Clinical Study Protocol

Drug Substance	Dapagliflozin
Study Code	D1692C00005
Edition Number	1
Date	

A multicenter, randomized, double-blind, placebo-controlled, parallel group, Phase 2 trial to evaluate the efficacy and safety of dapagliflozin as monotherapy in Japanese subjects with type 2 diabetes mellitus who have inadequate glycemic control

Sponsor:

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The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

Bristol-Myers Squibb AstraZeneca

PROTOCOL SYNOPSIS

A multicenter, randomized, double-blind, placebo-controlled, parallel group, Phase 2 trial to evaluate the efficacy and safety of dapagliflozin as monotherapy in Japanese subjects with type 2 diabetes mellitus who have inadequate glycemic control

Principal Investigator

The name of the investigators are described in Supplement A, "Investigations and Study Administrative Structure".

Study centre(s) and number of subjects planned

Study Centres: Approximately 40 centres are planned for participation

Number of Subjects: 275 randomised Japanese subjects (55 subjects per treatment group)

Study period		Phase of development
Estimated date of first subject enrolled	August 2009	Phase 2
Estimated date of last subject completed	June 2010	

Objectives and Outcome variable(s)

Primary Objectives

Primary Objectives	Primary Outcome variable(s)
To compare the mean changes from baseline in glycosylated hemoglobin (HbA1c) achieved with each dose of dapagliflozin vs placebo after 12 weeks of double-blind therapy.	The primary efficacy endpoint is the change in HbA1c from baseline to Week 12 or the last post-baseline measurement prior to Week 12, if no Week 12 assessment is available. The term "change" here and hereafter refers to absolute change.

Secondary Objectives

Secondary Objectives	Secondary Outcome variable(s)
To compare the differences of the change from baseline for each dose of dapagliflozin vs placebo after 12 weeks of oral administration of double-blind treatment for the following parameters: (a) Fasting plasma glucose (FPG) (b) Proportion of subjects achieving therapeutic glycemic response defined as HbA1c < 7%	(a) Change from baseline in FPG at Week 12. (b) Proportion of subjects achieving therapeutic glycemic response (HbA1c < 7.0%) at Week 12.

Tertiary Objectives

Tertiary Objectives	Tertiary Outcome variable(s)
1. To assess the differences of the change from baseline for each dose of dapagliflozin vs placebo after 12 weeks of oral administration of double-blind treatment for the following parameters: (a) Area under the curve (AUC) from 0 to 180 minutes for postprandial glucose, insulin, and C-peptide response to an oral glucose tolerance test (OGTT) (b) Fasting plasma insulin (c) Fasting plasma C-peptide (d) Beta-cell function (as measured by Homeostasis Model Assessment version 2 (HOMA2)) (e) Insulin resistance index (as measured by HOMA2)	1. (a) Change from baseline in AUC from 0 to 180 minutes for postprandial glucose, insulin, and C-peptide response to an OGTT at Week 12. (b) Change from baseline in fasting plasma insulin at Week 12. (c) Change from baseline in fasting C-peptide at Week 12. (d) Change from baseline in beta-cell function (as measured by HOMA2) at Week 12. (e) Change from baseline in insulin resistance (as measured by HOMA2) at Week 12.

Tertiary Objectives	Tertiary Outcome variable(s)
2. To assess each dose of dapagliflozin and placebo after 12 weeks of oral administration of double-blind treatment for the following:	2.
(a) Changes from baseline in glucose, C-peptide, and insulin concentrations at 0, 30, 60, 120 and 180 minutes during an OGTT	(a) Change from baseline in glucose, C-peptide and insulin concentrations at 0, 30, 60, 120, and 180 minutes postprandial values during an OGTT at Week 12.
(b) Change from baseline in the respective excretion profiles for plasma glucose, C-peptide, and insulin concentrations (defined as the difference between 0 and 30, 60, 120 and 180 minute postprandial values) during an OGTT	(b) Change from baseline in the respective excretion profiles for plasma glucose, C-peptide and insulin concentrations (defined as the difference between 0 and the 30, 60, 120, and 180 minutes postprandial values) during an OGTT at Week 12.
(c) Change from baseline in the insulin sensitivity and beta-cell function derived from measurements of insulin, C-peptide, and glucose during the OGTT	(c) Change from baseline in the insulin sensitivity and beta-cell function derived from measurements of insulin, C-peptide and glucose during the OGTT at Week 12.
(d) Change from baseline in body mass index (BMI), waist circumference, and total body weight	(d) Change from baseline in BMI, waist circumference, and total body weight at Week 12.
(e) Percent change from baseline in fasting lipids (total cholesterol (Total-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, (HDL-C), triglycerides (TG), and free fatty acids (FFA))	(e) Percent change from baseline in fasting lipids (Total-C, LDL-C, HDL-C, TG, and FFA) at Week 12.
(f) Change from base line in 24-hour urinary glucose/creatinine ratio.	(f) Change from base line in 24-hour urinary glucose/creatinine ratio at Week 12.

Safety objective

To assess the safety and tolerability of each dose of dapagliflozin in reference to that of placebo.

Exploratory objectives

To explore relationships between dapagliflozin plasma exposure measures and efficacy variables such as reduction in HbA1c from baseline. If necessary, Pharmacokinetic (PK) results will be documented in a separate population PK report.

Study design

This is a Phase 2b, multicenter, randomized, 5-arm, parallel-group, double-blind, placebo-controlled study to evaluate the efficacy and safety of dapagliflozin in Japanese T2DM subjects who have inadequate glycemic control.

Target subject population

The target population eligible to be randomized in this study is Japanese male and female subjects with T2DM aged ≥ 18 to ≤ 79 years, with inadequate glycemic control defined as HbA1c ≥ 7.0% and ≤ 10% on diet and exercise alone.

Investigational product, dosage and mode of administration

Each dose will be composed of 3 tablets. Investigational drug should be taken once daily in the morning.

Treatment Phase (Period C)

1 mg dose: 1 mg 1 tablet + 2.5 mg/5 mg placebo 1 tablet + 10 mg placebo 1 tablet

2.5 mg dose: 1 mg placebo 1 tablet + 2.5 mg 1 tablet + 10 mg placebo 1 tablet

5 mg dose: 1 mg placebo 1 tablet + 5 mg 1 tablet + 10 mg placebo 1 tablet

10 mg dose: 1 mg placebo 1 tablet + 2.5 mg/5 mg placebo 1 tablet + 10 mg 1 tablet

Comparator, dosage and mode of administration

Comparator dose will be composed of 3 tablets. Investigational drug should be taken once daily in the morning.

Placebo Lead-in Phase (Period B) and Treatment Phase (Period C)

Placebo dose: 1 mg placebo 1 tablet + 2.5 mg/5 mg placebo 1 tablet + 10 mg placebo 1 tablet

Duration of treatment

This study consists of an enrolment visit, a 6-week wash-out phase (Period A), a 4-week single-blind, placebo lead-in phase (Period B), a 12-week double-blind, placebo-controlled treatment phase (Period C), and a 4-week follow-up phase (Period D).

Statistical methods

The primary efficacy analysis will be based on the full analysis set, and the change from baseline in HbA1c at Week 12 will be analysed based on an analysis of covariance

(ANCOVA) model including treatment group as a fixed effect and baseline as a covariate. Based on the ANCOVA model, the point estimates and 2-sided 95% confidence intervals for the mean changes within each treatment group as well as for the differences in mean changes between each of dapagliflozin treatment group and the placebo treatment group will be calculated. Pair-wise comparisons of dapagliflozin treatment groups vs. placebo group will be made with multiplicity of tests adjusted by Dunnett's method at overall 2-sided significance level 0.05.

The change from baseline at Week 12 in FPG, 180 minutes AUC on postprandial glucose, insulin and C-peptide response to OGTT, fasting plasma insulin, fasting plasma C-peptide, beta-cell function (using HOMA2), and insulin resistance index (using HOMA2) will also be analysed based on the similar ANCOVA model as in the primary efficacy analysis for HbA1c.

All efficacy and safety variables will be summarised descriptively by treatment group.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.4.1)
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
CABG	Coronary Artery Bypass Graft
CEC	Clinical Event Committee
CHF	Congestive heart failure
CRF	Case Report Form (electronic/paper)
CTX	C-terminal cross-linking telopeptides of type I collagen
DAE	Discontinuation of Investigational Product due to Adverse Event
ECG	Electrocardiogram
FFA	Free fatty acids
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HbA1c	Glycosylated hemoglobin, Hemoglobin A1c
HCG	Human chorionic gonadotropin
HDL-C	High-density lipoprotein cholesterol
HOMA2	Homeostasis model assessment version 2
ICH	International Conference on Harmonization
IGT	Impaired Glucose Tolerance
LDL-C	Low density lipoprotein cholesterol
LLOQ	Lower Limit of Quantification
MDRD	Modification of Diet in Renal Disease
MI	Myocardial Infarction

Abbreviation or special term	Explanation
NAG	N-acetyl glucosamine
NPDR	Non-proliferative diabetic retinopathy
NYHA	New York Heart Association
OAE	Other Significant Adverse Event (see definition in Section 11.2.1)
OGTT	Oral glucose tolerance test
PCI	Percutaneous coronary intervention
PK	Pharmacokinetic
PT	Prothrombin Time
PTCA	Percutaneous transluminal coronary angioplasty
P1NP	Procollagen type-1 N-terminal propeptide
SAE	Serious adverse event (see definition in Section 6.4.2).
SMBG	Self monitoring blood glicose
TC	Total cholesterol
TG	Triglycerides
TIA	Transient ischemic attack
TSH	Thyroid Stimulating Hormone
T2DM	Type 2 diabetes mellitus
ULN	Upper limit normal
WBDC	Web Based Data Capture
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background

Recent estimates indicate that there were 150 million people in the world with type 2 diabetes mellitus (T2DM) at the beginning of the new millennium. It is believed that this number will double in the next 25 years.In Japan, diabetes mellitus patients and impaired glucose tolerance (IGT) is estimated as 8.9 million and 13.2 million, respectively, and in total, 22 million (The Summary of the National Health and Nutrition Survey 2007). The number of death caused by diabetes mellitus during 2007 was reported as 14,000 (Vital Statistics, 2007).

T2DM is characterized by beta-cell dysfunction and peripheral insulin resistance leading to hyperglycaemia(Matthaei et al 2000, Meier and Butler 2005). Chronic hyperglycaemia has been associated with the development of both macrovascular (myocardial infarction, stroke), and microvascular (nephropathy, retinopathy) complications (UKPDS Group 1998a). Every year, 3,500 people suffer from loss of eyesight caused by diabetic retinopathy (The 2005 Data on Diabetic Retinopathy by the Japan Ophthalmologists Association). Diabetic nephropathy was the top of the primary diseases that led to initiation of dialysis, with 15,750 patients (43% of total) (An Overview of regular dialysis treatment in Japan (as of December 31, 2007)).

Current treatment regimens aiming to reduce glucose levels in T2DM patients are categorized into 6 types, which have focussed on the stimulation of insulin secretion (e.g., sulfonylureas (SUs), rapid-acting insulin secretion stimulators (glinides)), the reduction of peripheral insulin resistance (e.g., biguanides (BGs), thiazolidine derivatives (TZDs)), the inhibition of intestinal glucose absorption(e.g. α-glucosidase inhibitors (AGIs)), or the addition of exogenous insulin. However, the limited efficacy as well as the induction of side effects (e.g., hypoglycaemia, induction of oedema, weight gain, etc.) clearly underline the need for novel antidiabetic treatment strategies with a new mechanism of action and more favourable risk/benefit profile.

Intestinal absorption and renal re-absorption of glucose are mediated through sodium-glucose transporters (Silverman 1991). Two sodium-dependent glucose transporters, SGLT1 and SGLT2, have been identified as the major transporters of glucose in the human (Wright 2001, Thomson and Wild 1997). SGLT1 is expressed in the gastrointestinal tract, heart, skeletal muscle, liver, lung, and kidney, while SGLT2 is expressed almost exclusively in the kidney. SGLT2 expression is localized to the S1 segment of the proximal tubule, where > 90% of renal glucose reabsorption occurs (Deetjen P et al 1992). Human mutations in SGLT2 are associated with familial renal glucosuria. These patients present with glucosuria secondary to a decrease in glucose reabsorption in the proximal tubule. They have normal plasma glucose levels. From the information available, these patients have normal life-span and no other abnormalities other than the increase urinary glucose excretion (Santer et al 2003, van den Heuvel et al 2002). Thus SGLT2 appears to be the major transporter responsible for renal glucose transport, mediating glucose re-uptake from the glomerular filtrate. Inhibition of SGLT2 therefore provides a promising novel treatment strategy to reduce high blood glucose levels via enhanced renal glucose excretion.

Dapagliflozin has been designed as a potent and selective inhibitor of the renal sodium-glucose transporter, SGLT2. This compound is being developed as an orally-active agent for the treatment of T2DM. Since this compound has the new mechanism of action, ie, induction of glucose excretion into urine independent of insulin action, it is expected to represent a novel therapeutic approach for the treatment of this disorder.

1.2 Research hypothesis

After 12 weeks of oral daily administration, there will be a greater mean reduction from baseline in glycosylated hemoglobin (HbA1c) achieved with dapagliflozin compared to placebo in Japanese subjects with T2DM with inadequate glycemic control.

1.3 Rationale for conducting this study

There is an unmet need in the treatment of diabetes mellitus. With the current medical therapy less than 50% of patients with diabetes reach glycemic control goals (UKPDS Group 1998a, UKPDS Group 1998b). Therefore, the development of medications with new mechanisms of action for the treatment of diabetes is desirable. Dapagliflozin, with its novel mechanism of action, inhibits SGLT2 and may result in lowering of plasma glucose regardless of the patient's insulin sensitivity and beta-cell functional secretory status.

In the global single ascending dose Phase 1 study in healthy volunteers (MB102001), there was a dose-dependent increase in urinary glucose excretion from 2.5 to 20 mg. Doses higher than 20 mg (50 to 500 mg) did not cause greater urinary glucose excretion than the 20 mg dose.

In the global multiple ascending dose Phase 1 study in healthy volunteers (MB102002), there was a dose-dependent increase in urinary glucose excretion from 2.5 mg to 20 mg/day. The urinary glucose excretion was similar for subjects taking 20 mg/day and 50 mg/day. It appears that in healthy subjects the peak effect in urinary glucose excretion is seen at 20 mg/day.

In the global Phase 2b study (MB102008), dose range from 2.5 to 50 mg was administered once daily oral ingestion over 12 weeks in patients with T2DM. A statistically significant reduction in HbA1c from baseline to Week 12 was achieved in all dapagliflozin groups compared with placebo ($p < 0.008$ or less for each dose group), but was not demonstrated to be dose dependent within the study dose range. In the global phase 2b study, dapagliflozin was demonstrated to be well-tolerated in subjects with T2DM.

In the Japan single ascending dose Phase 1 study (MB102010), dapagliflozin 2.5 mg, 10 mg, 20 mg and 50 mg was administrated to healthy volunteers. Preliminary data show that after single oral dose of dapagliflozin, urinary glucose excretion increased in proportion to dose while urinary glucose excretion remained constant following single oral dose of matching placebo.

In the Japan multiple ascending dose Phase 1 study (MB102025), multiple oral doses of dapagliflozin 2.5 mg, 10 mg and 20 mg for 14 days were generally safe and well tolerated in Japanese T2DM subjects. Preliminary data show that dosing with dapagliflozin increased the

amount of glucose excreted in urine almost dose-dependently and slightly increased the amount of calcium excreted in urine.

This study intends to evaluate the efficacy and safety of dapagliflozin as monotherapy in Japanese subjects with T2DM who have inadequate glycemic control. Based on a consideration of efficacy, pharmacodynamics, and safety data from the Japanese Phase 1 and the global Phase 1 and 2 studies, dapagliflozin doses of 1, 2.5, 5 and 10 mg were selected for this study (See Section 3.2). The study is also designed to be as similar as possible to the already completed overseas Phase 2b dose response study (MB102008), in order to enable comparison of the efficacy and safety results between the two studies.

1.4 Benefit/risk and ethical assessment

This study includes an experimental compound, dapagliflozin, being developed as a potential new therapy for hyperglycemia in subjects with T2DM. In the Japanese Phase 1 and the global Phase 1, 2a and 2b studies dapagliflozin was generally safe and well tolerated.

In the Japan Phase 1 (MB102025), multiple oral doses of dapagliflozin 2.5 mg, 10 mg and 20 mg for 14 days were generally safe and well tolerated in Japanese T2DM subjects. There were no deaths, serious adverse events (SAEs) or adverse events (AEs) leading to discontinuation of investigational product in this study. Fourteen (14) of 27 subjects experienced 19 AEs following administration of dapagliflozin, and 2 of 9 subjects experienced 3 AEs following the dose of placebo.

In the global Phase 2a study (MB102003), in which subjects received up to 100 mg of dapagliflozin, placebo or metformin daily for 2 weeks, AEs (AEs that began or worsened after treatment) were reported, gastrointestinal (GI) events were reported in the largest proportion of subjects. No SAE was reported during the double-blind period.

In the global Phase 2b study (MB102008), subjects with T2DM received dapagliflozin (up to 50 mg daily), placebo, or metformin, for 12 weeks. Subjects receiving dapagliflozin, in comparison to placebo, exhibited declines in HbA1c and dose-related decreases in fasting plasma glucose (FPG). In addition, subjects with dapagliflozin therapy exhibited decreases in body weight over the 12-week treatment period when compared to baseline weight as well as when compared to placebo. SAEs were reported in 4 subjects in the dapagliflozin-treatment arms, which were considered by the investigators not related to study medication. There were no deaths reported. Urinary tract infections were more common in dapagliflozin than in placebo but similar to that in the metformin group. Genital tract infections were more frequent in dapagliflozin-treated subjects compared with subjects receiving placebo, especially at the higher dapagliflozin doses of 20 and 50 mg/day. There were no reports of confirmed hypoglycemia, defined as symptoms of hypoglycemia with fingerstick glucose $\leq$ 50 mg/dL, during the double-blind period. The percentage of subjects with AEs of hypoglycemia was higher in the dapagliflozin treatment groups compared with the placebo group, but similar to that in the metformin treatment group. None of the events of hypoglycemia were assessed by the investigator to be of severe intensity. Dapagliflozin administration was associated with increases in urine production, accompanied by changes in clinical and laboratory data

consistent with mild plasma volume reduction. Changes in serum electrolyte concentrations were minor and infrequent.

Previous studies have indicated that dapagliflozin is effective in treatment of T2DM because of its new mechanism of action, ie, ability to reduce high blood glucose level via enhanced renal glucose excretion. Thus, it would be appropriate to move on to phase II clinical studies in Japanese T2DM patients.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objectives	Primary Outcome variable(s)
To compare the mean changes from baseline in HbA1c achieved with each dose of dapagliflozin vs placebo after 12 weeks of double-blind therapy.	The primary efficacy endpoint is the change in HbA1c from baseline to Week 12 or the last post-baseline measurement prior to Week 12, if no Week 12 assessment is available. The term "change" here and hereafter refers to absolute change.

2.2 Secondary objectives

Secondary Objectives	Secondary Outcome variable(s)
To compare the differences of the change from baseline for each dose of dapagliflozin vs placebo after 12 weeks of oral administration of double-blind treatment for the following parameters: (a) Fasting plasma glucose (FPG) (b) Proportion of subjects achieving therapeutic glycemic response defined as HbA1c < 7%	(a) Change from baseline in FPG at Week 12. (b) Proportion of subjects achieving therapeutic glycemic response (HbA1c < 7.0%) at Week 12.

2.3 Tertiary Objectives

Tertiary Objectives	Tertiary Outcome variable(s)
1. To assess the differences of the change from baseline for each dose of dapagliflozin vs placebo after 12 weeks of oral administration of double-blind treatment for the following parameters:	1.
(a) Area under the curve (AUC) from 0 to 180 minutes for postprandial glucose, insulin, and C-peptide response to an oral glucose tolerance test (OGTT)	(a) Change from baseline in AUC from 0 to 180 minutes for postprandial glucose, insulin, and C-peptide response to an OGTT at Week 12.
(b) Fasting plasma insulin	(b) Change from baseline in fasting plasma insulin at Week 12.
(c) Fasting plasma C-peptide	(c) Change from baseline in fasting C-peptide at Week 12.
(d) Beta-cell function (as measured by Homeostasis Model Assessment version 2 (HOMA2))	(d) Change from baseline in beta-cell function (as measured by HOMA2) at Week 12.
(e) Insulin resistance index (as measured by HOMA2)	(e) Change from baseline in insulin resistance (as measured by HOMA2) at Week 12.

Tertiary Objectives	Tertiary Outcome variable(s)
2. To assess each dose of dapagliflozin and placebo after 12 weeks of oral administration of double-blind treatment for the following:	2.
(a) Changes from baseline in glucose, C-peptide, and insulin concentrations at 0, 30, 60, 120 and 180 minutes during an OGTT	(a) Change from baseline in glucose, C-peptide and insulin concentrations at 0, 30, 60, 120, and 180 minutes postprandial values during an OGTT at Week 12.
(b) Change from baseline in the respective excretion profiles for plasma glucose, C-peptide, and insulin concentrations (defined as the difference between 0 and 30, 60, 120 and 180 minute postprandial values) during an OGTT	(b) Change from baseline in the respective excretion profiles for plasma glucose, C-peptide and insulin concentrations (defined as the difference between 0 and the 30, 60, 120, and 180 minutes postprandial values) during an OGTT at Week 12.
(c) Change from baseline in the insulin sensitivity and beta-cell function derived from measurements of insulin, C-peptide, and glucose during the OGTT	(c) Change from baseline in the insulin sensitivity and beta-cell function derived from measurements of insulin, C-peptide and glucose during the OGTT at Week 12.
(d) Change from baseline in body mass index (BMI), waist circumference, and total body weight	(d) Change from baseline in BMI, waist circumference, and total body weight at Week 12.
(e) Percent change from baseline in fasting lipids (total cholesterol (Total-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, (HDL-C), triglycerides (TG), and free fatty acids (FFA))	(e) Percent change from baseline in fasting lipids (Total-C, LDL-C, HDL-C, TG, and FFA) at Week 12.
(f) Change from base line in 24-hour urinary glucose:creatinine ratio.	(f) Change from base line in 24-hour urinary glucose:creatinine ratio at week 12.

2.4 Safety objective

To assess the safety and tolerability of each dose of dapagliflozin in reference to that of placebo.

2.5 Exploratory objectives

To explore relationships between dapagliflozin plasma exposure measures and efficacy variables such as reduction in HbA1c from baseline. If necessary, Pharmacokinetic (PK) results will be documented in a separate population PK report.

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

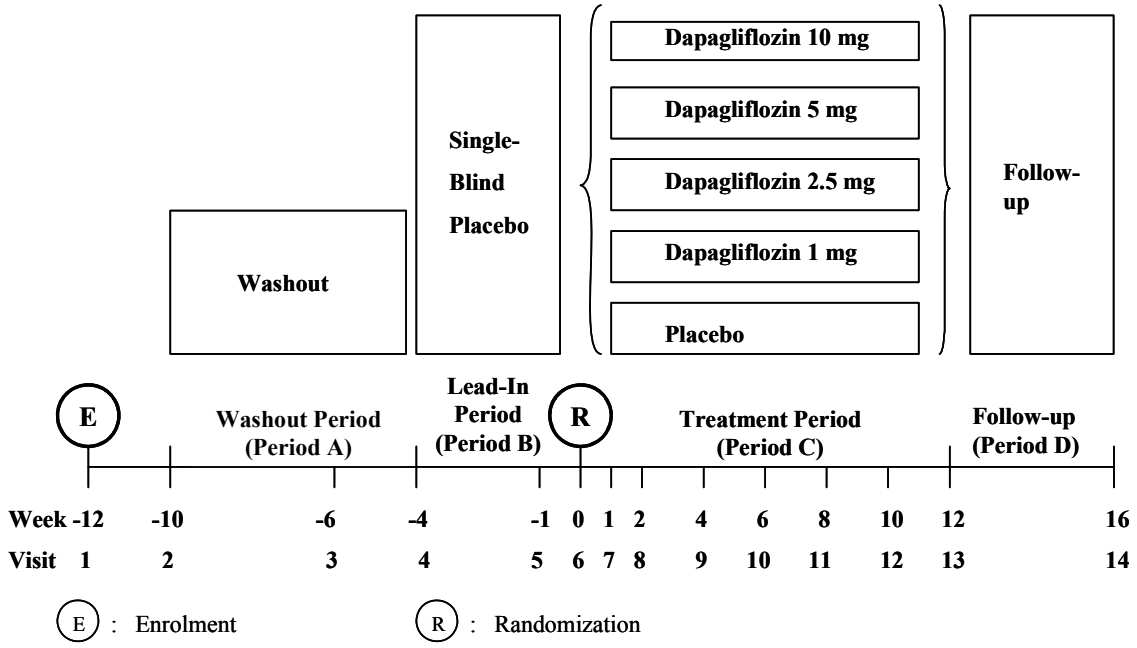
This is a Phase 2b, multicentre, randomized, 5-arm, parallel-group, double-blind, placebo-controlled study to evaluate the efficacy and safety of dapagliflozin in Japanese T2DM subjects with inadequate glycemic control on diet and exercise alone.

This study consists of an enrolment visit, a 6-week wash-out phase (Period A), a 4-week single-blind, placebo lead-in phase (Period B), a 12-week double-blind, placebo-controlled treatment phase (Period C), and a 4-week follow-up phase (Period D).

Subjects who have inadequate glycemic control (HbA1c ≥ 7% but ≤ 10%) on diet and exercise alone at Visit 5 (1 week before randomization) are eligible to be randomised.

The study design is shown in Figure 1.

Figure 1 Study flow chart



Enrolment visit (Visit 1)

Subjects will provide informed consent if not done before Visit 1, be enrolled and screened for all applicable inclusion and exclusion criteria, and submit laboratory samples.

There will be 4 types of subjects enrolled:

- Strictly treatment naïve subjects at enrolment, defined as never received medical treatment for diabetes (insulin and/or oral anti-hyperglycaemic agents)

- Relatively treatment naïve subjects at enrolment, defined as received medical treatment for diabetes for less than 30 days since diagnosis. In addition, during the 30-day period prior to enrolment did not receive oral anti-hyperglycemic medication for more than 3 consecutive or more than 7 non-consecutive days. Subjects also should not have a history of insulin therapy within 2 weeks of enrolment (with the exception of insulin therapy during a hospitalization for other causes or use in gestational diabetes).

- Subjects treated with anti-diabetic medication prior to enrolment, defined as previously treated with anti-diabetic medication but have not been treated within 6 weeks of enrolment

- Subjects treated with anti-diabetic medication up to enrolment. Only a single oral anti-hyperglycaemic agent or two agents with less than half of the approved maximal dose for each agent are allowed

Wash-out period - Period A (6 weeks; Visit 2 and Visit 3)

Subjects treated with anti-diabetic medication up to enrolment will enter Period A. Strictly treatment naïve subjects at enrolment, Relatively treatment naïve subjects at enrolment, or subjects treated with anti-diabetic medication prior to enrolment will skip this period and enter the Placebo Lead-in period (Period B).

Period A consists of Visit 2 and 3. If HbA1c is $\leq$ 8% and FPG $\leq$ 240 mg/dL at the enrolment visit, subjects will start wash-out at the latest from Visit 2 (Week -10). Washout means to stop taking oral anti-hyperglycaemic agent(s). Subjects will receive dietary counselling according to nutritional recommendations for a healthy lifestyle consistent with Japan Society of Diabetes or similar guidelines and a goal of weight maintenance to be followed for the study duration from the investigator(s). Also, subjects will be given a blood glucose meter and be instructed on its use by site personnel. FPG is measured at Visit 2 (Week -10), and Visit 3 (Week -6), and if FPG is > 240 mg/dL at either of these visits, subjects will be withdrawn from the study.

Single-blind, Placebo Lead-in Phase - Period B (4 weeks; Visit 4 and Visit 5)

Period B is a 4-week dietary and placebo lead-in phase.

Subjects treated with anti-diabetic medication up to enrolment will continue to this phase if FPG is ≤ 240 mg/dL during Period A (Visit 2 and 3). FPG is measured at Visit 4 (Week - 4) and Visit 5 (Week - 1), and if FPG is > 240mg/dl at either of these visits, subjects will be withdrawn from the study. The three other types of subjects will enter Period B if HbA1c is ≥ 7% and ≤ 10% at the enrolment visit.

Subjects will receive dietary counselling according to nutritional recommendations for a healthy lifestyle consistent with Japan Society of Diabetes or similar guidelines and a goal of weight maintenance to be followed for the study duration from the investigator(s). Subjects who skipped Period A will be given a blood glucose meter and be instructed on its use by site personnel.

In Period B, Single-blind placebo will be used to assess subject's compliance with treatment. Subjects must demonstrate good compliance with investigational products (≥ 80% and ≤ 120%) during Period B, and have HbA1c ≥ 7% but ≤ 10% at Visit 5 (1 week before randomisation) to be eligible for entry into Period C. Subjects will be withdrawn from the study if they do not meet these criteria, and must return all unused investigational products. The Investigators will assess adverse event and provide medical therapy that is clinically needed for the subject.

Double-blind, Placebo-controlled, Treatment Phase - Period C (12 weeks; Visit 6-13)

Eligible subjects will participate in a randomized, double-blind, placebo-controlled treatment phase (Period C). Subjects will be randomized to one of five treatment arms that include dapagliflozin 1 mg, 2.5 mg, 5 mg, 10 mg or placebo in a 1:1:1:1:1 ratio. Subjects will be followed for a total of 12 weeks on double-blind study medication, returning for a visit one week after start of treatment, and then approximately every 2 weeks for evaluation of safety and efficacy. Once a patient is randomised, all visits should be scheduled relative to Visit 6. Any slippage in time from one visit must not accumulate to affect other visits. Period C must be at least 81 days and at the most 87 days (12 weeks ± 3 days). Subject should not take investigational products prior to study visit at Visit 7, 10 and 12 (Week 1, 6 and 10). Investigational products should be taken soon after completing the study visit examinations.

All randomised Subjects who do not complete Period C will complete Visit 13 (Week 12) study procedures as soon as possible but at the latest within 7 days after discontinuation of investigational products.

Visit 6 (Week 0):

On the day of randomization, subjects will present in the morning after a 10-hour overnight fast including 12 hours abstinence from tobacco and caffeine and 24 hours abstinence from alcohol. Contact the registration centre to randomise eligible subjects. Fasting blood sample (for HbA1c, FPG, fasting insulin, C-peptide, fasting serum lipids, standard safety laboratory panel, markers of bone metabolism and cystatine C), and urine sample (for standard safety laboratory panel and spot urine and 24 hour urine for subjects who give consent) will be obtained. OGTT is performed in only those subjects whose FPG is less than 180 mg/dL at Visit 5 (Week -1). Blood samples for assays of glucose, insulin, and C peptide stipulated in

the protocol will be collected at baseline and throughout the duration of the OGTT, and all urine voided during OGTT will be collected. Subjects will receive their first dose of double-blind investigational products as soon as possible after completion of OGTT.

From Visit 7 (Week 1) to Visit 12 (Week 10):

Fasting blood samples and urine samples will be obtained at every visit. The investigators will assess adverse events, review concomitant medications and review subjects' dietary and exercise compliance. Compliance with investigational products will be assessed at every visit. Pill count will also be done at visits when new investigational products is dispensed and the old bottle returned.

Glucose control will be assessed and compared to the protocol-specific parameters for early termination (See Section 5.8) and subjects who meet the pre-specified hyperglycemia criteria will be discontinued from double-blind study medication and complete all Visit 13 (Week 12) study procedures (See Section 5.8).

Visit 13 (Week 12):

Fasting blood sample (for HbA1c, FPG, fasting insulin, C-peptide, fasting serum lipids, standard safety laboratory panel, markers of bone metabolism, and cystatine C), and urine sample (for standard safety laboratory panel and spot urine, and 24 hour urine for subjects who give consent) will be obtained. At Visit 13(Week 12), 24 hour urine is not performed in subjects who did not complete Period C. OGTT will be performed except for subjects who did not perform OGTT at Week 0, discontinued or whose FPG $\geq$ 180 mg/dl at Visit 12 (Week 10). PK samples are obtained at 60, 90, 120, 180 and 240 minutes after administration of investigational products. If OGTT is performed, the PK samples are obtained simultaneously with OGTT blood samples.

The investigators will assess adverse events, review concomitant medications, review subjects' dietary and exercise compliance, assess compliance with investigational products and collect all the investigational products.

Follow-up Phase – Period D (4 weeks; Visit 14)

All subjects completing period C or those who discontinue study medication during period C will be followed for an additional 4 weeks to assess safety parameters. Between weeks 12 and 16, the Investigator may add, at their discretion, any therapy that is clinically indicated to control the subject's hyperglycemia.

Table 1 Study Plan

Procedure	Scree-ning	Wash-out Period (Period A) [b]		Placebo Lead-in Period (Period B)		Double-blind, Placebo-controlled, Treatment Period (Period C) [c]								Follow-up period (Period D)
	Wk-12 ~ -10 [a]	Wk -10	Wk -6	Wk –4 Entry lead-in	Wk-1	Wk 0 Rando-misation	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12 End of Treatment	Wk 16
Visit	**1**	**2**	**3**	**4 (-4w)**	**5 (-1w)**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Informed Consent [a]	X													
Review In/Ex Criteria or Randomization Criteria	X					X								
Complete Medical History	X													
Complete Physical Examination	X			X		X							X	
Brief Physical Examination							X	X	X	X	X	X		X
Vital Signs, Body Weight	X			X		X	X	X	X	X	X	X	X	X
Orthostatic Blood Pressure, Heart rate						X		X	X				X	X
Height, Body Mass Index	X													
Waist Circumference	X					X							X	
ECG				X		X							X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dietary/exercise instruction/review		X	X	X	X	X	X	X	X	X	X	X	X	X
Contact Registration Centre	X [e]					X [e]							X [e]	
Dispense Glucose Meter and supplies/provide instructions [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events Assessment				X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test (urine) (WOCBP only)	X			X		X	X			X			X	

Table 1 Study Plan

Procedure	Screening	Wash-out Period (Period A) [b]		Placebo Lead-in Period (Period B)		Double-blind, Placebo-controlled, Treatment Period (Period C) [c]								Follow-up period (Period D)
	Wk-12 ~ -10 [a]	Wk -10	Wk -6	Wk –4 Entry lead-in	Wk-1	Wk 0 Randomisation	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12 End of Treatment	Wk 16
Visit	**1**	**2**	**3**	**4 (-4w)**	**5 (-1w)**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Standard Safety Laboratory Panel (Blood and urine)	X			X		X	X	X	X	X	X	X	X	X
HbA1c	X [f]				X [f]	X			X	X	X	X	X	X
FPG	X [g]	X [g]	X [g]	X [g]	X [g]	X	X	X	X	X	X	X	X	X
Fasting Insulin, C-peptide	X					X				X			X	
Oral Glucose Tolerance test (OGTT) with 75 g oral glucose solution						X [h]							X [h]	
Postprandial glucose, insulin and C-peptide (during OGTT)						X [h]							X [h]	
Collect urine for glucose, creatinine and sodium concentration (during OGTT)						X [h]							X [h]	
PK Sample collection							X [i]			X [i]		X [i]	X [i]	
Spot urine collection	X					X				X			X	X
24hr urine collection [j]						X							X	
Obtain serum sample for markers of bone metabolism						X					X		X	X
Assess glycemic targets (FPG)									X	X	X	X		
Fasting serum lipids: Total-C, LDL-C, HDL-C, TG, and FFA						X							X	
Hepatitis Screen Panel [k], TSH, and PT/APTT	X													

Table 1 Study Plan

Procedure	Screening	Wash-out Period (Period A) [b]		Placebo Lead-in Period (Period B)		Double-blind, Placebo-controlled, Treatment Period (Period C) [c]								Follow-up period (Period D)
	Wk-12 ~ -10 [a]	Wk -10	Wk -6	Wk –4 Entry lead-in	Wk-1	Wk 0 Randomisation	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12 End of Treatment	Wk 16
Visit	**1**	**2**	**3**	**4 (-4w)**	**5 (-1w)**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Cystatine C						X							X	X
Dispense Investigational products				X		X			X		X			
Review Medication Compliance						X	X	X	X	X	X	X	X	

a Screening procedures may be completed over multiple visit dates. IC should be obtained within 14 days before any study specific procedures performed.

b Wash-out period is only applicable to subjects treated with anti-diabetic medication up to enrolment, and strictly treatment naïve subjects at enrolment, Relatively treatment naïve subjects at enrolment, or subjects treated with anti-diabetic medication prior to enrolment could skip this period (Visit 2 and 3).

c All randomized subjects not completing the treatment period should have Visit 13 procedures done as soon as possible but at the latest within 7 days after discontinuation of investigational products, and subsequently enter the 4-week follow-up period.

d Glucose meter is provided to subjects and they check their blood glucose values if they have symptoms of hypoglycemia.

e Call Registration Center to enroll subjects when informed consent is obtained at Visit 1, to randomize subjects at Visit 6, and when subject completes Period C or early discontinue Period C.

f Subjects treated with anti-diabetic medication up to enrolment should have HbA1c ≤ 8% at Visit 1 to enter Period A, and the other type of subjects will enter Period B if HbA1c ≥ 7% but ≤ 10% at visit 1. All subjects should have HbA1c ≥ 7% but ≤ 10% at visit 5 to be randomized.

g Subjects treated with anti-diabetic medication up to enrolment will be withdrawn if FPG > 240 mg/dL.

h At Visit 6, OGTT is performed if FPG is <180 mg/dL at visit 5. At Visit 13, OGTT is not performed in subjects who did not perform OGTT at Visit 6, subjects who did not complete period C or subjects whose FPG is ≥ 180 mg/dL at Visit 12. At Visit 13, blood samples are drawn 60, 90, 120, 180 and 240 minutes after administration of 75 g oral glucose solution.

i Plasma samples for analysis of dapagliflozin are obtained before administration of dapagliflozin at Visit 7, 10 and 12. At Visit 13 plasma samples are obtained at 60, 90, 120, 180 and 240 minutes after administration of dapagliflozin. If the subjects perform OGTT at Visit 13, plasma samples are obtained simultaneously with OGTT blood samples.

j 24 hour urine collection is done in subjects who give consent. 24 hour urine is collected from the morning of the previous day to the visit up to the morning of the visit. 24 hour urine collection is allowed to be done on a separate day of the study visit if collected within 7 days before the visit. .Subjects do not need to perform 24 hour urine collection at visit 6 if they do not meet HbA1c ≥ 7% but ≤ 10% at Visit 5. At Visit 13(Week 12), 24 hour urine is not performed in subjects who did not complete Period C

k Includes anti-HAV (IgM, IgG), HBsAg, and anti-HCV, and anti-HBc

Table 2 Visit design and time windows

Visit ID	Visit description	Visit window
Visit 1	Enrolment (Screening) [a]	-12 weeks
Visit 2	Entry of washout [b]	-10 weeks ±3 days
Visit 3	Washout period [b]	-6 weeks ±3 days
Visit 4	Entry placebo lead-in	-4 weeks ±3 days
Visit 5	Placebo Lead-in Period	-1 week ±3 days
Visit 6	Randomisation/Start of treatment	±0 days
Visit 7	Treatment Period	1 week ±3 days after Visit 6
Visit 8	Treatment Period	2 weeks±3 days after Visit 6
Visit 9	Treatment Period	4 weeks ±3 days after Visit 6
Visit 10	Treatment Period	6 weeks ±3 days after Visit 6
Visit 11	Treatment Period	8 weeks ±3 days after Visit 6
Visit 12	Treatment Period	10 weeks ±3 days after Visit 6
Visit 13	Treatment Period/End of treatment	12 weeks ±3 days after Visit 6
Visit 14	Follow-up Period	16 weeks ±3 days after Visit 6

a If the results of central laboratory tests are available by Visit 2 (Week -10), Visit 1 can be done between 10 to 12 weeks before Visit 6.

b Strictly treatment naïve subjects at enrolment, Relatively treatment naïve subjects at enrolment, or subjects treated with anti-diabetic medication prior to enrolment can skip Visit 2 and Visit 3. If the results of central laboratory tests are available by Visit 4 (Week -4), Visit 1 can be done between 4 to 6 weeks before Visit 6.

3.2 Rationale for study design, doses and control groups

This study is a randomized, double-blind, placebo-controlled study to assess the efficacy and safety of dapagliflozin in Japanese subjects with T2DM who have inadequate glycemic control. This study is also designed to be as similar as possible to the global phase 2b study (MB102008) in order to enable comparison of the efficacy and safety results between the two studies.

Placebo lead-in period is set to remove any bias regarding placebo effect. Patients receiving prior therapy will complete a 6-week washout period, and 4 weeks of placebo lead-in for a total washout period of 10 weeks to eliminate effects of the prior therapy. The reason for 10 weeks of washout is as follows:

(a) Adequate washout of all prior oral anti-diabetic agents and their pharmacodynamic effects including the ones that have prolonged effects such as Pioglitazone

(b) Stabilization of HbA1c after discontinuation of any oral anti-diabetic agents takes 8-12 weeks. 10 weeks of washout allows for an adequate stabilization of HbA1c after washout of oral anti-diabetic agents prior to randomization of patients to dapagliflozin versus placebo treatment arms in this study.

The Follow-up period is set to examine the reversibility of potential adverse events after taking the last dose.

Doses of dapagliflozin and control groups

Placebo-controlled study is essential to evaluate the blood glucose-lowering effects of dapagliflozin.

In this study, dapagliflozin doses 1 mg, 2.5 mg, 5 mg and 10 mg were chosen based on efficacy, pharmacodynamic and safety data from the global phase 1 and 2 studies, and the Japan phase 1 studies. This dose range is supported by the following reasons:

- In the global phase 1and 2a studies, maximal glucosuria was seen at the 10 to 20 mg dose level. Doses ≥ 20 mg only increased the duration of glucosuria. In the global phase 2b study (MB102008), glucosuria appeared related to dose, with maximal glucosuria seen at the 20 and 50 mg doses.

- In the global phase 2b study (MB102008), dapagliflozin improved glycaemic parameters throughout the dose range of 2.5 mg to 50 mg daily, with most of the efficacy realized within the dose range of 2.5 mg to 10 mg. There was no apparent dose relationship beyond 10 mg for HbA1c, though there was evidence for a continued dose-response relationship up to 50 mg with respect to FPG change.

- In the global phase 2b study (MB102008), the sub-therapeutic dose for dapagliflozin was not identified. A global study including a 1 mg dose of dapagliflozin is being conducted to confirm a sub-therapeutic dose of dapagliflozin. The 1 mg dose is included in this study to confirm a sub-therapeutic dose in Japanese T2DM patients.

- The exposure levels of dapagliflozin in Japanese subjects obtained from the Phase 1 single dose study in Japanese healthy subjects (M102010) and the Phase 1 multiple dose study in Japanese patients with T2DM (MB102025) were compared with the exposure levels in non-Japanese subjects from the corresponding overseas studies (MB102001 and MB102003). It is judged from the comparison that there is negligible to modest difference in the exposure to dapagliflozin between Japanese and non-Japanese populations, in both healthy subjects and T2DM patients.

It is therefore judged that the doses investigated in the overseas Phase 2b study can be used for the Japanese Phase 2b dose response study. Doses of 2.5 mg and 5 mg are being repeated in the Japanese Phase 2b dose response study along with the top dose of 10 mg to have adequate data for comparison purposes between the overseas and Japanese Phase 2b studies. Having the 3 same doses in both studies is considered to allow adequate comparison of efficacy and safety of dapagliflozin between Japanese and non-Japanese patients with T2DM.

Just as in the global program, the Japanese Phase 2b study will also include the 1 mg dose as the lowest dose, to confirm a sub-therapeutic dose in Japanese patients with T2DM.

For the above reasons, the Japanese Phase 2b dose response study will investigate the 4 doses of 1, 2.5, 5 and 10 mg.

4. SUBJECT SELECTION CRITERIA

Investigator(s) should keep a record, the subject screening log, of subjects who entered pre-study screening.

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

4.1 Inclusion criteria

For inclusion in the study subjects should fulfil the following criteria:

1. Provision of informed consent prior to any study specific procedures

2. Female and male aged 18 to ≤ 79 years in Japanese (If the patient is younger than 20 years old, signed informed consent by the patient's legal representative (a person who exercises parental authority for the patient, or if no one is applicable, a guardian; the patient's parent in principle) is necessary.)

3. Subjects with T2DM **AND** meet one of the following criterion:

   - Strictly treatment naïve subjects at enrolment, and HbA1c ≥ 7.0% and ≤ 10% at the enrolment visit. Strictly treatment naïve is defined as never received medical treatment for diabetes (insulin and/or oral anti-hyperglycaemic agents)
     OR

   - Relatively treatment naïve subjects at enrolment, and HbA1c ≥ 7.0% and ≤ 10% at the enrolment visit. Relatively treatment naïve is defined as received medical treatment for diabetes for less than 30 days since diagnosis. In addition, during the 30-day period prior to enrolment did not receive oral anti-hyperglycemic medication for more than 3 consecutive or more than 7 non-consecutive days. Subjects also should not have a history of insulin therapy within 2 weeks of enrolment (with the exception of insulin therapy during a hospitalization for other causes or use in gestational diabetes)
     OR

   - Subjects treated with anti-diabetic medication prior to enrolment, and HbA1c ≥ 7.0% and ≤ 10% at the enrolment visit. Subjects treated with anti-diabetic medication prior to enrolment is defined as previously treated with anti-diabetic medication but have not been treated within 6 weeks of enrolment
     OR

- Subjects treated up to enrolment with a single oral anti-hyperglycaemic agent or with two agents with less than half of the approved maximal dose for each agent, HbA1c ≤ 8% at the enrolment visit, and FPG ≤ 240mg/dl at the enrolment visit

4. Fasting C-peptide > 1.0 ng/mL (0.33 nmol/L) at the enrolment visit

5. BMI ≤ 40 kg/m^2 at the enrolment visit

6. Scr < 1.5 mg/dL (132.6 μmol/L) for male subjects and < 1.4 mg/dL (123.8 μmol/L) for female subjects and glomerular filtration rate (GFR) calculated by the Modification in Diet in Renal Disease (MDRD) formula > 60 mL/min/1.73 m^2 at the enrolment visit.

7. No overt proteinuria defined as Spot urine Microalbumin/Cr ratio of < 300 mg/g at the enrolment visit.

Inclusion criteria for Randomization

8. No clinically significant abnormalities in any pre-randomization laboratory value, electrocardiogram (ECG), vital sign or physical examination, which in the Investigator's opinion, would preclude randomisation

9. Subject must demonstrate good compliance with study medication (≥ 80% and ≤ 120%) during Period B

10. Subjects having inadequate glycemic control on diet and exercise alone, defined as HbA1c ≥ 7.0% and ≤ 10% at 1 week before randomization (Visit 5)

4.2 Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca and Bristol Myers Squibb staff and/or staff at the study site)

2. Previous enrolment of treatment in the present study

3. Participation in another clinical study with an investigational product during the last 30 days

4. Previous participation in any clinical study of dapagliflozin

Sex and Reproductive Status Exclusions

5. Women who meet either of following criteria;

- Women of Child Bearing Potential (WOCBP) unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period.

- Women who are pregnant or breastfeeding

- Women with a positive pregnancy test on enrolment or prior to study drug administration.

Target Disease Exclusions

6. Any of the following target disease exclusions:

- Chronic insulin therapy within 30 days prior to the enrolment visit. Previous acute (≤ 2 weeks) intermittent use of insulin will be allowed, as long as last dose of insulin is administered more than 2 weeks before the enrolment visit or for the treatment during pregnancy for gestational diabetes.

- History of diabetic ketoacidosis or hyperosmolar nonketotic coma.

- Symptoms of poorly controlled diabetes that will preclude participation in this placebo-controlled trial including but not limited to marked polyuria and polydipsia with > 10% weight loss during the last 3 months prior to enrolment or other signs and symptoms.

- FPG > 240 mg/dL at Visit 2 (Week -10) or at Visit 3 (Week -6) or at Visit 4 (Week -4) or at Visit 5(Week -1) for subjects treated with anti-diabetic medication up to enrolment.

Medical History and Concurrent Disease Exclusions

Cardiovascular Disease:

7. Any of the following disease within 6 months of the enrolment visit:

- Documented history of myocardial infarction

- Cardiac surgery revascularization (coronary artery bypass graft/percutaneous transluminal coronary angioplasty (CABG/PTCA))

- Unstable angina

- Unstable congestive heart failure (CHF)

- New York Heart Association (NYHA) Class III or IV (See Appendix H for further guidance)

- Transient ischemic attack (TIA) or cerebrovascular disease

- Unstable or previously undiagnosed arrhythmias

Renal Disease:

8. Any of the following renal disease:

   - History of unstable or rapidly progressing renal disease
   - Congenital or iatrogenic renal glucosuria
   - History of diabetes insipidus

Retinopathy:

9. Greater than moderate Non-Proliferative Diabetic Retinopathy (NPDR) and Proliferative Diabetic Retinopathy. Moderate NPDR is defined as presence of microaneurysms plus cotton-wool posts and /or intraretinal microvascular abnormality documented within the previous year.

Hepatic Disease:

10. Any of the following hepatitic disease:

    - Significant hepatic disease (including chronic active hepatitis) with any 1 of the following elevated factors:
      - Aspartate aminotransferase (AST) > 2 x upper limit of normal (ULN)
      - Alanine aminotransferase (ALT) > 2 x ULN
      - Serum total bilirubin >2 mg/dL (34.2 mmol/L)
    - History of positive serologic evidence of current infectious liver disease including anti-HAV (IgM), hepatitis B surface antigen (HbsAg), or anti-HCV. Subjects who had isolated positive hepatitis B surface antibody (anti-HBs) will be included.
    - Documented history of hepatotoxicity with any medication
    - Documented history of severe hepatobiliary disease

Haematological Disease:

11. Clinically significant anaemia or any other abnormal haematological profile considered by the investigator to be of clinical consequence defined as haemoglobin ≤ 11.0 g/dL (6.8 mmol/L) or men and haemoglobin ≤ 10.0 g/dL (6.2 mmol/L) for women at the enrolment visit

12. Abnormal prothrombin time (PT) with international normalized ratio (INR) > 1.7 or activated partial thromboplastin time (APTT) > 5 seconds above ULN at the enrolment visit

13. History of haemoglobinopathies (sickle cell anaemia or thalassemias, sideroblastic anaemia)

14. Subject donated blood products to a blood bank within 3 months of the enrolment visit.

Other medical conditions

15. Any of the following medical conditions:

    – Unstable major psychiatric disorder

    – Malignancy within 5 years of the enrolment visit (with the exception of treated basal cell or treated squamous cell carcinoma)

    – Immunocompromised individuals such as subjects that underwent organ transplantation or were diagnosed with human immunodeficiency virus

16. Creatine kinase (CK) ≥ 3x ULN at the enrolment visit

17. Abnormal thyroid stimulation hormone (TSH) value at the enrolment will be further evaluated by free T4. Subjects with abnormal free T4 values will be excluded.

Procedures for withdrawal of incorrectly enrolled subjects see Section 5.3

5. STUDY CONDUCT

5.1 Restrictions during the study

- Subjects must make every attempt to adhere to the dietary and physical activity changes and goals as discussed with the Investigator(s).

- Subjects must be in a fasting state at least 10 hours prior to study visit, and abstain from tobacco and caffeine for 12 hours and alcohol for 24 hours prior to all study visits.

- 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.

5.2 Subject enrolment and randomisation

The Investigator(s) will:

1. Obtain signed informed consent from the potential subject before any study specific procedures are performed.

2. Assign potential subject a unique enrolment number "EXXXXYYY", which is composed of 4 digits (XXXX) of centre number and 3 digits (YYY) of consecutive number in order of enrolment registration at each study site.

3. Fill out the "Subject Registration Form" and fax to the registration centre.

4. Receive a "Registration Confirmation Form" from the registration centre. Keep the Registration Confirmation Form in the investigator's study file or elsewhere appropriately.

5. Determine subject eligibility. See Sections 4.1 and 4.2

6. Fill out the "Subject Randomisation Form" and fax to the registration centre. Registration centre will assign a unique randomization code to an eligible subject.

7. Receive a "Randomisation Confirmation Form" from the registration centre. Keep the Randomisation Confirmation Form in the investigator's study file or elsewhere appropriately.

If a subject withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused.

Information of the Registration Centre is given below:

5.2.1 Procedures for randomisation

Randomisation codes will be assigned at Week 0 of Period C.

The investigational product will be allocated by EPS Co., Ltd.. Key codes (drug number and the information of the allocated drugs) will be prepared by EPS Co., Ltd. and would be delivered together with the investigational product to the study sites.

Randomization to study treatment will be done in balanced blocks for each centre in order to ensure approximate balance among the 4 arms of dapagliflozin groups and the placebo group. Subjects will be randomized strictly sequentially, as subjects are eligible for randomization. If

a subject discontinues from the study, the subject number will not be reused, and the subject will not be allowed to re-enter the study.

5.3 Procedures for handling subjects incorrectly enrolled or randomised

Subjects who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or randomised. There can be no exceptions to this rule.

Where subjects that do not meet the selection criteria are randomised in error or incorrectly started on treatment, or where subjects subsequently fail to meet the study criteria post initiation, a discussion should occur between the AstraZeneca Study Delivery Team Physician and the Investigator regarding whether to continue or discontinue the subject from treatment.

The AstraZeneca Study Delivery Team Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the subject should have their study therapy stopped.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

For blinding purposes, this study incorporates a triple-dummy design throughout Period C. The Investigator(s), sponsor's personnel, and subjects will be blinded to treatment allocation throughout the study.

The only glycemic values measured at the central laboratory which will be provided to the investigators and sponser's personnel would be FPG throughout Period C and Period D.

HbA1c and urine glucose values measured at the central laboratory will not be provided to the Investigator, subject nor sponsor's personnel Period C and Period D.

Treatment allocation, HbA1c and urinary glucose values will be provided to the Investigator after the planned analysis of data has been completed.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomization for each randomized subject, will be available to the investigator(s) at the study centre. The treatment code must not be broken except in medical emergencies when the appropriate management of the subject necessitates knowledge of the treatment randomization. When breaking the treatment code, the investigator(s) should follow the manual of "Emergency Key Code Break Procedure" provided by AstraZeneca.

AstraZeneca and/or Bristol-Myers Squibb retain the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Dapagliflozin (BMS-512148) tablets are packed into HDPE bottle and are supplied by AstraZeneca. For details of the identity of the investigational product see below.

Investigational product	Dosage form and strength	Manufacturer
BMS-512148 tablet 1 mg	Contains 1 mg for dapagliflozin and Yellow, plain, round, film coated tablet	Bristol-Myers Squibb Company
BMS-512148 tablet 2.5 mg	Contains 2.5 mg for dapagliflozin and Green, plain diamond shaped, film coated tablet	Bristol-Myers Squibb Company
BMS-512148 tablet 5 mg	Contains 5 mg for dapagliflozin and Green, plain diamond shaped, film coated tablet	Bristol-Myers Squibb Company
BMS-512148 tablet 10 mg	Contains 10 mg for dapagliflozin and Green, plain diamond shaped, film coated tablet	Bristol-Myers Squibb Company
BMS-512148 tablet 1 mg placebo	Yellow, plain, round, film coated tablet	Bristol-Myers Squibb Company
BMS-512148 tablet 2.5 mg/5 mg placebo	Green, plain diamond shaped, film coated tablet	Bristol-Myers Squibb Company
BMS-512148 tablet 10 mg placebo	Green, plain diamond shaped, film coated tablet	Bristol-Myers Squibb Company

5.5.2 Doses and treatment regimens

Each dose will be composed of 3 tablets according to Table 3 and Table 4. Investigational drug should be taken once daily in the morning.

Period B:

Table 3 Composition of dose and number of tablets (Period B)

Dose	Investigational product
Placebo dose	1 mg placebo 1 tablet + 2.5 mg/5 mg placebo 1 tablet + 10 mg placebo 1 tablet

Period C:

Table 4 Composition of dose and number of tablets (Period C)

Dose	Investigational product
1 mg dose	1 mg 1 tablet + 2.5 mg/5 mg placebo 1 tablet + 10 mg placebo 1 tablet
2.5 mg dose	1 mg placebo 1 tablet + 2.5 mg 1 tablet + 10 mg placebo 1 tablet
5 mg dose	1 mg placebo 1 tablet + 5 mg 1 tablet + 10 mg placebo 1 tablet
10 mg dose	1 mg placebo 1 tablet + 2.5 mg/5 mg placebo 1 tablet + 10 mg 1 tablet
Placebo dose	1 mg placebo 1 tablet + 2.5 mg/5 mg placebo 1 tablet + 10 mg placebo 1 tablet

5.5.3 Labelling

Each packaging and bottle of investigational product will have a label indicating "For clinical study use".

Details of labelling and packaging of the study drug will be described in a separate document, 'Procedure of storage conditions for investigational product'.

5.5.4 Storage

All investigational products must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage conditions is specified on the investigational product pack label and the document 'Procedure of storage conditions for investigational product'.

5.6 Concomitant and post-study treatment(s)

Table 5 Prohibited and Restricted Therapies

Type of therapies	Timeline
Prohibited Therapies	
Anti-hyperglycemic medication (other than the study medication) with the exception of insulin for ≤ 5 days during a hospitalisation due to any reason. Subjects treated with anti-diabetic medication up to enrolment can continue their anti-diabetic medication from enrolment visit to Period A.	From the enrolment visit to Period C
Systemic corticosteroid therapy that will involve ≥ 5 days of therapy.	From the enrolment visit to Period D
Teriparatide (Forteo®)	From the enrolment visit to Period C
Restricted Therapies	

Table 5 Prohibited and Restricted Therapies

Type of therapies	Timeline
Subjects using herbal/over-the-counter preparations listed below at the time of enrolment may be used but must maintain stable doses.	From the enrolment visit to Period C
1. St. John's Wort	
2. Fenugreek	
3. Flaxseed	
4. Chromium	
5. Ginseng	
6. Natural agents marketed for lowering blood sugar	
Diuretics, where the dose has been stable for 30 days prior to the enrolment visit. No adjustment of dose is allowed.	From the enrolment visit to Period D
Inhalation of corticosteroid that has not been changed for the 30 days prior to the enrolment visit	From the enrolment visit to Period D
Bisphosphonates and calcium supplements where the dose has been stable for 30 days prior to the enrolment visit. No adjustment of dose is allowed	From the enrolment visit to Period D

Other medication, which is considered necessary for the subject's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the Case Report Form.

5.7 Treatment compliance

The administration of all medication (including investigational products) should be recorded in the appropriate sections of the Case Report Form.

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

5.7.1 Accountability

Investigational product will not be distributed to the medical institution until the contract is concluded between the medical institution and AstraZeneca. The investigational product provided to the medical institution must only be used as directed by the study protocol. The Investigational Product Storage Manager is responsible for managing the investigational product from receipt by the institution until the return of all unused investigational product to AstraZeneca. AstraZeneca will provide the study documents 'Procedures for investigational

product accountability' and 'Procedure of storage conditions for investigational product', which describe the specific requirements.

Investigator(s) are responsible for ensuring that the subject has returned all unused study drug. The subject must be asked to return unused study drug, empty cartons and packaging. Any investigational product materials returned by the subject must be promptly passed to the Investigational Product Storage Manager to complete drug accountability.

5.8 Discontinuation of investigational product

5.8.1 Criteria for discontinuation from the study

Subjects may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a subject are:

- Voluntary discontinuation by the subject who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment
- Risk to subjects as judged by the investigator and /or AstraZeneca and/or Bristol-Myers Squibb
- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca
- Incorrect enrolment, ie, the subject does not meet the required inclusion/exclusion criteria for the study
- Incorrectly randomized subjects, where appropriate following discussion between investigator and study team physician
- Subject lost to follow-up
- Adverse Event (including 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
- Development of study specific discontinuation criteria listed below

1. Use of (need for) any anti-hyperglycaemic medication other than investigational product, except of insulin for ≤ 5 days during a hospitalization due to any reason.
2. Requirement for oral glucocorticoid therapy that will involve ≥ 5 days of therapy
3. Major and/or frequent hypoglycaemic events, defined as ≥1 major event or recurring minor events (any recurrent events of hypoglycaemia, as judged by the investigator, not meeting the definition of major hypoglycaemic event) and if

contributing factors (eg, excessive physical activity) have been evaluated. See Section 6.4.3 for definition of hypoglycaemic events.

4. CK >10 x ULN confirmed at a repeated measurement, preferably within 24 hours, but not exceeding 72 hours, see Section 5.8.2 for further guidance

5. Increase of ALT and/or AST >5 x ULN more than two weeks after initiation of close monitoring of ALT and/or AST, see Section 5.8.2 for further guidance

6. Increase of ALT and/or AST >3 x ULN and increase of Total Bilirubin (TB) >1.5 x ULN confirmed at a repeated measurement within 72 hours, see Section 5.8.2 for further guidance

7. Increase of ALT and/or AST >8 x ULN confirmed at a repeated measurement within 72 hours, see Section 5.8.2 for further guidance

For all subjects who are discontinued from the study due to ALT/AST and TB increases, additional blood sampling should be done at the end of treatment visit, see Appendix I.

8. Serum Sodium ≤125 mmol/L (≤125 meq/L) and meet the discontinuation criteria on Appendix F. See Appendix F for further guidance

9. Haemoglobin ≤90 g/L (≤9.0 g/dL)

10. Confirmed increase in serum creatinine above the baseline value at a repeated measurement within one week:

    (i) For subjects with baseline creatinine of < 1.4 mg/dL (123 µmol/L), increase in serum creatinine level of ≥ 0.5 mg/dL (44 µmol/L)

    (ii) For subjects with baseline creatinine of ≥ 1.4 mg/dL (123 µmol/L), increase in serum creatinine level of ≥ 1.0 mg/dL (88 µmol/L)

    See Appendix G for further guidance.

11. Lack of glycemic control confirmed at a repeated measurement within 3-5 days, see Section 5.8.2 for further guidance

5.8.2 Procedures for discontinuation of a subject from investigational product

A subject that discontinues will always be asked about the reason(s) for discontinuation and the presence of any adverse events. The investigator(s) will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the subject. They will also immediately inform AstraZeneca of the withdrawal. Adverse events will be followed up (See Sections 6.4.3 and 6.4.4); and study drug should be returned by the subject.

Subjects with an increased CK >10 x ULN will have their investigational product withheld and repeated CK test within 24 hours, but not exceeding 72 hours. If repeated CK is still >10 x ULN the subject should discontinue the investigational product. Otherwise investigational product may be resumed unless otherwise contraindicated.

Subjects with increased ALT and/ or ALT > 3 x ULN will have repeated liver function tests within 72 hours.

- **If the repeat ALT and AST are ≤3 x ULN,** the subject should be monitored according to the clinical study protocol

- **If the repeat ALT and/or AST are >3 x ULN but ≤8 x ULN and TB ≤1.5 x ULN,** medical history including details of risk factors for liver disease will be requested, see Appendix I. The Investigator will follow the subject every 72 hours until the ALT and AST are ≤2 x ULN or until ALT and AST are back to the baseline levels*. The frequency of retesting can decrease to once a week or less if abnormalities stabilize and the patient is asymptomatic. **If ALT and/or AST is >5 x ULN more than two weeks after initiation of close monitoring of ALT and AST,** the subject must be discontinued from study medication, the Sponsor notified and the end of treatment visit performed within 72 hours. At the end-of treatment visit, medical history including details of risk factors for liver disease will be requested and additional blood sampling done, see Appendix I.

- **If the repeat ALT and/or AST are >3 x ULN AND TB >1.5 x ULN at any time point,** the subject must be discontinued from study medication, the Sponsor notified and the end of treatment visit performed within 72 hours. At the end of treatment visit, medical history including details of risk factors for liver disease will be requested and additional blood sampling done, see Appendix I. The Investigator will follow the subject every 72 hours until the ALT and AST are ≤2 x ULN or until ALT and AST are back to the baseline levels*. The frequency of retesting can decrease to once a week or less if abnormalities stabilize and the patient is asymptomatic.

- **If the repeat ALT and/or AST >8 x ULN at any time point,** the subject must be discontinued from study medication, the Sponsor notified and the end of treatment visit performed within 72 hours. At the end of treatment visit, medical history including details of risk factors for liver disease will be requested and additional blood sampling done (if not already done), see Appendix I. The Investigator will follow the subject every 72 hours until the ALT and AST are ≤2 x ULN or until ALT and AST are back to the baseline levels*. The frequency of retesting can decrease to once a week or less if abnormalities stabilize and the patient is asymptomatic.

* unless there are specific reasons for the ALT and/or AST elevations e.g. liver cancer

Subjects who meet discontinuation criteria for lack of glycemic control at specified visits (See Table 6) will be scheduled for a repeated measurement within 3-5 days. If the repeated FPG value still meets the criteria for discontinuation, the subject should discontinue the investigational product. Otherwise investigational product may be resumed unless otherwise contraindicated.

Table 6 Discontinuation criteria for lack of glycemic control

Visit (Period C)	FPG
Weeks 4 and 6	> 240 mg/dL (13.3 mmol/L)
Week 8	> 220 mg/dL (12.3 mmol/L)
Week 10	> 200 mg/dL (11.2 mmol/L)

All randomised subjects who do not complete the treatment period (Period C) will complete the end of treatment visit (Week 12) study procedures as soon as possible but at the latest within 7 days after discontinuation of study drug. All randomised subjects will enter the 4-week follow-up period (Period D).

If a subject is withdrawn from study, see Section 5.9.

5.9 Withdrawal from study

Subjects are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such subjects will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (See Sections 6.4.3 and 6.4.4); and study drug should be returned by the subject.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

Data will be entered in the Web Based Data Capture (WBDC) system at the study site. Trained study personnel will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the electronic Case Report Form (eCRF Instructions).

The eCRF Instructions will also guide the study site in performing data entry. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. Site personnel will enter the data in the eCRFs. The data will then be Source Data Verified (SDV), reviewed/ queried and updated as needed. The principal investigator will then sign the eCRF electronically.

When all data have been declared clean and signed by the investigator, the data will be frozen and then locked to prevent further editing. A copy of the eCRF will be archived at the study site when the study has been locked.

Dictionary coding

Medical coding is done using the most current version of MedDRA and the Bristol-Myers Squibb Drug Dictionary.

Management of external data

Data Management determines the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database (if applicable). Data Management will ensure that the data collection tool will be tested / validated as needed. External data reconciliation will be done with the clinical database as applicable.

The investigator(s) will record data on the observations, tests and assessments specified in the protocol on the electronic CRFs provided by AstraZeneca. The CRF will be accompanied with 'Instructions for the Investigator', which should be followed. These instructions provide guidance for the recording of study data in the CRF including how to change data incorrectly recorded.

6.2 Data collection and enrolment

6.2.1 Enrolment visit

Subjects will be screened for study participation (see Table 1) and eligibility will be determined by assessment of inclusion and exclusion criteria. The following assessments will be performed at the enrolment visit.

- Written informed consent
- Inclusion and exclusion criteria listed in Sections 4.1 and 4.2.
- Date of birth, sex, race
- Medical history and perform a complete physical examination (See Section 6.4.6).
- Height, body weight, waist circumference, BMI, vital signs (sitting blood pressure and sitting heart rate) (see Section 6.4.8)
- HbA1c, FPG, fasting insulin, C-peptide
- Hepatitis screen panel, TSH, PT and APTT
- Standard Safety Laboratory Panel (Blood and Urine) (See Section 6.4.5)
- Spot urine sample (See Section 6.4.9)

- Urine HCG (Human chorionic gonadotropin) pregnancy test for women of child bearing potential (WOCBP)

6.2.2 Wash-out period (Period A)

The following assessments will be performed at Period A.

- FPG (Week -10 and -6)

6.2.3 Lead-in period (Period B)

The following assessment will be performed at Period B.

- Complete physical examination (Week -4)
- Vital signs, body weight (Week -4)
- ECG (See Section 6.4.7) (Week -4)
- Urine HCG pregnancy test for WOCBP (Week -4)
- Standard Safety Laboratory Panel (Blood and Urine) (Week -4)
- HbA1c (Week -1)
- FPG (Week -4 and -1)

6.2.4 Treatment period (Period C)

The following assessment will be performed at Period C.

- Inclusion and exclusion criteria (Week 0)
- Brief/Complete physical examination
- Vital signs, body weight
- Orthostatic blood pressure and orthostatic heart rate (Week 0, 2, 4 and 12)
- Waist circumference (Week 0 and 12)
- ECG (Week 0 and 12)
- Urine HCG pregnancy test for WOCBP (Week 0, 1, 6 and 12)
- Standard Safety Laboratory Panel (Blood and Urine)
- Post-prandial glucose, insulin, C-peptide during OGTT (Week 0 and 12, if applicable) (See Section 6.3.1.2)

- Urine glucose, creatinine and sodium concentrations during OGTT (Week 0 and 12, if applicable) (See Section 6.3.1.2)
- PK sample collection (Week 1, 6, 10 and 12)
- Spot urine sample (See Section 6.4.9) (Week 0, 6 and 12)
- Serum sample for markers of bone metabolism (Week 0, 8 and 12)
- 24 hour urine collection (Week 0 and 12) (See Section 6.4.5)
- HbA1c, FPG, fasting insulin, fasting C-peptide, fasting serum lipids (See Section Table 7)
- Cystatine C (Week 0 and Week 12)

6.2.5 Follow-up procedures (Period D)

Subjects meeting one of the following criteria will participate in the Follow-Up Phase. Visit during this phase is scheduled to occur at Week 16.

(a) Subjects completing Period C (Week 12)

(b) Subject who discontinues double-blind study medication prior to Week 12 (will enter Period D after the last dose of study medication is administered)

The following assessment will be performed at Week 16.

- Brief physical examination
- Vital signs, body weight
- Orthostatic blood pressure
- Standard Safety Laboratory (Blood and Urine)
- HbA1c, FPG
- Spot urine sample
- Serum sample for markers of bone metabolism
- Cystatine C

6.3 Efficacy

6.3.1 Efficacy variable

6.3.1.1 Efficacy laboratory variable

The laboratory parameters that will be measured to assess efficacy are displayed in Table 7 by visit.

Table 7 Efficacy laboratory variable

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Week	**-12**	**-10**	**-6**	**-4**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**
HbA1c	X				X	X			X	X	X	X	X	X
FPG	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Total-C						X							X	
LDL-C						X							X	
HDL-C						X							X	
TG						X							X	
FFA						X							X	
Fasting Insulin	X					X				X			X	
C-peptide	X					X				X			X	

The laboratory parameters will be analyzed by a central laboratory. The result of HbA1c from Visit 6 (Week 0) and onwards will not be reported to subjects, the investigators and the sponsor. The results of FPG from baseline and onwards will not be reported to subjects.

6.3.1.2 Oral Glucose Tolerance Test (OGTT) Procedure

At Week 0, OGTT is performed in only those subjects whose FPG is less than 180 mg/dL at Week -1. At Week 12, OGTT is not performed in subjects who did not perform OGTT at Week 0, subjects who did not complete period C or subjects whose FPG ≥ 180 mg/dL at Week 10.

- At Week 0 (randomization), study medication is given as soon as possible AFTER OGTT is complete
- At Week 12 (or at end of study visit), the study medication is given 1 hour BEFORE administration of 75 g oral glucose solution.
- Instruct subject to empty bladder after obtaining urine sample.
- Insert saline lock, if appropriate.

- Draw Time 0 blood sample for glucose, insulin, C-peptide
- Immediately after Time 0 blood sample is drawn above: Administer 75 g of oral glucose.
- Draw blood specimens for post prandial glucose, insulin and C-peptide at 60, 90, 120, 180 and 240 minutes.
- Collect all urine voided after emptying of bladder up to and including attempted void after removal of saline lock for the measurement of total volume urinary glucose, creatinine, and sodium concentration.
- Remove saline lock.

6.3.1.3 Body weight and height

- The subject's weight will be recorded in kilograms (kg), to one decimal place. 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.
- The subject's height will be recorded in centimetres. Measurement of height should be performed with the subject's shoes removed. The subject's knees should be straightened, head held erect, and eyes forward.

6.3.1.4 Waist

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

6.4 Safety

It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The investigator is responsible for ensuring this.

6.4.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

For cases where it could be suspected that a tissue-derived medicine has been contaminated by a pathogen, information about any of the above conditions (including infection) should be collected.

The term AE is used to include both serious and non-serious AEs.

6.4.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

For reporting purposes, all cases of cancer and overdose must be reported immediately using the SAE module of eCRF.

- Cancer
- Overdose (defined as the accidental or intentional ingestion of any dose of the investigational product that is considered both excessive and medically important)

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

6.4.3 Recording of adverse events

Time period for collection of adverse events

All Adverse Events will be collected from the start of the Placebo lead-in Phase (Period B) throughout the treatment period including the Follow-up Phase (Period D). SAEs will be collected from the time when the informed consent is obtained until the Follow-up Phase.

Variables

The following variables will be collect for each AE;

- AE (verbatim)

- the date when the AE started and stopped
- maximum intensity
- whether the AE is serious or not
- investigator causality rating against the Investigational Product (yes or no)
- action taken with regard to investigational product
- outcome
- treatment required

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of AE

Maximum intensity will be graded according to the following definitions:

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities)

- very severe (debilitating, significantly incapacitates patient despite symptomatic therapy)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?”

Causal relationship in cases where the disease under study has deteriorated due to lack of effect will be classified as no reasonable possibility.

For SAEs causal relationship will also be assessed for other medication. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as “yes”.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: “Have you had any health problems since the previous visit?” or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events based on examinations and tests

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and other safety variables will only be reported as AEs if they are clinically significant, fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the investigational product, or require the patient to receive specific corrective therapy. If a deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Clinically relevant deterioration in non-protocol-mandated measurements will be reported as AE(s).

Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value).

Hypoglycaemic events

Signs and symptoms of hypoglycaemia, hypoglycaemia episodes, or discontinuation due to hypoglycaemia should not be reported on the AE eCRF page unless the event fulfils protocol criteria for a Serious Adverse Event (see Section 6.4.2), in which case an SAE must be reported in addition to the hypoglycaemic eCRF pages for hypoglycaemia. A separate section in the eCRF will be used to document all reported episodes of hypoglycaemia.

Subjects will be given glucometers and instructed on Self Monitoring of Blood Glucose (SMBG) technique. Subjects will be recommended to monitor their finger stick glucose at regular intervals. If subjects have hypoglycemic symptoms they should measure finger stick glucose. Hypoglycaemic events (symptoms and/or finger stick glucose measurements) should be recorded into the subject's card.

The investigator is responsible for questioning the patient about all symptoms reported in the subject's card and for determining if they meet the clinical definition of hypoglycaemia. Only symptoms and/or blood glucose values deemed by the Investigator to meet the definition of hypoglycaemia should be reported on the hypoglycaemia eCRF pages (see Section 6.4.9).

Follow-up of unresolved adverse events

Any AEs that are unresolved at the end of the study or at discontinuation are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.4.4 Reporting of serious adverse events

Investigators and other centre personnel must inform appropriate AstraZeneca representatives via the web based data capture (WBDC) system of any SAE which occurs in the course of the study within one calendar day (i.e., immediately but no later than the end of the next business day) of when he or she becomes aware of it. Follow-up information on SAEs must also be reported by the Investigator within the same time frame.

The AstraZeneca representative will work with the Investigator to compile all the necessary information and ensure that Bristol-Myers Squibb receives a report by day one for all SAEs. All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s). SAEs will be recorded from the time of informed consent. SAE information will be entered and submitted into the WBDC system on the relevant eCRF modules.

If the system is unavailable, the Investigator should contact the AstraZeneca representative immediately recognising that the same reporting time frames still apply. The Investigator is responsible for completing the eCRF as soon as the system becomes available again. The

AstraZeneca representative will forward all information relevant to the SAE to Bristol-Myers Squibb Pharmacovigilance via email.

AstraZeneca will provide the information on the serious adverse drug reactions collected domestically and abroad regarding the investigational product to the Head of the study site, Investigators and the regulatory agency as per local requirements. The Head of the study site must submit a written report to the IRB providing the information reported by AstraZeneca.

6.4.5 Laboratory safety assessment

Standard clinical laboratory tests (Standard Safety Laboratory Panel) for safety assessment will be performed at:

- Enrolment visit
- Week -4 of the lead-in phase
- Week 0, 1, 2, 4, 6, 8, 10 and 12 of the double-blind treatment phase.
- Week 16 of the follow-up phase.

Blood and urine samples will be obtained at specified time points for laboratory evaluations (see Table 1). The central laboratory for this study will perform the analysis of all scheduled laboratory tests except for urine HCG pregnancy test 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 10 hours prior to collection.

The following laboratory variables will be measured:

Screening

- Hepatitis Screening Panel
  - Hepatitis A Viral Antibody IgM and IgG
  - Hepatitis B Viral Antibody IgM (anti-HBc)
  - Hepatitis C Virus Antibody (anti-HCV)
  - Hepatitis B Surface Antigen (HBsAg)
- Tyroid stimulation hormone (TSH)
- Prothrombin time (PT)
- Activated partial thromboplastin time(APTT)

Standard Safety Laboratory Panel:

Hematology

- Hemoglobin
- Hematocrit
- Red blood cell count indices
- White blood cell count and differential
- Platelet count

Serum chemistry

- Aspartate Aminotransferase (AST, SGOT)
- Alanine Aminotransferase (ALT, SGPT)
- Alkaline phosphatase (ALK-P)
- Creatine Kinase (Creatine Phosphokinase, CK, CPK)
- Total Bilirubin (TB)
- Blood Urea Nitrogen (BUN)
- Bicarbonate
- Serum Creatinine (Scr)
- Electrolytes – sodium, potassium, chloride, calcium, magnesium and phosphate
- Total Protein, Albumin
- Uric acid

Cystatine C

Markers of bone metabolism:

- Parathyroid hormone
- Osteocalcin
- 25-vitamin D

- C-terminal cross-linking telopeptides of type I collagen (CTX)
- Bone-specific alkaline phosphates
- Procollagen type-1 N-terminal propeptide (P1NP)

Urinalysis by dipstick

- pH, protein, glucose, leukocyte esterase, blood
- Microscopy if dipstick positive for blood or leukocyte esterase
- 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.

Spot Urine Collection

On the day of the collection the subject is to urinate in the toilet and flush away the first urine in morning, and collect the second urine in the clinic or hospital. The specimen is kept in a refrigerator.

The following laboratory parameters will be analyzed by a central laboratory. The results of glucose concentration from baseline and onwards will not be reported to subjects, the investigator and the sponsor. At Visit 1, only albumin (calculated albumin to creatinine ratio) will be measured.

- Glucose concentration(glucose mg/dL x g creatinine)
- Albumin (calculated albumin to creatinine ratio)
- Total protein (calculated protein to creatinine ratio)
- Urinary Sodium (calculated sodium to creatinine ratio)
- Creatinine (mg/dL)
- α1-Microglobulin (mg/dL x g creatinine)
- N-acetyl glucosamine (NAG)
- Urine pH

24 hours Urine Collection

24 hour urine collection is done at Week 0 and Week 12 in subjects who give consent. 24 hour urine collection is allowed to be done on a separate day of the study visit if collected within 7 days before visit. On the day of the collection in the morning, the subject is to urinate in the toilet and flush away the first urine, and record the time. The subject will collect all urine day and night, including the urination on the next day up to the point 24-hours after the beginning of collection. The urine should be kept cool during the 24-hour period. After collecting the final urine, record the total urine volume. A portion of the 24 hour urine will be collected for a urine sample after fully mixing and uniforming the urine container. The urine sample should to be given to the investigators within 2 hours after removing from cold storage.

The following laboratory parameters will be analyzed by the central laboratory.

- Glucose concentration
- Creatinine

Specimen Collection and Transport

The detained 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.

For blood volume see Section 7.1

6.4.6 Physical examination

A brief physical examination includes the following: cardiovascular, lungs, abdomen, and extremities; and any organ systems pertinent to the subject's signs, symptoms or adverse events.

A complete physical examination includes the following: general appearance, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdomen, lymph nodes, extremities, neurological, skin, and musculoskeletal.

Baseline data for physical examination is collected at Week -4, and new findings at the following physical examinations are recorded as change from baseline.

6.4.7 ECG

6.4.7.1 Resting 12-lead ECG

A 12-lead ECG must be performed at Week –4, 0 and 12.

A 12-lead ECG will be taken after the subject has been lying down resting. The ECG will be evaluated by the investigator and entered as 'Normal' or 'Abnormal' in the eCRF. If the ECG is evaluated as "Abnormal" the investigator should document the specific abnormality.

6.4.8 Vital signs

6.4.8.1 Blood pressure and heart rate

For this study, sitting blood pressure/heart rate and orthostatic blood pressure/heart rate measurements are required. Sitting blood pressure will be assessed at the enrolment visit, Week –4, Period C and Week 16 and orthostatic blood pressure will be assessed at Week 0, 2, 4, 12 and 16.

Sitting Blood Pressure (BP) and heart rate

One heart rate measurement will be taken after the patient has been sitting and resting for at least 5 minutes and before blood samples are taken. The heart rate measurement will be followed by 3 blood pressure measurements, using a standardized cuff adapted to the size of the patient's arm. All 3 readings have to be recorded. For analysis the average of the 3 blood pressure readings will be used. blood pressure readings will be taken with the patients comfortably in a seated position with the arms raised to the level of the heart and in a supported position. All readings should be recorded as accurately as possible and the same blood pressure machine should be used for all assessments for a given patient.

Orthostatic Blood Pressure and Heart Rate

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

The supine blood pressure and heart rate must be measured prior to the standing blood pressure. The patient should rest in the supine position for at least 5 minutes prior to measurement of blood pressure and heart rate. Supine blood pressure will be determined from three replicate measurements obtained at least 1 minute apart. All 3 readings have to be recorded. For analysis the average of the 3 blood pressure and heart rate readings will be used.

The patient will then stand for 2 to 3 minutes. After this time, measure the blood pressure with the arm supported at the antecubital fossa at heart level. Standing blood pressure and heart rate will be determined from three replicate measurements obtained at least 1 minute apart. All 3 readings have to be recorded. For analysis the average of the 3 blood pressure and heart rate readings will be used. All readings should be recorded as accurately as possible and the same blood pressure machine should be used for all assessments for a given patient.

6.4.9 Other safety assessments

Urinary and Genital Infections

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

Asymptomatic bacteriuria is defined as the presence of $\geq 10^5$ colony forming units/mL of bacteria, in a properly collected voided urine specimen, without signs or symptoms typically attributed to urinary tract infection. Asymptomatic bacteriuria is prevalent among diabetic women, and is associated with pyuria in 70% of cases. Neither guidelines from the US

(Nicolle LE et al 2005) nor Europe (European Association of Urology 2008) recommend screening for, or treatment of, asymptomatic bacteriuria in non-pregnant diabetic patients. 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.

If based on suggestive signs or symptoms (dysuria, urgency or frequency of urination, suprapubic or perineal discomfort, flank, back, or abdominal pain, costovertebral angle tenderness, nausea, vomiting, fever, chills, or sepsis) the investigator believes that a urinary tract infection may be present, urine cultures (in a local laboratory) should be obtained to confirm a presumptive diagnosis of cystitis, urinary tract infection, pyelonephritis, or prostatitis. Mid-stream clean catch urine collections are recommended. Clinical judgment and local standards of care should apply to decisions concerning therapy.

Investigational product should be held in subjects with clinical evidence of upper tract UTI (e.g. pyelonephritis) or presumed urosepsis until the course of treatment of the infection has been completed and clinical recovery has occurred. It is recommended that a follow-up urine culture is obtained within 7 days of clinical recovery from a documented urinary tract infection.

Also, 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 6.4.3. 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.

Hypoglycemic events

The subject will be asked to always self-monitor fasting blood glucose in case of symptoms suggestive of hypoglycaemia and to register any signs of hypoglycaemia in the supplied subject’s card.

A hypoglycaemic event can be either

- An episode with symptoms and confirmed low glucose.
- An episode with low glucose.
- An episode with symptoms when glucose was not measured.

For the evaluation of hypoglycaemic events special attention will be given to as described below.

- Major hypoglycaemic events, defined as symptomatic events requiring external assistance due to severe impairment in consciousness or behaviour, with a capillary or plasma glucose value <3.0 mmol/L (<54 mg/dL), and prompt recovery after glucose or glucagons administration.

- Minor hypoglycaemic event, defined as either a symptomatic event with a capillary or plasma glucose value <3.5 mmol/L (<63 mg/dL), and no need for external assistance, or an asymptomatic blood glucose measurement <3.5 mmol/L (<63 mg/dL).

- Events suggestive for hypoglycaemia, with symptoms that the subject experiences as hypoglycaemia and no confirmative measurement.

Data to be collected for each hypoglycaemic event:

- Date of start and stop and time of the day for start

- If symptoms are present or not and which symptoms

- If finger stick value obtained and the plasma glucose value

- Intervention needed for recovery, max intensity, action taken, causality and possible contributing factors

- Time of last drug administration

- Time of last meal

The subject's card will be reviewed and data regarding hypoglycaemic events transcribed into the eCRFs at each clinical visit. A new subject's card for the next period will be handed over to the subject. If a major hypoglycaemic event occurs, or more than one minor event since last visit, the subject should contact the investigator. For recording of hypoglycaemic events/symptoms suggestive of hypoglycaemic events as AEs, see Section 6.4.3.

Hyperglycemic events

Fasting plasma glucose(FPG) will be measured at each visit. For the visits which pre-specified glycemic parameters on FPG are established (See Table 6), subjects are checked whether they have lack of glycemic control/hyperglycemic events.

6.4.10 Adjudication of Cardiovascular Adverse 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. The CEC will adjudicate events possibly related to the following events:

Death including:

(a) Cardiovascular Death

(b) Non-cardiovascular Death

Myocardial Infarction (MI)including:

(a) ECG and /or cardiac enzymes confirmed MI

(b) Sudden death

(c) Percutaneous coronary intervention (PCI)-related myocardial infarction

(d) CABG-related myocardial infarction

(e) MI diagnosed via pathologic criteria

(f) Silent MI

Fatal and Non-fatal Stroke including:

(a) Ischemic Stroke

(b) Hemorrhagic stroke

Serious Adverse Events of the following:

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

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

6.5 Patient reported outcomes – Not Applicable

6.6 Pharmacokinetics

6.6.1 Collection of samples

Blood samples (3 mL) for determination of dapagliflozin in plasma will be taken at the times presented in the study plan (See Table 1). At visit 7, 10 and 12, plasma samples will be taken before administration of dapagliflozin. At visit 13, plasma samples will be taken at 60, 90, 120, 180 and 240 minutes after administration of dapagliflozin.

Samples will be collected, labelled stored and shipped as detailed in Laboratory Manual.

For blood volume see Section 7.1.

6.6.2 Determination of drug concentration

Samples for determination of drug concentration in plasma will be analysed by AtlanBio, Route de Saint-André des Eaux, Z.I de Brais B.P 40309, 44605 SAINTNAZAIRE, Cedex FRANCE *on* behalf AstraZeneca, using liquid chromatography and mass spectrometric detection. The lower limit of quantification LLOQ of dapagliflozin in plasma is 1.0 ng/mL.

6.7 Pharmacodynamics – Not Applicable

6.8 Pharmacogenetics – Not Applicable

6.9 Health economics – Not Applicable

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each subject at maximum in this study is as follows:

Table 8 Volume of blood to be drawn from each subject

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
Assessment															
Haematology	2			2		2	2	2	2	2	2	2	2	2	22
Serum blood sampling [a]	10			5		13	5	5	5	10	5	5	13	10	86
HbA1c	2				2	2			2	2	2	2	2	2	18
FPG	2	2 [b]	2 [b]	2	2	2	2	2	2	2	2	2	2	2	28
Markers of bone metabolism [c]						10					10		10	10	40
PT, APTT	1.8														1.8

Table 8 Volume of blood to be drawn from each subject

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
Assessment															
OGTT [d]						10							10		20
PK sample [e]							3			3		3	15		24
Total	17.8	2	2	9	4	39	12	9	11	19	21	14	54	26	239.8

[a] Serum blood sampling for Clinical chemistry, Fasting Insulin, C-peptide, Fasting serum lipids (TC, LDL-C, HDL-C, TG, and FFA), Hepatitis Screen Panel (anti-HAV (IgM, IgG), HBsAg, anti-HCV, and anti-HBc), Thyroid Stimulating Hormone, Cystatine C. Blood volume depends on the assessment for each visit.

[b] If subject treated with anti-diabetic medication up to enrolment.

[c] Parathyroid hormone, osteocalcin, 25-vitamin D, C-terminal cross-linking telopeptides of type I collagen (CTX), Bone-specific alkaline phosphates and Procollagen type-1 N-terminal propeptide (P1NP)

[d] Visit 13, OGTT is not performed in subjects who did not perform OGTT at Visit 6, subjects who did not complete period C or subjects whose FPG is ≥ 180 mg/dL at Visit 12. At Visit 13, blood samples are drawn 60, 90, 120, 180 and 240 min after administration of 75 g oral glucose solution.

[e] Plasma samples for analysis of dapagliflozin are obtained before administration of dapagliflozin at Visit 7, 10 and 12. At Visit 13 plasma samples are obtained at 60, 90, 120, 180 and 240 after administration of dapagliflozin. If the subjects perform OGTT at Visit 13, plasma samples are obtained simultaneously with OGTT blood samples.

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses.

7.2.1 Clinical chemistry/ haematology samples

Samples will be disposed after the clinical study report has been finalised.

7.2.2 Pharmacokinetic samples

Samples will be disposed after the clinical study report has been finalised.

7.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C ‘IATA 6.2 Guidance Document’.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the subject unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

7.5 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented.
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site.
- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples. The applicable regulatory requirements in Japan are 'Good Clinical Practice for Trials on Drugs (MHLW Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications.

8.2 Subject data protection

The Master Informed Consent Form will explain that: Study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. ·Subject data will be maintaining confidentiality in accordance with national data legislation. For data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an Ethics Committee may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history. All data computer processed by AstraZeneca will be identified by study code and enrolment code (E-code).

8.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The Head of the study site will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The head of the study site should submit a notification of direction/determination as well as a copy of the IRB written approval to AstraZeneca before enrolment of any subject should into the study.

The Ethics Committee should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

The protocol should be re-approved by the IRB annually. The Principal Investigator should submit progress reports to the IRB via the head of the study site at the time of the protocol re-approval.

Before enrolment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

8.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.

- Ensure each subject is notified that they are free to discontinue from the study at any time.
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File.
- Ensure a copy of the signed Informed Consent Form is given to the subject.
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

If any new information on the study medication becomes available which may influence the decision of the subject to continue the study, the investigator(s) should inform the subject of such information immediately, record this in a written form, and confirm with the subject if he or she wishes to continue the participation in the study. In addition, if the investigator(s) deem it necessary to revise the Informed Consent Form, they should revise it immediately (Refer to Section 8.5). The investigator(s) should re-explain the subjects using updated Informed Consent Form even if although the subjects have already been informed of the new information verbally. Written informed consent to continue participation in the study should be provided separately.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca. If it is necessary for the study protocol to be amended, the amendment should be submitted to the Head of the Study Site and be approved by its IRB. If applicable, AstraZeneca should submit a notification to the regulatory authority before it is implemented. If a protocol amendment requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the centre's IRB should be notified. Approval of the revised Informed Consent Form by AstraZeneca and by the IRB is required before the revised form is used. If an administrative change is required, such a change should be notified to or approved by each IRB according to local requirements.

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical

Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

All study data may undergo a reliability review and onsite-GCP inspection by the regulatory authorities.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first subject is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate subjects for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in the contract between AstraZeneca and the head of the investigational study site.

9.2 Training of study site personnel

Before the first subject is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system(s) utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.3 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.

- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that investigational product accountability checks are being performed.

- Perform source data verification (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts).

- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The AstraZeneca representative will be available between visits if the investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.3.1 Source data

Source data are any data generated as a result of the subject's inclusion in the study (including run-in and/or follow up related to the study) and includes all related medical examinations and other records. Original data recorded on the CRFs and regarded as source data are specified in the Clinical Study Agreement between AstraZeneca and the investigator.

9.3.2 Direct access to source data in Japan

The Head of the institution and the investigator(s) will cooperate for monitoring and audit by AstraZeneca, and accept inspection by the IRB or regulatory authorities. All study documents such as raw data will be open for direct access to source data at the request of the monitor and the auditor of AstraZeneca, the IRB, or regulatory authorities.

The monitor(s) will verify data from the CRFs against source data before collecting the CRFs to ensure accuracy and completeness of documentation, and assure that the investigator(s) has submitted the CRFs to AstraZeneca. If the investigator wishes to amend the collected CRFs, the monitor will ensure that the investigator(s) has documented the amendment in writing (signed and dated) and provided this to AstraZeneca.

9.4 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or subjects are enrolled.

9.4.1 Archiving of study documents

(i) **Study files.** AstraZeneca will provide the Principal Investigator with a file in which to organise and retain all study-related documents. All study documents (including letters from AstraZeneca) should be retained in this file by the Principal Investigator. The monitor will regularly check the file to ensure that all relevant documents are retained. The contents of the file may be audited/inspected by AstraZeneca's auditor, regulatory authorities, or IRB.

(ii) **Period of record retention**. The study site (and the Principal Investigator) will retain the essential documents specified in the ICH GCP (eg, source document such as medical records, contract, signed consent form). Essential documents should be retained at the study site for at least 15 years following completion of the study, or per regulatory obligations if longer, and thereafter destroyed only after agreement with AstraZeneca. However this is not always applied to those that are not preservable such as blood samples. In the event of any inconsistency between the above-mentioned contents and the contract with the study site, the contract shall prevail. These documents should be retained for a longer period however if needed by AstraZeneca, and the specific period and method of retention will be separately discussed between the study site and AstraZeneca. AstraZeneca should notify the head of the study site in writing when the study related records are no longer needed. The records should be managed by a responsible person appointed by the head of the study site.

9.4.2 Deviation from the clinical study protocol in Japan

Investigator(s) must not deviate from or make any changes to the protocol without documented agreement between the principal investigator and AstraZeneca or the IRB approval based on its deliberations. However, this shall not apply to cases where the deviation or change is necessary to avoid an immediate hazard to the patients or for other compelling medical reasons, or where the changes involve only logistical or administrative aspects of the clinical trial (e.g. changes to the organisation/structure of the sponsor, the name/department name of the medical institution, the address or phone number of the medical institution or the sponsor, the job title of the investigator, and monitors). In such case, the principal investigator must notify details of the deviation or change, the reason, and a proposed revision in the protocol if required, to AstraZeneca. and the head of the study site and IRB via the head of the study site as soon as possible, in order to obtain their approval. A certificate of approval by the head of the study site as well as AstraZeneca. should be obtained via the head of the study site.

The investigator(s) should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to the patients or for other medically compelling reason, the investigator should prepare and submit the records explaining the reasons thereof to the sponsor, and retain a copy of the records.

9.5 Study timetable and end of study

The end of the study is defined as ”the last visit of the last subject undergoing the study”.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with dapagliflozin.

9.5.1 Planned duration of the study

Study period (First Subject In – Last Subject Last Visit): August, 2009 – June 2010

Registration period: August, 2009 - January, 2010

9.5.2 Discontinuation or suspension of the whole study programme

If AstraZeneca decides to prematurely terminate or suspend the study, the investigator(s), the head of the institution, and regulatory authorities should receive written notification of the reasons for the premature termination or suspension.

The investigator(s) will immediately notify the decision to the subjects, give appropriate medical treatment; take necessary measures, and record treatment or measures provided on the source documents.

9.5.3 Completion of the study

Upon terminating the study, the investigator(s) will report in writing the completion of the study as well as the summary of the results to the head of the study site in accordance with the institution’s rules. The head of the study site, who is informed of the termination by the investigator, will provide a written notification of the results to the IRB and AstraZeneca.

10. DATA MANAGEMENT BY ASTRAZENECA DATA MANAGEMENT CENTRE

Data management will be performed by AstraZeneca Data Management Centre staff.

The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the Bristol-Myers Squibb Drug Dictionary. All coding will be performed by the Medical Coding Team at Bristol-Myers Squibb.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

11.1 Calculation or derivation of efficacy variable(s)

Baseline is defined as the assessment performed at pre-dose on Week 0.

11.1.1 Beta-cell function and insulin resistance index

The beta-cell function and insulin resistance index will be calculated based on FPG and fasting plasma insulin using HOMA2.

The beta-cell function during an OGTT will be calculated using the insulinogenic index. The insulin sensitivity during an OGTT will be calculated using the Matsuda index or ISIcomp.

11.1.2 AUC from 0 to 180 minutes for postprandial glucose, insulin, and C-peptide response to an OGTT

The AUC from 0 to 180 minutes for postprandial glucose, insulin, and C-peptide response to an OGTT will be calculated using the trapezoidal rule.

11.2 Calculation or derivation of safety variable(s)

11.2.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs (Discontinuation of Investigational Product due to Adverse Event). Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

11.2.2 Creatinine clearance

To calculate Creatinine clearance using Cockcroft-Gault formula:

Male: $Ccr = [(140\text{-age}) \times \text{weight (kg)}]/[72 \times Scr]$

Female: Ccr = 0.85 x [140-age) x weight (kg)]/[72 x Scr]

11.2.3 Assessment of Renal Function and Calculation of the Glomerular Filtration Rate

Renal function must satisfy two criteria in this study for subjects who will receive placebo or study medication. These criteria are based on (1) Serum Creatinine (2) Calculated GFR

1. Serum Creatinine Criteria: To be eligible, a subject must have a Scr < 1.5 mg/dL (132.6 mmol/L) for males or < 1.4 mg/dL (123.8 mmol/L) for females.

2. GFR Criteria: To be eligible, a subject must also have a calculated GFR (Using Age, Sex, Race, and Scr) of > 60 ml/min/1.73 m^2. Appendix E has a listing of the serum creatinine values that (based on age, gender and race) would correspond to a GFR < 60 ml/min/1.73 m^2.

Glomerular filtration rate is considered to be the best method to measure the overall renal function in health and disease. The use of prediction formulas to calculate the GFR from serum creatinine and other variables, such as age gender and race is recommended by the National Kidney Foundation for the diagnosis and stratification of chronic renal diseases. The Modification of Diet in Renal Disease (MDRD) study equation can estimate highly accurately the GFR by including the subject's age gender, race and serum creatinine.

To calculate estimated GFR (eGFR) using MDRD:

Male: $eGFR\ (mL/min/1.73m^2) = 186.3 \times (Scr)^{-1.154} \times (Age)^{-0.203}$

Female: $eGFR\ (mL/min/1.73m^2) = eGFR\ (Male) \times 0.762$

11.3 Calculation or derivation of patient reported outcome variables – Not Applicable

11.4 Calculation or derivation of pharmacokinetic variables

The pharmacokinetic (PK) analyses will be performed at AstraZeneca R&D. The actual sampling times will be used in the PK calculations. If necessary, the PK properties of dapagliflozin will be evaluated by population PK methodology and reported in a separate PK report, including estimates of population mean PK parameters, between-patient variability as well as predictions of individual PK parameters (e.g. renal function on CL/F) may be identified and quantified. A detailed population PK analysis plan will be prepared prior to data base lock.

11.5 Calculation or derivation of pharmacodynamic variable(s) – Not Applicable

11.6 Calculation or derivation of pharmacogenetic variables – Not Applicable

11.7 Calculation or derivation of health economic variables – Not Applicable

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

A comprehensive Statistical Analysis Plan (SAP) will be prepared and finalised before the unblinding of the data.

The statistical analysis will be done by Statistics & Programming Department, AstraZeneca.

12.1 Description of analysis sets

The decision to include or exclude patients from each analysis set will be made at the clean file meeting, where the study team statistician and physician will attend, prior to the unblinding of the data.

12.1.1 Efficacy analysis set

The evaluation of efficacy will be performed for the full analysis set as well as for the per-protocol analysis set. The primary efficacy evaluation will be based on the full analysis set.

12.1.1.1 Full analysis set

The full analysis set will include all randomised patients who received at least one dose of study medication, and who have a non-missing baseline value and at least one post-baseline efficacy value for at least one efficacy variable. The patients will be analysed according to the treatment group to which they were randomised, regardless of the actually treatment taken.

12.1.1.2 Per protocol analysis set

The per-protocol analysis set – being a subset of the full analysis set – will include all patients of the full analysis set without major protocol deviations which may affect the study outcome significantly. Regardless of the number of patients not included in the per protocol analysis set, a set of pre-defined major protocol deviations which may affect the study outcome significantly will be used. The patients will be analysed according to the treatment group to which they were randomised, regardless of the actually treatment taken.

12.1.2 Safety analysis set

All randomised patients who received at least one dose of study medication will be included in the safety population. Throughout the safety results sections, erroneously treated subjects (eg,

those randomised to treatment A but actually given treatment B) will be accounted for in the actual treatment group.

12.2 Methods of statistical analyses

12.2.1 Analysis of efficacy data

All efficacy data will be listed by individual patient and summarised descriptively by treatment group.

Unless otherwise specified, for all changes (or percent changes) from baseline to a specific time point post-baseline as well as for glycemic therapeutic response definitions, analyses will be based on measurements available at that time point or the last post baseline measurement prior to the time-point, if no measurement is available at that time point, i.e., last observation carried forward (LOCF).

12.2.1.1 Primary analysis

For the primary efficacy analysis, the change from baseline in HbA1c at Week 12 will be analysed based on an analysis of covariance (ANCOVA) model including treatment group as a fixed effects and baseline as a covariate. Based on the ANCOVA model, the point estimates and 2-sided 95% confidence intervals for the mean changes within each treatment group as well as for the differences in mean changes between each of dapagliflozin treatment group and the placebo treatment group will be calculated. Pair-wise comparisons of dapagliflozin treatment groups vs. placebo group will be made with multiplicity of tests adjusted by Dunnett's method at overall 2-sided significance level 0.05.

12.2.1.2 Secondary analysis

The change from baseline to Week 12 in FPG will be analysed based on the similar ANCOVA model as in the primary efficacy analysis for HbA1c.

The proportion of subjects achieving a therapeutic glycemic response defined as HbA1c < 7.0% at Week 12 will be summarized by treatment groups. The 2-sided 95% confidence intervals for the response rate within each treatment group as well as for the difference in response rate between each of dapagliflozin treatment group and the placebo treatment group will be estimated. The proportions will be compared between each of dapagliflozin treatment groups versus placebo using a two-sided Fisher's exact test.

12.2.1.3 Tertiary analysis

The change from baseline to Week 12 in 180 minutes AUC on postprandial glucose, insulin and C-peptide response to OGTT, fasting plasma insulin, fasting plasma C-peptide, beta-cell function (using HOMA2), and insulin resistance index (using HOMA2) will be analysed based on the similar ANCOVA model as in the primary efficacy analysis for HbA1c.

At each time point, the observed value and changes from baseline for all continuous efficacy variables will be summarised using descriptive statistics. For categorical efficacy variables, the number of subjects in each category will be summarised at each time point.

12.2.2 Analysis of safety data

All safety data will be listed and summarised descriptively by treatment group.

The number and percentage of subjects who had any AEs, SAEs, AEs that lead to discontinuation, drug-related AEs and other significant AEs will be summarised.

Adverse events will be classified by body system and by preferred term using MedDRA. The number and percentage of subjects with AEs occurring after the first dosing date (including the first dosing date) by body system and by preferred term will be summarised. If necessary, similar summary will be made for SAEs and drug-related AEs.

For continuous safety variables, observed value and changes from baseline at each time point will be summarised using descriptive statistics. For categorical safety variables, the number of subjects in each category will be summarised at each time point.

All laboratory safety variables outside the reference range will be listed.

12.2.3 Analysis of PK data

The PK properties of dapagliflozin will be evaluated by population PK methodology and reported as necessary in a separate PK report, including estimates of population mean PK parameters, between-patient variability as well as predictions of individual PK parameters and exposures measures (ie, apparent clearance [CL/F], apparent volume of distribution [Vd/F] and exposure measures (ie, AUC, C_{min}). Possible covariate effects on PK parameters (e.g. renal function on CL/F) may be identified and quantified. A detailed population PK analysis plan will be prepared prior to data base lock.

12.3 Determination of sample size

The sample size for this study is calculated based upon the results observed in a similarly designed study for dapagliflozin (MB102008). From that study, the mean value and SD for the HbA1c change from baseline was –0.54% and 0.74%, respectively, as estimated from the the placebo-corrected change in the 5 mg group. The sample size calculation based on these results is considered appropriate, even though a smaller reduction in HbA1c could also be considered clinically meaningful. Then with 53 subjects per treatment group in the full analysis set, there is 90% power to detect a difference in mean change from baseline of 0.54% for HbA1c between any given dapagliflozin group and placebo using a 2-sample t-test at the overall 2-sided significance of 0.05, adjusted for multiplicity (4 tests against placebo) by Dunnett's method. Assuming a similar proportion (4%) of randomised patients are excluded from the full analysis set as seen in Study MB102008, 55 subjects per treatment group are needed to be randomised.

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2.

12.4 Data monitoring committee – Not Applicable

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4.4**

In the case of a medical emergency the investigator may contact the Monitors or the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the *Study* Delivery Team Physician/other physician at the AstraZeneca Research and development.

Name	Role in the study	Address & telephone number

13.2 Overdose

Overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. Once an investigator decides that a particular occurrences is an overdose, it must be reported using the SAE module of eCRF (see Section 6.4.4).

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

If a subject becomes pregnant during the course of the study investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day** ie, immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.4.4 and within 30 days for all other pregnancies

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

13.3.2 Paternal exposure – Not Applicable

14. LIST OF REFERENCES

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Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A multicenter, randomized, double-blind, placebo-controlled, parallel group, Phase 2 trial to evaluate the efficacy and safety of dapagliflozin as monotherapy in Japanese subjects with type 2 diabetes mellitus who have inadequate glycemic control

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol.

AstraZeneca Research and Development
site representative

ASTRAZENECA SIGNATURE(S)

A multicenter, randomized, double-blind, placebo-controlled, parallel group, Phase 2 trial to evaluate the efficacy and safety of dapagliflozin as monotherapy in Japanese subjects with type 2 diabetes mellitus who have inadequate glycemic control

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I agree to the terms of this study protocol.

AstraZeneca Research and Development site representativ

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D
Instruction For Sampling, Handling and Shipment of Pharmacokinetic Samples

1. TYPES OF SAMPLE

In this study, blood samples will be collected and transported to the laboratories in France to evaluate the concentration of dapagliflozin in plasma.

Any biological samples identified as Infectious Category A materials (see IATA 6.2 Regulations Guidance in Appendix C) are not allowed to be shipped (see Section 7.3 in the study protocol).

2. SAMPLING AND HANDLING

2.1 Sample Device

Disposable needles and disposable tubes shall be used. Needles and catheters will be prepared at each study centre, and sampling tubes will be prepared by AstraZeneca K.K.

2.2 Blood Sampling

Blood samples (3 mL per sample) will be collected by direct venipuncture or through an indwelling catheter into a properly labelled 3.0 mL tube with K2EDTA as the anticoagulant. If a catheter is used for blood collection, then approximately 1 mL of blood should be withdrawn initially and discarded. Immediately after collection, each blood sample will be gently inverted 8-10 times for complete mixing with the anticoagulant. Within 60 minutes, each blood sample will be centrifuged at room temperature for 15 minutes at approximately 1000 x g to separate plasma. The separated plasma will be transferred to an appropriately labelled transfer tube within 15 minutes of centrifugation. Samples must be stored immediately at or below -20°C in an upright position.

2.3 Labelling

On each sample tube the label with pre-printed information, including the sample identification, will be attached. The label can only be used for the intended sample and the pre-printed information must not be changed.

3. SHIPMENT

Samples will be packed in the dedicated package supplied by AstraZeneca K.K., and the appropriate requisition forms must be completed by the investigators or delegates.

Samples will be shipped by SRL Medisearch Inc. via its agreed courier to the laboratory. Where possible, the samples would be shipped in batches and would be coordinated to arrive within working hours of the receiving laboratory site.

Details of sample packing, documentation and shipping conditions are specified in the laboratory manual.

3.1 Bioanalytical laboratory

Appendix E
Serum Creatinine Exclusion

1. SERUM CREATININE EXCLUSION

Table 1 (Serum creatinine (Scr) in mg/dL) is derived from combining:

1. Metformin exclusion criteria for serum creatinine based on gender which would exclude a subject from the study. **AND**

2. Serum creatinine values based on subject's age, gender and race which would exclude the subject from the study because the GFR (as calculated by Simplified Modification in Diet and Renal Disease (MDRD) formula (Rigalleau et al 2005, Levey et al 1999)) is ≤ 60 mL/min/1.73 m^2.

Table 1 Serum creatinine

Age (years)	Male Scr (mg/dL)	Female Scr (mg/dL)
18	1.5	1.3
19	1.5	1.3
20	1.5	1.3
21	1.5	1.2
22	1.5	1.2
23	1.5	1.2
24	1.5	1.2
25	1.5	1.2
26	1.5	1.2
27	1.5	1.2
28	1.5	1.2
29	1.5	1.2
30	1.5	1.2
31	1.5	1.2
32	1.5	1.2
33	1.5	1.2
34	1.5	1.1
35	1.5	1.1
36	1.5	1.1
37	1.5	1.1
38	1.4	1.1

Table 1 Serum creatinine

Age (years)	Male Scr (mg/dL)	Female Scr (mg/dL)
39	1.4	1.1
40	1.4	1.1
41	1.4	1.1
42	1.4	1.1
43	1.4	1.1
44	1.4	1.1
45	1.4	1.1
46	1.4	1.1
47	1.4	1.1
48	1.4	1.1
49	1.4	1.1
50	1.4	1.1
51	1.4	1.1
52	1.4	1.1
53	1.4	1.1
54	1.4	1.1
55	1.4	1.1
56	1.4	1.1
57	1.3	1.1
58	1.3	1.1
59	1.3	1.0
60	1.3	1.0
61	1.3	1.0
62	1.3	1.0
63	1.3	1.0
64	1.3	1.0
65	1.3	1.0
66	1.3	1.0
67	1.3	1.0
68	1.3	1.0
69	1.3	1.0

Table 1 Serum creatinine

Age (years)	Male Scr (mg/dL)	Female Scr (mg/dL)
70	1.3	1.0
71	1.3	1.0
72	1.3	1.0
73	1.3	1.0
74	1.3	1.0
75	1.3	1.0
76	1.3	1.0
77	1.3	1.0
78	1.3	1.0
79	1.3	1.0

2. REFERENCE

Rigalleau et al 2005
Rigalleau V, Lasseur C, Perlemoine C, et al. Estimation of Glomerular Filtration Rate in Diabetic Subjects: Cockcroft formula or modification of diet in renal disease study equation. Diabetes Care 2005; 28(4):838-843.

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Appendix F
Algorithm on Management of Hyponatraemia

1. ALGORITHM ON MANAGEMENT OF HYPONATRAEMIA

If a subject experiences a serum sodium ≤125 mmol/L with or without symptoms, dosing of blinded investigational product will be interrupted. A repeat serum sodium concentration will be drawn within 3 days of the receipt of the result.

- If the repeat sodium concentration within 3 days is ≥130 mmol/L

  Investigational product may be restarted unless otherwise contraindicated. Serum sodium will be rechecked in 7 days after restarting the investigational product.

  o If the repeat sodium concentration within 7 days of restarting the investigational product is <130 mmol/L investigational product will be discontinued. Subjects will be prematurely discontinued from the study according procedures specified in Section 5.4.2 in the Clinical Study Protocol.

  o If the repeat sodium concentration within 7 days of restarting the investigational product is ≥130mmol/L further management should be based on composite of sodium concentration, clinical assessment of the subject and an evaluation of underlying cause of hyponatraemia.

- If the repeat sodium concentration within 3 days is <130 mmol/L

  If there is **no** suspected new, temporary, and reversible cause of hyponatraemia based on clinical assessment (other than investigational product), investigational product will be discontinued. Subjects will be prematurely discontinued from the study according procedures specified in Section 5.4.2 in the Clinical Study Protocol.

  If there is **a** suspected new, temporary, and reversible cause of hyponatraemia based on clinical assessment (other than investigational product), investigational product will continue to be interrupted. The suspected cause of hyponatraemia should be identified and corrected. The serum sodium will be rechecked in another 7 days.

  o If the repeat sodium concentration within 7 days is <130 mmol/L investigational product will be discontinued. Subjects will be prematurely discontinued from the study according procedures specified in Section 5.4.2 in the Clinical Study Protocol.

  o If the repeat sodium level concentration within 7 days is ≥130 mmol/L investigational product may be restarted unless otherwise contraindicated. Serum sodium will be rechecked in 7 days after restarting the investigational product, and further management should be based on composite of sodium concentration, clinical assessment of the subject and an evaluation of underlying cause of hyponatraemia.

For subjects whose serum sodium is in the range of 126-129 mmol/L the investigator's clinical judgment should apply concerning whether such subjects should be entered into this algorithm.

Appendix G
Case Identification and Management of Decreased Renal Function

1. CASE IDENTIFICATION AND MANAGEMENT OF DECREASED RENAL FUNCTION

The evaluation of renal function is an important part of the overall safety assessment in the dapagliflozin clinical development program. In order to standardize the definition and management of decreased renal function, the following guidelines has been developed:

a) For subjects with baseline creatinine of < 1.4 mg/dL (123 µmol/L), an absolute increase in serum creatinine level of ≥ 0.5 mg/dL (44 µmol/L) from baseline based on central laboratory results

b) For subjects with baseline creatinine of ≥ 1.4 mg/dL (123 µmol/L), an absolute increase in serum creatinine level of ≥ 1.0 mg/dL (88 µmol/L) from baseline based on central laboratory results

In either of these circumstances, the investigator should consider evaluating the subject for potentially reversible causes of renal dysfunction including but not limited to:

1. concurrent use of NSAIDS, antibiotics, or other medications known to affect measures of serum creatinine
2. volume depletion
3. urinary tract infection
4. obstructive uropathy

Subjects should return for repeat central laboratory testing as soon as possible, no later than 7 days after the abnormal result. Study drug should be interrupted pending the results of repeat testing. If after interruption the serum creatinine value remains above the increase limit described above (≥ 0.5 mg/dL (44 µmol/L) or ≥ 1.0 mg/dL (88 µmol/L) above baseline), the subject should permanently discontinue the medication and be withdrawn from the study (in which case an Adverse Event must be reported).

If after study drug interruption the serum creatinine value has decreased to below the increase limit (< 0.5 mg/dL (44 µmol/L) or < 1.0 mg/dL (88 µmol/L) above baseline), study drug can be re-started if appropriate in the investigator's judgment and after consultation with the study delivery team physician. If study drug is re-started, the subject should return for a follow-up central lab serum creatinine 7-14 days after re-start, although more frequent assessments may be done at investigator discretion. If the subject restarts study drug and the serum creatinine value increases again to the increase limit (≥0.5 mg/dL (44 µmol/L) or ≥ 1.0 mg/dL (88 µmol/L) above baseline), the subject should permanently discontinue the medication and be withdrawn from the study (in which case an Adverse Event must be reported).

Appendix H
New York Heart Association Functional Class

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 I
Additional Liver Related Investigations

1. ADDITIONAL LIVER RELATED INVESTIGATIONS

Additional investigations for all subjects with ALT and/or AST >3 x ULN confirmed at a repeated test within 72 hours

The following should be done within 72 hours:

- AE assessment
- Physical examination for jaundice and other signs of liver disease
- Review relevant predisposing factors and current history focusing on possible causes to increased ALT and/or AST and/or Bilirubin:
  - Illnesses (including infections) or surgery
  - New concomitant medication (including over-the-counter, herbal and vitamin preparations)
  - New physical activity or increase of intensity of usual physical activity (including housework, gardening etc) within 3 days prior to last sampling
  - Extent of alcohol consumption within 3 days prior to last sampling
  - Narcotic use within 3 days prior to last sampling
  - Other conditions which may cause liver disease (such as tattoos, travel, relevant sexual practices etc), or which may cause abnormal test results

For subjects who are discontinued from the study due to ALT/AST and Total Bilirubin increases, additional blood sampling should be done in addition to the above

The following additional blood sampling should be done within 72 hours:

- Conjugated Bilirubin
- Creatine kinase
- Antinuclear antibodies
- Smooth muscle antibodies
- Antibodies to hepatitis A, B, C, and E
- Antibodies to cytomegalovirus (CMV)

- Antibodies to Epstein Barr virus (EBV)
- Carbohydrate deficient transferrin (CDT)
- Prothrombin Time (PT)

Also, ultrasound, immunoglobulins: serum electrophoresis of IgA, IgG, and IgM including quantification of α1-antitrypsin should be considered.

Any additional tests and/or examinations should be carried out at the discretion of the investigator.

For any patient who discontinues taking investigational product due to suspected liver disease, a gastroenterologist (preferably a hepatologist) consultation should be considered.

For any patient who discontinues taking investigational product due to suspected liver disease, the Monitor/AstraZeneca Clinical Study Team Physician should be kept informed of the patient's clinical status including results of all assessments.

Any further investigations and laboratory results for patients who show abnormal laboratory values at the follow-up visit should be made available for BMS/AstraZeneca upon request.

Clinical Study Protocol: Supplement A

Drug Substance	Dapagliflozin
Study Code	D1692C00005
Supplement Edition Number	1
Supplement Date	

Supplement A
Investigators and Study Administrative Structure

STAFF AT STUDY SITE(S)

Centre No.	**Centre address**	**Name** (First name, Last name)	**Qualifications**	**Present position**	**Role in the study**

Centre No.	**Centre address**	**Name** (First name, Last name)	**Qualifications**	**Present position**	**Role in the study**

Centre No.	**Centre address**	**Name** (First name, Last name)	**Qualifications**	**Present position**	**Role in the study**

ASTRAZENECA STUDY PERSONNEL

Address	**Name** (First name, Last name)	**Qualifications**	**Present Position**	**Role in the study**

Address	**Name** (First name, Last name)	**Qualifications**	**Present Position**	**Role in the study**

Address	**Name** (First name, Last name)	**Qualifications**	**Present Position**	**Role in the study**

Address	**Name** (First name, Last name)	**Qualifications**	**Present Position**	**Role in the study**

DATA MONITORING OR SAFETY COMMITTEE(S)

Committee name and address	**Member name** (First name, Last name)	**Qualifications**	**Role in committee**

OTHER PARTICIPANTS

Organisation and address	Role in study

Clinical Study Protocol Amendment

Amendment Number	1
Drug Substance	Dapagliflozin
Study Code	D1692C00005
Date	
Protocol Dated	

A multicenter, randomized, double-blind, placebo-controlled, parallel group, Phase 2 trial to evaluate the efficacy and safety of dapagliflozin as monotherapy in Japanese subjects with type 2 diabetes mellitus who have inadequate glycemic control

Sponsor:

AstraZeneca K.K.

Bristol-Myers K.K.

Centres affected by the Amendment:

All centres

The protocol for the study is to be amended as follows:

Change 1

Section of protocol affected:

Section 5.8.1 Criteria for discontinuation from the study

Previous text:

5. Increase of ALT and/or AST >5 x ULN more than two weeks after initiation of close monitoring of ALT and/or AST, see Section 5.8.2 for further guidance

6. Increase of ALT and/or AST >3 x ULN and increase of Total Bilirubin (TB) >1.5 x ULN confirmed at a repeated measurement within 72 hours, see Section 5.8.2 for further guidance

7. Increase of ALT and/or AST >8 x ULN confirmed at a repeated measurement within 72 hours, see Section 5.8.2 for further guidance

   For all subjects who are discontinued from the study due to ALT/AST and TB increases, additional blood sampling should be done at the end of treatment visit, see Appendix I.

Revised text:

Subjects with a central laboratory ALT and/or AST >3x ULN will be scheduled for a follow-up visit within 3 calendar days following the receipt of the result. See Section 5.8.2 for further guidance. Subjects should be discontinued from study if the initial and repeat laboratory tests meet any of the following criteria:

5. ALT and/or AST are >3x ULN and Total Bilirubin (TB)>1.5x ULN

6. ALT and/or AST are >5x ULN for ≥14 consecutive days, at any time after initial confirmatory results

7. ALT and/or AST are >8x ULN

Reason for Amendment:

The purpose of this amendment is to expand existing procedures for the ongoing review of hepatic laboratory tests and hepatic events. A recent observation of the dapagliflozin program safety database revealed a slightly higher incidence of aminotransaminase elevations in dapagliflozin-treated subjects compared with placebo. An internal expert panel was convened which recommended implementation of additional hepatic laboratory monitoring across the program. Using the US Food and Drug Administration (FDA) Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009) as a reference, this amendment describes the changes being implemented in addition to the routine safety surveillance procedures already in place.

Change 2

Section of protocol affected:

Section 5.8.2 Procedures for discontinuation of a subject from investigational product

Previous text:

Subjects with increased ALT and/ or ALT > 3 x ULN will have repeated liver function tests within 72 hours.

- **If the repeat ALT and AST are ≤3 x ULN**, the subject should be monitored according to the clinical study protocol

- **If the repeat ALT and/or AST are >3 x ULN but ≤8 x ULN and TB ≤1.5 x ULN**, medical history including details of risk factors for liver disease will be requested, see Appendix I. The Investigator will follow the subject every 72 hours until the ALT and AST are ≤2 x ULN or until ALT and AST are back to the baseline levels*. The frequency of retesting can decrease to once a week or less if abnormalities stabilize and the patient is asymptomatic. **If ALT and/or AST is >5 x ULN more than two weeks after initiation of close monitoring of ALT and AST**, the subject must be discontinued from study medication, the Sponsor notified and the end of treatment visit performed within 72 hours. At the end-of treatment visit, medical history including details of risk factors for liver disease will be requested and additional blood sampling done, see Appendix I.

- **If the repeat ALT and/or AST are >3 x ULN AND TB >1.5 x ULN at any time point**, the subject must be discontinued from study medication, the Sponsor notified and the end of treatment visit performed within 72 hours. At the end of treatment visit, medical history including details of risk factors for liver disease will be requested and additional blood sampling done, see Appendix I. The Investigator will follow the subject every 72 hours until the ALT and AST are ≤2 x ULN or until ALT and AST are back to the baseline levels*. The frequency of retesting can decrease to once a week or less if abnormalities stabilize and the patient is asymptomatic.

- **If the repeat ALT and/or AST >8 x ULN at any time point**, the subject must be discontinued from study medication, the Sponsor notified and the end of treatment visit performed within 72 hours. At the end of treatment visit, medical history including details of risk factors for liver disease will be requested and additional blood sampling done (if not already done), see Appendix I. The Investigator will follow the subject every 72 hours until the ALT and AST are ≤2 x ULN or until ALT and AST are back to the baseline levels*. The frequency of retesting can

* unless there are specific reasons for the ALT and/or AST elevations e.g. liver cancer

decrease to once a week or less if abnormalities stabilize and the patient is asymptomatic.

Revised text:

The monitoring for liver safety will be performed using the serum levels of AST, ALT and TB (see Appendix I for algorithm flow chart).

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

- **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**

Note: See Appendix I for further discontinuation procedures

Reason for Amendment:

The purpose of this amendment is to expand existing procedures for the ongoing review of hepatic laboratory tests and hepatic events. A recent observation of the dapagliflozin program safety database revealed a slightly higher incidence of aminotransaminase elevations in dapagliflozin-treated subjects compared with placebo. An internal expert panel was convened which recommended implementation of additional hepatic laboratory monitoring across the program. Using the US Food and Drug Administration (FDA) Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009) as a reference, this amendment describes the changes being implemented in addition to the routine safety surveillance procedures already in place.

Change 3

Section of protocol affected:

Appendix I 1. ADDITIONAL LIVER RELATED INVESTIGATIONS

Previous text:

Additional investigations for all subjects with ALT and/or AST >3 x ULN confirmed at a repeated test within 72 hours

The following should be done within 72 hours:

- AE assessment
- Physical examination for jaundice and other signs of liver disease
- Review relevant predisposing factors and current history focusing on possible causes to increased ALT and/or AST and/or Bilirubin:
  - Illnesses (including infections) or surgery
  - New concomitant medication (including over-the-counter, herbal and vitamin preparations)
  - New physical activity or increase of intensity of usual physical activity (including housework, gardening etc) within 3 days prior to last sampling
  - Extent of alcohol consumption within 3 days prior to last sampling
  - Narcotic use within 3 days prior to last sampling
  - Other conditions which may cause liver disease (such as tattoos, travel, relevant sexual practices etc), or which may cause abnormal test results

For subjects who are discontinued from the study due to ALT/AST and Total Bilirubin increases, additional blood sampling should be done in addition to the above

The following additional blood sampling should be done within 72 hours:

- Conjugated Bilirubin
- Creatine kinase
- Antinuclear antibodies
- Smooth muscle antibodies
- Antibodies to hepatitis A, B, C, and E
- Antibodies to cytomegalovirus (CMV)
- Antibodies to Epstein Barr virus (EBV)
- Carbohydrate deficient transferrin (CDT)
- Prothrombin Time (PT)

Also, ultrasound, immunoglobulins: serum electrophoresis of IgA, IgG, and IgM including quantification of α1-antitrypsin should be considered.

Any additional tests and/or examinations should be carried out at the discretion of the investigator.

For any patient who discontinues taking investigational product due to suspected liver disease, a gastroenterologist (preferably a hepatologist) consultation should be considered.

For any patient who discontinues taking investigational product due to suspected liver disease, the Monitor/AstraZeneca Clinical Study Team Physician should be kept informed of the patient's clinical status including results of all assessments.

Any further investigations and laboratory results for patients who show abnormal laboratory values at the follow-up visit should be made available for BMS/AstraZeneca upon request.

Revised text:

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 (i.e., 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

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 above, study medication will be discontinued, the Sponsor notified and the early termination (End-of-Treatment) visit performed within 3 days of the confirmed laboratory results. Additional blood sampling must be done within 3 days of the confirmed laboratory results in conjunction with an early termination (End-of-Treatment) visit, in addition to the procedures noted above. A “Liver Discontinuation” visit laboratory kit , in addition to the Specialized Liver Panel kit as noted below, 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. Patient should also be scheduled for a Follow-up visit (i.e. procedures of Visit 14) 4 weeks after discontinuation of investigational product. 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 safety follow-up visit should be made available to the Sponsor upon request.

Following the Early Termination (End-of-Treatment) 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.

Specialized Liver Panel

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

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

Liver Discontinuation Panel

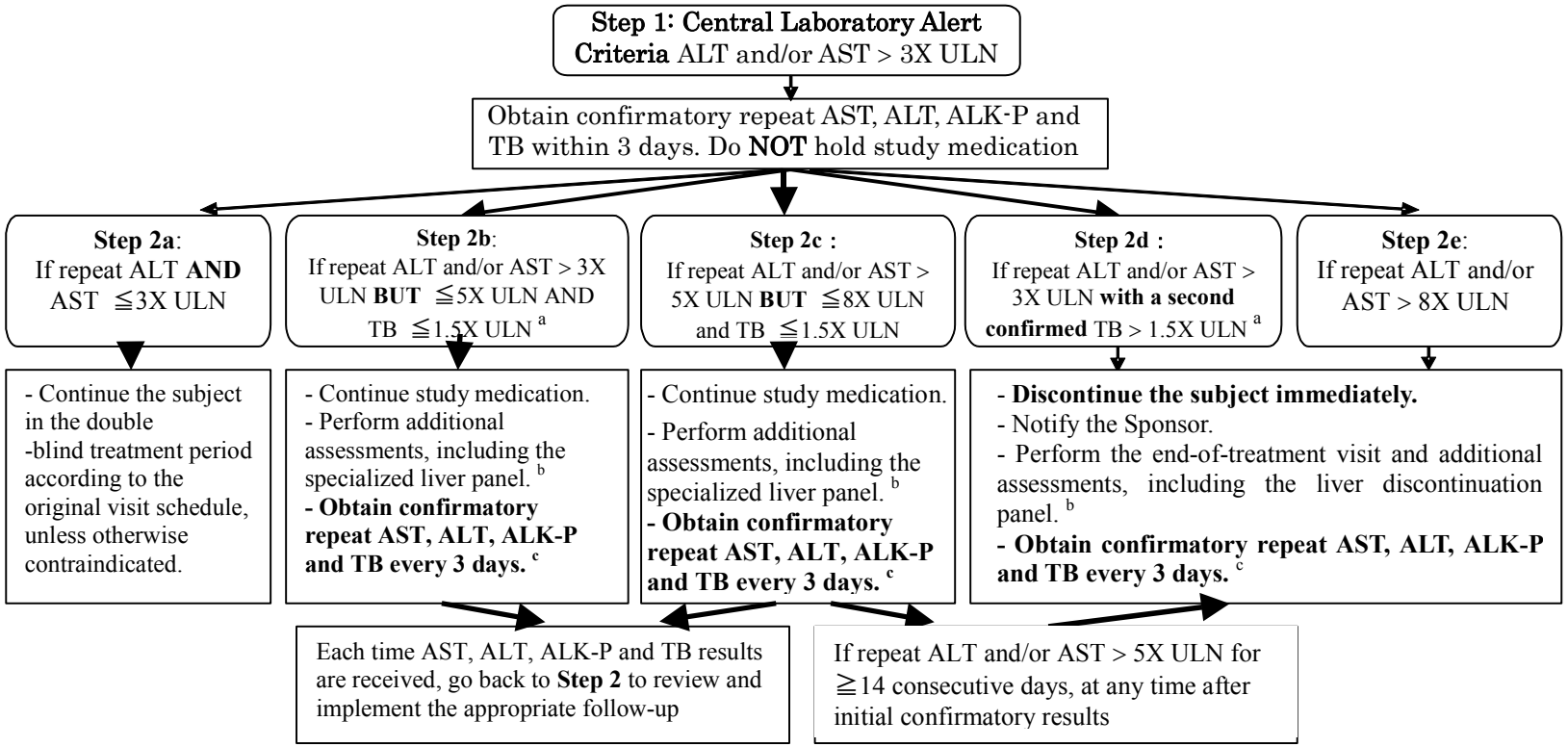
For subjects who are discontinued from the study as a result of sustained elevated liver safety abnormalities, additional central laboratory tests will be performed at the time of Early Termination (End-of-Treatment) visit. Similar to the Specialized Liver Panel, these laboratory tests will study the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

- Cytomegalovirus (CMV) IgM Ab
- Herpes Simplex Virus (HSV) 1 and 2 IgG antibody
- Ceruloplasmin

- Toxoplasmosis IgG and IgM
- 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.

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 this Appendix I 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.

Reason for Amendment:

The purpose of this amendment is to expand existing procedures for the ongoing review of hepatic laboratory tests and hepatic events. A recent observation of the dapagliflozin program safety database revealed a slightly higher incidence of aminotransaminase elevations in dapagliflozin-treated subjects compared with placebo. An internal expert panel was convened which recommended implementation of additional hepatic laboratory monitoring across the program. Using the US Food and Drug Administration (FDA) Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009) as a reference, this amendment describes the changes being implemented in addition to the routine safety surveillance procedures already in place.

Persons who initiated the Amendment:

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A multicenter, randomized, double-blind, placebo-controlled, parallel group, Phase 2 trial to evaluate the efficacy and safety of dapagliflozin as monotherapy in Japanese subjects with type 2 diabetes mellitus who have inadequate glycemic control

---

This Clinical Study Protocol and all Amendments to the CSP has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development
site representative

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