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A 16-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Safety and Efficacy of Dapagliflozin 2.5 mg BID, 5 mg BID and 10 mg QD Versus Placebo in Patients with Type 2 Diabetes Who Are Inadequately Controlled on Metformin-IR Monotherapy

Sponsor: *AstraZeneca AB, 151 85 Södertälje, Sweden*

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 16-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Safety and Efficacy of Dapagliflozin 2.5 mg BID, 5 mg BID and 10 mg QD Versus Placebo in Patients with Type 2 Diabetes Who Are Inadequately Controlled on Metformin-IR Monotherapy

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Study centre(s) and number of subjects planned

This international study will be conducted at approximately 65 study centres. It is estimated that 940 patients will be screened and 654 patients will be enrolled to reach the target of 392 randomised patients during an enrolment period of approximately 6.5 months. It is expected that 5 to 7 patients will be randomised per centre.

Study period	Phase of development
Estimated date of first subject enrolled	III
Estimated date of last subject completed	

Objectives

Primary Objective

To compare the change from baseline in HbA1c achieved with each of the 2 BID doses of dapagliflozin (2.5 mg BID and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment.

"BID" means twice daily administration. Baseline is defined as the last value collected on/or prior the date of the first dose of the double-blind study. It is expected that baseline value is from the randomisation visit (Visit 4), at week 0. Metformin-IR means that immediate release formulation tablets of metformin will be administered BID, however "metformin" will be used throughout the protocol text.

Key Secondary Objectives

- To compare the percent change from baseline in body weight achieved with each of the 2 BID doses of dapagliflozin (2.5 mg BID, and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment.

- To compare the change from baseline in fasting plasma glucose (FPG) achieved with each of the 2 BID doses of dapagliflozin (2.5 mg BID and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 1 week of double-blind treatment.

- To compare the change from baseline in fasting plasma glucose (FPG) achieved with each of the 2 BID doses of dapagliflozin (2.5 mg BID and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment.

- To compare the proportion of patients with HbA1c <7.0% achieved with each of the 2 BID doses of dapagliflozin (2.5 mg BID and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment, in patients who had HbA1c ≥7.0% at baseline.

Other Secondary Objective

Efficacy

- To compare the change from baseline in seated systolic and diastolic blood pressure (BP) achieved with each of the 2 BID doses of dapagliflozin (2.5 mg BID and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment.

- To compare the proportion of patients with seated systolic blood pressure <130 mmHg reached with each of the 2 BID doses of dapagliflozin (2.5 mg BID and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment, in patients who had seated systolic blood pressure ≥130 mmHg at baseline.

- To compare the change from baseline in body weight achieved with each of the 2 BID doses of dapagliflozin (2.5 mg BID and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment.

- To compare the change from baseline in HbA1c achieved with 10 mg dapagliflozin QD (once daily) co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment.

- To compare the change from baseline in fasting plasma glucose (FPG) achieved with 10 mg of dapagliflozin QD co-administered with metformin versus placebo co-administered with metformin after 1 week and 16 weeks of double-blind treatment.

- To compare the proportion of patients with HbA1c <7.0% achieved with 10 mg of dapagliflozin QD co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment, in patients who had HbA1c ≥7.0% at baseline.

- To compare the percent change from baseline in body weight achieved with 10 mg of dapagliflozin QD co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment.

- To compare the change from baseline in body weight achieved with 10 mg of dapagliflozin QD co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment.

- To compare the change from baseline in seated systolic and diastolic blood pressure (BP) achieved with 10 mg of dapagliflozin QD co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment.

- To compare the proportion of patients with seated systolic blood pressure <130 mmHg reached with dapagliflozin 10 mg QD co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment, in patients who had seated systolic blood pressure ≥130 mmHg at baseline.

Safety

- To examine the safety and tolerability of dapagliflozin co-administered with metformin versus placebo co-administered with metformin by assessment of AEs, laboratory values, electrocardiogram, pulse, blood pressure, hypoglycaemic events, calculated creatinine clearance, estimated glomerular filtration rate and physical examination findings.

Pharmacogenetic Objective

- To collect and store DNA for future exploratory research into genes that may influence response, eg, safety, tolerability and efficacy of dapagliflozin treatment and genetic factors that may influence susceptibility to type 2 diabetes and/or associated conditions.

Study design

This is a 16-week randomised, double-blind, double dummy, placebo-controlled, 4-arm, parallel-group, multicentre study with a 4 week open label placebo lead-in period, and a 16 week treatment period. Patients will be stratified by HbA1c measurement at randomisation (HbA1c <7.0%, HbA1c ≥7.0%). With respect to recruitment, one stratum will represent patients with an HbA1c value <7.0% (Stratum 1), up to a maximum size of 20% of all randomised patients. The other recruitment stratum (Stratum 2) consist of patients with an HbA1c value at randomisation ≥7.0% and ≤10.0%. Randomisation strata will be combined in the analysis of the primary endpoint.

Target subject population

Men and women with type 2 diabetes who:

- Are ≥18 to ≤77 years old at time of consenting

- Have inadequate glycaemic control, defined as HbA1c ≥6.7% and ≤10.5% at week –4 (HbA1c ≥7.2% and ≤10.5%, after randomisation Stratum 1 complete)

- Have inadequate glycaemic control, defined as HbA1c ≥6.5% and ≤10.0% at week –1 (HbA1c ≥7.0% and ≤10.0%, after randomisation Stratum 1 complete)

- Are on stable treatment with a total daily dose of immediate release formulation of metformin ≥1500 mg taken BID as monotherapy for at least 10 weeks prior to enrolment

Investigational product, dosage and mode of administration

Dapagliflozin 2.5 mg, and 5 mg tablets, administered orally twice daily, and dapagliflozin 10 mg tablet administered orally once daily, together with food and metformin.

Comparator, dosage and mode of administration

Matching placebo for dapagliflozin 2.5 mg and 5 mg administered orally twice daily as well as matching placebo for dapagliflozin 10 mg administered once daily with food and metformin.

Study drug, dosage and mode of administration

Open-label metformin IR 500 mg tablets administered orally twice daily with food to achieve total daily doses of 1500 to 2500 mg/day during the 4-week placebo lead-in period and during the 16-week double-blind treatment period.

Duration of treatment

Following initial screening and a 1-week enrolment period, patients will enter a 4-week placebo lead-in period, after which they will be randomised to the 16-week double-blind treatment period. After either completion of the randomised treatment period or early discontinuation from treatment, patients will enter a 4-week follow-up period.

The total planned study duration starting with enrolment and including the follow-up period will be 25 weeks.

Outcome variable(s):

Primary outcome variable:

- Change in HbA1c from baseline to week 16

Key secondary outcome variables:

- Percent change in body weight from baseline to week 16

- Change in FPG from baseline to week 1

- Change in FPG from baseline to week 16

- Proportion of patients with HbA1c<7.0% at week 16, in patients who had HbA1c ≥7.0% at baseline.

Other secondary outcome variables:

- Change in seated systolic and diastolic blood pressure (BP) from baseline to week 16

- Proportion of patients with seated systolic blood pressure <130 mmHg at week 16 in patients who had seated systolic blood pressure ≥130 mmHg at baseline

- Change in body weight from baseline to week 16

The following secondary outcome variables apply to dapagliflozin 10 mg only:

- Change in HbA1c from baseline at week 16

- Change in FPG from baseline at week 1 and 16

- Proportion of patients with HbA1c<7.0% at week 16, in patients who had HbA1c ≥7.0% at baseline

 – Percent change in body weight from baseline to week 16

 – Change in body weight from baseline to week 16

 – Change in seated systolic and diastolic blood pressure (BP) from baseline to week 16

 – Proportion of patients with seated systolic blood pressure <130 mmHg at week 16 in patients who had seated systolic blood pressure ≥130 mmHg at baseline

Safety

Adverse Events (AE) laboratory values, electrocardiogram, pulse, blood pressure, hypoglycaemic events, cardiovascular events, calculated creatinine clearance, estimated glomerular filtration rate and physical examination findings.

Statistical methods

The primary outcome variable, change from baseline to week 16 in HbA1c, will be analyzed by an analysis of covariance (ANCOVA) model which will include terms for treatment group and covariate for baseline HbA1c. 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.

A Hochberg procedure will be used to control the overall Type I error rate for the two treatment group comparisons (dapagliflozin 2.5 mg BID and 5 mg BID) versus placebo for the primary efficacy variable. Further testing of treatment group(s) versus placebo for key secondary variables will be performed using a hierarchical, fixed sequence testing procedure, but only with respect to the treatment group(s) found significant for the primary efficacy variable.

The sample size for this study was selected to demonstrate a difference in the mean change in HbA1c from baseline to week 16 between one of the dapagliflozin treatment groups (2.5 mg BID and/or 5 mg BID) versus placebo in combination with metformin. A review of variability estimates from BMS studies MB102013 and MB102014 suggests that the standard deviation associated with change in HbA1c from baseline to week 16 using LOCF will not be more than 0.97%. Since the overall Type I error will be controlled for the two treatment comparisons using a Hochberg procedure, sample size estimation is based on the conservative assumption that one dose comparison may not reach statistically significance. In this situation, in order to detect a 0.5% difference in mean change from baseline in HbA1c between one of the dapagliflozin treatment groups (2.5 mg BID or 5 mg BID) versus placebo using a 2-sample t-test at a 0.025, two-sided significance level with 90% power, 95 evaluable patients are required per treatment group in the Full Analysis Set. If one assumes 3% of the subjects will not have a baseline and post-baseline efficacy measurement, 98 subjects per group (392 total subjects) will need to be randomised.

Further, if 40% of subjects fail to meet entry criteria for randomisation (as seen in study MB102014), then approximately 654 subjects must be enrolled.

TABLE OF CONTENTS   PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

Appendix A   Signatures

Appendix B   Additional Safety Information

Appendix C   IATA 6.2 Guidance document

Appendix D   New York Heart Association Classification

Appendix E   Optional Genetic Research

Appendix F   Algorithm on Management of Hyponatraemia

Appendix G   Case Identification and Management of Decreased Renal Function

Appendix H   Algorithm on Management of Sustained Elevated Liver Safety Abnormalities

Appendix I   Visit to Visit Guide

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)
AZ	AstraZeneca
ANCOVA	Analysis of covariance model
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC	Area under curve
BID	Twice daily
BMI	Body Mass Index
BP	Blood pressure
BUN	Blood urea nitrogen
CEC	Clinical Event Committee
CHMP	Committee for Medicinal Products for Human Use
CK	Creatin kinase
Cm	Centimetre
CPMP	Committee for Proprietary Medicinal Products
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation due to Adverse Event
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECRF	Electronic Case Report Form
EGFR	Estimated glomerular filtration rate
EMEA	European Medicines Agency
FDA	Food and Drug Administration

Abbreviation or special term	Explanation
FDC	Fixed Dose Combination
FPG	Fasting plasma glucose
FSH	Follicle simulating hormone
GCP	Good Clinical Practice
HbA1c	Glycosylated Haemoglobin A1c
ICH	International Conference on Harmonisation
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IWRS	Interactive Web Response System
Kg	Kilogram
LLOQ	Lower Limit of Quantification
LOCF	Last observation carried forward
MC	Marketing Company
MDRD	Modification of Diet in Renal Disease
MI	Myocardial infarction
MODY	Maturity-onset diabetes of the young
NYHA	New York Heart Association
OAD	Oral antidiabetic drug
PGx	Pharmacogenetics
QD	Once daily
SAE	Serious adverse event (see definition in Section 6.4.2).
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SGLT	Sodium-Glucose Transporter
SmPC	Summary of Product Characteristics
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
UACR	Urine albumin: creatinine ratio
ULN	Upper limit of normal
UTI	Urinary Tract Infection
WBDC	Web Based Data Capture
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background

Type 2 diabetes is characterised by beta-cell dysfunction and peripheral insulin resistance leading to hyperglycaemia (Matthaei et al 2000, Meier and Butler 2005). Chronic hyperglycaemia is associated with the development of both macrovascular (myocardial infarction, stroke, peripheral arterial disease), and microvascular (nephropathy, retinopathy, neuropathy) complications (UKPDS group 1998). Current treatment regimens aiming to reduce glucose levels in patients with type 2 diabetes have focused on the stimulation of insulin secretion (eg, sulphonylureas, glinides, GLP-1 analogs, DPP-4 inhibitors), improvement in insulin sensitivity (eg, metformin, thiazolidinediones), inhibition of intestinal glucose absorption (eg, acarbose), or the replacement of insulin. However, the limited efficacy of currently available antihyperglycaemic agents, as well as associated side effects (eg, hypoglycaemia, oedema, weight gain, etc.) clearly underline the need for novel antihyperglycaemic treatment strategies (ACCORD 2008, Koro et al 2004). In addition, the majority of patients with type 2 diabetes require more than one antihyperglycaemic agent to achieve glycaemic 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 hypoglycaemic 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 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 FPG, postprandial glucose, and HbA1c levels throughout the entire dose range, and was associated with weight loss (Ferrannini, 2010). Similar findings were observed in a 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). One of the conclusions is that dapagliflozin can be used in combination with conventional metformin treatment in T2DM.

Metformin (dimethylbiguanide) is a widely used oral antihyperglycaemic agent for twice daily use in the treatment of T2DM; its major effect is to decrease hepatic glucose output resulting in lower fasting plasma glucose and HbA1c levels (Garber, 1997). It is recommended as the initial pharmacological therapy as adjunct to diet and lifestyle measures in both the US and the EU because of its glycaemic efficacy, weight neutrality, low risk of hypoglycaemia, good tolerability and relatively low cost. Efficacy and safety of metformin are well characterized and adverse events are primarily digestive disturbances (Garber, 1997). Long-term metformin treatment resulted in a reduction of diabetic complications in overweight T2DM patients after diet failure (UKPDS group 1998). Long-term metformin treatment is associated with impaired absorption of vitamin B12 and folic acid but the clinical significance (such as anaemia) is unclear. Lactic acidosis has been identified as a very rare complication, for instance in patients with hypoxia, a reduced creatinine clearance below <60ml/min, or with an overdose.

With disease progression, however, many patients with T2DM who initially respond well to metformin monotherapy subsequently require an additional agent, with a different mechanism of action, to reach glycaemic goals. The combination of an agent that inhibits renal glucose reabsorption (dapagliflozin) with an agent that decreases hepatic glucose output (metformin) may have additive glucose-lowering effects. Concomitant treatment with both agents may offer potential advantages such as improved compliance and eventually better glycaemic control.

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

1.2   Research hypothesis

After 16 weeks of treatment, there will be a greater mean reduction from baseline in HbA1c achieved with dapagliflozin 2.5 or 5 mg twice daily (BID) compared to placebo in patients with T2DM who have inadequate glycaemic control on metformin alone.

1.3   Rationale for conducting this study

This Phase III trial is being conducted to evaluate the efficacy and safety of dapagliflozin given twice a day, in patients with T2DM who are inadequately controlled on metformin alone. The primary objective supports the registration requirement for approval of a fixed dose

combination of dapagliflozin with metformin. In addition, this is the first Phase III study in which dapagliflozin is administered twice a day and therefore important to establish efficacy and safety with this dosing regimen. The secondary endpoints are recognized additional attributes of SGLT2 inhibition when dapagliflozin is administered once daily.

Moreover, in one of the double-blind randomised treatment arms, patients will receive 10 mg dapagliflozin once daily (QD) co-administered with metformin as a 'positive control', a measure of assay sensitivity. Efficacy and safety in the 10 mg QD dapagliflozin treatment arm will be compared only to placebo co-administered with metformin.

To ensure that efficacy will be studied over a wide range of HbA1c levels, recruitment has been stratified. One recruitment stratum (Stratum 1) is characterized by HbA1c levels at randomisation of <7.0% (blood samples taken at Visit 3, or one week before randomisation) and will comprise up to 20% of recruited patients. The second stratum (Stratum 2) is characterized by HbA1c levels at randomisation of ≥7.0% (blood samples taken at Visit 3, or one week before randomisation) and consists of the remainder of the randomised patients.

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 patients 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 Phase III programme to monitor and/or minimize these risks, are included in the Investigator Brochure.

Inhibition of SGLT2 results in increased urinary glucose excretions, which is commonly believed to increase the risk of urinary tract infections (UTIs). In clinical 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 Phase III studies, the proportions of subjects treated with dapagliflozin who reported AEs that matched a predefined list of MedDRA preferred terms (PTs) that were indicative of genital infection were higher than those seen for placebo.

Imbalances of liver function test parameters in Phase-III studies were observed with diabetic patients in some but not all studies. Most elevations have been reversible. The enzyme elevations have not shown any specific pattern with regards to time of exposure. In addition in the ongoing blinded Phase 2/3 studies, expedited safety reports were issued concerning 1

subject with acute hepatitis, 1 subject with hepatic neoplasm malignant, and 1 subject with hepatic enzyme increased.

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.

In addition, all patients in this study will receive metformin as background medication. This medication is a widely used anti-diabetic treatment and will be prescribed according to the approved label.

Thus, the benefits and risks associated with the background medication and comparator treatment are well established and presented in their respective approved prescribing information. No study procedure will put patients 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 patients. In order to ensure the safety of all patients participating in this study, AstraZeneca and Bristol-Myers Squibb are conducting a real-time review of all safety information from all ongoing clinical dapagliflozin studies as they become available. Safety signal detection will include the integration of all available sources of safety information, including clinical study data, adverse event reports, pre-clinical data, epidemiological studies and literature reports, to identify and characterize unrecognized safety risks or changes in those which are currently expected Adverse Drug Reactions. Any information that may affect the benefit-risk profile of dapagliflozin will be immediately communicated to relevant Health Authorities and appropriate actions will be taken regarding the clinical program as needed. 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 patient risk management plan that includes the temporary and if necessary permanent discontinuation of investigational product in individual patients 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 hypoglycaemia (Section 6.4.10.1), urinary tract and genital infections (Section 6.4.10.2), hyponatraemia (Appendix F), decreased renal function (Appendix G) and liver function abnormalities (Appendix H).

Potential benefits to patients

All patients will receive active background antihyperglycaemic therapy; however, a direct benefit from randomised treatment cannot be assured as one quarter of patients will receive

placebo, and the efficacy of dapagliflozin in this clinical setting is assumed but has yet to be established. In this study, the doses of dapagliflozin (2.5 mg BID, 5 mg BID and 10 mg QD) were chosen to provide efficacy in reducing hyperglycaemia 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 especially in patients with elevated baseline blood pressure. Patients are also expected to receive some benefit in the form of increased medical care/attention when participating in study procedures, which includes at least 10 clinic visits with at least 10 physical examinations over the 25-week study. Patients will also receive counselling on dietary and life-style modifications. It is commonly observed that even patients receiving placebo in diabetes studies show some improvement in glycaemic control, likely due to their increased compliance to dietary and life-style counselling while they are participating in a clinical study.

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 patient 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 patients who meet the inclusion/exclusion criteria and consent to take part in the study.

2. STUDY OBJECTIVES

The purpose of this study is to examine the dapagliflozin treatment regimens of 2.5 mg BID and 5 mg BID as add-on to metformin therapy. The dapagliflozin 10 mg QD treatment group is provided as a measure of assay sensitivity. Comparisons of dapagliflozin 10 mg QD to placebo will be performed with nominal p-values but are not part of the primary or key secondary objectives of the study.

2.1 Primary objective

The primary objective of this study is to compare the change from baseline in HbA1c achieved with each of the 2 BID doses of dapagliflozin (2.5 mg BID and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment.

2.2 Secondary objectives

2.2.1 Key Secondary Objectives

Four key secondary efficacy objectives are identified a priori for special consideration in this study, in addition to the primary objective:

- To compare the percent change from baseline in body weight achieved with each of the 2 BID doses of dapagliflozin (2.5 mg BID and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment.

- To compare the change from baseline in fasting plasma glucose (FPG) achieved with each of the 2 BID doses of dapagliflozin (2.5 mg BID and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 1 week of double-blind treatment.

- To compare the change from baseline in fasting plasma glucose (FPG) achieved with each of the 2 BID doses of dapagliflozin (2.5 mg BID and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment.

- To compare the proportion of patients with HbA1c <7.0% achieved with each of the 2 BID doses of dapagliflozin (2.5 mg BID and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment, in patients with an HbA1c ≥7.0% at baseline.

2.2.2 Other Secondary Objectives

- To compare the change from baseline in seated systolic and diastolic blood pressure (BP) achieved with each of the 2 BID doses of dapagliflozin (2.5 mg BID and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment.

- To compare the proportion of patients with seated systolic blood pressure <130 mmHg reached with each of the 2 BID doses of dapagliflozin (2.5 mg BID and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment, in patients who had seated systolic blood pressure ≥130 mmHg at baseline.

- To compare the change from baseline in body weight achieved with each of the 2 BID doses of dapagliflozin (2.5 mg BID and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment.

- To compare the change from baseline in HbA1c achieved with 10 mg dapagliflozin QD (once daily) co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment.

- To compare the change from baseline in fasting plasma glucose (FPG) achieved with 10 mg of dapagliflozin QD co-administered with metformin versus placebo co-administered with metformin after 1 week and 16 weeks of double-blind treatment.

- To compare the proportion of patients with HbA1c <7.0% achieved with 10 mg of dapagliflozin QD co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment, in patients with an HbA1c ≥7.0% at baseline.

- To compare the percent change from baseline in body weight achieved with 10 mg of dapagliflozin QD co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment.

- To compare the change from baseline in body weight achieved with 10 mg of dapagliflozin QD co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment.

- To compare the change from baseline in seated systolic and diastolic blood pressure (BP) achieved with 10 mg of dapagliflozin QD co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment.

- To compare the proportion of patients with seated systolic blood pressure <130 mmHg reached with dapagliflozin 10 mg QD co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment, in patients who had seated systolic blood pressure ≥130 mmHg at baseline.

2.3   Safety objective

To examine the safety and tolerability of dapagliflozin co-administered with metformin versus placebo co-administered with metformin by assessment of AEs, laboratory values, electrocardiogram, pulse, blood pressure, hypoglycaemic events, calculated creatinine clearance, estimated glomerular filtration rate and physical examination findings.

2.4   Pharmacogenetic Objective

To collect and store DNA for future exploratory research into genes that may influence response, eg, safety, tolerability and efficacy of dapagliflozin treatment and genetic factors that may influence susceptibility to type 2 diabetes and/or associated conditions.

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 16-week, international, multicentre, randomised, double-blind, double dummy, parallel-group, placebo-controlled, pivotal Phase III study to evaluate the efficacy and safety of dapagliflozin 2.5 mg BID, 5 mg BID and 10 mg QD in patients with type 2 diabetes. Dapagliflozin or placebo will be added to the therapy of patients who have inadequate glycaemic control on metformin therapy alone.

For the definition of inadequate glycaemic control see Section 4.1, Inclusion Criterion 5.

Figure 1   Study flow chart
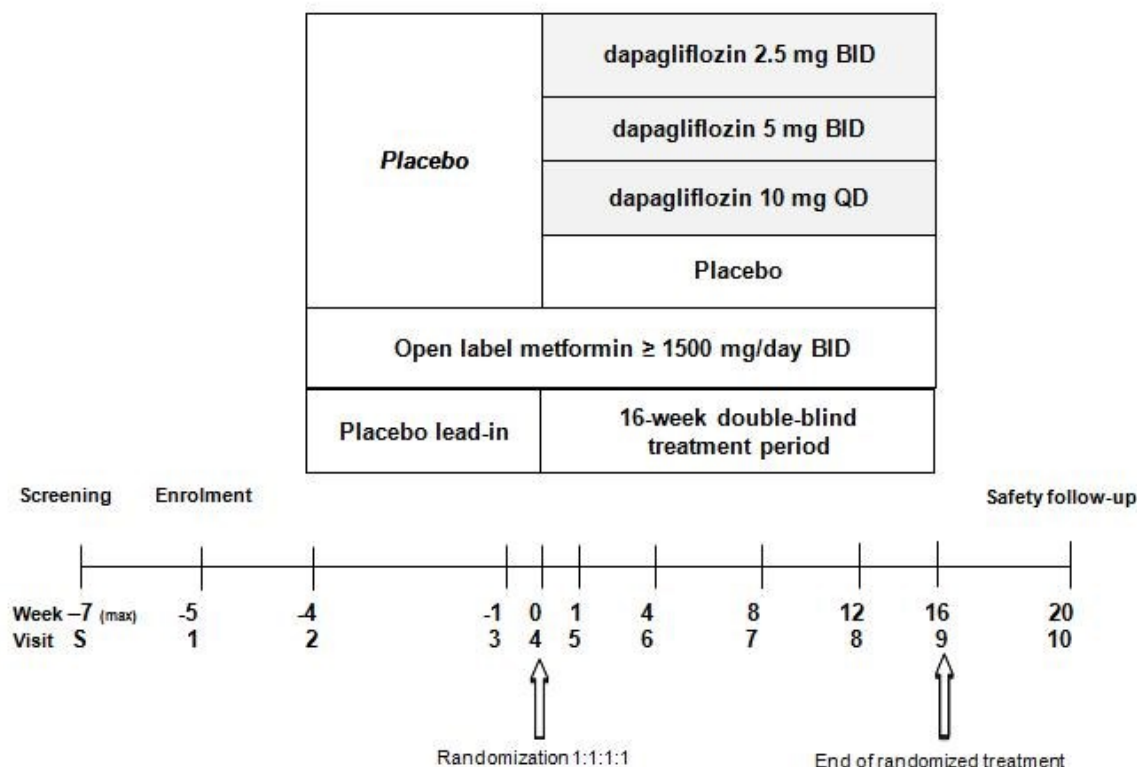
Before entry into the study, patients will be screened for an HbA1c level. Patients who meet the HbA1c inclusion criterion can be enrolled and examined for all inclusion and exclusion criteria.

At the start of the open-label treatment (Visit 2), pre-study metformin will be discontinued and replaced with metformin 500 mg tablets provided by the sponsor. In addition, patients will receive two different type of placebo tablets ('double-dummy'), matching placebo for dapagliflozin 2.5 mg and 5 mg (9 mm) BID and matching placebo for dapagliflozin 10 mg

23(89)

(11 mm) QD (see Section 5.5.2.). The objective of the placebo lead-in period is to ensure that patients are compliant with background therapy, and that only patients who continue to meet the inclusion and exclusion criteria are randomised and receive investigational product or placebo. Criteria for randomisation will be checked at Visit 3.

Upon meeting these criteria, patients will be randomised to the 16-week double blind treatment period.

After either completion of the treatment period, or discontinuation from treatment, patients will enter a 4-week follow-up period. The follow-up visit provides the opportunity to further evaluate changes in physical signs, symptoms or laboratory parameters that may be related to dapagliflozin treatment.

The total planned study duration from Visit 1 to the safety follow-up (Visit 10) will be 25 weeks.

This international study will be conducted at approximately 65 study centres. It is estimated that 940 patients will be screened to achieve 654 enrolled patients, to reach the target of 392 randomised patients during an enrolment period of approximately 6.5 months.

It is expected that 5 to 7 patients will be randomised per centre. Globally patients will be randomised to ensure a 1:1:1:1 ratio of patients in the 4 arms. Recruitment will be competitive between sites and countries. Centres may be discontinued from the study if recruitment rates are poor and new centres may be added if necessary to achieve recruitment goals.

3.1.1 Study Periods

3.1.1.1 Screening Visit

Failure to meet the HbA1c inclusion criterion is one of the main reasons for screening failure in diabetes treatment studies. Discrepancies between locally and centrally determined HbA1c values are common. Therefore, in this study screening activity will comprise submission of one blood sample to determine the HbA1c at the central laboratory.

A screening informed consent form will be provided by AstraZeneca to all the centres, and implemented locally based on all applicable regulatory requirements and laws. The written screening informed consent must be obtained prior to conducting screening visit (Visit S) activities.

Patients will be allowed to proceed to Visit 1 only if they meet HbA1c inclusion criteria (Inclusion criterion 5, Section 4.1). Patients are not allowed to be re-screened.

If the target number of randomised patients within Stratum 1 is reached (up to 20% of randomised patients), communication will be sent out to all sites that screening and enrolment will only continue for patients in Stratum 2 with an HbA1c $\geq 7.2\%$ and $\leq 10.5\%$ (see Section 4.1, inclusion criterion no. 5, Note 1). For patients in Stratum 2, the randomisation criterion of HbA1c $\geq 7.0\%$ and $<10.0\%$ will apply (see Section 4.1, inclusion criterion no. 6, Note 2).

If the target number of enrolled patients for both strata combined is reached, enrolment will be stopped by AstraZeneca in IWRS and central laboratory processing.

All patients who are screened should be listed on a patient screening log, with an S number allocated in consecutive order, having a tick-box for confirmation if the patient was enrolled or not. See also Section 6.2.

3.1.1.2 Enrolment Visit (Visit 1, week –5)

Eligible patients should be seen for Visit 1 within 3 to 14 days after screening. Patients will sign informed consent, undergo repeated check for all applicable inclusion and exclusion criteria, and submit laboratory samples. Diet and lifestyle advice will be given.

The existing patient's metformin medication and dose will remain unchanged. No other anti-diabetic drugs are allowed. If applicable, anti-hypertensive medication need to be reviewed and can be adjusted.

3.1.1.3 Placebo lead-in period (Visit 2-3, week –4 to week 0)

At the beginning of the placebo lead-in period (Visit 2, week –4) patients will undergo repeated checks for inclusion/exclusion criteria. Appropriate diet and exercise counselling will be reviewed with all patients at this visit.

At Visit 2, all eligible subjects will stop their original metformin treatment, they will be provided with study drug open-label 500 mg metformin tablets and continue their metformin dose for the duration of the study. Subjects, whose current therapy is not based on 500 mg metformin tablets, will have their dose modified as noted in Table 1.

The open-label metformin dose will remain stable throughout the study. If the metformin dose will require unequal BID dosing, it is up to the investigator and patient to decide when the larger dose should be taken, to decrease the risk of undesired gastrointestinal effects.

Table 1   Adjustment of metformin dose

If patients' pre-study metformin dose is	Adjust open-label metformin therapy to
≥1500 and ≤1749 mg/day	1500 mg/day
≥1750 and ≤2249 mg/day	2000 mg/day
≥2250 mg/day	2500 mg/day

In addition, patients will receive two different type of placebo tablets ('double-dummy'), matching placebo for dapagliflozin 2.5 mg and 5 mg (9 mm) BID and matching placebo for dapagliflozin 10 mg (11 mm) QD (see Section 5.5.2.). Placebo will be used to assess subject's compliance with treatment. Subjects should demonstrate good compliance with study medication (≥80% and ≤120%) during the lead-in period. For other subjects the Investigator should ensure that there are no systematic factors which may result in unacceptable

compliance with study medication during the treatment period of the trial, such cases should be discussed with the Study Team Physician prior to randomisation.

At Visit 2, a glucometer and a patient diary will also be provided to patients and they will be instructed to monitor their FPG at least every second day and to enter the results into the patient diary. Investigators may instruct patients to monitor their FPG more often, according to their local treatment guidelines or clinical judgement. For FPG monitoring procedures and assessment of hypoglycaemic events, refer to Section 6.4.10.1.

During the placebo lead-in period, background antihypertensive medications should be adjusted in patients with seated systolic BP ≥160 mmHg or seated diastolic BP ≥100 mmHg. Only those patients with seated systolic BP <160 mmHg and diastolic BP <100 mmHg at the end of placebo lead-in period will be randomised.

At Visit 3 assessments are performed primarily to check eligibility for randomisation, following one week later. HbA1c, FPG and CK measured by the central laboratory in a sample taken at Visit 3 will be used for assessment of corresponding eligibility criteria at randomisation.

3.1.1.4 Randomisation and Double-blind Treatment Period (Visits 4-9, week 0 to week 16)

Randomisation visit (Visit 4, week 0)

Eligible patients will be randomised at Visit 4 (week 0, baseline) in a 1:1:1:1 ratio to receive either dapagliflozin 2.5 mg BID, or dapagliflozin 5 mg BID, or dapagliflozin 10 mg QD, or placebo. At Visit 3, one week before randomisation, patients will be stratified based on 1 recruitment factor:

Factor 1: HbA1c value (determined in the blood sample taken at Visit 3, one week before randomisation).

- Stratum 1 (HbA1c <7.0% at randomisation)

- Stratum 2 (HbA1c ≥7.0% at randomisation)

Stratum 1 is planned to be a maximum of 20% of the randomised patients. If the number of patients in Stratum 1 reaches 20% (n=78) of the total number of planned randomised patients (20% of 392 anticipated is: 78 patients), communication will be sent out to all sites that screening and enrolment will only continue for patients in Stratum 2 with an HbA1c ≥7.2% and <10.5% (see Section 4.1, inclusion criterion no. 5, Note 1). For these patients in Stratum 2, the randomisation criterion for HbA1c ≥7.0% and <10.0% will apply (see Section 4.1 inclusion criterion no. 6, Note 2).

Maintenance Treatment Period (Visits 5-9)

Patients will follow up at week 1 (Visit 5), week 4 (Visit 6), week 8 (Visit 7), week 12 (Visit 8) and week 16 (Visit 9) after randomisation, completing the randomised treatment period.

Patients will continue to monitor their FPG levels at least every second day and will continue to enter the results into the patient diary. Investigators may instruct patients to monitor their FPG more often, according to their local treatment guidelines or clinical judgement. Hypoglycaemic events should also be entered into the patient diary. For FPG monitoring procedures and assessment of hypoglycaemic events please refer to Section 6.4.10.1. Diet and lifestyle modification will be reinforced at each visit during the double-blind treatment period.

The following table displays criteria for lack of glycaemic control during the double-blind treatment period. For Visit 6 measurement FPG >240 mg/dL (13.2 mmol/L), and for Visit 8 measurement FPG >200 mg/dL (11.1 mmol/L) will be considered as threshold. Subjects who lack glycaemic control as defined below will be discontinued from the study and will have follow up visit procedures performed. Up-titration of metformin dose during the study will not be allowed.

Table 2   Definition of lack of glycaemic control during the randomised treatment period

Period	Central Laboratory FPG
From week 1 (Visit 5) to week 4 (Visit 6)	FPG >270 mg/dL (15 mmol/L)
From week 4 (Visit 6) to week 12 (Visit 8)	FPG >240 mg/dL (13.2 mmol/L)
From week 12 (Visit 8) to week 16 (Visit 9)	FPG >200 mg/dL (11.1 mmol/L)

Changes in antihypertensive medication may be made as needed for appropriate blood pressure management. All medication changes, including dose modifications and the last blood pressure value measured before a medication change should be recorded in the Electronic Case Report Form (eCRF).

End of Treatment Visit (Visit 9)

Patients will stop taking all study drugs at the end of the treatment period (Visit 9, week 16). The End of Treatment Visit procedures should be performed as soon as possible but at the latest 7 days after discontinuation, for any reason (see Section 4.3.1).

3.1.1.5   Follow-up period (Visit 10, week 20)

Patients will be followed up for 4 weeks after discontinuing investigational product. During this time patients can be treated for their type 2 diabetes according to country-specific or

regional guidelines as necessary without any further protocol restrictions. It is at the discretion of the investigator to continue with the metformin at the dosing schedule used during the double blind treatment period.

Table 3   Study Plan

Visit	Screening	Enrolment	Open label metformin/ placebo lead in		16-week double blinded treatment period						Follow-up visit
	S	1 (E)	2	3	4 (R)	5	6	7	8	9 (EoT)[f]	10
Week	-7 max	- 5	-4	-1	0	1	4	8	12	16	20
Visit window (days) [e]	(-14 to -3)	(0)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)
Screening informed consent and blood sample HgbA1c	X										
Informed consent		X									
Demography and medical history		X									
Inclusion/Exclusion criteria		X	X	X	X						
Randomisation					X						
Brief physical examination			X	X		X	X	X	X		X
Complete physical examination		X			X					X	
Vital signs		X	X		X	X	X	X	X	X	X
Weight		X	X	X	X	X	X	X	X	X	X
Height		X									
12-lead ECG		X			X					X	
Concomitant medication		X	X	X	X	X	X	X	X	X	X
Laboratory assessments [a]		X	X	X	X	X	X	X	X	X	X
Pregnancy test [b]		X	X	X	X	X	X	X	X	X	X

29(89)

Visit	Screening	Enrolment	Open label metformin/ placebo lead in		16-week double blinded treatment period						Follow-up visit
	S	1 (E)	2	3	4 (R)	5	6	7	8	9 (EoT)[f]	10
Week	-7 max	- 5	-4	-1	0	1	4	8	12	16	20
Visit window (days) [e]	(-14 to -3)	(0)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)
AEs			X	X	X	X	X	X	X	X	X
SAEs		X	X	X	X	X	X	X	X	X	X
Dispense open label metformin			X		X		X	X	X		
Dispense investigational product/placebo			X		X		X	X	X		
Drug accountability				X	X	X	X	X	X	X	
Diet and life-style advice		X	X	X	X	X	X	X	X	X	
Dispense glucometer at V2; provide supplies and instructions			X	X	X	X	X	X	X		
Dispense patient diary			X	X	X	X	X	X	X		
Patient diary review for/glucometer values/ hypoglycaemic events [c]				X	X	X	X	X	X	X	
Informed consent, blood sample for genetic research [d]					X						

a) Specifications of laboratory parameters will be shown in separate tables

b) Pregnancy test will be done on all female patients who are not postmenopausal or hysterectomised.

c) Patients should be instructed to contact investigator by phone if a hypoglycaemic event occurs, in cases specified in the patient diary.

d) Genetic informed consent must be obtained before genetic blood sample is taken. Blood sample donation is optional and can be done any time from Visit 4 (ie, randomisation) to Visit 9.

e) Once a patient is randomised, all visits should be scheduled relative to Visit 4. Any slippage in time from one visit must not accumulate to affect other visits.

f) EoT visit procedures should be performed in case if a patient is discontinued after randomisation, for any reason

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 BID versus matching placebo BID in patients with T2DM who have inadequate glycaemic control on metformin alone.

Moreover, efficacy and safety of dapagliflozin QD co-administered with metformin will be compared with matching placebo QD co-administered with metformin.

The study has standard design features for a confirmatory pivotal Phase III FDC diabetes study (eg, multi-centre, randomised, double-blind, parallel group, co-administration of each of the active components, and placebo comparisons with the active add-on components) and incorporates the relevant features of the Committee for Proprietary Medicinal Products' guidance for investigations of diabetes (CPMP 2002) with regard to duration of treatment, choice of study population, and choice of outcome variables. The dapagliflozin 10 mg QD arm is a 'positive control with placebo', a measure of assay sensitivity, and not contributory to the primary objective and key secondary objectives.

3.2.2 Study doses and control groups

Investigational product doses

Dapagliflozin 2.5 mg and 5 mg tablets, administered orally BID and dapagliflozin 10 mg tablets administered orally QD with metformin, just prior to, or with, meals for the 16-week double-blind treatment period.

Control group

Matching placebo for dapagliflozin 2.5 mg and 5 mg tablets administered orally BID and matching placebo for dapagliflozin 10 mg tablet administered orally QD with metformin, just prior to, or with, meals for the 4-week placebo lead-in period and the 16-week double-blind treatment period.

Background therapy

Open-label metformin IR 500 mg tablets administered orally BID just prior to, or with meals, at doses ≥1500 mg/day for the 4-week placebo lead in/open label metformin period and the 16-week double-blind treatment period. Metformin is approved for use at doses up to 3000 mg/day but this can differ between countries. In several countries, metformin is not indicated for use in patients with a creatinine clearance <60 ml/min because of metformin accumulation and an increased risk of lactic acidosis, a very rare condition that is associated with increased mortality. Metformin is contra-indicated for use in diseases which may cause sudden hypoxia such as dehydration, severe infection, respiratory failure, or a recent myocardial infarction. Efficacy, safety and tolerability of metformin are well documented in the literature.

Dapagliflozin

The 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 and 2-week multiple ascending-dose studies in healthy patients and patients with type 2 diabetes), dapagliflozin was safe and well tolerated with a favourable pharmacokinetic and pharmacodynamic profile. A Phase IIb study in patients with type 2 diabetes demonstrated good glycaemic efficacy and an acceptable safety profile over a wide range of doses. Based on considerations of efficacy, pharmacodynamic, and safety data from the Phase I and II programs, daily doses up to 10 mg daily of dapagliflozin have been chosen for the Phase III studies. Daily doses of 5 and 10 mg were chosen for this study as they have been extensively studied in Phase III trials. A recent publication has reported on the efficacy, tolerability and safety of dapagliflozin 2.5 mg, 5 mg and 10 mg once daily as add on therapy to metformin (Bailey 2010).

3.2.3 Choice of outcome variables

HbA1c is the variable of choice for assessment of glycaemic control and is required for registration purposes, but fasting plasma glucose will also be measured at each visit.

Because of its novel, complementary mechanism of action, dapagliflozin may have additive or synergistic HbA1c-lowering effects when given in combination with other antihyperglycaemic agents. Additionally, as beneficial effects on weight, systolic blood pressure (SBP) and FPG have been observed in other dapagliflozin studies, these variables have been chosen as key and non-key secondary objectives (see Table 4).

Table 4   Efficacy variables with related objectives and rationale

Efficacy variable	Related objective	Rationale
HbA1c	Change in HbA1c from baseline at week 16. Proportion of patients with HbA1c <7.0% at 16 weeks, in patients who had HbA1c ≥7.0% at baseline.	HbA1c is the clinical and regulatory parameter used to estimate glycaemic efficacy in patients with type 2 diabetes (CPMP 2002). HbA1c targets for patients with type 2 diabetes range from <6.5% (IDF 2005, AACE 2007) to <7.0% (ADA 2009, ADA 2010). The degree of change in HbA1c in patients with type 2 diabetes is related to the baseline HbA1c level; patients with higher HbA1c at baseline tend to have greater reductions in HbA1c when treated with any antihyperglycaemic agent (Bailey 2010, Bloomgarden 2006)

Efficacy variable	Related objective	Rationale
Fasting Plasma Glucose	Change in FPG from baseline at week 1. Change in FPG from baseline at week 16.	Fasting plasma glucose is a well-established measure of glycaemic efficacy, and is considered by the CHMP (Committee for Medicinal Products for Human Use) to be acceptable as secondary endpoint (CPMP 2002).
Weight	Percent change in body weight from baseline at week 16. Change in body weight from baseline at week 16.	More than 85% of patients with T2DM are overweight (BMI ≥ 25 kg/m^2) or obese (BMI ≥ 30 kg/m^2) (CDC 2004). Weight loss is a fundamental goal for the majority of patients with type 2 diabetes since it has been shown to improve comorbid conditions such as hypertension, dyslipidemia, heart disease, osteoarthritis, and sleep apnea
Blood pressure	Change in seated SBP and DBP from baseline at week 16 Proportion of patients with seated systolic blood pressure <130 mmHg, at week 16 who had seated systolic blood pressure ≥ 130 mmHg at baseline	The American Diabetes Association and the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 2004) guidelines recommend a blood pressure target of <130/80 in patients with diabetes (ADA 2009, JNC 2004). Lowering blood pressure in patients with diabetes has been shown to reduce the risk of coronary heart disease events, stroke, retinopathy and nephropathy (JNC 2004).

Age

The prevalence of type 2 diabetes increases with age; it is therefore important to assess the safety of antihyperglycaemic agents in elderly patients. In this study upper age limit for patients is 77 years, taking into account the upper age limit based on local metformin prescribing guidelines, as well as the upper age limit used in a phase III dapagliflozin monotherapy study.

HbA1c

The HbA1c inclusion criterion at randomisation was selected to include patients with a wide range of glycaemic control. The lower bound of this HbA1c inclusion window (ie, 6.5%) reflects the most recent treatment guidelines (IDF 2005, AACE 2007) as well as the HbA1c threshold (6.5%) to diagnose T2DM (ADA 2010). Other guidelines recommend treatment to somewhat higher HbA1c targets such as HbA1c <7.0% (ADA 2009). Results of recent studies suggest that a rigorous lowering of HbA1c to stricter targets may not be appropriate for all patients, suggesting that the pathophysiology of type 2 diabetes needs to be considered in pharmacological treatment combinations (ACCORD 2008, ADA 2009, Hanefeld and Forst, 2010). The upper limit of the HbA1c inclusion window (ie, 10.0%) was chosen because insulin is generally the treatment of choice for patients with HbA1c values above this level (ADA 2009). The HbA1c inclusion window allows the evaluation of dapagliflozin co-administered with metformin versus placebo co-administered with metformin over a wide range of HbA1c. To ensure that dapagliflozin's and metformin's efficacy, safety and tolerability are studied over the entire range of HbA1c, patients will be stratified according to their HbA1c at randomisation, limiting the number of patients in Stratum 1 (HbA1c <7.0%) at randomisation to 20% of the total study population (see Section 3.1.1.4).

Kidney Function

The exclusion criteria that relate to creatinine and creatinine clearance are consistent with prescribing guidelines for metformin ≥1500 mg/day.

Pregnancy or breastfeeding

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 T2DM, haemoglobinopathies that would interfere with the HbA1c analyses) or to exclude patients whose safety could be compromised by participation in the study.

4.   SUBJECT SELECTION CRITERIA

Patient population should be selected without bias.

Investigator(s) must keep a record of patients who entered pre-trial screening but were never enrolled eg, patient screening log.

Each patient 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

The following criteria apply to the enrolment (Visit 1), whereas inclusion criterion no. 6 applies to Visit 3 and Visit 4 (Randomisation).

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

2.   Diagnosis of T2DM

3.   Men or women age ≥18 to ≤77 years old at time of consenting

4.   Current antihyperglycaemic treatment with metformin immediate release formulation monotherapy ≥1500mg/day at a stable dose for at least 10 weeks prior to enrolment. Other treatment with OADs within the 10 weeks prior to enrolment is not permitted.

5.   HbA1c ≥6.7% and ≤10.5%, based on central laboratory values from Screening Visit, and Enrolment Visit 1. **Note 1**: In the case that Stratum 1 has met its goal for randomised patients, communication will be sent out to all sites that screening and enrollment will only continue for patients in Stratum 2 with an HbA1c ≥7.2% and ≤10.5%. For these patients in Stratum 2, randomisation criteria of HbA1c ≥7.0% and ≤10.0% will apply (see also inclusion criterion no. 6, Note 2, below).

6.   HbA1c ≥6.5% and ≤10.0%, based on central laboratory values obtained at Visit 3, one week prior to randomisation. **Note 2**: In the case that Stratum 1 has met its goal for randomised patients, HbA1c randomisation criteria will change to those applicable for Stratum 2: HbA1c ≥7.0% and ≤10.0%, based on central lab values at Visit 3, one week prior to randomisation.

7.   Women of childbearing potential (WOCBP) who comply with the following:

  –   Use a highly effective method of birth control (see below) 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 HCG) within 72 hours prior to the start of study medication and at each visit

Definitions:

Women of Child Bearing Potential - Women between menarche and menopause who have not been permanently or surgically sterilized and are capable of procreation.

Women NOT of Childbearing Potential - Women who are permanently or surgically sterilized or postmenopausal. Permanent sterilisation includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion. Tubal occlusion is considered a highly effective method of birth control but does not absolutely exclude possibility of pregnancy. (The term occlusion refers to both occluding and ligating techniques that do not physically remove the oviducts).

Post Menopausal Women - Women will be considered postmenopausal if they are amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women under 50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and have FSH levels ≥40 mIU/mL.

- Women over 50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments.

Highly effective method of birth control is defined as one that results in a low failure rate (eg, less than 1 percent per year) when used consistently and correctly. The following are considered acceptable methods of contraception: Total sexual abstinence; Vasectomised sexual partner; Tubal occlusion (ligation); IUD; IUS levonorgestrel Intra Uterine System (eg, Mirina); Etonogestrel implants (eg, Implanon, Norplan); Normal and low dose combined oral contraceptive pills; Norelgestromin/EE transdermal system; Intravaginal device (eg, EE and etonogestrel); Cerazette (desogestrel)

4.2 Exclusion criteria

Patients must not enter the study if any of the following exclusion criteria are fulfilled.

The following criteria apply to enrolment (Visit 1).

Laboratory value criteria apply at the start of placebo lead in/ open label metformin treatment period (Visit 2, using laboratory values from Visit 1).

Laboratory value criterion no. 27 should be repeatedly checked including at Randomisation (Visit 4, using laboratory value from Visit 3).

Endocrine and metabolic disorders

1. Diagnosis of Type 1 diabetes mellitus, known diagnosis of Maturity Onset Diabetes of the Young (MODY) or secondary causes of 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 >270 mg/dL (>15.0 mmol/L)

5.   BMI >45 kg/m^2

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) and free T4 values outside normal range. An abnormal TSH value needs to be followed up with a free T4 test. Patients with abnormal free T4 values will be excluded. Patients with an elevated TSH and normal free T4 will be allowed if referred to their family doctor for thyroid hormone replacement therapy prior to randomisation.

Kidney disorders

9.   Creatinine Clearance: <60 mL/min (calculated by Cockcroft-Gault formula) or a measured serum creatinine value of ≥1.5 mg/dL (133 μmol/L) for male patients and ≥1.4 mg/dL (124 μmol/L) for female patients

10.   Urine albumine: creatinine ratio >1800 mg/g

11.   History of unstable or rapidly progressing kidney disease

12.   Known condition of familial renal glucosuria

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) >3xULN

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

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

16.   History of drug-induced liver enzyme elevations

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 III or IV (see Appendix D), unstable or acute congestive heart failure. Note: eligible patients 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 3 months prior to the screening visit, 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, patients who have unstable cardiovascular disease at enrolment in the judgment of the investigator are excluded from the study.

20.   Blood pressure:

- *At enrolment (Visit 1):* Systolic BP $\geq$170 mmHg and/or diastolic BP $\geq$110 mmHg

- *At randomisation (Visit 4):* Systolic BP $\geq$160 mmHg and/or diastolic BP $\geq$100 mmHg

Hematologic/oncologic disorders/conditions

21.   Haemoglobin $\leq$10 g/dL ($\leq$100 g/L) for men; haemoglobin $\leq$9.0 g/dL ($\leq$90 g/L) for women

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

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

24.   Donation or transfusion of blood, plasma, or platelets within the past 3 months prior to Visit 1

25.   History of malignancy within the last 5 years, excluding successful treatment of basal or squamous cell skin carcinoma or in situ carcinoma of the cervix.

Infectious disease/immunologic disorders

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

Musculoskeletal disorders

27.   Creatine Kinase (CK) >3xULN

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

Reproductive status

29.   Pregnant or breastfeeding patients

Prohibited medications

30.   Use of antihyperglycaemic medications other than metformin during the 10 weeks prior to enrolment

31.   Use of insulin within 24 weeks of enrolment (with the exception of insulin use during a hospitalization or during pregnancy in patients with past history of gestational diabetes).

32.   Use of weight loss medication, including but not limited to sibutramine, phentermine, orlistat, rimonabant, benzphetamine, diethylproprion, methamphetamine, and/or phendimetrazine, within 60 days prior to enrolment.

33.   Treatment with 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; topical or inhaled corticosteroids are allowed

34.   Treatment with unstable doses of teriparatide, bisphosphonates and/or calcitonin (note: teriparatide, bisphosphonates and calcitonin are allowed provided the dose has not changed within 30 days prior to enrolment).

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

Other

36.   Intolerance, contraindication or potential allergy or hypersensitivity to metformin, placebo, or formulation excipients

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

38.   Patients who, in the judgement of the investigator, 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

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 screening, enrolment or randomisation to treatment in the present study

43.   Previous participation in a clinical study with dapagliflozin (BMS-512148) and/or with any other SGLT2 inhibitor in which the patient received at least one dose of investigational product

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

For the participation in the optional genetic research, patients must not have had:

45.   Previous bone marrow transplant

46.   Whole blood transfusion within 120 days of the date of genetic sample collection

4.3   Withdrawal of patients

4.3.1   Criteria for discontinuation from the study

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

General discontinuation criteria:

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

2.   Risk to patients as judged by the investigator and /or AstraZeneca

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

4.   Incorrectly enrolled patients (see Section 5.3)

5.   Patient lost to follow-up as defined by inability to reach the patient after 3 documented phone calls, faxes, or emails; inability to contact the patient through patient locator agencies (if allowed per national regulation); and lack of response by the patient to one letter by registered/certified mail. All attempts at contact should be documented in the patient's medical records

6.   Adverse Events, 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 patient

7.   Withdrawal of informed consent to the use of biological samples collected as an integral part of the study, see Section 7.5

Study-specific discontinuation criteria:

8.   Use of (need for) any antihyperglycaemic medication other than investigational product or open-label metformin. However, insulin use is permitted in the following situations:

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

   (b)   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 glycaemic control.

   (c)   For up to 14 days total during the study and up to 7 continuous days if patients have to temporarily stop investigational product and/or open-label metformin due to recommendations made in this clinical study protocol.

   (d)   For up to 7 days during hospitalisation as long as the primary reason for hospitalisation is not management of the patient's glycaemic control.

9.   Treatment with glucocorticoids equivalent to oral prednisolone >10 mg/day (one temporary period of higher daily doses for no longer than 7 days is allowed)

10.   Major and/or frequent hypoglycaemic events, defined as ≥1 major event or recurring minor events (see Section 6.4.10.1 for definition of minor and major). This definition should be applied after possible contributing factors (eg, excessive physical activity) have been excluded by the investigator

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

12.   Patients who have an FPG >270 mg/dL (15 mmol/L) between week – 4 and week 4 (visits 2 to 6), have an FPG >240 mg/dL (13.2 mmol/L) between week 4 and week 12 (visits 6 to 8), and have an FPG >200 mg/dL (11.1 mmol/L) between week 12 and week 16 (visits 8 to 9). See Section 3.1.1.4, Table 2 for definition of lack of glycaemic control.

13.   Change in kidney function (Please see Appendix G for further guidance): calculated creatinine clearance <60 mL/min or an increase in serum creatinine of ≥0.5 mg/dL

above the baseline value confirmed by a repeated measurement within one week or increase in creatinine that would preclude continued treatment with metformin according to local guidance.

14.   CK >10xULN confirmed at a repeated measurement preferably within 24 hours, but not exceeding 72 hours, see Section 6.4.14

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

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

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

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

16.   Serum Sodium ≤125 mmol/L with or without symptoms; see Appendix F for further guidance

17.   Since intravascular administration of iodinated contrast agents in radiologic studies can lead to renal failure, metformin should be discontinued prior to or at the time of the test and restarted 48 hours later, after renal function has been re-evaluated and confirmed to be normal.

18.   Metformin should be discontinued 48 hours before elective surgery with general anaesthesia and should not be resumed within 48 hours of the procedure.

4.3.2   Procedures for discontinuation of a patient from the study

Pre-randomisation

A patient that discontinues will always be asked about the reason(s) for discontinuation and the presence of any AEs. If possible, they will be seen and assessed by an investigator(s). AEs will be followed up (See Sections 6.4.1 and 6.4.4); patient diaries and study drug should be returned by the patient.

Randomised patients

Randomised patients who discontinue the study before week 16 should return and complete the procedures described for Visit 9 as soon as possible but at the latest 7 days after discontinuation. These patients should also be scheduled for a follow-up visit (ie, procedures of Visit 10) four weeks after discontinuation of investigational product. In addition the investigator should follow patients who discontinue the study due to an AE including a laboratory abnormality until the event has been resolved or stabilised.

After discontinuation of investigational product and open-label metformin, alternative antihyperglycaemic treatment should be considered according to the investigator's judgement and according to local medical practice.

Patients with an increased CK >10xULN will have their investigational product withheld and repeated CK test preferably within 24 hours, but not exceeding 72 hours. If repeated CK is still >10xULN the patient should permanently discontinue 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.

Patients who use an HMG-CoA-reductase inhibitor (a 'statin') will be advised to promptly report muscle pain, tenderness or weakness, and discontinue the statin if signs or symptoms appear. The statin should be discontinued if markedly elevated CK levels occur, for instance CK >5xULN. CK elevations that are greater than 3xULN but less than 10xULN need to be confirmed by a repeated measurement preferably within one week, after which a decision is made to discontinue the statin treatment, or resume the treatment, perhaps at a lower dose, according to country-specific guidelines.

Patients with increased liver function tests as defined in Section 6.4.15 will be scheduled for a follow-up visit within 3 calendar days following the receipt of the result. Patients may remain on study medication until the confirmatory results are obtained. See Appendix H for further guidance. If repeat liver function tests still are increased as outlined in Section 6.4.15 the patient should permanently discontinue study medication and be withdrawn from the study (see Appendix H for further guidance).

4.3.2.1 Procedures for discontinuation from genetic aspects of the study

A patient may withdraw from the genetic research at any time, independent of any decision concerning participation in other aspects of the main study described in this protocol. Voluntary discontinuation by the patient will not prejudice further treatment.

Patients who discontinue from the study should always be asked specifically whether they are also withdrawing or continuing their consent for genetic research. It must be established whether the patient:

- Agrees to the genetic sample and any DNA extracted from the sample being kept for genetic research in the future.

- Withdraws consent for the sample to be kept for genetic research in the future and wishes the sample to be destroyed. Destruction of the sample (or the DNA extracted from the sample) will only be possible as long as the particular sample is traceable. In the event that genetic research has already been performed, AstraZeneca and Bristol-Myers Squibb will retain the results and associated data for regulatory reasons.

The principal investigator is responsible for providing written notification to AstraZeneca and Bristol-Myers Squibb of any patient who has withdrawn consent for the use of the sample taken for genetic research. AstraZeneca and Bristol-Myers Squibb will provide written confirmation to the investigator of the actions taken with the sample, which must be filed in the investigator study file.

Procedures for withdrawal of incorrectly enrolled subjects see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

All patients will visit the clinic fasting, in the morning, before 11 a.m. if possible. Patients will be instructed to abstain from all food and beverages for 12 hours prior to each clinic visit (drinking water is allowed). Permitted medications may be taken with water only.

Patients should not drink alcohol within 24 hours prior to each visit and should not use tobacco/nicotine within 12 hours prior to each visit.

Patients should not take investigational product or open-label metformin on the morning of the clinic visit. These medications should be taken with their first meal of the day.

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

Approximately 152 ml of blood will be drawn from each patient during the entire duration of the clinical study (excluding optional genetic blood sample and extra blood samples taken at unscheduled visits), patients 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 Sections 4.2 and 4.3.1. Fasting prior to laboratory assessments is described in Section 6.4.6.

5.2 Subject enrolment and randomisation

The principal investigator or delegate will:

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

2.   Perform enrolment call in Interactive Web Response System (IWRS), to obtain the unique enrolment number assigned, beginning with "E#"(E-code).

3.   From Visit 1 to Visit 4 determine patient eligibility. See Sections 4.1 and 4.2.

4.   Perform drug allocation call for assigning Placebo Lead-In and Metformin at Visit 2 in IWR system

The E-code will be used to identify the patient throughout study participation. Patient eligibility will be established before treatment randomisation.

Randomisation codes will be assigned strictly sequentially as patients are eligible for randomisation.

If a patient discontinues participation in the study, then his/her enrolment/randomisation code cannot be reused.

If patients have discontinued their participation in the study then they cannot re-enter into the study.

5.2.1 Procedures for randomisation

Randomisation to study treatment will be done via an IWRS on Visit 4, in balanced blocks in order to ensure approximate balance among treatment arms. Patients will be stratified by HbA1c at randomisation (Stratum 1, Stratum 2). The IWRS will allocate a randomisation code according to a randomisation scheme prepared by AstraZeneca.

The number and size of tablets will be identical between dapagliflozin 2.5 mg and 5 mg tablets and its matching placebo. Dapagliflozin tablets 10 mg will be identical in size and number to its matching placebo.

The size of the dapagliflozin tablets 2.5 mg and 5 mg and matching placebo (all 9 mm) is slightly smaller than the dapagliflozin tablet 10 mg and matching placebo (both 11 mm).

Patients will receive 3 bottles together with instruction to take one tablet in the morning and one tablet in the evening from the 2.5 mg, 5 mg and matching placebo bottles containing smaller tablets (with white booklet label) and 1 tablet in the morning from the 10 mg and matching placebo bottle (with yellow booklet label).

For treatment A, patients will receive dapagliflozin 2.5 mg BID and matching placebo for dapagliflozin 10 mg QD in the morning.

For treatment B, patients will receive dapagliflozin 5 mg BID and matching placebo for dapagliflozin 10 mg QD in the morning.

For treatment C, patients will receive matching placebo for dapagliflozin 2.5 mg and 5 mg BID and dapagliflozin 10 mg QD in the morning.

For treatment D, patients will receive matching placebo for dapagliflozin 2.5 mg and 5 mg BID and matching placebo for dapagliflozin 10 mg QD in the morning.

Random kit numbers will be identified by clinical supplies, where each kit number is specific to a treatment arm. For randomised patients, the IWRS will provide an appropriate kit number to match the assigned randomised treatment from those kits available at the centre.

Forced randomisation is not allowed. If a patient is dispensed with a wrong drug supply, the centre must immediately notify the IWRS contact. Corrections for the patient and the IWRS will be made as required. Until resolution, the patient should continue taking study medication, but at the latest until the next scheduled visit.

If a patient discontinues from the study, the patient E-code and randomisation number (if applicable) will not be reused, and the patient will not be allowed to re-enter the study.

5.3 Procedures for handling subjects incorrectly enrolled or randomised

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

Patients who are incorrectly enrolled but are not yet randomised should be withdrawn from the study.

If a patient not meeting the study criteria is randomised in error, the patient should complete the study unless there are safety concerns or if the patient withdraws consent. Data collected for patients randomised in error will be included in the analyses. Once the error is identified a discussion must occur between the AZ Study Team Physician and the Investigator regarding whether to continue or discontinue the patient from the study. The AstraZeneca Study Team Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the patient should have their randomised therapy stopped and be discontinued from the study.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The study will be conducted in a double blind and double dummy fashion. The dapagliflozin 2.5 mg and 5 mg tablets and the matching placebo will be identical in size, whereas dapagliflozin 10 mg tablets and matching placebo are slightly larger. Colour, smell, taste is identical.

Packaging and labeling will ensure blinding. Patients will receive 2 types of bottles, with instruction to take one tablet in the morning and one tablet in the evening from the 2.5 mg, 5 mg or matching placebo bottle containing smaller tablets (with white booklet label) and 1 tablet in the morning from the 10 mg or matching placebo bottle containing larger tablets (with yellow booklet label)

Metformin treatment will be open-label.

Until after the completion of all subjects in the study of the 16-week randomised treatment period, no member of the extended study delivery team at AstraZeneca or Bristol-Myers Squibb, at the investigational centres or any Contract Research Organization handling data will have access to the randomisation scheme, with the exception of the Investigational

Products department at AstraZeneca or their designee, where the information is needed to package study medication, and the drug safety departments at Bristol-Myers Squibb and AstraZeneca. See Section 5.4.2 for further details.

The treatment codes and results will be kept strictly within AstraZeneca and Bristol-Myers Squibb to safeguard the integrity of the blind of the investigators and patients, and hence to minimize any possible bias in data handling.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigator(s) from the IWRS. In case if the investigator(s) are not available, AstraZeneca MC safety department has the right to perform unblinding. Routines for this will be described in the IWRS user manual that will be provided to each centre.

The treatment code must not be broken except in medical emergencies when the appropriate management of the patient necessitates knowledge of the treatment allocation. If the treatment code is broken then the investigator(s) must document and report it to AstraZeneca.

Bristol-Myers Squibb 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 after all patients have completed, all data are clean, and all decisions on the evaluability of the data from each individual patient during the 16-week randomised treatment period have been made and documented.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Table 5 Identity of investigational products and study drugs

Investigational product/ Study Drug	Dosage form and strength	Manufacturer
Dapagliflozin 2.5 mg	Biconvex, diamond shape, green tablet 2.5 mg (Size: 9 mm)	Bristol-Myers Squibb,
Dapagliflozin 5 mg	Biconvex, diamond shape, green tablet 5 mg (Size: 9 mm)	Bristol-Myers Squibb,
Dapagliflozin 10 mg	Biconvex, diamond shape, green tablet 10 mg (Size: 11 mm)	Bristol-Myers Squibb,
Matching placebo for dapagliflozin 5 mg and 2.5 mg	Biconvex, diamond shape, green tablet (Size: 9 mm)	Bristol-Myers Squibb,
Matching placebo for dapagliflozin 10 mg	Biconvex, diamond shape, green tablet (Size: 11 mm)	Bristol-Myers Squibb,

Investigational product/ Study Drug	Dosage form and strength	Manufacturer
Glucophage® (metformin hydrochloride, immediate release) 500 mg	Film coated, white to off-white round tablet, 500 mg	Merck Santé, Semoy

The formulation number and batch number will be recorded in the Study Master File and identified in the Clinical Study Report.

The investigational product will be supplied by Bristol-Myers Squibb Pharmaceutical Research Institute or their designee. Investigational product will be packed in bottles. The dapagliflozin/placebo bottles will contain 35 tablets. The tablets may contain lactose, which may cause discomfort in lactose-intolerant individuals. Primary packing of the investigational product will be carried out by Bristol-Myers Squibb or their designee, secondary packed in IPS Mölndal in accordance with current Good Manufacturing Practice (GMP).

Commercial packs of metformin will be supplied by AstraZeneca or their designee. The packs will contain 100 tablets and will be labelled with labels or booklets, depending on availability. The labels will fulfil GMP Annex 13 requirements and local regulatory guidelines.

5.5.2   Doses and treatment regimens

The investigational product dapagliflozin (2.5 mg and 5 mg) or matching placebo small size will be taken twice daily, the investigational product dapagliflozin (10 mg) or matching placebo with larger size will be taken once daily in the morning. Metformin will be taken orally together with food twice daily with breakfast and with the evening meal during the study period.

Patients should be instructed to abstain from all food and beverages for 12 hours prior to each clinical visit; however, drinking water is allowed. In the morning prior to each visit, acceptable concomitant medications can be taken with water only.

The doses are:

- Dapagliflozin 2.5 mg and 5 mg tablets, administered orally twice daily for the 16-week double-blind treatment period

- Dapagliflozin 10 mg tablets, administered orally once daily in the morning for the 16-week double-blind treatment period

- Matching placebo for dapagliflozin 2.5 mg and 5 mg tablets administered orally twice daily for the 4-week placebo lead-in period, and the 16-week double-blind treatment period

- Matching placebo for dapagliflozin 10 mg tablets administered orally once daily in the morning for the 4-week placebo lead-in period, and the 16-week double-blind treatment period

- Open-label metformin IR 500 mg tablets administered orally twice daily at doses ≥1500mg/day for the 4-week placebo lead in/open label period and the 16-week double-blind treatment period.

Table 6   Drug dispensing scheme:

Visit ID	No. of bottles to dispense of dapagliflozin 2.5mg, or 5 mg or matching placebo, for morning and evening	No. of bottles to dispense of dapagliflozin 10 mg or matching placebo for morning	No. of commercial packs to be dispensed of metformin 500 mg, open label
Visit 1	N/A	N/A	N/A
Visit 2	2 bottles (Placebo lead-in)	1 bottle (Placebo lead-in)	2 commercial packs
Visit 3	NA	NA	NA
Visit 4	2 bottles	1 bottle	2 commercial packs
Visit 5	NA	NA	NA
Visit 6	2 bottles	1 bottle	2 commercial packs
Visit 7	2 bottles	1 bottle	2 commercial packs
Visit 8	2 bottles	1 bottle	2 commercial packs

5.5.3   Additional study drug

N/A

5.5.4   Labelling

Labelling of the investigational product and study drugs will be carried out by AstraZeneca or a Contract Research Organization (CRO) in accordance with current Good Manufacturing Practice (GMP), Annex 13 and or local regulatory requirements. Label text will be translated into local languages. All investigational products will be labelled.

The labels will include at least the following information:

- Name of sponsor (AstraZeneca)

- Study drug(s) dosage form, route of administration, and quantity of dosage units

- Study code

- Order number (to identify the contents and packaging operation)

- Enrolment code (will be added by the investigator when product is dispensed)

- Kit ID (if applicable)

- Visit number, if applicable (will be added by the investigator when product is dispensed)

- Directions for use. (For oral use.)

- The name of the principal investigator, if applicable (will be added by the investigator when product is dispensed)

- The period of use, eg, expiry date

- Storage conditions, if applicable

- The following standard statements

  - "for clinical trial use only"

  - "keep out of reach of children".

5.5.5 Storage

All study drugs must be kept in a secure place under appropriate storage conditions. The labels on the bottles of investigational product and boxes of open-label and study drugs and the Investigator Brochure specify the appropriate storage and shipment.

5.6 Concomitant and post-study treatment(s)

Changes in concomitant medication should be avoided unless medically indicated. If concomitant medication must be changed - including but not limited to diuretics, antihypertensive drugs and lipid lowering therapy – these changes must be recorded in the appropriate sections of the eCRF.

The administration of all medication must be recorded in the appropriate sections of the eCRF. The specific medication, the indication for use, and the dates of usage should also be reported. Trade name of the medication should be recorded in the eCRF. Generic name can be used if trade name is unknown. Additionally, the total daily dose of the following medications should be reported: metformin, insulin, diuretics, anti-hypertensive agents, and HMG-CoA reductase inhibitors (statins).

Other medications considered necessary for the patient's safety and well-being may be given at the discretion of the investigator. (With the exception of medications listed in the Exclusion Criteria in Section 4.2).

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

For prohibited and restricted medication, see Exclusion Criteria (Section 4.2) and Discontinuation Criteria (Section 4.3).

5.7 Treatment compliance

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

Patients will be asked to return all unused investigational product, metformin and empty packages and bottles to the clinic at each visit. The patient 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. Patients 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

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all drugs dispensed and returned.

The investigational product and study drugs are to be prescribed only by the investigator. Under no circumstances will the investigator allow the investigational product and study drugs to be used other than as directed by the protocol without AstraZeneca approval.

Investigational product and study drugs will only be delivered to the centre when the required regulatory approvals have been obtained. Ethic committee approvals may also be required, depending on local regulations. It is the investigator and/or institution's responsibility to establish a system for handling study treatments, including investigational product and study drugs, so as to ensure that:

- Deliveries of products from AstraZeneca or their designee are correctly received by the investigator or his or her designee;

- Such deliveries are recorded on an appropriate drug log.

The investigator must maintain accurate records accounting for the receipt and for the disposition of the investigational products and study drugs. This record is in addition to any drug accountability information recorded in the eCRFs. It must be possible to reconcile delivery records with records of usage and returned stocks. Any discrepancies must be accounted for. Certificates of delivery and return should be signed by the investigator or a designated person.

The investigator is responsible for making sure

- That the investigational product and study drugs are handled and stored safely and properly (see Section 5.5.5)

- That the investigational product and study drugs are only dispensed to study patients in accordance with this protocol.

Patients must return all unused investigational product and study drugs and empty containers to the investigator.

At the termination of the Clinical Study or at the request of AstraZeneca, the investigator will either return any unused investigational products and study drugs to AstraZeneca, or destroy investigational products and study drugs at the site depending on local regulations. If the Investigational Product is destroyed at site, the site personnel will account for all unused drugs and for appropriate destruction. Certificates of delivery, destruction and return must be signed. If the Investigational Product is returned to AstraZeneca, the Study site personnel or the AstraZeneca monitor will return all unused drugs to AstraZeneca. Certificates of delivery and return must be signed.

5.8 Withdrawal from study

Subjects are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such subjects will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (See Sections 6.4.4 and 6.4.5); diaries and all study drugs should be returned by the subject.

Withdrawn subjects will not be replaced.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

Data must be entered into the Web Based Data Capture (WBDC) system at the investigational centre within 72 hours after the scheduled visit (except for SAEs that should be entered within 1 calendar day). Trained study personnel will be responsible for entering data into the WBDC system according to the Instructions for the Investigator including the data entry instructions. Data includes observations, tests and assessments specified in the protocol.

When data have been entered, reviewed, edited and Source Data Verification (SDV) has been performed by an AstraZeneca representative, the data will be frozen to prevent further editing. Principal Investigator is responsible for signing the eCRF and this can be delegated to a trained Investigator. The eCRF is signed electronically as per the eCRF instructions. A copy of the eCRF data will be archived at the study site.

Data from the central laboratory assessments will be either loaded into WBDC or returned to AstraZeneca directly as datasets, and validated to ensure that it is consistent with the clinical data. Any queries on the data will be raised and resolved within the WBDC system or other designated systems.

Data verification and validation will be performed. The Investigator should answer any external queries raised by AstraZeneca in a timely manner, and query resolutions will be saved in the central database.

The patients will be instructed to monitor their FPG at least every second day between Visits 2-6 and at least once a week between visits 6-9. The results and information about hypoglycaemic events should be entered by the patient into a paper diary.

6.2 Data collection, screening and enrolment

During the screening visit a separate Screening Informed Consent will be obtained before the screening procedure is performed, which consists of a blood sample for determination of HbA1c.

During the Enrolment, in addition to what is specified in Table 4 for enrolment, the following demographic data will be collected and recorded in the appropriate sections of the eCRF:

- Date of birth, sex, race and ethnicity

- Information about smoking, alcohol, medical history, specific disease history and family history on coronary heart disease

6.2.1 Follow-up procedures

A follow-up (Visit 10) will be performed 25-31 days (4 weeks ±3 days) after the end of the double-blind treatment period, see Table 3 for further details.

6.3 Efficacy

6.3.1 Efficacy laboratory variables

Table 7   Efficacy laboratory variables

Visit	S	1	2	3	4	5	6	7	8	9	10
Study Week	-7	-5	-4	-1	0	1	4	8	12	16	20
HbA1c	X	X		X	X		X	X	X	X	
FPG		X	X	X	X	X	X	X	X	X	X

The laboratory parameters that will be measured to assess efficacy are displayed in Table 7 by visit. The results from baseline and onwards will not be reported to the investigator unless the values meet the defined discontinuation criteria in Section 4.3.1.

HbA1c

HbA1c is the primary assessment for the determination of glycaemic efficacy accepted by the FDA and the EMEA. The primary outcome variable for this study is the change in HbA1c from baseline to the end of the 16-week randomised treatment period. 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.

FPG

Fasting plasma glucose (FPG) is a well established measure of glycaemic efficacy and considered by the CHMP to be an acceptable secondary endpoint.

6.3.2 Blood pressure

As BP is both an efficacy and safety variable in this study, measurement of systolic and diastolic BP is described in Section 6.4.9.1

6.3.3 Weight and height

The patient's weight will be recorded in kilograms (kg) to one decimal place, fasting, with light clothing and no shoes. The patient's height will be recorded in centimetres (cm), 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 patient.

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.

6.4.2 Definitions of serious adverse event

A serious adverse event (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-patient hospitalisation or prolongation of existing hospitalisation

- Results in persistent or significant disability or incapacity

- Is a congenital abnormality or birth defect

- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

- Cancer

- Drug dependency/abuse.

6.4.3   Definitions of overdose

An overdose (defined as the accidental or intentional ingestion of any dose of the investigational product that is considered both excessive and medically important) should be reported as an SAE using the most relevant SAE criteria, as judged by the Investigator.

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

6.4.4   Recording of adverse events

Time period for collection of adverse events

All AEs will be collected from the start of the placebo led-in period (Visit 2) throughout the treatment period and including the follow-up period (Visit 10).

SAEs will be collected from the time when the informed consent is obtained until the end of the study (Visit 10).

Variables

The following variables will be recorded in the eCRF for each AE;

- description of the AE,

- the date when the AE started and stopped,

- maximum intensity,

- whether the AE is serious or not,

- causality rating (yes or no),

- action taken with regard to investigational product and

- outcome.

Maximum intensity will be graded according to the following definitions:

- mild (awareness of sign or symptom, but easily tolerated)

- moderate (discomfort sufficient to cause interference with normal activities)

- severe (incapacitating, with inability to perform normal activities)

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

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

- Causality assessment in relation to Study Drug

- Description of AE.

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 Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

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

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

Adverse Events based on signs and symptoms

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

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. 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 patient to receive specific corrective therapy. If a deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Any new or aggravated clinically relevant abnormal medical finding at a physical examination 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).

Hypoglycaemic events

A separate section in the eCRF will be used to document all reported episodes of hypoglycaemia (see Section 6.4.10.1). In addition, hypoglycaemic episodes should only be reported on the AE eCRF page if the event fulfils protocol criteria for a Serious Adverse

Event (see Section 6.4.2). In this case, an SAE must be reported in addition to the hypoglycaemia eCRF pages for hypoglycaemia.

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 patient 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.

AE dictionary

The latest version of the AE dictionary, Medical Dictionary for Regulatory Activities (MedDRA), will be used for the classification and analysis of AEs entered in the study database. For regulatory reporting, SAEs will be processed at the Bristol-Myers Squibb Pharmacovigilance database and coded using MedDRA.

Cardiovascular events

Cardiovascular (CV) events will be monitored in the study population and an independent CV adjudication committee will review events (See Section 6.4.16).

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.

CV events will be analyzed in conjunction with CV events observed in other Phase II and Phase III dapagliflozin studies and reported elsewhere.

6.4.5   Reporting of serious adverse events

Investigators and other study site personnel must inform appropriate AstraZeneca representatives via the web based data capture (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 about the SAE as per local requirements. Reporting of SAEs to the Regulatory Authority is the responsibility of Bristol-Myers Squibb.

Investigators or other site personnel send automated email alert to the designated AstraZeneca representative (when the page with SAE information is saved in WBDC system).

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.

6.4.6 Laboratory safety assessment

Blood and urine specimens will be collected for laboratory analyses. The date and time of sampling will be recorded on the laboratory requisition form. The samples will be processed by a central laboratory and results will be reported back to the clinic within 72 hours.

Due to the fasting laboratory assessments, all patients will visit the clinic fasting in the morning, before 11 a.m. Patients will be instructed not to eat or drink anything for 12 hours before visiting the clinic (drinking water is allowed). Patients should not drink alcohol within 24 hours prior to each visit and should not use tobacco/nicotine within 12 hours prior to each visit.

In addition, patients will be instructed not to take investigational product or metformin in the morning before visiting the clinic. Permitted concomitant medication can be taken with water only.

All samples should be taken by adequately trained study personnel and handled in accordance with instructions in the laboratory manual. Up to date reference ranges will be provided during the study and laboratory results will be compared to the laboratory standard normal ranges and flagged if they are outside the normal range. The Investigator should make an assessment of any clinically significant abnormalities in the laboratory reports. The laboratory reports should be signed, dated and retained at the study site as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.4.4

The complete list of safety laboratory tests is displayed in Table 8 below.

Table 8 **Safety laboratory variables**

Visit	1	2	3	4	5	6	7	8	9	10
Study Week	**-5**	**-4**	**-1**	**0**	**1**	**4**	**8**	**12**	**16**	**20**
Haematology										
Haemoglobin	X			X	X	X	X	X	X	X
Haematocrit	X			X	X	X	X	X	X	X
Red blood cell count	X			X	X	X	X	X	X	
White blood cell county and differential	X			X	X	X	X	X	X	
Platelet count	X			X	X	X	X	X	X	
Clinical Chemistry										
Aspartate Aminotransferase (AST, SGOT)	X			X	X	X	X	X	X	X
Alanine Aminotransferase (ALT, SGPT)	X			X	X	X	X	X	X	X
Alkaline Phosphatase (AP)	X			X	X	X	X	X	X	X
Creatine Kinase (CK)	X		X	X	X	X	X	X	X	X
Total Bilirubin (TB)	X			X	X	X	X	X	X	X
Blood Urea Nitrogen (BUN)	X			X	X	X	X	X	X	X
Electrolytes: (- Sodium - Bicarbonate - Potassium - Chloride - Calcium - Magnesium - Phosphate)	X			X	X	X	X	X	X	X
Total protein	X			X		X	X	X	X	
Albumin	X			X		X	X	X	X	
Uric acid	X			X	X	X	X	X	X	X
Serum Creatinine (SCr)	X			X	X	X	X	X	X	X

Visit	1	2	3	4	5	6	7	8	9	10
Study Week	-5	-4	-1	0	1	4	8	12	16	20
Calculated creatinine clearance (Cockroft-Gault formula)[a]	X			X	X	X	X	X	X	X
Estimated Glomerular Filtration Rate (MDRD formula)	X			X			X	X	X	
FSH[b]	X									
TSH, T4[c]	X									
Hepatitis Screen Panel[d]	X									
Urinalysis										
Glucose[e]	X			X	X	X	X	X	X	X
Blood by dipstick[f]	X			X	X	X	X	X	X	X
Albumin	X			X	X	X	X	X	X	X
Creatinine	X			X		X	X	X	X	X
Calculated Urinary albumine: creatinine ratio (UACR)	X			X		X	X	X	X	X
Pregnancy test[g]	X	X	X	X	X	X	X	X	X	X

a) Creatinine clearance will be calculated by the method of Cockcroft and Gault., preferentially using the most recent body weight. Patients with a calculated creatinine-clearance <60 ml/min or an increase in serum creatinine of ≥0.5 mg/dL (≥44.2 μmol/L) above the baseline value, will have their metformin withheld and a repeated serum creatinine test will be done within one week. For details, see Section 4.3.2. The eGFR will be estimated by the abbreviated Modification of Diet in Renal Disease (MDRD) formula and reported by central laboratory.

b) FSH levels are to be measured in women who are under 50 years of age who have been amenorrheic for 12 months or more.

c) Free T4 will be measured only in cases when TSH is abnormal, see detailed in Section 4.2

d) Includes Hepatitis B viral antibody IgM, Hepatitis B surface antigen and Hepatitis C virus antibody

e) Results will be blinded

f) Microscopy if dipstick positive for blood.

g) Urine HCG pregnancy test for WOCBP (HCG minimum sensitivity of 25 IU/L) (dipstick analyzed at the study centre).

For blood volume see Section 7.1

In case of patient reported signs and/or symptoms suggestive of an urinary or genital tract infection, a urine sample will be collected for culture at a scheduled or at an unscheduled visit, as described in Section 6.4.10.2.

6.4.7 Physical examination

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

Baseline data is collected at Visit 4, and new findings discovered on subsequent physical examinations should be recorded as changes from baseline.

6.4.8 ECG

Resting 12-lead ECG

A 12-lead ECG will be taken (supine position, standard ECG with a recommended paper speed of 50 mm/second covering at least 6 sequential beats) after the patient has been lying down resting for at least 5 minutes. Heart rate, QRS durations, PR, QT and QTc intervals will be recorded from standard lead of the computerised ECG and will be entered in the eCRF. 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. Clinically relevant abnormalities should be reported as AE-s, see Section 6.4.4.

6.4.9 Vital signs

6.4.9.1 Pulse and blood pressure

Seated pulse and blood pressure measurements will be performed before blood samples are taken. One pulse measurement will be taken over a minimum 30 seconds after the patient has been sitting and resting for at least 5 minutes The pulse measurement will be followed by three blood pressure (BP) measurements separated by 2 minutes each. All three BP readings should be recorded. At Visit 1, before entry into the placebo lead-in period, 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. The average of the three BP readings will be used for study analyses. BP readings should be taken while the patient is in a comfortable seated position with the arm supported at the level of the heart. All readings should be recorded. Ideally, blood pressure 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 patient's arm is recommended. Oscillometric devices (such as Dinemap) 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.

New oscillometric devices must be recalibrated when the certificate of calibration provided by the vendor expires. Thereafter the devices must be calibrated with a frequency according to local regulation but at least annually, and calibration must be documented.
Aneroid devices should not be used.

6.4.10 Other safety assessments

Self-monitored plasma glucose readings and hypoglycaemic events will be collected in a patient diary and reviewed by the investigator at each visit. The investigator will also ask the patient about symptoms of urinary tract and genital infections at every scheduled visit starting at Visit 4.

6.4.10.1 Fasting plasma glucose concentrations and hypoglycaemic events

Patient self-monitoring of FPG is performed in order to reduce the risks associated with prolonged hyperglycaemia and to confirm symptoms of hypoglycaemia. Patients will be asked to perform self-monitoring of FPG using glucometers provided by AstraZeneca. The patients 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 9. The results should be recorded in the patient 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. A new diary will be dispensed to the patient at each of these visits.

The memory of the glucometer should be reviewed and compared with the readings in the patient'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 patient. If fingerstick glucose values are discordant with central laboratory results or with clinical symptoms, the patient's glucometer should be tested and the glucometer instructions should be re-reviewed with the patient.

If self-monitored FPG is above 270 mg/dL (15 mmol/L) from week - 4 (Visit 2) up to week 4 (Visit 6), above 240 mg/dL (13.2 mmol/L) from week 4 (Visit 6) up to week 12 (Visit 8), or above FPG >200 mg/dL (11.1 mmol/L) from week 12 (Visit 8) up to week 16 (Visit 9) the patient should repeat the FPG on the same day. If the second FPG measurement is above the stated value, the patient should contact the study centre and be scheduled for a central laboratory FPG measurement within one week.

If central laboratory values confirm that the FPG is above the threshold value, the patient should be discontinued.

A separate section in the eCRF will be used to document all reported episodes of hypoglycaemia. The patients will be asked to always check their blood glucose if they develop symptoms suggestive of hypoglycaemia and to record specific symptoms in the patient diary. The Investigator is responsible for questioning the patient about all symptoms reported in the diary and for determining if they meet the clinical definition of hypoglycaemia. Only symptoms and/or blood glucose values that meet the definition of hypoglycaemia should be reported on the hypoglycaemia eCRF pages.

A hypoglycaemic event can be either:

- Symptoms of hypoglycaemia 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 hypoglycaemia without a blood glucose reading

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

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

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

- **Minor hypoglycaemic event,** defined as either a symptomatic episode with a capillary or plasma glucose measurement <63mg/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 hypoglycaemia,** defined as a symptomatic event without a confirmatory blood glucose measurement.

Data to be collected for each **hypoglycaemic** event:

- Date and time of episode (start and stop)

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

- Whether symptoms were present, and a 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 antihyperglycaemic drug administration

- Time of last meal and its contents

The patient diary will be reviewed and the hypoglycaemic 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 patient if needed. If a major hypoglycaemic event or more than one minor event has occurred since the previous visit, the patient should contact the investigator.

6.4.10.2 Urinary and Genital Infections

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

Urinary Tract Infections

During enrolment and follow up of patients in this trial, the investigator may discover a patient 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 patients. In this study, the central laboratory will report urinary dipstick test results for hemoglobin but will not routinely report the results of urinary dipstick tests for leukocyte esterase as a screening test for pyuria in surveillance urine examinations.

At every scheduled visit starting from the randomisation visit, the investigator will question patients about symptoms of urinary tract infections, including but not limited to pain or burning or uncomfortable pressure in the lower abdomen/pelvic area while passing urine,

blood in the urine, and symptoms of urinary urgency (a strong and uncontrolled urge to pass urine). If based on the response to these questions or other suggestive signs or symptoms (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.

Investigational product should be temporarily stopped in patients 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

In addition, at every scheduled study visit starting from the randomisation visit, the investigator will question patients about symptoms of genital infections including but not limited to itching, soreness or redness in the genital area and a change or increase in genital discharge. The diagnosis of vaginitis, vulvovaginitis, vulvitis or balanitis can be made based on physical examinations, culture of secretions or a therapeutic response to treatment of fungal or other vaginal pathogens. A urine culture is not required for diagnosis of genital infections if the diagnosis is confirmed by physical examination, culture of secretions, or a therapeutic response to treatment of fungal or other vaginal pathogens.

Also, it is the investigator's responsibility to report, as applicable based on investigator's judgement and patient'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.

Patient reported signs or symptoms suggestive of Urinary or Genital Tract Infection.

Between scheduled visits, patients may experience signs or symptoms that are potentially indicative of urinary or a genital tract infection. The patient should contact the investigator by telephone. In either instance, an unscheduled visit will be planned as soon as possible, preferably within 24 h. The investigator will follow local guidelines to evaluate and treat suspected urinary or genital tract infections.

6.4.11 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 patients who are taking loop diuretics. These patients should have careful monitoring of electrolytes, volume status, and renal function. Loop diuretic dose adjustments should be made if clinically indicated. Metformin is not indicated in diseases that may cause tissue hypoxia such as clinically serious heart failure (see Section 4.2, exclusion criterion 18).

6.4.12 Change in kidney function

Please see Appendix G for further guidance.

6.4.13 Hyponatremia

Please see Appendix F for further guidance.

6.4.14 CK abnormalities

Please see Section 4.3.2, "Procedures for discontinuation of a patient from the study."

6.4.15 Liver function test abnormalities

Please see Appendix H for further guidance.

6.4.16 Independent Adjudication Committee

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

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

Serious Adverse Events 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.*

6.5   Pharmacogenetics

AstraZeneca and Bristol-Myers Squibb intend to perform genetic research in the dapagliflozin clinical development programme to explore how genetic variations may affect the clinical parameters associated with dapagliflozin response. Collection of DNA samples from populations with well described clinical characteristics may aid in the identification of future drug targets and projects to validate identified targets. Future research may suggest other genes or gene categories as candidates for influencing not only response to dapagliflozin but also susceptibility to T2DM and other metabolic disease for which dapagliflozin may be evaluated. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to disease susceptibility and drug action.

6.5.1   Collection of pharmacogenetic samples

The blood sample for optional genetic research will be obtained from the patients after randomisation. For further information, see Appendix E.

For blood volume see Section 7.1.

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 9 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety/Efficacy	Clinical chemistry	8.5	9	76.5
	Haematology	4.0	9	36
FPG		4.0	10	40
Genotyping [a]		10.0	1	10
Total [b]				152.5 (162.5)

[a] Genetic blood sample donation is optional.
[b] The total blood volume stated within brackets includes the optional genetic blood sample.
Extra blood samples in case of unscheduled visits are not included.

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed after analyses or retained for further use as described here.

Biological samples for future research will be retained at the Bristol-Myers Squibb Sample Bank and/or secure Central Laboratory owned by AstraZeneca for a maximum of 15 year after the blood sample collection date or according to local legislation. Samples may be destroyed prior to this timeframe if the patient has withdrawn consent.

For information on genetic samples, see Appendix E.

7.2.1 Pharmacogenetic samples

Patients who provide written informed consent related to genetic research will provide a blood sample according to the Study Plan, see Table 4. Individual patients will not be identified. Samples and data will be kept confidential and stored separately. For more information, see Appendix E.

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 (materials containing or suspected to contain infectious substances that do not meet Category A criteria (see IATA 6.2 Regulations Guidance in Appendix C).

Any samples identified as Infectious Category A materials are not shipped and further samples taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

7.4 Chain of custody of biological samples

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

The principal investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment and keeps documentation of receipt of arrival.

The sample receiver keeps full tractability of the samples while in storage and during use until used or disposed.

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 is registered in AstraZeneca bio bank system during the entire life cycle.

All genetic samples will be stored under secure conditions with restricted access at Bristol-Myers Squibb and/or AstraZeneca. The blood, DNA or data derived from the samples may be made available to groups or organisations working with AstraZeneca and Bristol-Myers Squibb on this study or as part of the development drug project. However, the samples and any results will remain the property of Bristol-Myers Squibb and AstraZeneca at all times. Bristol-Myers Squibb or AstraZeneca will not give blood, DNA samples or data derived from the samples to any other parties, except as required by law. All samples and DNA will be destroyed within 15 years after the blood sample collection date or according to local legislation. Samples may be destroyed prior to this timeframe if the patient has withdrawn consent.

7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of biological samples donated the samples will be disposed/destroyed, if not already analyzed and documented.

If collection of the biological samples is an integral part of the study then the patient is withdrawn from further study participation.

If collection of the biological samples is a voluntary part of the study then the patient may continue in the study.

The principal investigator:

- Ensures patients withdrawal of informed consent is notified immediately to AstraZeneca

- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed/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/destructed and the action documented returned to the study site.

In the event that analysis/research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

All genetic samples stored at the central lab must be shipped to Bristol Myers-Squibb for registration in the Sample Bank system. Bristol Myers-Squibb is responsible for destroying (and documenting) all genetic samples.

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 International Conference on Harmonisation (ICH) /Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

For studies including genetic analysis special precautions are taken as described in Appendix E.

8.2 Subject data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, patients will authorise the collection, use and disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

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. All data computer processed by AstraZeneca and Bristol-Myers Squibb will be identified by E-code and study code.

The Master Informed Consent Form will also explain that for data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an Ethics Committee may require direct access to parts of the hospital or practice records relevant to the study, including patients' medical history.

Strict data protection and confidentiality principles, described in detail in Appendix E, are applicable to the optional genetic research component of this study.

Reference to participation in genetic research should not be recorded into the patients' general medical records. All notes should be kept within the clinical study records.

Due to the exploratory nature of this genetic research that may be associated with this study, there will be no routine communication of results to patients.

AstraZeneca and Bristol-Myers Squibb will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

8.3   Ethics and regulatory review

An Ethics Committee must approve the final study protocol, including the final version of the Informed Consent Form and any other written information to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee must be given in writing. The investigator must submit the written approval to AstraZeneca before enrolment of any patient into the study.

The Ethics Committee must approve all advertising used to recruit patients for the study.

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

If required by local regulations, the protocol must be re-approved by the Ethics Committee annually.

Before enrolment of any patient 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.

The distribution of any of these documents to the national regulatory authorities will be handled by AstraZeneca.

Where genetic research and/or sample collection is included, approval must be obtained for this genetic research and the associated genetic informed consent from the Ethics Committee. It must be clearly stated in the approval that this genetic research is approved. The investigator must submit written approval to AstraZeneca before any patient participates in this genetic research.

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

Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to the Ethics Committee according to local regulations and guidelines.

8.4   Informed consent

A screening informed consent form will be provided to all the sites, and implemented locally, when possible, based on all applicable regulatory requirements and laws.

The main informed consent form will be signed at or prior to Visit 1, based on eligibility of HbA1c taken at screening visit. It should always be checked if closure of enrolment was announced by AstraZeneca, before the main informed consent form is handed to a patient.

The principal investigator(s) at each centre will:

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

- Ensure that the patient is notified that they are free to discontinue from the study at any time

- Ensure that the patient is given the opportunity to ask questions and allowed time to consider the information provided

- Ensure that the patient's signed and dated informed consent is obtained before conducting any procedure specifically for the study, including the following:

    – Withholding or discontinuation of treatment

    – Collection of blood and urine samples

    – Physical examination including ECG

- Obtain and document the patient's signed and dated informed consent before conducting any procedure specifically for the study

- Ensure the original, signed Informed Consent Form is stored in the Investigator's Study File

- Ensure a copy of the signed Informed Consent Form is given to the patient.

The genetic research is optional and the patient may participate in the main study without participating in the genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for the main study (non-genetic components of the study) and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that he/she may freely discontinue the genetic aspect of the study at any time.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator and AstraZeneca /Bristol-Myers Squibb.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment should be approved by each Ethics Committee and if applicable, also the national regulatory authority, before implementation. Local requirements should be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 8.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee should approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

The distribution of these documents to the regulatory authority will be handled according to local practice.

8.6 Audits and inspections

Authorized 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, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first patient 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

- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator.

- Discuss the specific requirements of the genetic research with the investigator(s) (and other personnel involved with the study).

9.2 Training of study site personnel

Prior to the study start, regional meetings will be held with all investigators and/or other staff involved from each study centre and AstraZeneca representatives. During the meeting, participants will have an opportunity to discuss the procedures associated with the study, the requirements for collection of blood samples and the genetics part in accordance with Appendix E. The importance of the informed consent process will be made clear.

Before the first patient 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 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, and that investigational product accountability checks are being performed

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

- Perform source verification of the genetic consent of participating patients and ensure that the investigational team is adhering to the specific requirements of this genetic research

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

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

Refer to Clinical Study Agreement for location of source data.

9.4 Study agreements

The principal investigator at each/the centre must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol shall prevail.

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

9.5 Study timetable and end of study

The end of the entire study is defined as "the last visit of the last patient undergoing the study".

The study is expected to start in QIV 2010 and to be completed by QI 2012.

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.

10. DATA MANAGEMENT BY COGNIZANT

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

Data will be entered in the Web Based Data Capture (WBDC) system at the study site. Trained study personnel will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the 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 and this can be delegated to a trained Investigator. The eCRF is signed 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. Any treatment revealing data may thereafter be added 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. Following database lock, required amendments to the database due to critical errors will only be allowed with the appropriate supporting documentation. Non-critical errors will not result in amendments to the database but will be captured via the appropriate documentation.

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

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications

will be classified according to the Bristol-Myers Squibb Drug Dictionary. All coding will be performed by the coding team at Bristol-Myers Squibb.

Management of genotype data

Genotype data generated in this study will be stored in the Bristol-Myers Squibb and/or AstraZeneca database, or other appropriate secure system, separate from the database used for the main study. Some or all of the clinical datasets from the main study may be duplicated within the Bristol Myers Squibb and/or AstraZeneca secure databases to facilitate exploratory genetic analyses.

Any results from this genetic research will be reported separately from the clinical study report for the main study.

Data associated with biological samples

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca and Bristol-Myers Squibb.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

11.1 Calculation or derivation of safety variable(s)

11.1.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Drug Safety Physician, be considered OAEs and reported as such in the Clinical Study Report.

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.

A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

11.1.2 Other safety variables

The safety evaluations will include analyses of AEs, laboratory parameters, ECG, vital signs (pulse and BP), seated systolic BP, hypoglycaemic events, calculated creatinine clearance, estimated GFR (eGFR) and physical examination. The analysis of safety will be based on the safety analysis set. Safety data gained during the 16-week double-blind treatment period and the 4-week safety follow-up period will be evaluated. Safety variables will be summarized descriptively.

The Cockcroft-Gault formula will be used to calculate creatinine clearance.

Males:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \, x \, (140 - \text{Age})}{72 \, x \, \text{serum creatinine (mg/dL)}}$$

Females:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \, x \, (140 - \text{Age})}{72 \, x \, \text{serum creatinine (mg/dL)}} \, x0.85$$

The MDRD equation will be used to calculate eGFR.

The mean of the 3 seated systolic BP measurements will be computed by AstraZeneca for each patient at each visit.

Patients reporting at least one episode of hypoglycaemia between baseline and week 16 will be tabulated using counts and proportions.

All other safety variables will be summarized descriptively.

11.2 Calculation or derivation of efficacy variables

Please see Section 6.3 for a description of specific efficacy variables.

11.2.1 Change and percent change from baseline

Change from baseline will be calculated as absolute difference 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/or prior the date of the first dose of the double-blind study

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.

11.2.2 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.

11.3 Calculation or derivation of pharmacogenetic variables

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

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

12.1 Description of analysis sets

12.1.1 Safety Analysis Set

The Safety Analysis Set consists of all subjects who received at least one dose of double-blind study medication. The Safety Analysis Set would include any subject who accidentally received double-blind study medication but was not randomised in the study. In cases where information was available which indicated that a subject received a different treatment for the entire course of his/her participation in the study the subject will be analyzed according to the treatment actually received. In case a subject never received the treatment as assigned by randomisation, then the safety data for that subject will be presented by the first treatment received. The Safety Analysis Set will be used for safety summaries.

12.1.2 Full Analysis Set

The Full Analysis Set will include all randomised subjects (as randomised) who received at least one dose of double-blind study medication and who have a non-missing baseline value and at least one post-baseline value for at least one efficacy variable. The intention-to-treat principle will be preserved despite the exclusion of subjects who took no study medication, as the decision of whether or not to begin treatment during the randomised treatment period could not be influenced by knowledge of the assigned treatment. All efficacy analyses will be based on the Full Analysis Set.

12.1.3 Per-Protocol Analysis Set

The Per-Protocol Analysis Set will be a subset of the Full Analysis Set consisting of subjects who do not violate the terms of the protocol which may affect the primary efficacy variable significantly, ie, subjects who do not have relevant protocol deviations. 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 unblinding of the study and agreed by the study team.

The analysis of the primary efficacy variable of change from baseline in HbA1c will be repeated using the Per-Protocol Analysis Set if more than 10% of the subjects in any regimen are found to significantly violate the terms and conditions of the protocol. The Per-Protocol Analysis does not replace the primary analysis, but would be a sensitivity analysis. Otherwise, efficacy analysis will be restricted to the Full Analysis Set.

12.2 Methods of statistical analyses

All efficacy analyses will be based on the Full Analysis Set. The primary efficacy variable of change from baseline in HbA1c will also be analyzed using the Per-Protocol Analysis Set if more than 10% of the subjects in any regimen are found to significantly violate the terms and

conditions of the protocol (see description of Per-Protocol Analysis Set). Treatment effects will be determined through pair-wise treatment group comparisons: each dapagliflozin dose group versus placebo. No statistical comparisons will be made amongst the three dapagliflozin groups (2.5 mg BID, 5 mg BID and 10 mg QD).

The dapagliflozin 10 mg QD treatment group is provided as a measure of assay sensitivity. Comparisons of dapagliflozin 10 mg QD to placebo will be performed with nominal p values, outside of the controls, for multiplicity for the two dapagliflozin BID groups.

For efficacy variables, missing values at week 16 will be replaced by the last observation carried forward (LOCF) approach (see 11.2.2).

The primary objective of the study is to assess the efficacy of dapagliflozin 2.5 mg BID and 5 mg BID compared to placebo as add-on therapy to metformin in improving glycaemic control in subjects with type 2 diabetes, as determined by the primary efficacy variable change in HbA1c from baseline to week 16.

The null hypotheses H_{01} and H_{02} given below will be tested against the alternative hypotheses H_{A1} and H_{A2} respectively ($\alpha \leq 0.050$, two-sided):

$$H_{01}: \quad \mu_{D1} - \mu_P = 0, \qquad\qquad H_{02}: \quad \mu_{D2} - \mu_P = 0,$$

$$H_{A1}: \quad \mu_{D1} - \mu_P \neq 0, \qquad\qquad H_{A2}: \quad \mu_{D2} - \mu_P \neq 0,$$

where μ_{D1} and μ_{D2} denote the mean change in HbA1c from baseline to week 16 in the two dapagliflozin dose groups (2.5 mg BID and 5 mg BID) and μ_P denotes the mean change in HbA1c from baseline to week 16 in the placebo group. D1 denotes the dapagliflozin 2.5 mg BID dose group, and D2 denotes the dapagliflozin 5 mg BID dose group

The following key secondary efficacy variables have been identified:

1.   Percent change in body weight from baseline to week 16

2.   Change in FPG from baseline to week 1

3.   Change in FPG from baseline to week 16

4.   Proportion of patients with HbA1c<7.0%, in patients with HbA1c ≥7.0% at baseline.

A Hochberg procedure will be used to control the overall Type I error rate ≤0.050 for the two treatment group (2.5 mg BID and 5 mg BID) comparisons versus placebo for the primary efficacy variable (Hochberg 1988). Nominal p-values for the differences between the two dapagliflozin dose groups (2.5 mg BID and 5 mg BID) and the placebo group will be determined. If the largest of the two p-values is ≤0.050 (two-sided), then the two treatment group comparisons (2.5 mg BID and 5 mg BID) versus placebo will be declared statistically significant. If the largest of the p-values is >0.050 (two-sided), then the corresponding

treatment group comparison (2.5 mg BID or 5 mg BID) versus placebo is not significant. Then, the smaller p-value will be assessed for significance at a 0.025 level (two-sided).

Further testing of treatment groups (2.5 mg BID and/or 5 mg BID) versus placebo for key secondary variables will be performed using a hierarchical, fixed sequence testing procedure, but only with respect to the treatment group(s) found significant for the primary efficacy variable. The testing of the key secondary variables will be performed in the order listed above. The level of significance used for key secondary variables will be 0.050. The testing procedure is described below.

If at least one of the comparisons between a dapagliflozin treatment group (2.5 mg BID and/or 5 mg BID) and the placebo treatment group is significant for the primary efficacy variable, all statistical tests for the key secondary efficacy variables 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 variable will be done using a step-wise procedure. Within each dose group (2.5 mg BID and/or 5 mg BID) that was significantly superior to placebo for the primary efficacy variable, testing of key secondary variables will be performed in a fixed order sequence (see above). The testing sequence will be applied separately for each dose group (2.5 mg BID and/or 5 mg BID) with an $\alpha=0.05$ for each testing stream. Inference for hypothesis testing for the key secondary objectives will stop at the first occurrence of a failed test using the order stated above for, regardless of how testing has progressed in the other dose group.

Other secondary efficacy variables and safety variables shall provide supportive efficacy and safety information regarding the differences of the three dapagliflozin dose groups versus placebo.

The primary efficacy variable, change in HbA1c from baseline to week 16, will be analyzed using an analysis of covariance (ANCOVA) model with factor for treatment group (fixed effect) and covariate for baseline HbA1c. All treatment groups will be included in the model. The model will be used to derive a least squares estimate of the treatment difference in mean change with two-sided 95% confidence interval and corresponding p-value. Further, two-sided 95% confidence intervals for the mean change within each treatment group will be calculated.

The same method will be applied for analyzing other continuous efficacy variables, eg, change in systolic blood pressure from baseline to week 16. Nominal p-values for the difference of the dapagliflozin dose groups (2.5 mg BID, 5 mg BID and 10 mg QD) versus placebo will be provided.

For variables analyzed as percent change from baseline, the ANCOVA model will apply to logarithm-transformed data and resulting least-squares means and confidence intervals back-transformed to provide estimates in the original scale.

The change (or percent change) from baseline will be analyzed for important continuous efficacy variables at each scheduled time of assessment (using observed data and LOCF). For

each time point under consideration, summary statistics, adjusted mean changes (or percent changes) within each treatment group as well as means and 95% confidence intervals for the differences of the dapagliflozin dose groups (2.5 mg BID, 5 mg BID and 10 mg QD) versus placebo will be derived from an ANCOVA model with treatment group as a fixed effect, HbA1c at randomisation stratum and the baseline measurement as a covariate.

Proportions will be analyzed using the methodology of Zhang et al 2008 and Tsiatis et al 2008 when there are at least 5 subjects on average by treatment group. Estimates for treatment effects and differences between treatment groups will be obtained along with 95% confidence intervals and nominal p-values using this methodology with adjustment for baseline value. When there are less than 5 responders on average by treatment group, the unadjusted proportions and differences between proportions, exact 95% confidence intervals, and nominal p-values from the Fisher's exact test (when applicable) will be provided.

Other discrete variables will be summarized by counts, proportions and corresponding two sided 95% confidence intervals for each treatment group. Comparisons between treatments will be performed using two-sided Fisher's exact test, when applicable.

Due to the large number of centres and the expected low number of subjects per centre it will not be appropriate to explore centre effects. In order to assess effects of geographic region the primary efficacy variable will be analyzed using an ANCOVA model with additional factors for geographic region and treatment-by-geographic region interaction.

The safety evaluations will include analyses of AEs, laboratory parameters, vital signs, physical examination, ECG and hypoglycaemic events. The analysis of safety will be based on the Safety Analysis Set. Safety variables will be summarized descriptively.

12.2.1   Interim analyses

No interim analyses are planned.

12.3   Determination of sample size

The sample size for this study was selected to demonstrate a difference in the mean change in HbA1c from baseline to week 16 between one of the dapagliflozin treatment groups (2.5 mg BID and/or 5 mg BID) versus placebo co-administered with metformin. A review of variability estimates from BMS studies MB102013 and MB102014 suggests that the standard deviation associated with change in HbA1c from baseline to week 16 using LOCF will not be more than 0.97%. Since the overall Type I error will be controlled for the two treatment comparisons using a Hochberg procedure, sample size estimation is based on the conservative assumption that one dose comparison may not reach statistically significance. In this situation, in order to detect a 0.5% difference in mean change from baseline in HbA1c between one of the dapagliflozin treatment groups (2.5 mg BID and 5 mg BID) versus placebo using a 2-sample t-test at a 0.025, two-sided significance level with 90% power, 95 evaluable patients are required per treatment group in the Full Analysis Set. If one assumes 3% of the subjects will not have a baseline and post-baseline efficacy measurement, 98 subjects per group (392 total subjects) will need to be randomised.

Further, if 40% of subjects fail to meet entry criteria for randomisation (as seen in study MB102014), then approximately 654 subjects must be enrolled.

12.4 Data monitoring committee

The need for a data monitoring committee was considered, using both the CHMP's Guideline on Data Monitoring Committees (http://www.emea.europa.eu/pdfs/human/ewp/587203en.pdf) and the FDA's Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees(http://www.fda.gov/CBER/gdlns/clintrialdmc.pdf) as guidance.

Taking into account the available knowledge about dapagliflozin; the indication being studied; the study endpoints, duration, and population; and the patient safety assessment measures in place, AstraZeneca and our co-development partner Bristol-Myers Squibb have concluded that a data monitoring committee is not required for this study.

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 6.4.5

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 at the AstraZeneca Research and Development site shown below.

Name	Role in the study	Address & telephone number
Maria Gergely MD	Study Delivery Team Leader responsible for the protocol	AstraZeneca Kft. Hungary Bocskai u. 134-146. 1113 Budapest, Hungary Phone: +36 1 8836518 Fax: +36 1 8833337 Mobile: +36 20 9812 978
Veronika Hruba MD	Study Delivery Team Physician responsible for the protocol at central R&D site	AstraZeneca Czech Republic s.r.o. Smichov Gate - Prague Plzenska 3217/16 150 00 Praha 5, Czech Republic Phone: +420 222 807 230 Fax: +420 222 322287 Mobile: +420724110370

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 patients with type 2 diabetes. Once an investigator decides that a particular occurrence is an overdose, it must be reported as a Serious Adverse Event (see Sections 6.4.3 and 6.4.5). 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 should 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 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 patient was discontinued from the study.

If any pregnancy occurs in the course of the study, the patient 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 CRF 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.

14.   LIST OF REFERENCES

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