committee for approval/positive opinion. I will use the new consent form for any new subjects prior to enrollment, and for subjects currently enrolled in the study if they are affected by the Amendment.

_____ _____

Investigator's printed name and signature *Date*

_____ _____

Medical Monitor/Study Director *Date*
(If required by applicable regulations and guidelines.)

Protocol Number: MB102077
Site Number:
Amendment Number: 08

Protocol Number: MB102077
IND Number: IND 68,652
EUDRACT Number 2010-019798-13
Date:

Protocol MB102077: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Subjects with Type 2 Diabetes with Inadequately Controlled Hypertension treated with an Angiotensin-Converting Enzyme Inhibitor (ACEI)or Angiotensin Receptor Blocker (ARB) and an Additional Antihypertensive Medication

Amendment Number 09
Site Number: All

Study Director / Central Medical Monitor

Telephone (office):
Fax:

24-hr Emergency Telephone Number:
USA:
International:

Bristol-Myers Squibb Research and Development
Metabolic Diseases Clinical Research and Development

This amendment must be maintained with the referenced protocol.

Amendment Rationale:

The primary purpose of this amendment is to revise the statistical method for the primary efficacy analysis in the MB102077 study. Comments received from FDA regarding protocol MB102077 amendment 8 that was submitted on November 10, 2011, to IND 68652 for dapagliflozin stated: "Single imputation methods like last observation carried forward and baseline observation carried forward should not be used as the primary approach to the treatment of missing data unless the assumptions that underlie them are scientifically justified" as described by the National Academy of Sciences (NAS) in the report on missing data which was commissioned by FDA in July 2010.

In line with the NAS 2010 recommendations for missing data report, the primary efficacy analysis will be a longitudinal repeated measures analysis using direct likelihood instead of using ANCOVA model based on the last observation carried forward (LOCF). The LOCF based analysis will be included as a sensitivity analysis. The details of the analysis will be described in the Statistical Analysis Plan.

Additionally, this amendment will decrease the minimum number of subjects to be randomized in the study. A total of at least 408 subjects (204 subjects each in the dapagliflozin 10 mg and placebo treatment groups) need to be randomized into the MB102077 study. Assuming 5% of the subjects do not have a post-baseline assessment, the study will have at least 80% power to detect a difference of 4 mmHg in mean change from baseline in seated systolic blood pressure between the dapagliflozin 10 mg treatment group and placebo treatment group at significance level of 0.05, assuming a standard deviation (SD) of 14 mmHg and at least 94% power to detect a difference of 0.4% in mean change from baseline in HbA1c between the dapagliflozin 10 mg treatment group and the placebo treatment group at significance level of 0.05, assuming a SD of 1.1%.

This amendment also removes Section 5.3.5 Guidance on Assessment of Cancer Cases. This section was added in amendment 8 with the expectation that there would be a change in the way cancer cases were evaluated across the dapagliflozin clinical trial program. However, while additional information has been collected and consultation with oncology experts has occurred for some specific cancer cases, a cancer adjudication

committee was not established for this trial. All cancer cases will be adjudicated in a separate large dapagliflozin cardiovascular outcomes trial.

This amendment will also include clarification on the appropriate use and monitoring of insulin as a background medication during the study.

Lastly, the amendment will correct the below listed typographical errors in the protocol, include minor clarifications as well as administrative changes.

This amendment has no impact on the study conduct or subject's safety. There is no urgency with the implementation of this amendment and it will apply to all subjects in all countries once approved.

Changes to the Protocol:

1) Cover page: Central Medical Monitor, Change in name of BMS Medical Monitor and contact details.
2) Synopsis: Study Assessments and Primary Endpoints, the last post-baseline measurement prior to Week 12 if no Week 12 assessment is available has been removed.
3) Synopsis: Study Population, clarify to say total insulin dose each day not varying by more than 20% from the mean daily dose of insulin during the previous 8 weeks.
4) Synopsis: Statistical Methods, re-sizing of study from 722 subjects to 408 subjects.
5) Protocol Section 3.1, Study Design and Duration: Change from 722 subjects randomized to at least 408.
6) Protocol Section 3.1.3, Double Blind Treatment and Randomization: clarification of section in regard to the appropriate use and monitoring of insulin as a background medication during the study.
7) Protocol Section 3.3.1, Inclusion Criteria: Correct typo in criteria #2 upper range of HbA1c, ≤ 10.5%. Inclusion criteria number 3, clarify to say total insulin dose each day not varying by more than 20% from the mean daily dose of insulin during the previous 8 weeks.
8) Protocol Section 3.5.2.1, Changes in insulin dose: correct typo in second sentence, hyperglycemia change to hypoglycemia. Clarify section in regard to the appropriate use and monitoring of insulin as a background medication during the study.
9) Protocol Section 3.5.4, Discontinuation Guidelines due to Protocol-Defined Major Hypoglycemia Episode or Recurrent Non-Major Hypoglycemia Episodes: Under

Insulin Dose Reduction clarify 2 bullets to read **capillary** or plasma blood glucose values.

10) Protocol Section 5.3.1, Self-Monitoring of Blood glucose (SMBG)- clarify language in 2nd paragraph.
11) Protocol Section 5.3.5, Guidance on Assessment of Cancer Cases: remove entire section.
12) Protocol Sections renumbering as follows;
    a) Section 5.3.6 Physical Examination becomes section 5.3.5
    b) Section 5.3.7 BP and Heart Rate becomes section 5.3.6
    c) Section 5.3.7.1 Seated BP and Heart Rate becomes section 5.3.6.1
    d) Section 5.3.7.2 Orthostatic BP and Heart Rate becomes section 5.3.6.2
    e) Section 5.3.8 12-Lead Electrocardiogram (ECG) becomes section 5.3.7
    f) Section 5.3.9 Early Termination visits and supplemental visits becomes section 5.3.8
    g) Section 5.3.9.1 Early Termination Visit (Week 12/ET visit) becomes section 5.3.8.1
    h) Section 5.3.9.2 Supplemental visits becomes section 5.3.8.2
13) Protocol Section 6.1.1, Serious Adverse Event Reporting: Update Medical Monitor contact and information.
14) Protocol Section 8.1, Sample Size Determination: the statement, “last post-baseline measurement prior to Week 12, if no Week 12 assessment is available”, has been removed. Revised to reflect changes in the power calculation and added “mean change from baseline at Week 12 between dapagliflozin 10 mg treatment group and the placebo treatment group in seated systolic blood pressure ”. Changed from 722 subjects randomized to at least 408 (204 per treatment group).
15) Protocol Section 8.2, Populations for Analyses: First bullet clarified.
16) Protocol Section 8.3, Endpoint Definitions: Endpoint analysis has been clarified.
17) Protocol Section 8.4.2, Efficacy Analyses: Analyses model has been changed and section revised.
18) Protocol Section 8.4.2.1, Primary Analysis: Section revised to reflect change in primary analysis method.
19) Protocol Section 8.4.2.2, Secondary Analyses: Section revised to reflect change in secondary analysis method.
20) Protocol Section 8.4.2.3, Exploratory Analyses: Section revised to reflect change in exploratory analysis method.
21) Appendix 5, Eligible Daily Doses of Angiotensin Converting Enzyme Inhibitors (ACE-I) and Angiotensin Receptor Blockers; added new to market medication, Azilsartan ≥ 40 mg/day to the list of ARBs.

22) Appendix 6, Automated Blood Pressure Monitors Acceptable For Blood Pressure Measurements, added OMRON HEM 705 cpn monitor to the list of acceptable blood pressure monitors.

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.

AMENDMENT ACKNOWLEDGMENT

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_____ _____

Investigator's printed name and signature *Date*

_____ _____

Medical Monitor/Study Director *Date*
(If required by applicable regulations and guidelines.)

Protocol Number: MB102077
Site Number:
Amendment Number: 09