Clinical Study Protocol

Drug Substance	Dapagliflozin
Study Code	D1692C00006
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Date	

A 24-week randomised, double-blind, parallel-group, multi-centre, placebo-controlled phase III trial to evaluate the efficacy and safety of dapagliflozin as monotherapy in Japanese subjects with Type 2 diabetes who have inadequate glycemic control with diet and exercise

Sponsor:

AstraZeneca K.K.
Bristol-Myers K.K.

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

PROTOCOL SYNOPSIS

A 24-week randomised, double-blind, parallel-group, multi-centre, placebo-controlled phase III trial to evaluate the efficacy and safety of dapagliflozin as monotherapy in Japanese subjects with Type 2 diabetes who have inadequate glycemic control with diet and exercise

Principal Investigator

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

Study centre(s) and number of subjects planned

Study Centres: Approximately 35 centres are planned for participation

Number of Subjects: 255 randomised Japanese subjects

Study period		Phase of development
Estimated date of first subject enrolled	February 2011	Phase III
Estimated date of last subject completed	April 2012	

Objectives

Primary Objective:

- The primary objective of this study is to compare the change from baseline in haemoglobin A1c (HbA1c) achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.

Key Secondary Objectives:

- To compare the change from baseline in fasting plasma glucose (FPG) achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.
- To compare the change from baseline in total body weight achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.

Secondary Objectives:

- To compare the percent change from baseline in total body weight achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.

- To compare the change from baseline in seated systolic blood pressure (SBP) in subjects with baseline seated SBP ≥130 mmHg achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.

- To compare the change from baseline in total body weight in subjects with baseline body mass index (BMI) ≥25 kg/m^2 achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.

- To compare the change from baseline in HbA1c achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment in subjects with baseline HbA1c ≥7.5%.

- To compare the proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c <6.5%, achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.

- To compare the proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c <7%, achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment in subjects with baseline HbA1c ≥7%.

- To compare the change from baseline in seated SBP achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.

- To compare the proportion of subjects with baseline elevated blood pressure (BP) (baseline SBP ≥130 mmHg and/or baseline diastolic blood pressure (DBP) ≥80 mmHg) who achieve a seated BP of <130/80 mmHg achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.

- To compare the change in waist circumference achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.

- To compare the proportion of subjects discontinued for lack of efficacy or rescued for failing to maintain FPG below pre-specified rescue criteria achieved with each dose of dapagliflozin versus placebo after 12, 16 and 24 weeks double-blind treatment.

- To compare the percent change from baseline in fasting lipids (total cholesterol [TC] low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C]and triglycerides [TG]) achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.

- To compare the change from baseline in fasting insulin and C-peptide achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.

- To compare the change from baseline in glycoalbumin achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.

Safety Objectives:

- To evaluate the safety and tolerability of dapagliflozin by assessment of adverse event (AE), safety laboratory values, electrocardiogram (ECG), pulse, BP, hypoglycemic events, estimated glomerular filtration rate (eGFR) and physical examination findings.

Study design

This is a 24-week randomised, double-blind, placebo-controlled, 3-arm, parallel-group, multi-centre Phase III study to evaluate the efficacy and safety of dapagliflozin as monotherapy in Japanese subjects with T2DM who have inadequate glycemic control with diet and exercise.

Target subject population

Japanese subjects with type 2 diabetes (T2DM) who have inadequate glycemic control on diet and exercise

Either gender needs to be 40% or higher of total number of randomised subjects. Also, the proportion of subjects with HbA1c ≥6.5% but ≤7% at Visit 5 needs to be at most approximately 25% of the total number of randomised subjects.

Investigational product, dosage and mode of administration

Each dose will be composed of 2 tablets. Investigational drug should be taken once daily in the morning.

Treatment Phase

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

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

Comparator, dosage and mode of administration

Comparator dose will be composed of 2 tablets. Investigational drug should be taken once daily in the morning.

Placebo Lead-in Phase

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

Treatment Phase

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

Duration of treatment

This study consists of a 2-week Screening Period, a 4-week single-blind, placebo lead-in period, a 24-week double-blind, placebo-controlled treatment period and a 3-week follow-up period.

The total planned study duration starting with enrolment and including the follow-up period will be 33 weeks.

The subjects who received ongoing medical treatment for diabetes within 6 weeks of enrolment, except for thiazolidinedions (TZD) (a single oral anti-diabetic agent or two agents with less than half of the approved maximal dose for each agent) need a 6-week wash-out period before a 4-week placebo lead-in period.

Outcome variable(s):

Efficacy

Primary outcome variables:

- Change from baseline in HbA1c at 24 weeks

Key secondary outcome variables:

- Change from baseline in FPG at 24 weeks
- Change from baseline in total body weight at 24 weeks

Other secondary outcome variables:

- Percent change from baseline in total body weight at 24 weeks
- Change from baseline in seated SBP at 24 weeks (only subjects with baseline seated SBP ≥130)
- Change from baseline in total body weight at 24 weeks (only subjects with baseline BMI ≥25 kg/m^2)
- Change from baseline in HbA1c at 24 weeks (only subjects with baseline HbA1c ≥7.5%)
- Proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c <6.5%, at 24 weeks
- Proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c <7%, at 24 weeks in subjects with baseline HbA1c ≥7%
- Change from baseline in seated SBP at 24 weeks
- Proportion of subjects with baseline elevated BP who achieve a seated BP of <130/80 mmHg at 24 weeks
- Change from baseline in waist circumference at 24 weeks

- Proportion of subjects discontinued for lack of efficacy or rescued for failing to maintain FPG
- Percent change from baseline in fasting lipids (TC, LDL-C, HDL-C and TG) at 24 weeks
- Change from baseline in fasting insulin and C-peptide at 24 weeks
- Change from baseline in glycoalbumin at 24 weeks

Safety

- AEs and Serious adverse events (SAEs)
- Hypoglycemic events
- Safety Laboratory values
- ECG
- Vital Signs (pulse and BP)
- eGFR
- Physical examination

Statistical methods

For the primary variable, the change from baseline in HbA1c to Week 24, each pair wise treatment group comparison will be tested at a significance level of approximately 0.027, according to Dunnett's method, in order to maintain an overall Type I error rate <0.050 for the primary objective. A hierarchical closed testing procedure will be used to control the Type I error rate across the primary and key secondary objectives within each dapagliflozin treatment group.

The change in HbA1c from baseline to Week 24 (Last Observation Carried Forward [LOCF]), will be analyzed by an analysis of covariance (ANCOVA) model including treatment group and gender as effect and baseline as covariate. The ANCOVA model will be used to derive a least squares estimate of the treatment difference with 95% confidence interval and corresponding 2-sided p-value. Efficacy will primarily be evaluated using a full analysis set.

To detect a difference of 0.5% between each dapagliflozin group versus placebo for changes in HbA1c from baseline to Week 24, assuming a SD=0.9%, and at a two-sided significance level of 0.027, 80 evaluable subjects are needed in each treatment group to provide 90% power. The assumed SD=0.9 is considered to be appropriate based on Japan Phase IIb study and Global monotherapy Phase III study result where SD was approximately 0.52% and 0.91%, respectively. Assuming that approximately 5% of the subjects will not have a post-baseline efficacy measurement, 85 subjects per treatment group (255 subjects total) are planned for randomization.

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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
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BP	Blood Pressure
CEC	Clinical Event Committee
CK	Creatinine Kinase
DBP	Diastolic Blood Pressure
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
FFA	Free Fatty Acid
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HbA1c	Haemoglobin A1c
HCG	Human Chorionic Gonadotropin
HDL-C	High-Density Lipoprotein Cholesterol
IATA	International Air Transport Association
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LDL-C	Low-Density Lipoprotein Cholesterol
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare

Abbreviation or special term	Explanation
MI	Myocardial Infarction
NGSP	National Glycohemoglobin Standardization Program
OAE	Other Significant Adverse Event (see definition in Section 11.2.2)
PT	Prothrombin Time
PTH	Parathormome
PTT	Partial Thromboplastin Time
SAE	Serious Adverse Event (see definition in Section 6.4.2).
SBP	Systolic Blood Pressure
SCr	Serum Creatinine
SGLT	Sodium-glucose Transporters
TB	Total Bilirubin
TC	Total Cholesterol
TG	Triglyceride
TSH	Thyroid Stimulating Hormone
TZD	Thiazolidinedions
T2DM	Type 2 Diabetes
UACR	Urine Albumin: Creatinine Ratio
ULN	Upper Limit of Normal
UTI	Urinary Tract Infections
WBDC	Web Based Data Capture
WOCBP	Women of child bearing potential

1. INTRODUCTION

1.1 Background

Type 2 diabetes (T2DM) is characterised by beta-cell dysfunction and peripheral insulin resistance leading to hyperglycemia (Matthaei et al 2000, Meier and Butler 2005). Chronic hyperglycemia is associated with the development of both macrovascular (myocardial infarction [MI], stroke, peripheral arterial disease), and microvascular (nephropathy, retinopathy, neuropathy) complications (UKPDS group 1998). Current treatment regimens aiming to reduce glucose levels in patients with T2DM have focused on the stimulation of insulin secretion (eg, sulphonylureas, glinides, glucagon-like peptide-1 agonists [GLP-1] analogs, dipeptidyl peptidase-4 inhibitors [DPP-4] inhibitors), improvement in insulin sensitivity (eg, metformin, thiazolidinediones [TZD]), inhibition of intestinal glucose absorption (eg, acarbose), or the replacement of insulin. However, the limited efficacy of currently available antihyperglycemic agents, as well as associated side effects (eg, hypoglycemia, oedema, weight gain, etc.) clearly underline the need for novel antihyperglycemic treatment strategies (ACCORD 2008, Koro et al 2004). In addition, the majority of patients with T2DM require more than one antihyperglycemic agent to achieve glycemic targets (Nathan 2006).

Intestinal absorption and renal reabsorption of glucose are mediated through sodium-glucose transporters (SGLT) (Silverman 1991). Two sodium glucose transporters, SGLT1 and SGLT2, have been identified as the major transporters of glucose in humans. SGLT1 is expressed in the gastrointestinal tract, heart, skeletal muscle, liver, lung, and kidney, while SGLT2 is expressed almost exclusively in the kidney (Silverman 1991, Wright 2001). SGLT2 expression is localized in the S1 segment of the proximal tubule, where according to animal data, >90% of renal glucose reabsorption occurs (Wright 2001). Thus, SGLT2 appears to be the major transporter responsible for the reabsorption of glucose from the glomerular filtrate.

Human SGLT2 mutations are associated with a condition known as familial renal glucosuria. These individuals have varying degrees of glucosuria; those who have loss of function in both alleles can excrete 100 g of glucose or greater per day. The majority of patients are asymptomatic, and their condition is diagnosed incidentally. Typically they do not have hypoglycemic episodes, electrolyte imbalance or increased risk of urinary tract infections (Santer et al 2003). Even the most severe form of the condition appears to be associated with a favourable prognosis (Scholl-Burgi et al 2004) although very few patients have been described in the literature. This human model of SGLT2 inhibition supports the potential safety of this mechanism as a treatment approach for type 2 diabetes by demonstrating that mild to moderate glucosuria in itself is not associated with significant adverse health consequences.

Dapagliflozin is a rationally designed, potent, highly selective and orally active inhibitor of the human renal SGLT2. Dapagliflozin lowers plasma glucose by inhibiting the renal reabsorption of glucose and thereby by promoting its urinary excretion. This compound is being developed as an oral agent for the treatment of T2DM, and represents a novel therapeutic approach for the treatment of this disorder. Proof of concept for dapagliflozin in patients with T2DM has been established in a global Phase IIb study over a dose range from 2.5 to 50 mg over 12 weeks,

administered orally once daily as monotherapy. In this study, dapagliflozin treatment led to significant and clinically relevant reductions in fasting plasma glucose (FPG), postprandial glucose, and haemoglobin A1c (HbA1c) levels throughout the entire dose range, and was associated with weight loss (Ferrannini, 2010). Similar findings were observed in a global Phase III study with administration of once daily dapagliflozin 2.5 mg, 5 mg and 10 mg as an add-on to metformin in T2DM subjects inadequately controlled on metformin alone (Bailey 2010).

In a Phase IIb study in Japan, similar results were also seen in Japanese subjects with T2DM who had inadequate glycemic control. A statistically significant mean reduction from baseline in HbA1c was seen in all dapagliflozin treatment groups (1, 2.5, 5 and 10 mg) compared to the placebo group, and a clinically relevant effect on HbA1c (>0.5% placebo corrected reduction) over 12 weeks was seen in the dapagliflozin 5 mg and 10 mg groups. In addition, treatment with dapagliflozin as monotherapy for 12 weeks was safe and well tolerated for Japanese subjects with T2DM and the overall safety profile is similar to other reported dapagliflozin clinical studies with no unexpected findings.

For additional details on the background of dapagliflozin, please see the Investigator's Brochure.

1.2 Research hypothesis

After 24 weeks of treatment, there will be a greater mean reduction from baseline in glycosylated HbA1c achieved with dapagliflozin compared to placebo in Japanese subjects with T2DM who have inadequate glycemic control with diet and exercise alone.

1.3 Rationale for conducting this study

This study will be performed as part of the clinical development programme for dapagliflozin for the treatment of T2DM. This study intends to compare efficacy and safety of dapagliflozin with placebo in treatment of Japanese subjects with T2DM who have inadequate glycemic control with diet and exercise alone.

This study has standard design features for a confirmatory Phase III diabetes study (eg, multi-centre, randomised, double-blind, parallel group) and incorporates the relevant features of the Japanese Guideline on Clinical Evaluation methods on Oral Hypoglycemic Agents which was issued 9th July 2010 with regard to duration of treatment, choice of study population, and choice of outcome variables.

1.4 Benefit/risk and ethical assessment

Risk category

Considering dapagliflozin's mechanism of action, the previous clinical experience with dapagliflozin, the study's design features (including the inclusion, exclusion, and discontinuation criteria), and the planned safety procedures, participation in this study presents a minimal and thus acceptable risk to the individual subjects that will be included.

Potential risks

The potential risks associated with dapagliflozin that have been identified based upon the mechanism of action, the preclinical results, and the clinical experience to date, as well as precautions included in the global Phase III programme to monitor and/or minimize these risks, are included in the Investigator's Brochure.

Inhibition of SGLT2 results in increased urinary glucose excretions, which is commonly believed to increase the risk of urinary tract infections (UTIs). In some of the global Phase III studies, events suggestive of UTI were reported in a slightly higher proportion of dapagliflozin-treated subjects than the placebo group. Increased urinary glucose excretion may also lead to an increased risk of developing genital infections. In global Phase III studies, the proportions of subjects treated with dapagliflozin who reported adverse events (AEs) that matched a predefined list of Medical dictionary for regulatory activities (MedDRA) preferred terms that were indicative of genital infection were higher than those seen for placebo.

Based on the mechanism of action of dapagliflozin and results of animal and clinical studies, there may be a potential risk for this compound to cause hypovolaemia or electrolyte imbalance. As a precaution, subjects at risk for hypovolaemia or electrolyte disturbance should not receive dapagliflozin until more clinical information is available from human studies. In subjects already receiving dapagliflozin who develop conditions that may cause hypovolaemia or electrolyte imbalance, decisions to interrupt or discontinue dapagliflozin therapy and management of subjects should be based on clinical judgment.

Bone health was evaluated in the dapagliflozin clinical development program due to the possible effects of dapagliflozin on body weight, renal tubular handling of calcium and phosphorus, metabolism of vitamin D. Fractures were reported infrequently and the frequency was similar between the dapagliflozin groups and control in the clinical trials with dapagliflozin. Mean change from baseline in the markers of bone resorption was found to be slightly higher in dapagliflozin-treated subjects compared with placebo-treated subjects. However, change in bone formation markers was inconsistent. Therefore, a definitive conclusion on the net effect of treatment of humans with dapagliflozin on bone turnover (resorption/formation) cannot be made at this time.

Higher proportions of subjects with marked laboratory abnormalities of hyperphosphatemia were reported in dapagliflozin vs. placebo but the clinical meaning of this is unclear.

Hepatic laboratory markers were assessed in all the clinical studies with dapagliflozin. In the pooled analyses, the proportion of subjects with elevated liver function tests was similar in the dapagliflozin and comparator groups and no clinically meaningful or consistent mean changes from baseline in liver function tests were observed in the dapagliflozin and placebo groups across the Phase IIb and III clinical studies. One subject had an serious adverse event (SAE) reported as drug-induced acute hepatitis and was later also diagnosed with probable autoimmune hepatitis.

No study procedure will put subjects at a risk beyond those ordinarily encountered during the performance of routine medical examinations or routine tests.

Protection against risks

This study has been designed with appropriate measures in place so as to monitor and minimize any of the potential health risks to participating subjects. In order to ensure the safety of all subjects participating in this study, AstraZeneca and Bristol-Myers Squibb will conduct a real-time review of all safety information from all ongoing clinical dapagliflozin studies as they become available. Safety signal detection will include the integration of all available sources of safety information, including clinical study data, AE reports, pre-clinical data, epidemiological studies and literature reports, to identify and characterize unrecognized safety risks or changes in those which are currently expected Adverse Drug Reactions. Any information that may affect the benefit-risk profile of dapagliflozin will be immediately communicated to relevant Health Authorities and appropriate actions will be taken regarding the clinical program as needed. Thus real-time, active safety surveillance will be conducted during the entire duration of this study. In addition, all dapagliflozin studies are subject to a carefully designed subject risk management plan that includes the temporary and if necessary permanent discontinuation of investigational product in individual subjects in whom a potential health risk or a laboratory abnormality of clinical concern has been identified. Investigators are also provided guidance on appropriate management of potential risks such as hypoglycemia (Section 6.4.9.1) urinary tract and genital infections (Section 6.4.9.2) hyponatraemia (Appendix E), decreased renal function (Appendix F) and increased liver function tests (Appendix G).

Potential benefits to subjects

All subjects will receive counseling on dietary and life-style modifications; both Japan phase II and global studies that have established the effect, but it needs to be confirmed in Japan phase III studies. In this study, the doses of dapagliflozin (5 mg and 10 mg) were chosen to provide efficacy in reducing hyperglycemia while mitigating the potential for AEs, based on previous clinical experience. In addition, dapagliflozin is expected to help decrease body weight (or prevent weight gain) as well as help lower blood pressure (BP) especially in subjects with elevated baseline BP. Subjects are also expected to receive some benefit in the form of increased medical care/attention when participating in study procedures, which includes at least 12 clinic visits (14 clinical visits for subjects who need a 6-week wash-out period) with at least 11 physical examinations (13 physical examinations for subjects who need a 6-week wash-out period) over the 33-week study (39-week study for subjects who need a 6-week wash-out period). Subjects will also receive counselling on dietary and life-style modifications.

Informed consent and alternatives to participation

All prospective participants will be fully informed of the possible risks and benefits associated with this study, and their consent will be received prior to performing any study-related activity. Should a prospective participant elect to not participate in the study or to withdraw from the study, other medications are available to treat their diabetes, and the subject will not be disadvantaged in any way.

Conclusion

Considering the pre-clinical and clinical experience with dapagliflozin and the precautions included in the study protocol, participation in this study presents a minimal and thus acceptable risk to subjects who meet the inclusion/exclusion criteria and consent to take part in the study.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:

- The primary objective of this study is to compare the change from baseline in HbA1c achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.

2.2 Secondary objectives.

Key Secondary Objectives:

- To compare the change from baseline in FPG achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.
- To compare the change from baseline in total body weight achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.

Secondary Objectives:

- To compare the percent change from baseline in total body weight achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.
- To compare the change from baseline in seated systolic blood pressure (SBP) in subjects with baseline seated SBP ≥130 mmHg achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.
- To compare the change from baseline in total body weight in subjects with baseline body mass index (BMI) ≥25 kg/m^2 achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.
- To compare the change from baseline in HbA1c achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment in subjects with baseline HbA1c ≥7.5%.
- To compare the proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c <6.5%, achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.

- To compare the proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c <7%, achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment in subjects with baseline HbA1c ≥7%.

- To compare the change from baseline in seated SBP achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.

- To compare the proportion of subjects with baseline elevated BP (baseline SBP ≥130 mmHg and/or baseline diastolic blood pressure (DBP) ≥80 mmHg) who achieve a seated BP of <130/80 mmHg achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.

- To compare the change in waist circumference achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.

- To compare the proportion of subjects discontinued for lack of efficacy or rescued for failing to maintain FPG below pre-specified rescue criteria achieved with each dose of dapagliflozin versus placebo after 12, 16 and 24 weeks double-blind treatment.

- To compare the percent change from baseline in fasting lipids (total cholesterol [TC] low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C]and triglycerides [TG]) achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.

- To compare the change from baseline in fasting insulin and C-peptide achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.

- To compare the change from baseline in glycoalbumin achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment.

2.3 Safety and tolerability

To evaluate the safety and tolerability of dapagliflozin by assessment of AE events, safety laboratory values, electrocardiogram (ECG), pulse, BP, hypoglycemic events, estimated glomerular filtration rate (eGFR) and physical examination findings.

2.4 Exploratory objectives – Not applicable

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 24-week randomised, double-blind, placebo-controlled, 3-arm, parallel-group, multi-centre phase III study to evaluate the efficacy and safety of dapagliflozin as monotherapy in Japanese subjects with T2DM who have inadequate glycemic control with diet and exercise.

This study consists of a 2-week Screening Period, a 4-week single-blind, placebo lead-in period, a 24-week double-blind, placebo-controlled treatment period and a 3-week follow-up period.

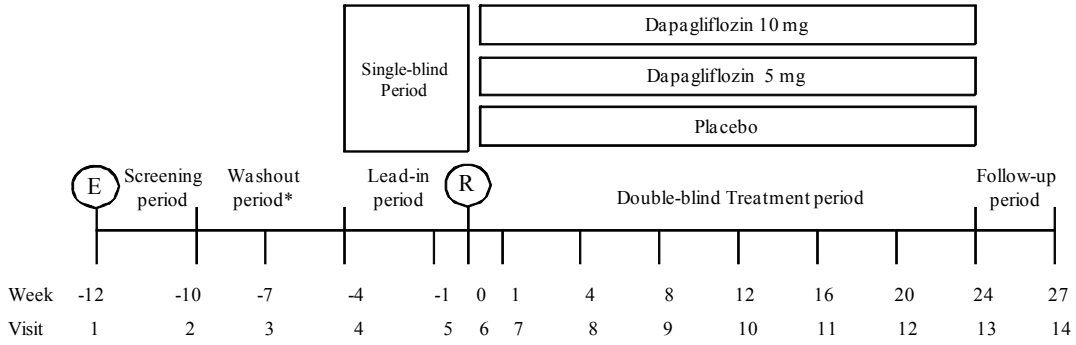
The subjects who received ongoing medical treatment for diabetes within 6 weeks of enrolment, except for TZD (a single oral anti-diabetic agent or two agents with less than half of the approved maximal dose for each agent) need a 6-week wash-out period before a 4-week placebo lead-in period.

Subjects who have inadequate glycemic control (HbA1c ≥6.5% but ≤10%) on diet and exercise alone at Visit 5 (1 week before randomization) are eligible to be randomised at Visit 6.

The study consists of three treatment arms: dapagliflozin 5 mg, 10 mg and placebo.

The study design is shown in Figure 1.

Figure 1 Study flow chart



E: Enrolment, R: Randomization

* Wash-out period is applicable only for subjects with ongoing anti-diabetic treatment at enrolment. Drug-naive subjects skip the period and directly proceed to Placebo Lead-in period.

3.1.1 Screening Period (2 weeks)

Subjects who are treatment-naïve (see Inclusion criteria No.4) are required to have HbA1c ≥6.5% but ≤10% and meet all inclusion and exclusion criteria at Visit 1.

Subjects who are under ongoing medical treatment for diabetes within 6 weeks of enrolment, except for TZD (single oral anti-diabetic agent or two agents with less than half of the approved maximal dose for each agent) (see Inclusion criteria No.4) are required to have HbA1c ≤8.0% at Visit1 and meet all inclusion and exclusion criteria. Subjects treated with TZD within 6 months prior to enrolment are not eligible for this study.

If the subjects have FPG>240 mg/dL at Visit 1, the subjects are withdrawn from the study.

3.1.2 Wash-out Period (6 weeks, it is applicable exclusively for subjects receiving anti-diabetic agent)

Subjects, who are treatment-naïve or previously treated with anti-diabetic agents but have not been treated within 6 weeks of enrolment (see Inclusion criteria No.4), can skip wash-out period and proceed to the lead-in period.

The subjects who received ongoing medical treatment for diabetes within 6 weeks of enrolment, except for TZD (a single oral anti-diabetic agent or two agents with less than half of the approved maximal dose for each agent) (see Inclusion criteria No.4) should have a 6-week washout period before a placebo lead-in period (10-week washout before randomization).

Washout means to stop taking oral anti-diabetic agent(s). Subjects will receive dietary counseling according to nutritional recommendations consistent with Japan Society of Diabetes or similar guidelines. Also, subjects will be given a blood glucose meter and diary, and be instructed on its use by site personnel.

If the subjects have FPG >240 mg/dL at Visit 2 or 3, the subjects are withdrawn from the study.

3.1.3 Single-blind, Dietary and Exercise Placebo Lead-in Period (4 weeks)

Eligible subjects are enrolled in a 4-week placebo lead-in period, while diet and exercise instruction will be provided and placebo tablets will be taken.

Subjects will receive dietary counseling from the investigators according to nutritional recommendations consistent with Japan Society of Diabetes or similar guidelines. Subjects who are treatment-naïve or previously treated with anti-diabetic agents but have not been treated within 6 weeks of enrolment (see Inclusion criteria No. 4) (skipped wash-out period) will be given a blood glucose meter and diary, and be instructed on its use by site personnel.

If the subjects have FPG >240 mg/dL at Visit 4 or 5, the subjects are withdrawn from the study.

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 Lead in Period.

Subjects who have inadequate glycemic control (HbA1c ≥6.5% but ≤10%) on diet and exercise alone at Visit 5 (1 week before the start of the treatment period) and who meet the eligibility criteria are eligible to entry into the double-blind randomized period at Visit 6.

3.1.4 Double-blind Placebo-controlled Treatment Period (24 weeks)

Subjects randomized (1:1:1) to 1 of 3 treatment groups (dapagliflozin 5 mg, 10 mg and placebo).

Either gender needs to be 40% or higher of total number of randomised subjects. Also, the proportion of subjects with HbA1c ≥6.5% but ≤7% at Visit 5 needs to be at most approximately 25% of the total number of randomised subjects.

After the randomization visit, subjects will be followed up at Visit 7 (Week 1) and then at the subsequent visits at 4-week intervals between Visit 6 (Week 0) and Visit 13 (Week 24).

3.1.4.1 Rescue Treatment

Subjects with inadequate glycemic control based on glycemic criteria as outlined in Table 1 can remain in the study and can receive rescue therapy with metformin following Japanese local regulation and treatment guideline. In case of intolerability, contraindication or hypersensitivity to metformin or in case of eGFR<60 ml/min, glymepiride can be used as rescue therapy. In case of inappropriateness of using both metformin and glymepiride, subjects will be withdrawn from this study. If glycemic control is not improved by the rescue therapy, the investigators can consider the discontinuation of the study after consulting with study delivery physician of AZKK.

During Visit 10 (Week 12) to Visit13 (Week 24), if the results of FPG at the visit show more than 200 mg/dL twice in a row, the investigator consider to start rescue treatment.

Table 1 Criteria for initiation of rescue therapy during the randomised treatment period

Period	Central Laboratory FPG
From Visit 10 (Week 12) to Visit 13 (Week 24)	FPG >200 mg/dL (twice in a row [a])

a During Visit 10 to 13, if the results of FPG at the visit show more than 200 mg/dL, the investigators should set up acting visit at some other day in order to recheck the FPG at central laboratory. If the results of FPG show more than 200 mg/dL consecutively at this second visit, the investigators can consider to start rescue treatment.

3.1.5 Follow-up period (3weeks)

Subjects will stop taking investigational products at Visit 13 (Week 24) and will be re-evaluated 3 weeks later for AEs and laboratory parameters. Subjects who discontinue study medication during the treatment period will also be re-evaluated 3 weeks later for AEs and laboratory parameters. Open-label use of anti-diabetic agents are permitted during the follow-up period.

Table 2 Study plan

	Screening Period	Wash-out Period [a]		Lead-in Period		Double-blind, Placebo-controlled Treatment Period								Follow-up Period
Procedure	**Wk -12 or Wk -6 [a]**	**Wk -10**	**Wk -7**	**Wk -4**	**Wk -1**	**Wk 0**	**Wk 1 [b]**	**Wk 4 [b]**	**Wk 8 [b]**	**Wk 12 [b]**	**Wk 16 [b]**	**Wk 20 [b]**	**Wk 24**	**Wk 27**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Visit window (days)	+7	**±3**	**±3**	**±3**	**±3**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Eligibility Assessments														
Informed Consent	X													
Review Inclusion/Exclusion Criteria or Randomization Criteria	X	X	X	X	X	X								
Randomisation						X								
Complete Medical History	X													
Complete Physical Examination	X			X		X							X	
Brief Physical Examination		X	X				X	X	X	X	X	X		X
Vital Signs, Body Weight	X			X		X	X	X	X	X	X	X	X	X
Height	X													
Orthostatic Blood pressure						X	X	X	X				X	X
BMI	X					X							X	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
General														
Dietary/exercise instruction/review		X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Glucose Meter, diary and provide instructions		X	X	X	X	X	X	X	X	X	X	X	X	

Table 2 Study plan

	Screening Period	Wash-out Period [a]		Lead-in Period		Double-blind, Placebo-controlled Treatment Period								Follow-up Period
Procedure	**Wk -12 or Wk -6 [a]**	**Wk -10**	**Wk -7**	**Wk -4**	**Wk -1**	**Wk 0**	**Wk 1 [b]**	**Wk 4 [b]**	**Wk 8 [b]**	**Wk 12 [b]**	**Wk 16 [b]**	**Wk 20 [b]**	**Wk 24**	**Wk 27**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Visit window (days)	+7	**±3**	**±3**	**±3**	**±3**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Safety Assessments														
AE Assessment				X	X	X	X	X	X	X	X	X	X	X
SAE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycemic Events Assessment				X	X	X	X	X	X	X	X	X	X	X
Laboratory Tests														
Pregnancy Test (urine) (WOCBP only)	X			X		X	X	X	X	X	X	X	X	X
Standard Safety Laboratory Panel (Blood and urine)	X			X		X	X	X	X	X	X	X	X	X
HbA1c	X				X	X		X	X	X	X	X	X	X
FPG	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting Insulin, C-peptide	X					X			X		X		X	
Glycoalbumin	X					X		X	X	X	X	X	X	
Spot urine collection for glucose, sodium and creatinine	X					X			X		X		X	
Fasting serum lipids: TC, LDL-C, HDL-C, TG, and FFA						X							X	
Hepatitis Screen Panel [c], TSH, and PT/PTT	X													
Cystatine C						X							X	
Parathormome (PTH)						X							X	X

Table 2 Study plan

	Screening Period	Wash-out Period [a]		Lead-in Period		Double-blind, Placebo-controlled Treatment Period								Follow-up Period
Procedure	**Wk -12 or Wk -6 [a]**	**Wk -10**	**Wk -7**	**Wk -4**	**Wk -1**	**Wk 0**	**Wk 1 [b]**	**Wk 4 [b]**	**Wk 8 [b]**	**Wk 12 [b]**	**Wk 16 [b]**	**Wk 20 [b]**	**Wk 24**	**Wk 27**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Visit window (days)	+7	**±3**	**±3**	**±3**	**±3**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Clinical Drug Supplies														
Dispense Study Medication				X		X		X	X	X	X	X		
Review Medication Compliance					X	X	X	X	X	X	X	X	X	

FFA:free fatty acid, TSH:thyroid stimulating hormone, PT: prothrombin time, PTT: partial thromboplastin time, WOCBP: Women of child bearing potential

a Wash-out period is applicable only for subjects with ongoing treatment with anti-diabetic agents. For treatment-naïve subjects, screening period is Week -6 to -4.

b Subjects not completing the treatment period should complete the procedures described for Visit 13 within 7 days after discontinuation. These subjects should also complete the procedures described for a follow-up visit (ie, Visit 14) three weeks after discontinuation of investigational product.

c Includes anti-HAV (IgM, IgG), HBsAg, anti-HBc (igG, IgM) and anti-HCV.

3.2 Rationale for study design, doses and control groups

3.2.1 Study design and regulatory requirement

The current study is designed to demonstrate the efficacy and safety of dapagliflozin versus placebo in Japanese subjects of T2DM who have inadequate glycemic control with diet and exercise.

Placebo lead-in period is set to remove any bias regarding placebo effect. Subjects who received ongoing medical treatment for diabetes within 6 weeks of enrolment, except for TZD (single oral anti-diabetic agent or two agents with less than half of the approved maximal dose for each agent) 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.

(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 except for TZDs prior to randomization of subjects to dapagliflozin versus placebo treatment arms in this study.

The Follow-up period is set to examine the reversibility of potential AE and laboratory values after taking the last dose.

This study has standard design features for a confirmatory Phase III diabetes study (eg, multi-centre, randomised, double-blind, parallel group) and incorporates the relevant features of the Japanese Guideline on Clinical Evaluation methods on Oral Hypoglycemic Agents which was issued 9th July 2010 with regard to duration of treatment, choice of study population, and choice of outcome variables.

3.2.2 Study doses and control groups

Control group

This is a placebo-controlled study.

Dapagliflozin

Results of pre-clinical pharmacokinetic and toxicology studies support the safety of conducting a Phase III clinical development program for dapagliflozin. In Phase I clinical pharmacology studies (single ascending-dose study in healthy Japanese subjects and 2-week multiple ascending-dose study in Japanese subjects with T2DM), dapagliflozin was safe and well tolerated with favourable pharmacokinetic and pharmacodynamic profile. A Japan Phase IIb study in subjects with T2DM demonstrated good glycemic efficacy and acceptable safety profile over a dose range from 1 mg to 10 mg. In addition, 5 mg and 10 mg of dapagliflozin showed clinically relevant effect on HbA1c (>0.5% placebo corrected reduction) over 12 weeks. Based

on considerations of efficacy, pharmacodynamic, and safety data from the Phase I and II programs, doses of 5 mg and 10 mg of dapagliflozin have been chosen for the Phase III studies.

3.2.3 Choice of outcome variables

In the Japanese Guideline on Clinical Evaluation methods on Oral Hypoglycemic Agents, HbA1c is the prescribed measure for determination of glycemic control and is therefore chosen as the primary variable. Certain secondary variables have been selected for additional assessment because of their clinical relevance and importance. Outcome variables related to body weight and BP changes will be investigated considering dapagliflozin's novel insulin independent mechanism of action that leads to loss of glucose and associated calories in urine along with a diuretic effect.

3.2.4 Choice of study population

Age

The prevalence of T2DM increases with age; it is therefore important to assess the safety of anti-diabetic agents in elderly subjects. In this study there is no upper age limit for subjects.

HbA1c

The HbA1c inclusion criterion at randomisation was selected to include patients with a wide range of glycemic control. The lower limit of this range (ie, 6.5%) reflects the suggestion of the International Expert Committee, which was based on the results of DETECT2 study (Gillett MJ, 2009). The upper limit of this interval (ie, 10%) was chosen because insulin is generally the treatment of choice for patients with HbA1c values above this level (ADA 2009). To avoid potential bias in the subject characteristics which may be caused by excessive randomisation of subjects with low level of HbA1c, a limitation was added to the inclusion criterion, ie, randomisation of subjects for each arm with HbA1c ≥6.5% but ≤7% was limited to at most approximately 25%. The measurement of HbA1c is National Glycohemoglobin Standardization Program (NGSP).

Pregnancy or breastfeeding

Data from rat pre- and postnatal development and juvenile toxicity studies indicate that direct administration of dapagliflozin to weanling juvenile rats and indirect exposure during late pregnancy are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny, although the long-term functional consequences of these effects are unknown. Dapagliflozin has not been tested in pregnant women and the risks to embryo, foetus, and infant are unknown. For this reason, women who are pregnant or breastfeeding are excluded and women of childbearing age are instructed to take precautions to avoid becoming pregnant during the study.

Other

The purpose of the majority of the inclusion and exclusion criteria is to limit confounding factors that may complicate the interpretation of the study results (eg, corticosteroid-induced diabetes,

haemoglobinopathies that would interfere with the HbA1c analyses) or to exclude subjects whose safety could be compromised by participation in the study.

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. Diagnosis of type 2 diabetes

3. Men or women age ≥20 years old (Either gender needs to be 40% or higher of total number of treated subjects)

   Women not of childbearing potential (postmenopausal, and/or have undergone hysterectomy and/or bilateral oophorectomy or salpingectomy/tubal ligation) or women of childbearing potential who comply with the following:

   – Use a highly effective method of birth control to avoid pregnancy throughout the study and for up to 4 weeks after the study

   – Have a negative urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin (HCG) within 72 hours prior to the start of study medication and at each visit

   Women will be defined as postmenopausal if last menstruation period was >1 year ago and serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) are within the postmenopausal range, or if age >50 years and with last menstruation period >2 years ago.

4. Current condition at enrolment (Visit 1)

   - Drug naïve defined as:

     - Never received medical treatment for diabetes (insulin and/or other anti-diabetic agents [oral or injection])

       OR

- Received medical treatment for diabetes for less than 30 days since diagnosis. In addition, during the 30-day period prior to screening did not receive oral anti-diabetic agents 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 screening (with the exception of insulin therapy during a hospitalization for other causes or use in gestational diabetes)

OR

- Previously received medical treatment for diabetes but have not been treated within 6 weeks of enrolment

OR

- Ongoing medical treatment for diabetes within 6 weeks of enrolment, except for TZD (single oral anti-diabetic agent or two agents with less than half of the approved maximal dose for each agent)

5. HbA1c (The proportion of randomised subjects with HbA1c ≥6.5% but ≤7% at Visit 5 needs to be at most approximately 25%.):

   - At enrolment (Visit 1):
     - ≥6.5% and ≤10% for patients with drug naïve
     - ≤8% for patients with ongoing treatment
   - At Week -1 (Visit 5) for randomization:
     - ≥6.5% and ≤10% for all patients

6. Subject must demonstrate good compliance with study medication (≥80% and ≤120%) during Lead in period.

4.2 Exclusion criteria

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

Endocrine and metabolic disorders

1. Diagnosis of Type 1 diabetes mellitus, known diagnosis of maturity onset diabetes of the young (MODY) or secondary diabetes mellitus

2. History of diabetic ketoacidosis

3. Symptoms of poorly controlled diabetes including, but not limited to, marked polyuria, polydipsia, and/or greater than 10% weight loss during the 3 months prior to enrolment

4. FPG >240 mg/dL (Visit 1, 2, 3, 4 and 5)

5. BMI ≥45.0 kg/m^2 at Visit 1

6. History of bariatric surgery (ie, any surgery to treat obesity; for example, gastric banding or procedures that involve bypassing or transposing sections of the small intestine). History of liposuction is allowed.

7. Diabetes insipidus

8. Thyroid-stimulating hormone (TSH) values outside normal range at Visit 1. An abnormal TSH value needs to be followed up with a free T4 test. Subjects with abnormal free T4 values will be excluded. Subjects with an elevated TSH and normal free T4 will be allowed if referred to their family doctor for thyroid hormone replacement therapy prior to randomization

Kidney disorders

9. eGFR: <45 mL/min (calculated by Japanese guideline formula) or a measured serum creatinine (SCr) value of >1.5 mg/dL (133 μmol/L) for male subjects and >1.4 mg/dL (124 μmol/L) for female subjects at Visit 1.

10. Urine albumin: creatinine ratio (UACR) >1800 mg/g (>203.4 mg/mmol) at Visit 1

11. History of unstable or rapidly progressing kidney disease

12. Familial renal glucosuria. This condition is diagnosed as glucosuria (glucose >1 mmol/L urine) in the presence of normoglycemia in a patient without the diagnosis of diabetes mellitus

Hepatic disorders

13. Severe hepatic insufficiency and/or significant abnormal liver function defined as aspartate aminotransferase (AST) >3X upper limit of normal (ULN) and/or alanine aminotransferase (ALT) >3X ULN at Visit 1

14. Total bilirubin (TB) >2.0 mg/dL (>34.2 μmol/L) at Visit 1

15. Positive serologic evidence of current infectious liver disease including Hepatitis A viral antibody IgM, Hepatitis B surface antigen and Hepatitis C virus antibody at Visit 1

16. History of drug-induced liver enzyme elevation

17. History of severe hepatobiliary disease or hepatotoxicity with any medication

Cardiovascular disorders

18. Congestive heart failure defined as New York Heart Association (NYHA) class IV, unstable or acute congestive heart failure. Note: eligible subjects with congestive heart failure, especially those who are on diuretic therapy, should have careful monitoring of their volume status throughout the study.

19. Significant cardiovascular history within the past 2 months prior to enrolment, defined as: myocardial infarction, unstable angina pectoris, transient ischemic attack, unstable or previously undiagnosed arrhythmia, cardiac surgery or revascularization (coronary angioplasty or bypass grafts), or cerebrovascular accident. In addition, subjects who have unstable cardiovascular disease at enrolment in the judgment of the investigators are excluded from the study.

20. SBP ≥160 mmHg and/or DBP ≥100 mmHg at Visit 1

Hematologic/oncologic disorders/conditions

21. Haemoglobin <10 g/dL (<100 g/L) for men; haemoglobin <9 g/dL (<90 g/L) for women at Visit 1

22. History of chronic haemolytic anaemia or haemoglobinopathies (for example, sickle cell anaemia, thalassemia, sideroblastic anaemia)

23. Iron deficiency anemia with iron therapy started in the past 12 weeks prior to enrolment, or a recent diagnosis of iron deficiency anemia that requires therapeutic management within the next 6 months in the judgement of the investigators

24. Donation or transfusion of blood, plasma, or platelets within the past 3 months prior to enrolment

25. History of malignancy within the last 5 years prior to enrolment, excluding successful treatment of basal or squamous cell skin carcinoma

Infectious disease/immunologic disorders

26. Known immunocompromised status, including subjects who have undergone organ transplantation

Musculoskeletal disorders

27. Creatinine Kinase (CK) >3X ULN at Visit 1

28. History of drug-induced myopathy or drug-induced CK elevation

Reproductive status

29. Pregnant or breastfeeding patients

Prohibited medications

30. Treatment with TZD within 6 month prior to enrolment

31. Use of weight loss medication, including but not limited to mazindol, sibutramine, phentermine, orlistat, rimonabant, benzphetamine, diethylproprion, methamphetamine, and/or phendimetrazine, within 30 days prior to enrolment

32. Treatment with systemic glucocorticoids equivalent to oral prednisolone ≥10 mg (betametasone ≥1.2 mg, dexamethasone ≥1.5 mg, hydrocortisone ≥40 mg) per day within 30 days prior to enrolment; single systemic doses, topical and inhaled corticosteroids are allowed

33. Treatment with unstable doses of teriparatide, bisphosphonates and/or calcitonin within 30 days prior to enrolment

34. Treatment for Human Immunodeficiency Virus (HIV) and/or use of antiviral drugs (delavirdine, indinavir, nelfinavir, ritonavir, saquinavir)

Other

35. Intolerance, contraindication or potential allergy or hypersensitivity to dapagliflozin

36. Intolerance, contraindication or potential allergy or hypersensitivity to both metformin and glymepiride

37. Any clinically significant abnormality identified on physical examination, ECG or laboratory tests, which in the judgement of the investigator would compromise the subject's safety or successful participation in the clinical study

38. Sibjects who, in the judgement of the investigators, may be at risk for dehydration

39. Acute or chronic metabolic acidosis

40. History of alcohol abuse or illegal drug use within the past 12 months prior to enrolment

41. Involvement in the planning and conduct of the study (applies to both AstraZeneca and Bristol-Myers Squibb staff or staff at the study centre)

42. Previous enrolment or randomisation to treatment in the present study

43. Previous participation in a clinical study with dapagliflozin (BMS-512148) in which the subject received at least one dose of study medication except for placebo

44. Participation in another clinical study during the last 1 month prior to enrolment

Procedures for withdrawal of incorrectly enrolled subjects see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

- Subjects must be in a fasting state at least 10 hours prior to study visit (however, drinking water is allowed). Permitted medications may be taken with water only.
- Subjects must abstain from tobacco for 12 hours prior to all study visits.
- Subjects must make every attempt to adhere to the dietary and physical activity changes and goals as discussed with the Investigator(s).
- 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.
- The subjects should not take investigational products on the morning of the clinic visit.

If a subject arrives for a visit without having followed the above instructions, the entire visit should be rescheduled (within the allowed time-window, if possible).

As up to approximately 201 mL of blood will be drawn from each subject during the entire duration of the clinical study, subjects should be instructed to abstain from donating any blood during the clinical study and for 3 months following their last study visit.

Prohibited and restricted concomitant medications are listed in Section 5.6.

5.2 Subject enrolment and randomisation

Procedures for enrolment

The Principal Investigator will:

1. Obtain signed informed consent from the potential subject before any study specific procedures are performed.
2. Perform enrolment call in Interactive Web Response System (IWRS).
3. Assign potential subject a unique enrolment number “E43XXYYY”, which is composed of 4 digits (43XX) of centre number and 3 digits (YYY) of consecutive number in order of enrolment registration at each study site.
4. Determine subject eligibility. See Sections 4.1 and 4.2.
5. Perform drug allocation call for assigning Placebo Lead-In at Visit 4 in IWRS.

Routines for this will be described in the IWRS user manual that will be provided to each centre.

Procedures for randomisation

The randomisation list will be generated at AstraZeneca using the global randomisation system (GRand). The randomization will be done in balanced blocks and stratified according to gender (male, female) and HbA1c at Visit 5 category (≥6.5% and ≤7%, >7% and ≤10%).

Assign eligible subjects with a unique randomisation code (patient number) through IWRS at Visit 6. (Randomisation codes will be assigned strictly sequentially as subjects become eligible for randomisation.)

Routines for this will be described in the IWRS user manual that will be provided to each centre.

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

Randomisation codes will be assigned strictly sequentially as subjects become eligible for randomisation.

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

Medication will be labeled using a unique material pack code which is linked to the randomization scheme. The Centralized Registration/ Randomization Center will assign the bottle of study material to be dispensed to each subject according to Table 5. Each dose will be identical and presented in the same packaging to ensure blinding of the medication.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised subject, will be available to the investigator(s) or pharmacists from the IWRS. Routines for this will be described in the IWRS user manual that will be provided to each centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomisation. The investigator

documents and reports the action to AstraZeneca, without revealing the treatment given to subject to the AstraZeneca staff.

AstraZeneca retains 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 or their designee. For details of the identity of the investigational product see below.

Table 3 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
BMS-512148 tablet 5 mg	Contains 5 mg of dapagliflozin and Green, plain diamond shaped, film coated tablet	Bristol-Myers Squibb Company
BMS-512148 tablet 10 mg	Contains 10 mg of dapagliflozin and Green, plain diamond shaped, film coated tablet	Bristol-Myers Squibb Company
BMS-512148 tablet 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 2 tablets according to Table 4. Investigational drug should be taken once daily in the morning.

Table 4 Composition of dose and number of tablets :

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

Table 5 Drug Dispensing Scheme

Visit ID	1	2	3	4	5	6	7	8	9	10	11	12
Number of bottles to dispense dapagliflozin 5 mg, 10 mg and/or matching placebo	0	0	0	2 (Placebo Lead-in)	0	2	0	2	2	2	2	2

5.5.3 Additional study drug – Not applicable

5.5.4 Labelling

Labelling of the investigational product will be carried out by AstraZeneca or Contract Research Organisation (CRO) in accordance with current Good Manufacturing Practice (GMP). Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling and text will be translated into local language. Details of labelling and packaging of the study drug will be described in a separate document, 'Procedure of storage conditions for investigational product'.

5.5.5 Storage

All study drugs should 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.

5.6 Concomitant and post-study treatment(s)

Changes in concomitant medication should be avoided during study participation, with the exception of situations defined in this protocol, but medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the investigators, who must decide if the subject should remain in study or need to be dismissed from study due to subject's safety or interference with study objectives.

The administration of all medication must be recorded in the appropriate sections of the electronic case report form (eCRF) with trade names, dosages, dates of starting and ending of medication and reason for therapy.

After having completed or discontinued the study, subjects will receive usual care and anti-diabetic agents according to the investigator's judgement and according to local medical practice.

Prohibited Therapies

- Weight loss medication, including but not limited to mazindol, sibutramine, phentermine, orlistat, rimonabant, benzphetamine, diethylproprion, methamphetamine, and/or phendimetrazine
- Antiviral drugs (delavirdine, indinavir, nelfinavir, ritonavir, saquinavir)

- Treatment with systemic glucocorticoids equivalent to oral prednisolone ≥10 mg (betametasone ≥1.2 mg, dexamethasone ≥1.5 mg, hydrocortisone ≥40 mg) per day (two temporary periods of higher daily doses for no longer than 7 days each are allowed).

- Anti-diabetic agents except for the study medication and rescue therapies (Anti-diabetic agents planned to be stopped for wash-out are allowed to be used until the beginning of wash-out period. After completion of the treatment period, alternative anti- diabetic treatment will be initiated according to standard medical practice.)

Restricted Therapies

- Insulin use is permitted in the following cases:

  – For up to 14 days total during the study and up to 7 continuous days if subjects are unable to take oral medications (for example during a gastrointestinal illness)

  – For up to 14 days total during the study and up to 7 continuous days if there is a documented illness or infection that requires additional therapy for maintaining glycemic control

  – For up to 14 days total during the study and up to 7 continuous days if subjects have to temporarily stop investigational product and rescue therapies due to requirements of this clinical study protocol.

  – For up to 7 days during hospitalisation as long as the primary reason for hospitalisation is not management of the subject's glycemic control.

- Teriparatide, bisphosphonates and/or calcitonin are allowed if only the dose has not changed within 30 days prior to enrolment)

5.7 Treatment compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the eCRF.

Subjects will be asked to return all unused investigational product and empty packages and bottles to the clinic at each visit. The subject will be asked about compliance at each study visit; compliance will also be assessed based on returned tablet counts. Tablet counts will be recorded in the eCRF. Subjects judged to be non-compliant (defined as taking less than 80% or more than 120% of the prescribed dose of investigational product) may continue in the study, but should be counselled on the importance of taking their study medication as prescribed.

5.7.1 Accountability

Study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The Investigational Product Storage Manager is responsible for managing the study drug from receipt by the institution until the return of all unused study drug

to AstraZeneca. AstraZeneca will provide the study documents 'Procedures for drug accountability' and 'Procedures for drug storage' which describes the specific requirements. The investigator(s) is responsible for ensuring that the subject has returned all unused study drug.

5.8 Discontinuation of investigational product

Subjects who discontinue study medication during the treatment period will be performed the procedures scheduled at Visit 13 (Week 24) and will be re-evaluated 3 weeks later for AEs. Open-label use of anti-diabetic agents are permitted.

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:

General discontinuation criteria:

1. Voluntary discontinuation by the subject who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment

2. Risk to subjects as judged by the investigator, AstraZeneca and/or Bristol-Myers Squibb

3. Severe non-compliance to protocol as judged by the investigator, AstraZeneca and/or Bristol-Myers Squibb

4. Incorrectly enrolled subjects (See Section 5.3)

5. Subject lost to follow-up defined by inability to reach the subject after 3 documented phone calls, faxes, or emails. All attempts at contact should be documented in the subject's medical record.

6. AE, ie, any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject

Study-specific discontinuation criteria:

7. Use of (need for) any anti-diabetic agents, except for rescue treatment, other than investigational product.

8. Treatment with systemic glucocorticoids equivalent to oral prednisolone ≥10 mg/day (two temporary periods of higher daily doses for no longer than 7 days each are allowed)

9. Major and/or frequent hypoglycemic events; If more than one event of severe hypoglycemia, defined as symptomatic events requiring external assistance due to severe impairment in consciousness or behaviour, with a capillary or plasma glucose value <3 mmol/L (<54 mg/dL), and prompt recovery after glucose or glucagon

administration occurs, or if the investigators decides that current treatment poses the subject at risk of either repeated hypoglycemic events or severe hypoglycemia.

10. Pregnancy confirmed by a positive pregnancy test or otherwise verified

11. Change in kidney function (see Appendix F for further guidance):

- For subjects treated with metformin: For subjects with a central laboratory eGFR <60 mL/min or with an increase in SCr of ≥0.5 mg/dL (44.2 µmol/L) above the baseline value (Visit 6), an increase in SCr of ≥0.5 mg/dL above the baseline value (Visit 6) confirmed by a repeated measurement within one week or eGFR <60 mL/min

- For subjects not treated with metformin: Subject with following criteria will be scheduled for an additional visit within one week.

  (a) eGFR <45 ml/min

  (b) Subjects with baseline creatinine ≥1.4 mg/dL (≥123 µmol/L) an absolute increase in SCr of ≥1.0 mg/dL (≥88 µmol/L), or

  (c) Subjects with baseline creatinine <1.4 mg/dL (<123 µmol/L) an absolute increase in SCr of ≥0.5 mg/dL (≥44 µmol/L).

  Subjects should be discontinued from study if the repeat laboratory tests meet SCr ≥0.5 mg/dL or eGFR <45 mL/min.

12. Subjects with a central laboratory CK >10X ULN will be scheduled for an additional visit within 24 hours, but not exceeding 72 hours. Subjects should be discontinued from study if the repeat laboratory tests meet CK >10X ULN.

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

  (a) ALT and/or AST are >3X ULN and TB>1.5X ULN

  (b) ALT and/or AST are >5X ULN for ≥14 consecutive days, at any time after initial confirmatory results

  (c) ALT and/or AST are >8X ULN.

14. Serum Sodium ≤125 mmol/L with or without symptoms (see Appendix E 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 AEs. The Principal Investigator/sub-investigator 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. AEs will be followed up (See Sections 6.4.3 and 6.4.4); diary, glucometer and study drug should be returned by the subject.

Randomised subjects

Randomised subjects who discontinue the study treatment before Week 24 should return and complete the procedures described for Visit 13 as soon as possible but at the latest 7 days after discontinuation. These subjects should also be scheduled for a follow-up visit (ie, procedures of Visit 14) three weeks after discontinuation of investigational product. In addition subjects who discontinue the study due to an AE including a laboratory abnormality should be followed by the investigator until the event has been resolved or stabilised.

After discontinuation of investigational product alternative anti-diabetic treatment will be initiated according to the investigator's judgement and according to local medical practice.

Subjects with an increased CK >10X ULN will have their investigational product held and repeated CK test preferably within 24 hours, but not exceeding 72 hours. If repeated CK is still >10X ULN the subject should permanently discontinue all study medication and be withdrawn from the study (in which case an Adverse Event must be reported). Otherwise investigational product may be resumed unless otherwise contraindicated.

Subjects with increased liver function tests as defined in Section 5.8.1 under listing No.13 will be scheduled for a follow-up visit within 3 days following the receipt of the result. Subjects may remain on study medication until the confirmatory results are obtained. If repeat liver function tests still are increased as outlined in Appendix G the subject should permanently discontinue study medication and be withdrawn from the study (see Appendix G for further guidance).

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 AEs. If possible, they will be seen and assessed by an investigator. AEs will be followed up (See Sections 6.4.3 and 6.4.4); diary, glucometer and all study drugs should be returned by the subject.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRF as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness and timeliness of the data recorded and of the provision of answers to data queries. The investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site.

The Principal Investigator/sub-investigator will record data on the observations, tests and assessments specified in the protocol on the eCRFs provided by AstraZeneca. The eCRF will be accompanied with 'Instructions for the Investigator', which should be followed. These instructions provide guidance for the recording of study data in the eCRF including how to change data incorrectly recorded.

6.2 Data collection and enrolment

For full details please see the study plan (Table 2).

6.2.1 Follow-up procedures

A follow-up (Visit 14) will be performed 3 weeks (±3 days) after the end of the double-blind treatment period, see Table 2 for further details.

6.3 Efficacy

6.3.1 Efficacy laboratory variables

The laboratory parameters that will be measured to assess efficacy are displayed in Table 6 by visit. The results from baseline and onwards will not be reported to the investigator unless FPG value is above 270 mg/dL (15 mmol/L) from Week 0 (Visit 6) to Week 4 (Visit 8), above 240 mg/dL (13.2 mmol/dL) from Week 4 (Visit 8) to Week 12 (Visit 10) and above 200 mg/dL (11.1 mmol/L) from Week 12 (Visit 10) to Week 24 (Visit 13), except for TC, HDL-C, LDL-C and TG which will be reported.

Table 6 Efficacy laboratory variables

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Study week	**-12 or -6**	**-10**	**-7**	**-4**	**-1**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**27**
HbA1c	X				X	X		X	X	X	X	X	X	X
FPG	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Insulin	X					X			X		X		X	
C-peptide	X					X			X		X		X	
Glycoalbumin	X					X		X	X	X	X	X	X	

Table 6 Efficacy laboratory variables

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Study week	-12 or -6	-10	-7	-4	-1	0	1	4	8	12	16	20	24	27
TC						X							X	
LDL-C						X							X	
HDL-C						X							X	
TG						X							X	
FFA						X							X	

6.3.2 HbA1c

HbA1c is the primary assessment for the determination of glycemic efficacy accepted referred by the Japanese Guideline on Clinical Evaluation methods on Oral Hypoglycemic Agents. HbA1c will be analysed by a central laboratory according to the procedures described in the Laboratory Manual which will be distributed to each study site during site initiation. The measurement of HbA1c is NGSP.

6.3.3 FPG

FPG is a well established measure of glycemic efficacy and considered to be an acceptable secondary endpoint.

6.3.4 Weight and height

The subject's weight will be recorded in kilogram (kg) to one decimal place, on a fasting stomach with light clothing and no shoes. The subject's height will be recorded in centimetres, with no shoes. All readings should be recorded as accurately as possible and the same scale should be used for all assessments for a given subject.

6.3.5 BMI

BMI is a calculated ratio between weight and height (weight / height^2, where weight is measured in kg, and height in metres) and will be computed by AstraZeneca.

6.3.6 Blood pressure

As BP is both an efficacy and safety variable in this study, measurement of BP is described in Sections 6.4.8.1 and 6.4.8.2.

6.3.7 Waist circumference

The waist circumference 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 a normal inspiration.

6.3.8 Glycoalbumin

Glycoalbumin is a well established measure of glycemic efficacy and considered to be an acceptable secondary endpoint.

6.4 Safety

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

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.

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

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.

6.4.2 Definitions of serious adverse event

A SAE 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-subject hospitalisation or prolongation of existing hospitalisation (including hospitalisation for tests related to AEs), except hospitalisation that has been planned before enrolment
- 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.
- Cancer
- Drug Dependency/ abuse

- 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

AEs will be collected from the start of the placebo lead-in period (Visit 4 to 5) throughout the treatment period (Visit 6 to 13) and including the follow-up period (Visit 14).

SAEs will be recorded from the time of informed consent is obtained until the end of the study (Visit 14).

Follow-up of unresolved adverse events

Any AEs that are unresolved at the end of the study (Visit 14) or at discontinuation visit in the study 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.

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.

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 subject 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 a 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 a SAE.

Causality collection

The Investigator will assess causal relationship between Investigational Product and each AE, 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?’

For SAEs causal relationship will also be assessed for other medication and study procedures and additional study drug (rescue 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 subject or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. 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 or are the reason for discontinuation of treatment with the investigational product, or require the subject 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 or ECG evaluation 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).

Hypoglycemic events

A separate section in the eCRF will be used to document all reported episodes of hypoglycemia (See Section 6.4.9). Hypoglycemic episodes should only be reported on the AE eCRF page if the event fulfils protocol criteria for a SAE (See Section 6.4.2). In this case, an SAE must be reported in addition to the hypoglycemia eCRF pages for hypoglycemia.

Follow-up of unresolved adverse events

All AEs and SAEs, including those that are ongoing at the end of the study or at discontinuation, will be followed up until resolution or until the Investigator decides that no further follow-up is necessary. AstraZeneca retains the right to request additional information for any subject with ongoing AEs/SAEs at the end of the study, if judged necessary. The requirement to follow-up is not intended to delay database lock or production of the clinical study report. Both these activities should proceed as planned with ongoing AEs if necessary.

Any follow-up of ongoing SAEs after database lock will be reported to AstraZeneca, who will notify the appropriate Bristol-Myers Squibb Pharmacovigilance contact.

Cardiovascular events

Cardiovascular events will be monitored in the study population and an independent cardiovascular adjudication committee will review events. Cardiovascular events will be analyzed in conjunction with cardiovascular events observed in other Phase II and Phase III dapagliflozin studies and reported separately.

6.4.4 Reporting of serious adverse events

Investigators and other study site personnel must inform appropriate AstraZeneca representatives via the WBDC system of any SAE that occurs in the course of the study within 1 calendar day (ie, 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 with the same time frame.

The AstraZeneca representative will work with the investigator to compile all the necessary information and ensure that all the necessary information is provided to Bristol-Myers Squibb Global Pharmacovigilance and Epidemiology within one calendar day of initial receipt for fatal and life threatening events and within three calendar days of initial receipt for all other SAEs.

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF. SAEs will be recorded from the time of informed consent.

The investigator and/or Sponsor are responsible for informing the Ethics Committee (EC) about the SAE as per local requirements. Reporting of SAEs to the Regulatory Authority is the responsibility of Bristol-Myers Squibb.

An automated email alert will be sent to the designated AstraZeneca representative, when the page with SAE information is saved in WBDC system by the Investigators or other site personnel. If the WBDC system is not available, then the Investigator or other study site personnel reports by fax an SAE to the appropriate AstraZeneca representative. A paper back-up SAE report is used for this purpose. 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 fax or email.

6.4.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis will be taken at the times indicated in the Study Plan (see Table 2).

The following laboratory variables will be measured. For blood volume see Section 7.1

Table 7 Safety laboratory variables

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Study week	**-12 or -6**	**-10**	**-7**	**-4**	**-1**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**27**
Haematology														
Haemoglobin	X			X		X	X	X	X	X	X	X	X	X
Haematocrit	X			X		X	X	X	X	X	X	X	X	X
Red blood cell count	X			X		X	X	X	X	X	X	X	X	X
White blood cell count and differential	X			X		X	X	X	X	X	X	X	X	X
Platelet count	X			X		X	X	X	X	X	X	X	X	X
Clinical chemistry (serum)														
AST (SGOT)	X			X		X	X	X	X	X	X	X	X	X
ALT (SGPT)	X			X		X	X	X	X	X	X	X	X	X
Alkaline Phosphatase (ALP)	X			X		X	X	X	X	X	X	X	X	X
CK	X			X		X	X	X	X	X	X	X	X	X
TB	X			X		X	X	X	X	X	X	X	X	X
Blood Urea Nitrogen (BUN)	X			X		X	X	X	X	X	X	X	X	X
Electrolytes [a]	X			X		X	X	X	X	X	X	X	X	X
Total protein	X			X		X	X	X	X	X	X	X	X	X
Albumin	X			X		X	X	X	X	X	X	X	X	X
Uric acid	X			X		X	X	X	X	X	X	X	X	X
Serum Creatinine (SCr)	X			X		X	X	X	X	X	X	X	X	X
eGFR (Japanese guideline formula) [b]	X			X		X	X	X	X	X	X	X	X	X
Serum Cystatin C						X							X	
PTH						X							X	X
TSH	X													
PT	X													
PTT	X													
Hepatitis Screen Panel [c]	X													
Urinalysis (dipstick)														
Glucose [d]	X			X		X	X	X	X	X	X	X	X	X
Blood [e]	X			X		X	X	X	X	X	X	X	X	X
Pregnancy test [f]	X			X		X	X	X	X	X	X	X	X	X
Urinalysis (spot urine)														
Creatinine	X					X			X		X		X	
Albumin	X					X			X		X		X	
UACR	X					X			X		X		X	

Table 7 Safety laboratory variables

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Study week	-12 or -6	-10	-7	-4	-1	0	1	4	8	12	16	20	24	27
Na	X					X			X		X		X	
Glucose [d]	X					X			X		X		X	

a Electrolytes: Sodium, Bicarbonate, Potassium, Chloride, Calcium, Magnesium, Phosphorus
b The eGFR will be estimated by the abbreviated Japanese guideline formula and reported by central laboratory.
c Includes anti-HAV (IgM, IgG), HBsAg, anti-HBc (igG, IgM) and anti-HCV.
d Result will be blinded after Visit 6.
e Microscopy if dipstick positive for blood
f Urine HCG pregnancy test for WOCBP (HCG minimum sensitivity of 25 IU/L) (dipstick analyzed at the study centre)

6.4.6 Physical examination

- A brief physical examination should include the cardiovascular system, lungs, abdomen, and extremities, and any organ system pertinent to the subject's signs, symptoms, or AEs. The subject should always be evaluated for the presence of oedema.

- A complete physical examination should include general appearance, head, eyes, ears, nose, throat, neck, cardiovascular system, lungs, abdomen, lymph nodes, extremities, neurological system, skin, and musculoskeletal system. The subject should always be evaluated for the presence of oedema.

Baseline data is collected at Visit 6, and new findings discovered on subsequent physical examinations should be recorded as changes from baseline.

6.4.7 ECG

Resting 12-lead ECG

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 Pulse and blood pressure

One pulse measurement will be taken after the subject has been sitting and resting for at least 5 minutes and before blood samples are taken. The pulse measurement will be followed by three BP measurements separated by 2 minutes each. All three BP readings should be recorded. At Visit 1 the seated BP will be recorded three times in both the left and the right arms. All three measurements should be made in one arm before transferring the cuff to the other arm. The arm with the highest mean seated BP readings will be the one used for all subsequent readings throughout the study. BP readings should be taken while the subject is in a comfortable seated

position with the arm supported at the level of the heart. All readings should be recorded. Ideally, BP should be measured with the same machine, at the same time of day, and by the same personnel at each visit. A standard mercury sphygmomanometer with a standardised cuff adapted to the size of the subject's arm is recommended. Oscillometric devices (such as Dynamap) may be used at sites where:

- a mercury sphygmomanometer is not available, or
- a mercury sphygmomanometer is available, but site staff is not practiced in its use
- use of mercury devices is restricted by local law.

6.4.8.2 Orthostatic blood pressure

At selected visits where orthostatic BP and pulse are collected, supine and standing measurements should be made after the seated BP and pulse measurements have been made, using the same arm that was used for the seated BP measurements. All readings should be recorded. Ideally, BP should be measured with the same machine, at the same time of day, and by the same personnel at each visit.

Supine BP and pulse

The supine BP and pulse must be measured prior to the standing BP and pulse. After the subject rests in the supine position for at least 5 minutes, supine BP and pulse will be determined from three replicate measurements obtained at least 1 minute apart. All three readings must be recorded. For study analyses, the average of the three BP and pulse readings will be used.

Standing BP and pulse

After the supine BP and pulse measurements are obtained, the subject will stand for 2 to 3 minutes. After this time, the BP will be measured with the arm supported at the level of the heart. Standing BP and pulse will be determined from three replicate measurements obtained at least 1 minute apart. All 3 readings must be recorded. For study analyses, the average of the three BP and pulse readings will be used.

6.4.9 Other safety assessments

Self-monitored plasma glucose readings and hypoglycemic events will be collected in a subject diary and reviewed by the investigator at each visit.

6.4.9.1 Fasting plasma glucose concentrations and hypoglycemic events

Subject self-monitoring of FPG is performed in order to reduce the risks associated with prolonged hyperglycemia and to confirm symptoms of hypoglycemia. Subjects will be asked to perform self-monitoring of FPG using glucometers provided by AstraZeneca. The subjects will receive instructions for the use of the glucometer according to the manufacturer's instructions.

FPG should be self-monitored at least every second day between Visits 2 and 6 and at least once a week between Visits 6 and 8. The results should be recorded in the subject diary, which will be

collected and reviewed by the study personnel at each visit starting with Visit 3; a print out will be stored in the investigator study file.

The memory of the glucometer should be reviewed and compared with the readings in the subject's diary. The glucose values should be reviewed by the study personnel to identify any unusually high or low values, and to confirm that self-monitoring was performed by the subject. If fingerstick glucose values are discordant with central laboratory results or with clinical symptoms, the subject's glucometer should be tested and the glucometer instructions should be re-reviewed with the subject.

If self-monitored FPG is above 270 mg/dL (15 mmol/L) from Week - 4 (Visit 4) to Week 4 (Visit 8), and above 240 mg/dL (13.2 mmol/L) from Week 4 (Visit 8) to Week 24 (Visit 13), the subject should repeat the FPG on the same day. If the second FPG value is above 270 mg/dL (15 mmol/L), or 240 mg/dL (13.2 mmol/L), respectively, the subject should contact the study centre and be scheduled for a central laboratory FPG measurement within one week.

If central laboratory values show similar values, the subject should be discontinued.

A separate section in the eCRF will be used to document all reported episodes of hypoglycemia after Week - 4 (Visit 4). The subjects will be asked to check their blood glucose if they develop symptoms suggestive of hypoglycemia and to record specific symptoms in the subject diary. The Investigator is responsible for questioning the subject about all symptoms reported in the diary and for determining if they meet the clinical definition of hypoglycemia. Only symptoms and/or blood glucose values that meet the definition of hypoglycemia should be reported on the hypoglycemia eCRF pages.

A hypoglycemic event can be either:

- Symptoms of hypoglycemia with a low blood glucose reading (<63 mg/dL [<3.5 mmol/L])
- A low blood glucose reading (<63 mg/dL [<3.5 mmol/L])
- Symptoms of hypoglycemia without a blood glucose reading

Hypoglycemic episodes or discontinuation due to hypoglycemia should not be reported on the AE eCRF page unless the event fulfils protocol criteria for a SAE (See Section 6.4.2). In this case, an SAE must be reported in addition to the hypoglycemia eCRF pages for hypoglycemia.

Symptoms suggestive of hypoglycemia with an associated capillary or plasma glucose value ≥63 mg/dL (≥3.5 mmol/L), should be recorded as an AE rather than as a hypoglycemic event. If the physician does not consider the glucose measurement to be accurate, however, the event should be documented as a hypoglycemic event in the hypoglycemia eCRF.

For the evaluation of hypoglycemic events, this study will use the definitions provided in the CPMP guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus, as described below.

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

- Minor hypoglycemic event, defined as either a symptomatic episode with a capillary or plasma glucose measurement <63 mg/dL (<3.5 mmol/L) regardless of need for external assistance or an asymptomatic capillary or plasma glucose measurement below 63 mg/dL (3.5 mmol/L) , that does not qualify as a major episode

- Events suggestive of hypoglycemia, defined as a symptomatic event without a confirmatory blood glucose measurement.

Data to be collected for each hypoglycemic event:

- Date and time of episode (start and stop)

- Whether the subject was sleeping at the time of the event

- Whether symptoms were present, and list of symptoms

- Possible contributing factors

- Whether a fingerstick value was obtained, and if so, the plasma glucose value

- Whether intervention was needed for recovery

- How the episode was treated

- Whether recovery was prompt after treatment

- Time of last anti-diabetic agents administration

- Time of last meal and its contents

The subject diary will be reviewed and the hypoglycemic event data will be transcribed into the eCRFs at each clinical visit. A new diary for the next period will be handed over to the subject if needed. If a major hypoglycemic event or more than one minor event has occurred since the previous visit, the subject should contact the investigator.

6.4.9.2 Urinary and Genital Infections

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

Urinary Tract Infections

If based on the 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 judgement and local standards of care should apply to decisions concerning therapy. It is strongly recommended that a diagnosis of a recurrent urinary tract infection, defined either as two infections in a 6-month period or three infections in a 12-month period, should result in referral to a gynecologist (women) or urologist (men) for further diagnosis and treatment. Any treatment needs to be documented in the eCRF.

Between scheduled visits, subjects may experience novel signs or symptoms that are potentially indicative of urinary or a genital tract infection. The subject should contact the investigator by telephone. An unscheduled visit will be planned as soon as possible, preferably within 24 h. The investigator will take the subject's recent history, a midstream urine sample will be obtained for urine analyses and a mandated urine culture, and it is also recommended that a genital swab is done, if indicated. Analyses and culture(s) are to be performed at the local laboratory. The investigator will follow local guidelines to recommend treatment for urinary tract infection or genital tract infection.

Investigational product should be temporary stopped in subjects with clinical evidence of upper urinary tract infection (eg, pyelonephritis) or presumed urosepsis until the course of treatment of the infection has been completed and clinical recovery has occurred. It is recommended that a follow-up urine culture is obtained within 7 days of clinical recovery from a documented UTI. Whether additional therapy is prescribed because of culture results should be determined by Investigator judgement.

Genital Tract Infections

The diagnosis of vaginitis, vulvovaginitis, vulvitis or balanitis can be made based on physical examinations, culture of secretions or a therapeutic response to treatment of fungal or other vaginal pathogens. A urine culture is not required for diagnosis of genital infections if the diagnosis is confirmed by physical examination, culture of secretions, or a therapeutic response to treatment of fungal or other vaginal pathogens. A recurrent genital tract infection, defined as more than 2 infections in a 6 month period, should result in a referral to a gynecologist (women) or urologist (men) for further diagnosis and treatment. Any treatment needs to be documented in the eCRF.

Also, it is the investigator's responsibility to report, as applicable based on investigator's judgement and subject's medical history, related AEs as defined in Section 6.4.5. Additional information, including but not limited to completion of supplemental eCRFs may be requested for certain AEs and/or laboratory abnormalities which are reported/identified during the course of the study.

Asymptomatic bacteriuria

During enrolment, treatment and follow up of subjects in this trial, the investigator may discover a subject with asymptomatic bacteriuria. Asymptomatic bacteriuria is defined as the presence of $\geq 10^5$ 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 et al 2005, USPST 2004) nor Europe (European Association of Urology 2008) recommend screening for, or treatment of, asymptomatic bacteriuria in non-pregnant diabetic subjects. In this study, the central laboratory will report urinary dipstick test results for hemoglobin but will not routinely report the results of urinary dipstick tests for leukocyte esterase as a screening test for pyuria in surveillance urine examinations.

6.4.10 Congestive Heart Failure

The risk of electrolyte abnormalities, volume depletion, and impaired renal function is enhanced when two diuretics are used in combination. For this reason, caution should be exercised when administering dapagliflozin, which has a modest diuretic effect, to subjects who are taking loop diuretics. These subjects should have careful monitoring of electrolytes, volume status, and renal function. Loop diuretic dose adjustments should be made if clinically indicated.

6.4.11 Change in kidney function

Please see Appendix F for further guidance.

6.4.12 Hyponatremia

Please see Appendix E for further guidance.

6.4.13 CK abnormalities

Please see Section 5.8

6.4.14 Liver function test abnormalities

Please see Section 5.8 and Appendix G.

6.4.15 Independent Adjudication Committee

A Clinical Event Committee (CEC), blinded to the treatment of the subjects, will independently adjudicate certain cardiovascular AEs, 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:

Death including:

1. Cardiovascular Death
2. Non-cardiovascular Death

Myocardial Infarction (MI) including:

1. ECG and /or cardiac enzymes confirmed MI
2. Sudden death
3. Percutaneous coronary intervention-related MI
4. Coronary artery bypass graft-related MI
5. MI diagnosed via pathologic criteria
6. Silent MI

Fatal and Non-fatal Stroke including:

1. Ischaemic Stroke
2. Haemorrhagic Stroke

SAEs of the following:

1. Heart failure
2. Cardiac arrhythmia
3. Unstable angina
4. Unplanned arterial revascularization (coronary, carotid and peripheral)
5. Cardiac arrest with successful resuscitation
6. Deep Vein Thrombosis and Pulmonary Emboli
7. Systemic non-stroke arterial embolism/thrombosis including systemic arterial occlusion
8. 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.

6.4.16 Hepatic Adjudication Committee

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

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

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

6.5 Patient reported outcomes (PRO) – Not applicable

6.6 Pharmacokinetics – Not applicable

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 in this study is as follows:

Table 8 Volume of blood to be drawn from each subject (mL)

Visit	1	2 [a]	3 [a]	4	5	6	7	8	9	10	11	12	13	14	Maximum volume
Sample volume	26	2	2	13.5	5	21.5	13.5	16.5	16.5	16.5	16.5	16.5	21.5	13.5	201

a Only for subjects who received ongoing medical treatment for diabetes within 6 weeks of enrolment, except for TZD (a single oral anti-diabetic agent or two agents with less than half of the approved maximal dose for each agent)

7.2 Handling, storage and destruction of biological samples

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

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 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.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

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 EC 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 EC 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 investigator/The Head of the study site will ensure the distribution of these documents to the applicable EC, and to the study site staff.

The opinion of the EC should be given in writing. The head of the study site should submit a notification of direction/determination as well as a copy of the Institutional Review Board (IRB) written approval to AstraZeneca before enrolment of any subject should into the study.

The EC 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, ECs, the head of the study site and Principal Investigators with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Reactions (SUSARs), where relevant.

The Head of the study site should submit a written report to the IRB providing the details of all adverse event case(s) reported by AstraZeneca.

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 EC.

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.

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 eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs 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 eCRFs and regarded as source data are as follows.

- Reason for therapy or medication
- Any Comments on eCRF
- Evaluation for inclusion/exclusion criteria

- AE (Yes/No, Maximum intensity, Serious, Treatment required, Outcome, Causality)
- Description of AE on SAE form
- Main reason for premature discontinuation

9.3.2 Direct access to source data in Japan

The Head of the institution and the Principal Investigator/sub-investigator 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 eCRFs against source data before collecting the eCRFs to ensure accuracy and completeness of documentation, and assure that the Principal Investigator/sub-investigator has submitted the eCRFs to AstraZeneca. If the investigator wishes to amend the collected eCRFs, the monitor will ensure that the Principal Investigator/sub-investigator 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, or equivalent, 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

The investigator(s) must not deviate from or make any changes to the protocol without documented agreement between the principal investigator and AstraZeneca K.K. 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 subjects or for other compelling medical reasons, or where the changes involve only logistical or administrative aspects of the clinical trial (eg, 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).

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 subjects 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.

The investigator(s) may deviate from or make a change to the protocol without documented agreement between the principal investigator and AstraZeneca K.K. or the IRB approval, only in the event of a medical emergency, eg, it is only way to avoid an immediate hazard to the subjects. 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 K.K. 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 K.K. should be obtained via the head of the study site.

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.

Planned duration of the study:

Study period: February 2011 – April 2012

Registration period: February 2011 – August 2011

Discontinuation or suspension of the whole study programme

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

The Principal Investigator 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.

Completion of the study

Upon terminating the study, the Principal Investigator 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.

Data will be entered in the 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 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. The data will then be Source Data Verified (SDV), reviewed, queried and updated as needed. Principal Investigator is responsible for signing the eCRF electronically as per the eCRF instructions.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail. Quality assurance procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

The data will be frozen and then locked to prevent further editing. When all data have been coded, validated, signed and locked, clean file will be declared. All editing accesses will be revoked and the final database will be locked. Copy of the eCRF will be archived at the study site when the study has been locked.

The study Data Management Plan will describe in greater detail the methods used to collect, check and process clinical data. It will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

Prior to breaking the treatment codes, all decisions on the evaluability of the data from each individual patient must have been made and documented.

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 (eg, IWRS etc) will be tested / validated as needed. External data reconciliation will be done with the clinical database as applicable.

Dictionary coding

AEs and medical/surgical history will be classified according to the terminology of the latest version the MedDRA. Medications will be classified according to the Bristol-Myers Squibb Drug Dictionary. All coding will be performed by the coding team at Bristol-Myers Squibb.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

11.1 Calculation or derivation of efficacy variable(s)

11.1.1 Change and percent change from baseline

Change from baseline will be calculated as absolute difference (or percentage change) between the value measured at or derived for a specific time point after baseline minus baseline value. Baseline is defined as the last value collected on Visit 6 but also before during intake.

Percent change from baseline will be computed as 100*(value measured at or derived for a specific time point after baseline - baseline value)/baseline value.

11.1.2 Last observation carried forward (LOCF)

If no measurement is available at a time point, the last post-baseline measurement prior to the specific time-point will be used instead for analysis. Unless otherwise specified, if a subject initiates rescue medication, the last value taken on or before the first rescue dose will be used for analysis.

11.2 Calculation or derivation of safety variable(s)

11.2.1 Calculation of eGFR

The following Japan guideline recommended equation will be used to calculate eGFR.

$$eGFR\ (mL/min/1.73m^2) = 194 \times (SCr)^{-1.094} \times (age)^{-0.287} \times (0.739\ \text{if female})$$

11.2.2 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 Discontinuation of Investigational Product due to

Adverse Event (DAEs). Based on the expert's judgement, significant AEs 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.

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

11.4 Calculation or derivation of pharmacokinetic variables – Not applicable

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 will be finalized prior to the clean file.

12.1 Description of analysis sets

Protocol deviations will be reviewed in a blinded fashion by the study team prior to database lock. All decisions to exclude subjects and/or data from the Full Analysis Set to form the Per Protocol Analysis Set will be made prior to the unblinding of the study and agreed by the study team.

12.1.1 Efficacy analysis set

The evaluation of efficacy will be performed primarily for the full analysis set.

12.1.1.1 Full analysis set

The full analysis set will include all randomised subject 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 subjects will be analysed according to the treatment group to which they were randomised, regardless of the actual 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 subjects of the full analysis set without major protocol deviations which may affect the study outcome significantly. The subjects will be analysed according to the treatment group to which they were randomised, regardless of the actual treatment taken. All decisions to exclude subjects from the per-protocol data set will be made prior to the unblinding of the study.

12.1.2 Safety analysis set

The safety analysis set will include all subjects who received at least one dose of randomised study medication and who provide any safety records. Subjects who were dispensed the same wrong treatment for the entire treatment period (ie, those randomised to dapagliflozin 10 mg but actually given placebo, or vice versa) will be counted in the treatment group for which they received medication.

12.2 Methods of statistical analyses

12.2.1 Demographics and baseline characteristics

Descriptive summaries of demographics and baseline characteristics will be presented by treatment group and for all subjects combined using the full analysis set.

12.2.2 Efficacy analysis

For the primary variable, the change from baseline in HbA1c to Week 24, each pair wise treatment group comparison will be tested at a significance level of approximately 0.027, according to Dunnett's method, in order to maintain an overall Type I error rate <0.050 for the primary objective.

A hierarchical closed testing procedure will be used to control the Type I error rate across the primary and key secondary objectives within each dapagliflozin treatment group. Key secondary objectives are to compare the effects of each dose of dapagliflozin versus placebo after a 24-week double-blind treatment period by evaluation of:

1. The change from baseline in FPG at Week 24 (LOCF).

2. The change from baseline in total Body weight at Week 24 (LOCF).

The statistical testing of the primary and key secondary efficacy endpoints will proceed in a sequential manner, to control the type I error rate within each dapagliflozin group at the 0.05 level. Specifically, the significance or non-significance of the treatment comparisons for the primary efficacy endpoint will determine which, if any, statistical inferences are made for the key secondary efficacy endpoints. Only those dapagliflozin groups significantly superior to placebo for the primary efficacy endpoint will have statistical inference vs placebo for the first key secondary endpoint, (1). Then, the testing for the other key secondary efficacy endpoints will proceed so that the significance or non-significance of the treatment comparisons for (1) will determine which, if any, statistical inferences are made in treatment comparisons for (2). If a result for one of the dapagliflozin treatment groups is not significant, statistical inference ends at

that endpoint and no statistical inference will be applied to the subsequent key secondary endpoints for that treatment group.

If at least one of the primary comparisons between a dapagliflozin treatment group and the placebo treatment group is significant at the 0.027 level for the primary endpoint, all statistical tests for the two key secondary efficacy endpoints will be performed and nominal p-values will be reported. However, in order to protect the global type I error rate of the hierarchical testing procedure, the interpretation of the statistical significance of treatment comparisons for each key secondary efficacy endpoint will be done using the step-wise procedure described above.

Other secondary outcome variables and exploratory outcome variables shall provide supportive efficacy and safety information regarding the differences between the treatment groups. For other secondary efficacy variables, supportive statistical test will be made at nominal significance level 0.05 and nominal p-values will be reported.

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, ie, last observation carried forward (LOCF). For rescued subjects, values collected after initiation of rescue medication will not be considered in calculating the LOCF values for glycemic endpoints.

The time course of all continuous variables will be presented using standard descriptive summary statistics.

12.2.2.1 Primary efficacy analysis

The change in HbA1c from baseline to Week 24 (LOCF), will be analyzed by an analysis of covariance (ANCOVA) model including treatment group and gender as fixed effect and baseline as covariate. The ANCOVA model will be used to derive a least squares estimate of the treatment difference with 95% confidence interval and corresponding 2-sided p-value.

12.2.2.2 Key secondary varibles

The changes from baseline to Week 24 (LOCF) in FPG and total body weight will be analyzed and presented in similar way as the primary efficacy analysis described in Section 12.2.2.1.

12.2.2.3 Other secondary efficacy variables

The following variables, except for the percent changes from baseline in lipids and body weight, will be analysed based on similar ANCOVA model as the primary efficacy analysis described in Section 12.2.2.1. The percent changes from baseline to Week 24 (LOCF) in lipids (TC, LDL-C, HDL-C and fasting TG) and body weight will be analysed on a log scale in an ANCOVA model with terms similar to the primary efficacy analysis.

- the percent change from baseline in total body weight at Week 24 (LOCF)

- the change from baseline in seated SBP in subjects with baseline seated SBP ≥130 mmHg at Week 24 (LOCF)
- the change from baseline in total body weight in subjects with baseline BMI≥25 kg/m^2 at Week 24 (LOCF)
- the change from baseline in HbA1c at Week 24 (LOCF) in subjects with baseline HbA1c ≥7.5%
- the change from baseline in seated SBP at Week 24 (LOCF)
- the change from baseline in waist circumference at Week 24 (LOCF)
- the percent change from baseline in fasting lipids (TC, LDL-C, HDL-C and TC) at Week 24 (LOCF)
- the change from baseline in fasting insulin and C-peptide at Week 24 (LOCF)
- the change from baseline in glicoalbumin at Week 24 (LOCF)

For the following proportions, estimates, confidence intervals, and tests will be obtained using the methodology of Zhang, Tsiatis and Davidian (Zhang M et al 2007) and Tsiatis, Davidian, Zhang and Lu (Tsiatis A et al 2007) with adjustment for gender and baseline variable (eg, adjustment for baseline HbA1c). For each treatment group, the probability of response is first modeled using a logistic regression model with gender and baseline (eg, baseline HbA1c) as the covariate. Treatment group estimates of response rate are then obtained by integrating each group's modeled probability of response over the observed distribution of baseline covariate (combined across groups). The difference in response rate between each of the dapagliflozin treatment groups and the placebo group will be displayed along with the 95% confidence intervals. Nominal p-values for the difference between the dapagliflozin treatment groups versus placebo will be provided (if applicable). When there are less than 5 responders on average by treatment group, the unadjusted (and difference) proportions, exact 95% confidence interval, and p-values from the Fisher's exact test (when applicable) will be provided.

- the proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c < 6.5%, at Week 24 (LOCF)
- the proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c <7% at Week 24 (LOCF) in subjects with baseline HbA1c ≥7%.
- the proportion of subjects discontinued for lack of efficacy or rescued for failing to maintain FPG below pre-specified rescue criteria at Week 12, 16, and 24 (LOCF)
- the proportion of subjects with baseline elevated BP (baseline SBP ≥130 mmHg and/or baseline DBP ≥80mmHg) who achieve a seated BP of <130/80mmHg at Week 24 (LOCF)

12.2.3 Safety analysis

The safety evaluations will include analyses of AEs, laboratory parameters, ECG, vital signs (pulse and BP), hypoglycemic events, eGFR and physical examination.

The analysis of safety will be based on the safety analysis set. Safety data gained during the 24-week double-blind treatment period and the 3-week safety follow-up period will be evaluated. Safety variables will be summarized descriptively and missing data will be replaced using the LOCF approach where appropriate. Information about adjudicated cardiovascular events will be combined with the results from other dapagliflozin Phase II and Phase III studies to monitor cardiovascular safety. Results of analyses will be reported elsewhere.

12.3 Determination of sample size

Each pairwise treatment group comparison will be tested at a significance level of approximately 0.027, according to Dunnett's method, in order to maintain an overall type I error rate < 0.050 for the primary objective. To detect a difference of 0.5% between each dapagliflozin group versus placebo for changes in HbA1c from baseline to Week 24, assuming a SD = 0.9%, and at a two-sided significance level of 0.027, 80 evaluable subjects are needed in each treatment group to provide 90% power. The assumed SD=0.9 is considered to be appropriate based on Japan Phase IIb study and Global monotherapy Phase III study result where SD was approximately 0.52% and 0.91%, respectively. Assuming that approximately 5% of the subjects will not have a post-baseline efficacy measurement, 85 subjects per treatment group (255 subjects total) are planned for randomization.

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 Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician.

Name	Role in the study	Address & telephone number
	Study Delivery Team Leader	
	Study Delivery Team Physician	
Monitor	Study Delivery Team Monitor	See Supplement A, "Investigators and Study Administrative Structure".

13.2 Overdose

Overdose is defined as the accidental or intentional ingestion of any dose of investigational product that is considered both excessive and medically important. Dapagliflozin has been well tolerated at doses of up to 500 mg/day in single dose testing in healthy volunteers and up to 100 mg/day in repeat dose testing for 14 days in healthy volunteers and subjects with T2DM. Once an investigator decides that a particular occurrence is an overdose, it must be reported as a SAE. If an overdose is suspected, monitoring of vital functions as well as treatment as appropriate should be performed.

13.3 Pregnancy

All outcomes of pregnancy must be reported to AstraZeneca.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study and/or metformin and/or glymepiride 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, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, the subject should be discontinued, the investigational product should be stopped and then investigators or other site personnel must inform appropriate AstraZeneca representatives immediately but no later than the end of the next business day of when he or she becomes aware of it.

The PREGREP module in the eCRF is used to report the pregnancy. This module in the eCRF should be completed by the investigator and the AstraZeneca representative will forward the information to Bristol Myers Squibb using the same procedure as for SAE reporting. An

AstraZeneca paper Pregnancy Outcome Report, part 2, is used to report the outcome of the pregnancy.

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Clinical Study Protocol Appendix A	
Drug Substance	Dapagliflozin
Study Code	D1692C00006
Edition Number	1
Date	
Protocol Dated	

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A 24-week randomised, double-blind, parallel-group, multi-centre, placebo-controlled phase III trial to evaluate the efficacy and safety of dapagliflozin as monotherapy in Japanese subjects with Type 2 diabetes who have inadequate glycemic control with diet and exercise

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

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A 24-week randomised, double-blind, parallel-group, multi-centre, placebo-controlled phase III trial to evaluate the efficacy and safety of dapagliflozin as monotherapy in Japanese subjects with Type 2 diabetes who have inadequate glycemic control with diet and exercise

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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

Clinical Study Protocol Appendix B

Drug Substance	Dapagliflozin
Study Code	D1692C00006
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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.

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Clinical Study Protocol Appendix C	
Drug Substance	Dapagliflozin
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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.

Clinical Study Protocol Appendix D	
Drug Substance	Dapagliflozin
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Appendix D
New York Heart Association (NYHA) Classification

NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION

The NYHA classification will be based on the following definitions:

Class I	No limitation: Ordinary physical exercise does not cause undue fatigue, dyspnoea or palpitations.
Class II	Slight limitation of physical activity: Comfortable at rest but ordinary activity results in fatigue, palpitations, dyspnoea.
Class III	Marked limitation of physical activity: Comfortable at rest but less than ordinary activity results in symptoms.
Class IV	Unable to carry out any physical activity without discomfort: Symptoms of congestive heart failure are present even at rest with increased discomfort with any physical activity.

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Clinical Study Protocol Appendix E	
Drug Substance	Dapagliflozin
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Appendix E
Algorithm on Management of Hyponatraemia

ALGORITHM ON MANAGEMENT OF HYPONATRAEMIA

If a patient 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.

  – If the repeat sodium concentration within 7 days of restarting the investigational product is <130 mmol/L, investigational product will be discontinued. Patients will have an end of treatment visit and a follow-up visit three weeks after discontinuation of investigational product as specified in Section 5.8.2 in the CSP.

  – If the repeat sodium concentration within 7 days of restarting the investigational product is ≥130 mmol/L, further management should be based on composite of sodium concentration, clinical assessment of the patient 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. Patients will have an end of treatment visit and a follow-up visit three weeks after discontinuation of investigational product as specified in Section 5.8.2 in the CSP.

  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.

  – If the repeat sodium concentration within 7 days is <130 mmol/L, investigational product will be discontinued. Patients will have an end of treatment visit and a follow-up visit three weeks after discontinuation of investigational product as specified in Section 5.8.2 in the CSP.

  – 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 patient and an evaluation of underlying cause of hyponatraemia.

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

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Clinical Study Protocol: Appendix F	
Drug Substance	Dapagliflozin
Study Code	D1692C00006
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Appendix F
Case Identification and Management of Decreased Renal Function

CASE IDENTIFICATION AND MANAGEMENT OF DECREASED RENAL FUNCTION

In order to standardise the definition and management of decreased renal function, the following guideline has been developed. Please note separate sections for patients who are treated with metformin and for those who are not treated with metformin.

FOR PATIENTS WHO ARE TREATED WITH METFORMIN:

If calculated eGFR is <60 ml/min or if there is an increase in serum creatinine of ≥0.5 mg/dL (≥44.2 µmol/L) above the baseline value based on central laboratory results, this will be considered a case of "decreased renal function".

In this circumstance, the investigator should consider evaluating the patient for potentially reversible causes of renal dysfunction including:

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.

Patients should return for repeat central laboratory testing as soon as possible, no later than 7 days after the abnormal result. Investigational drug and metformin should be interrupted pending the results of repeat testing. If after interruption eGFR is still <60 ml/min or if the serum creatinine value remains ≥0.5 mg/dL (≥44.2 µmol/L) above the baseline value, the patient should permanently discontinue the study medication and be withdrawn from the study (in which case an Adverse Event must be reported).

If after interruption of investigational drug and metformin eGFR is ≥60 ml/min or if the serum creatinine value has decreased to <0.5 mg/dL (<44.2 µmol/L) above baseline, investigational drug and metformin can be re-started if appropriate in the judgement of the investigator and following consultation with the study team physician. If the patient restarts investigational drug and metformin and eGFR is again <60 ml/min or the serum creatinine value increases again to ≥0.5 mg/dL (≥44.2 µmol/L) above baseline, the patient should permanently discontinue the study medication and be withdrawn from the study (in which case an Adverse Event must be reported).

FOR PATIENTS WHO ARE NOT TREATED WITH METFORMIN:

If a) eGFR is <45 ml/min or b) in subjects with baseline creatinine ≥1.4 mg/dL (≥123 µmol/L) there is an absolute increase in serum creatinine of ≥1.0 mg/dL (≥88 µmol/L), or c) in subjects with baseline creatinine <1.4 mg/dL (<123 µmol/L) there

is an absolute increase in serum creatinine of ≥0.5 mg/dL (≥44 µmol/L), this will be considered a case of "decreased renal function".

In this circumstance, the investigator should consider evaluating the patient for potentially reversible causes of renal dysfunction including:

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.

Patients should return for repeat central laboratory testing as soon as possible, no later than 7 days after the abnormal result. Investigational drug should be interrupted pending the results of repeat testing. If after interruption eGFR is still <45 ml/min or if the serum creatinine value remains ≥0.5 mg/dL (≥44.2 µmol/L) above the baseline value, the patient should permanently discontinue the study medication and be withdrawn from the study (in which case an Adverse Event must be reported).

If after interruption of investigational drug eGFR is ≥45 ml/min or if the serum creatinine value has decreased to <0.5 mg/dL (<44.2 µmol/L) above baseline, investigational drug can be re-started if appropriate in the judgement of the investigator and following consultation with the study team physician. If the patient restarts investigational drug and eGFR is again <45 ml/min or the serum creatinine value increases again to ≥0.5 mg/dL (≥44.2 µmol/L) above baseline, the patient should permanently discontinue the study medication and be withdrawn from the study (in which case an Adverse Event must be reported).

Clinical Study Protocol Appendix G	
Drug Substance	Dapagliflozin
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Appendix G
Algorithm on Management of Sustained Elevated Liver Safety Abnormalities

ALGORITHM ON MANAGEMENT OF SUSTAINED ELEVATED LIVER SAFETY ABNORMALITIES

The monitoring for liver safety will be performed using the serum levels of AST, ALT and TB (see Figure 1 Sustained Elevated Liver Safety Abnormalities flow chart).

Patients with a 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. Patients should remain on study medication until confirmatory results are obtained, unless otherwise contraindicated.

- **If the repeat ALT and AST are ≤3X ULN,** patient should continue double-blind treatment 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 patient's medical history, including details of risk factors for liver diseases, should be evaluated for potential underlying aetiologies. 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 patient'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 patient is asymptomatic. Patients 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.

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

- ALT and/or AST are >3 x ULN and TB >1.5 x ULN

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

- ALT and/or AST are >8 x ULN

In each of these situations, study medication will be discontinued, the Sponsor notified and the End of Treatment Visit performed within 3 days of the confirmed laboratory results (see Section 5.8.2 in the CSP). At the End of Treatment Visit, medical history including details of risk factors for liver diseases (if not previously assessed) will be requested and additional

blood sampling performed (**Specialized Liver Panel** and **Liver Discontinuation Panel**, see detailed below). Patient should also be scheduled for a Follow-up Visit (ie, procedures of Visit 14) 3 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 patients with abnormal laboratory values at the Follow-up Visit should be made available to the Sponsor upon request.

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.

Following the 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 ≤2 x 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.

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

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

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

- Specialized Liver Laboratory Panel (see below)

Specialized Liver Panel
For patients 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

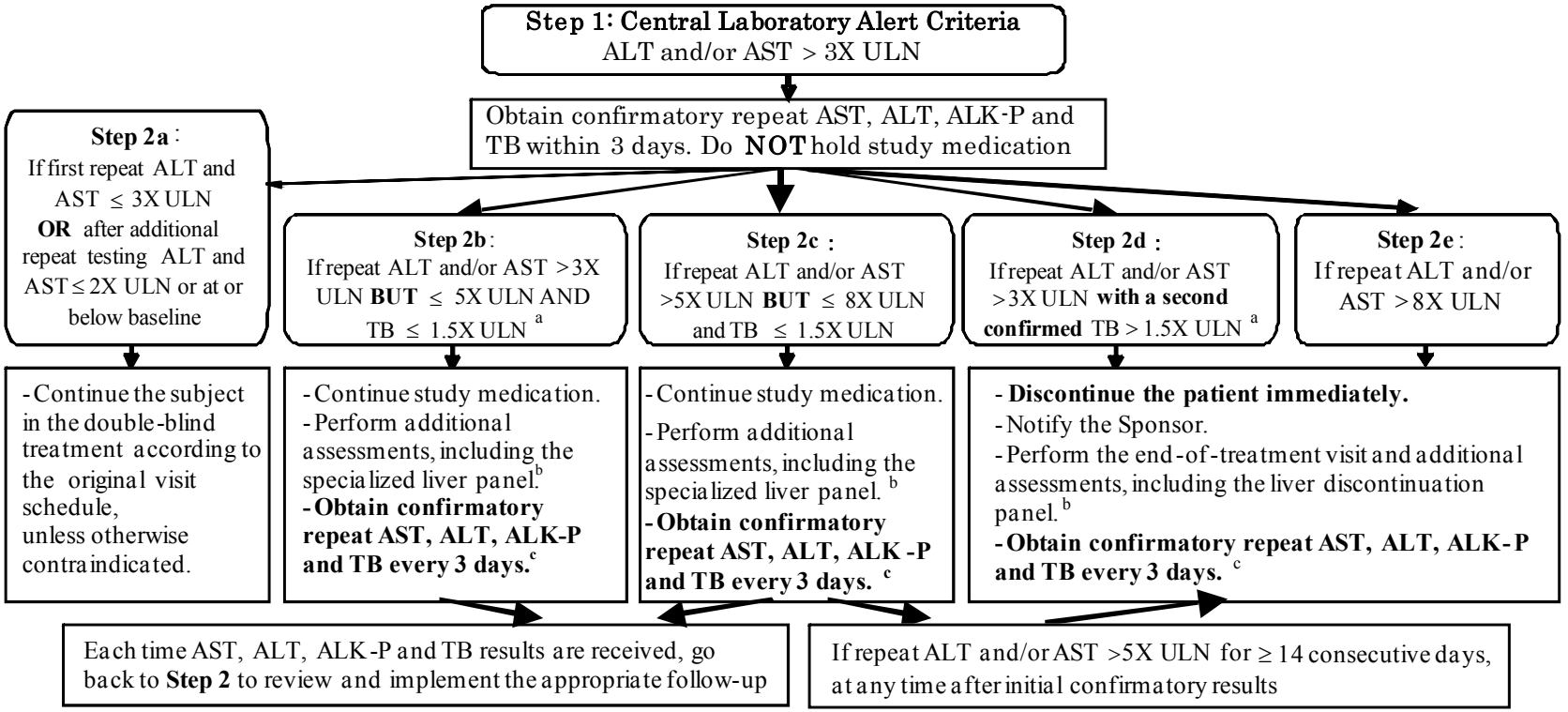
Liver Discontinuation Panel
For patients who are discontinued from the study as a result of sustained elevated liver safety abnormalities, additional central laboratory tests will be performed at the time of End of Treatment Visit. Similar to the Specialized Liver Panel, these laboratory tests will study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

- Cytomegalovirus (CMV) IgM Ab

- Herpes Simplex Virus (HSV) 1 and 2
- Ceruloplasmin
- Toxoplasmosis
- Alpha-1 antitrypsin

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

Figure 1 Sustained elevated liver safety abnormalities flow chart



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

b Please see text above in the Appendix 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 patient is asymptomatic.

Clinical Study Protocol: Supplement A

Drug Substance	Dapagliflozin
Study Code	D1692C00006
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**

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**

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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)

Address	**Member name** (First name, Last name)	**Present position**	**Role in committee**
External Medical Advisor			

OTHER PARTICIPANTS

Organisation and address	Role in study

Clinical Study Protocol Amendment

Amendment Number	1
Drug Substance	Dapagliflozin
Study Code	D1692C00006
Date	
Protocol Dated	

A 24-week randomised, double-blind, parallel-group, multi-centre, placebo-controlled phase III trial to evaluate the efficacy and safety of dapagliflozin as monotherapy in Japanese subjects with Type 2 diabetes who have inadequate glycemic control with diet and exercise

Sponsor:

AstraZeneca K.K.

Bristol-Myers K.K.

Centres affected by the Amendment:

All centres in the study

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

"Previous text" and "Revised text" include only information that has been changed.

Change 1

Section of protocol affected:

6.3.1 Efficacy laboratory variables

Previous text:

The laboratory parameters that will be measured to assess efficacy are displayed in Table 6 by visit. The results from baseline and onwards will not be reported to the investigator unless FPG value is above 270 mg/dL (15 mmol/L) from Week 0 (Visit 6) to Week 4 (Visit 8), above 240 mg/dL (13.2 mmol/dL) from Week 4 (Visit 8) to Week 12 (Visit 10) and above 200 mg/dL (11.1 mmol/L) from Week 12 (Visit 10) to Week 24 (Visit 13), except for TC, HDL-C, LDL-C and TG which will be reported.

Revised text:

The laboratory parameters that will be measured to assess efficacy are displayed in Table 6 by visit. The FPG results from baseline and onwards will not be reported to the investigator unless FPG value is above 270 mg/dL (15 mmol/L) from Week 0 (Visit 6) to Week 4 (Visit 8), above 240 mg/dL (13.2 mmol/dL) from Week 4 (Visit 8) to Week 12 (Visit 10) and above 200 mg/dL (11.1 mmol/L) from Week 12 (Visit 10) to Week 24 (Visit 13).

Reason for Amendment:

To correct error

Persons who initiated the Amendment:

Study Delivery Team Leader

Clinical Study Protocol Amendment No 1
Appendix A

Drug Substance	Dapagliflozin
Study Code	D1692C00006
Edition Number	1
Date	
Protocol Dated	

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A 24-week randomised, double-blind, parallel-group, multi-centre, placebo-controlled phase III trial to evaluate the efficacy and safety of dapagliflozin as monotherapy in Japanese subjects with Type 2 diabetes who have inadequate glycemic control with diet and exercise

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

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

AstraZeneca Research and Development
site representative

ASTRAZENECA SIGNATURE(S)

A 24-week randomised, double-blind, parallel-group, multi-centre, placebo-controlled phase III trial to evaluate the efficacy and safety of dapagliflozin as monotherapy in Japanese subjects with Type 2 diabetes who have inadequate glycemic control with diet and exercise

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