AstraZeneca

Revised Clinical Study Protocol	
Drug Substance	Dapagliflozin
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A 24-week international, randomized, parallel-group, double-blind, placebo-controlled Phase III study with a 80-week extension period to evaluate the efficacy and safety of dapagliflozin therapy when added to the therapy of patients with type 2 diabetes with inadequate glycaemic control on insulin.

Sponsor: AstraZeneca AB 15185 Södertälje, Sweden

AstraZeneca Marketing Compagny site representative

The following Amendment(s) and Administrative Changes are included in this amended protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1			
2			
3			
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Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change
1			

PROTOCOL SYNOPSIS

A 24-week international, randomized, parallel-group, double-blind, placebo-controlled Phase III study with a 80-week extension period to evaluate the efficacy and safety of dapagliflozin therapy when added to the therapy of patients with type 2 diabetes with inadequate glycaemic control on insulin

International coordinating investigator

Study centre(s) and number of subjects planned

This international study will be conducted at approximately 150 study centres. Approximately 1610 patients will be enrolled to reach the target of 644 randomized patients during an enrolment period of approximately 6 months. It is expected that approximately 4 to 5 patients will be randomized per centre. Centres may be discontinued from the study if recruitment rates are poor and new centres will be added if necessary to achieve recruitment goals. Recruitment will be competitive and centres will stop enrolment when enough patients are screened to provide the globally projected number randomized.

Approximately 700 patients will be offered to enter the long-term extension period II. This estimate is based on the number of actually randomised patients (808) amd the assumption that approximately 14 % of the randomised patients will have been withdrawn at week 48 (visit 12).

Study period		**Phase of development**
Estimated date of first subject enrolled	Q2 2008	IIIa
Estimated date of last subject completed)	Q1 2011	

Objectives

Primary Objective

The primary objective of this study is to assess the efficacy of 2.5 mg, 5 mg and 10 mg dapagliflozin compared to placebo as add-on therapy to insulin in improving glycaemic control in subjects with type 2 diabetes who have inadequate glycaemic control on ≥ 30 IU injectable insulin daily for at least 8 weeks prior to enrolment, as determined by the change in HbA1c levels from baseline to Week 24.

Secondary objectives

Key secondary objectives

Four key secondary objectives are identified a priori for special consideration in this study, in addition to the primary objective (superiority for HbA1c). A hierarchical closed testing procedure will be applied in order to control the type I error rate to support secondary superiority claims of dapagliflozin plus insulin treatment over placebo plus insulin treatment for the following key secondary objectives, for each dose of dapagliflozin:

- to examine whether treatment with dapagliflozin in combination with insulin is superior in reducing body weight or causing less weight gain as compared to placebo added to insulin treatment after 24 weeks of treatment.
- to examine whether treatment with dapagliflozin in combination with insulin leads to a lower absolute calculated mean daily insulin dose as compared to placebo added to insulin treatment alone, from baseline to week 24.
- to examine whether treatment with dapagliflozin in combination with insulin leads to higher percentage of patients with calculated mean daily insulin dose reduction from baseline to week 24 as compared to placebo added to insulin treatment
- to examine whether treatment with dapagliflozin in combination with insulin is superior in reducing Fasting Plasma Glucose (FPG) as compared to placebo added to insulin treatment after 24 weeks of treatment.

Other secondary objectives

To compare the effects of each dose of dapagliflozin versus placebo given as add-on therapy to insulin on additional weight and glycaemic outcome variables, as well as changes in blood pressure and lipid values:

- Percentage change of calculated mean daily insulin dose from baseline to week 24
- Mean change in HbA1c from baseline to week 24 in patients with baseline HbA1c ≥9%
- Proportion of patients achieving a therapeutic glycaemic response defined as HbA1c <7% at week 24

- Mean change in HbA1c from baseline to week 24 in patients with HbA1c ≥7.5% and <9% at baseline
- Mean change in HbA1c from baseline to week 24 in patients with BMI ≥27 kg/m^2 at baseline
- Mean change in HbA1c from baseline to week 24 in patients with BMI ≥30 kg/m^2 at baseline
- Mean change in body weight from baseline to week 24 in patients with a baseline BMI ≥30 kg/m^2
- Mean change in body weight from baseline to week 24 in patients with a baseline BMI ≥27 kg/m^2
- Mean change in waist circumference from baseline to week 24
- Mean change of FPG after 1 week of treatment
- Mean change in seated systolic BP and seated diastolic BP from baseline to week 24
- Mean change in seated systolic BP and seated diastolic BP from baseline to week 24 in patients with baseline seated systolic BP >140 mmHg
- Percentage change in total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG) and free fatty acids (FFA) from baseline to week 24

Safety Objectives

- To evaluate the safety and tolerability by assessment of adverse events (AE), laboratory values, electrocardiogram (ECG), pulse, blood pressure (BP), hypoglycaemic events, calculated creatinine clearance, estimated glomerular filtration rate (eGFR), total protein/creatinine ratio (mg/g) and physical examination findings (e.g. oedema).

Pharmacokinetic objectives

- To explore the relationships between exposure measures and efficacy endpoints such as reduction in HbA1c from baseline

Objectives of the 24-week extension period I

- To assess the safety and tolerability parameters over 48 weeks of treatment
- To assess the maintenance of efficacy of each dose of dapagliflozin plus insulin over 48 weeks of treatment

Objectives of the 56-week extension period II

- To assess the safety and tolerability of dapagliflozin 2.5 and 10 mg compared with placebo as add-on therapy to insulin over 104 weeks of treatment
- To assess the maintenance of efficacy of dapagliflozin 2.5 and 10 mg compared with placebo as add-on therapy to insulin over 104 weeks of treatment
- To assess the influence of switching dapagliflozin 5 mg to 10 mg on the safety and efficacy parameters compared with placebo as an add-on therapy to insulin over 56 weeks of treatment

All glycemic efficacy objectives will be based on values measured by central laboratory. Self monitored plasma glucose (SMBG) measured by the patient and FPG measured by the site using glucometer will be used only for safety purposes.

Study design

This is a 24-week, international, randomized, parallel-group, double-blind, placebo-controlled Phase III study with a 24-week double -blind extension period I and a 56-week double-blind-extension period II incorporating a switch of dapagliflozin 5 mg to 10 mg during extension period II to evaluate the efficacy and safety of dapagliflozin as add-on therapy in adult patients with type 2 diabetes who have inadequate glycaemic control (HbA1c ≥7.5% and ≤10.5%) on ≥ 30 IU injectable insulin daily for at least 8 weeks prior to enrolment, with or without OADs.

Target subject population

Male and female patients with type 2 diabetes and age ≥18 to ≤80 years, with inadequate glycaemic control defined as HbA1c ≥7.5% and ≤10.5% are eligible to enter the Enrolment period. Patients must be according to investigators judgement on a stable insulin regimen with the mean insulin dose of ≥ 30 IU injectable insulin for at least 8 weeks prior to enrolment. Additional treatment with OADs according to their approved prescribing information is allowed. Patients will be stratified according to whether their treatment regimen includes OADs or not. No more than 60% of the enrolled patients can be taking insulin plus OADs. Enrolment in the strata with OADs may be stopped to ensure adequate numbers of patients who are not taking any OADs. OADs must be at a stable dose for at least 8 weeks prior to the enrolment visit. Patients on metformin therapy should be on at least 1500 mg/day of metformin or at the maximum tolerable dose for a period of at least 8 weeks prior to enrolment. Patients on other OAD medications should be on at least half maximum daily recommended dose of the OAD for a period of at least 8 weeks prior to enrolment. Patients on more than 2 background OADs may not be included in the study.

Target subject population for the long-term, double blind extension period II

Patients who are still on active study treatment after the first 48 weeks of double-blind treatment, have not developed any criterion for study discontinuation and are willing to participate in the second extension period for another 56 weeks.

Investigational product, dosage and mode of administration

- Dapagliflozin tablets, 2.5 mg, 5 mg and 10 mg, administered orally, once daily for the 24-week double-blind treatment period and the 24-week long term double-blind extension period I .
- Dapagliflozin tablets 2.5 and 10 mg, administered orally, once daily for the 56-week long term double-blind extension period II.
- Matching placebo for dapagliflozin tablets, 2.5 mg, 5 mg and 10 mg, administered orally, once daily for the 24-week double-blind treatment period and the 24-week long term double-blind extension period I
- Matching placebo for dapagliflozin tablets 2.5 mg and 10 mg, administered orally, once daily for the 56-week long term double-blind extension period II.

Comparator, dosage and mode of administration

Patients will continue their prior insulin and if applicable OAD dose throughout the entire study period unless insulin dose reduction or up-titration of insulin is indicated in patients with inappropriate glycaemic control.

Duration of treatment

The randomized treatment period will be 104 weeks in total:

- 24 weeks double-blind treatment period (dapagliflozin 2.5 mg, 5 mg, 10 mg, or placebo),
- 24 weeks first double-blind extension period I (dapagliflozin 2.5 mg, 5 mg, 10 mg, or placebo),
- 56 weeks second double-blind extension period II (dapagliflozin 2.5 mg or10 mg, or placebo).

Patients will have an enrolment period of 2 weeks, and a follow up period of 3 weeks off of study medication. The 3-week follow up period allows for a further understanding of any changes in physical signs and symptoms or laboratory parameters that can be potentially attributed to the use of the investigational product.

Outcome variables

Efficacy

Primary outcome variable:

- Change in HbA1c from baseline to week 24.

Secondary outcome variables:

Key secondary outcome variables

- Change in body weight from baseline to week 24
- Absolute change in calculated mean daily insulin dose from baseline to week 24
- Proportion of patients with calculated mean daily insulin dose reduction from baseline to week 24
- Change in FPG from baseline to week 24.

Other secondary outcome variables

Efficacy

- Percent change of calculated mean daily insulin dose from baseline to week 24
- Change in HbA1c from baseline to week 24 in patients with a HbA1c of ≥9% at baseline
- Proportion of patients achieving HbA1c <7% at week 24
- Change in HbA1c from baseline to week 24 in patients with a HbA1c of ≥7.5% and <9% at baseline
- Change in HbA1c from baseline to week 24 in patients with BMI ≥27 kg/m2 at baseline
- Change in HbA1c from baseline to week 24 in patients with BMI ≥30 kg/m2 at baseline
- Change in body weight from baseline to week 24 in patients with a baseline BMI ≥30 kg/m2
- Change in body weight from baseline to week 24 in patients with a baseline Body Mass Index (BMI) ≥27 kg/m2
- Change in waist circumference from baseline to week 24
- Change of FPG after 1 week of treatment
- Change in seated systolic BP and seated diastolic BP from baseline to week 24

- Change in seated systolic BP and seated diastolic BP from baseline to week 24 in patients with baseline seated systolic BP >140 mmHg

- Percent change in total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG) and free fatty acids (FFA) from baseline to week 24

Safety

- Adverse events (AEs), laboratory values, electrocardiogram (ECG), pulse, blood pressure (BP), hypoglycaemic events, calculated creatinine clearance, estimated glomerular filtration rate (eGFR), total protein/creatinine ratio (mg/g) and physical examination findings (e.g. oedema).

Pharmacokinetics

Relationships between exposure measures (e.g. AUC) and efficacy endpoints (e.g. changes from baseline in HbA1c).

Variables for the long-term, double-blind extension period I

- AEs, laboratory values, ECG, pulse, BP, hypoglycaemic events, calculated creatinine clearance, eGFR, total protein/creatinine ratio (mg/g) and physical examination findings (e.g. oedema) from baseline to week 48

- Change in HbA1c from baseline to week 48

- Change in HbA1c from week 24 to week 48

- Change in FPG from baseline to week 48

- Change in body weight from baseline to week 48

- Proportion of patients with calculated mean daily insulin dose reduction from baseline to week 48

- Change in calculated mean daily insulin dose from baseline to week 48

- Percent change of calculated mean daily insulin dose from baseline to week 48

- Change in HbA1c from baseline to week 48 in patients with a HbA1c of ≥9% at baseline

- Proportion of patients achieving HbA1c <7% at week 48

- Change in HbA1c from baseline to week 48 in patients with a HbA1c of ≥7.5% and <9% at baseline

- Change in HbA1c from baseline to week 48 in patients with BMI ≥27 kg/m2 at baseline

- Change in HbA1c from baseline to week 48 in patients with BMI ≥30 kg/m2 at baseline

- Change in body weight from baseline to week 48 in patients with a baseline BMI ≥30 kg/m2

- Change in body weight from baseline to week 48 in patients with a baseline Body Mass Index (BMI) ≥27 kg/m2

- Change in waist circumference from baseline to week 48

- Change in seated systolic BP and seated diastolic BP from baseline to week 48

- Change in seated systolic BP and seated diastolic BP from baseline to week 48 in patients with baseline seated systolic BP >140 mmHg

- Percent change in total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG) and free fatty acids (FFA) from baseline to week 48

Variables for the long-term, double-blind extension period II

- AEs, laboratory values, ECG, pulse, BP, hypoglycaemic events, calculated creatinine clearance, eGFR, total protein/creatinine ratio (mg/g) and physical examination findings (e.g. oedema) from baseline to week 104, and from week 48 to week 104

- Change in HbA1c from baseline to week 104.

- Change in HbA1c from week 24 to week 104.

- Change in HbA1c from week 48 to week 104.

- Change in FPG from baseline to week 104 and from week 48 to week 104..

- Change in body weight from baseline to week 104, and from week 48 to week 104.

- Proportion of patients with calculated mean daily insulin dose reduction from baseline to week 104, and from week 48 to week 104.

- Mean change and percentage change in calculated mean daily insulin dose from baseline to week 104

- Mean change and percentage change of calculated mean daily insulin dose from week 48 to week 104.

- Change in HbA1c from baseline to week 104, and from week 48 to week 104 in patients with a HbA1c of ≥9% at baseline

- Proportion of patients achieving HbA1c <7% at week 104 and from week 48 to week 104

- Change in HbA1c from baseline to week 104, and from week 48 to week 104 in patients with a HbA1c of ≥7.5% and <9% at baseline

- Change in HbA1c from baseline to week 104, and from week 48 to week 104 in patients with BMI ≥27 kg/m2 at baseline

- Change in HbA1c from baseline to week 104, and from week 48 to week 104 in patients with BMI ≥30 kg/m2 at baseline

- Change in body weight from baseline to week 104, and from week 48 to week 104 in patients with a baseline BMI ≥30 kg/m2

- Change in body weight from baseline to week 104, and from week 48 to week 104 in patients with a baseline Body Mass Index (BMI) ≥27 kg/m2

- Change in waist circumference from baseline to week 104, and from week 48 to week 104

- Change in seated systolic BP and seated diastolic BP from baseline to week 104, and from week 48 to week 104

- Change in seated systolic BP and seated diastolic BP from baseline to week 104, and from week 48 to week 104 in patients with baseline seated systolic BP >140 mmHg

- Percent change in total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG) and free fatty acids (FFA) from baseline to week 104, and from week 48 to week 104

Patient reported outcomes

(PROs) (not applicable)

Health economics (not applicable)

Pharmacokinetics

Plasma samples for analysis of dapagliflozin will be obtained at the Week 8 and Week 20 visits immediately prior to dosing, 60 minutes post-dose and 180 minutes post dose.

Genetics

Blood samples will be taken from patients who separately consent to optional blood sampling donation for deoxyribonucleic acid (DNA) analysis. The purpose is to enable future pharmacogenetic research studies. DNA collected from the samples and health information collected from the main clinical study may be used to investigate the effects of DNA variation on response to study treatments and the causes and further progression of type 2 diabetes and other metabolic diseases. Samples from this and other clinical studies may also be used in conjunction to accomplish these objectives. The samples will be destroyed after 15 years.

Statistical methods

The primary outcome variable, change from baseline to week 24 in HbA1c, will be analyzed by an analysis of covariance model (ANCOVA) which will be used to derive least squares estimates of the treatment differences (each dapagliflozin dose group versus placebo) in mean change with corresponding p-values and two-sided 95% confidence intervals. A hierarchical closed testing procedure will be used to control the Type I error rate across the primary and key secondary objectives. Efficacy will primarily be evaluated using the full analysis set.

Each pair-wise treatment group comparison will be tested at a significance level of approximately 0.019, according to Dunnett's method, in order to maintain an overall Type I error rate <0.050 for the primary objective. To detect a difference of 0.5% between each dapagliflozin group versus placebo for changes in HbA1c from baseline to week 24, assuming a SD = 1.2%, and at a two-sided significance level of 0.019, 153 evaluable subjects are needed in each treatment group to provide 90% power. Assuming that 5% of the subjects will not be evaluable in the full analysis set , 161 subjects per treatment group (644 subjects total) are planned for randomization.

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* Supplement might be updated during the course of the study. This will not be considered as an amendment to the Clinical Study Protocol.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 4.7.1.1)
ANCOVA	Analysis of covariance model
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under curve
BP	Blood pressure
BUN	Blood urea nitrogen
CK	Creatine Kinase
CPMP	Committee for Proprietary Medicinal Products
CRO	Contract research organization
eCRF	Electronic Case Report Form
CSA	Clinical Study Agreement
ECG	Electrocardiogram
Ethics Committee	Synonymous to Institutional Review Board and Independent Ethics Committee
FFA	Free fatty acids
FPG	Fasting plasma glucose
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HbA1c	Glycosylated haemoglobin A1c
HDL-C	High density lipoprotein-cholesterol
HIV	Human immunodeficiency virus
hs-CRP	High sensitivity C-reactive protein
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.
Kg	Kilogram

Abbreviation or special term	**Explanation**
LDL-C	Low density lipoprotein-cholesterol
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MODY	Maturity onset Diabetes of the Young
NYHA	New York Heart Association
OAD	Oral anti-diabetic drug
PPG	Postprandial glucose
PTH	Parathyroid hormone
SAE	Serious adverse event (see definition in Section **4.7.1.1**).
SAP	Statistical analysis plan
SDV	Source data verification
SMBG	Self monitored blood glucose
TB	Total bilirubin
TC	Total cholesterol
TG	Triglycerides
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
WBDC	Web Based Data Capture
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background

Type 2 diabetes is characterized by beta-cell dysfunction and peripheral insulin resistance leading to hyperglycaemia (**Matthaei et al 2000**, **Meier et al 2005**). Chronic hyperglycaemia has been associated with the development of both macrovascular (myocardial infarction, stroke), and microvascular (nephropathy, retinopathy, neuropathy) complications (**The Diabetes Control and Complications** Trial Research Group 1993, **UK Prospective Diabetes Study (UKPDS)** Group 1998). Current treatment regimens aiming to reduce glucose levels in patients with type 2 diabetes have focussed on the stimulation of insulin secretion (e.g. sulphonylureas, glinides, DPP-4 inhibitors), the reduction of peripheral insulin resistance (e.g. metformin, thiazolidinediones), the inhibition of intestinal glucose absorption (e.g. acarbose), or the substitution of insulin. However, the limited efficacy as well as the induction of side effects (e.g., hypoglycaemia, oedema, weight gain, etc.) clearly underline the need for novel antidiabetic treatment strategies (**Standards of medical care in** diabetes 2006, **Koro et al 2004**).

Intestinal absorption and renal reabsorption of glucose are mediated through sodium glucose transporters (SGLT) (**Silverman 1991**). Two sodium-dependent 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 >90% of renal glucose reabsorption occurs (**Wright 2001**). Human mutations in SGLT2 are associated with familial renal glucosuria (**Santer et al 2003**). These patients present with glucosuria secondary to a decrease in glucose reabsorption in the proximal tubule. They have normal plasma glucose levels. From the information available, these patients have a normal life-span and the majority of them have no abnormalities other than an increased urinary glucose excretion (**Santer et al 2003**, **van den Heuvel et al** 2002). Thus SGLT2 appears to be the major transporter responsible for renal glucose transport, mediating glucose re-uptake from the glomerular filtrate. Inhibition of SGLT2 therefore provides a promising novel treatment strategy to reduce high blood glucose levels via enhanced renal glucose excretion.

Dapagliflozin has been designed as a potent and selective inhibitor of the renal sodium-glucose transporter, SGLT2. This compound is being developed as an orally-active agent for the treatment of type 2 diabetes, and represents a novel therapeutic approach for the treatment of this disorder.

Proof of concept for dapagliflozin in patients with type 2 diabetes has been established in a phase IIb study over a dose range from 2.5 to 50 mg over 12 weeks, administered as once daily oral ingestion. In this study, dapagliflozin treatment led to significant and clinically relevant reductions of fasting glucose concentration and HbA1c levels throughout the entire dose range, and was associated with weight loss. Adverse events and serious adverse events were balanced between the dapagliflozin and placebo groups with the exception of an increased incidence of dizziness (5.0% for dapagliflozin vs. 1.9% for placebo), and vulvovaginal infections (1.8% for dapagliflozin vs. 0% for placebo).

Overall, these findings support the further development of dapagliflozin and the implementation of pivotal trials of sufficient duration to more fully characterize the safety and efficacy of the 2.5, 5, and 10 mg doses.

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

1.2 Rationale

This study is one of the Phase III studies that will be performed concurrently as part of a full Phase III clinical development program for dapagliflozin for the treatment of type 2 diabetes.

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 subjects and in patients with type 2 diabetes), dapagliflozin was safe and well tolerated with a favourable pharmacokinetic and pharmacodynamic profile. In Phase IIb studies in patients with type 2 diabetes dapagliflozin demonstrated good glycaemic efficacy, significant weight loss and an acceptable safety profile over a wide range of doses. Based on a consideration of efficacy, pharmacodynamics, and safety data from the Phase I and Phase II programs, daily doses of 2.5 mg, 5 mg and 10 mg of dapagliflozin have been chosen for the Phase III studies.

Insulin is a frequently chosen antidiabetic therapy for Type 2 diabetes patients with insufficient glycaemic control on OAD therapy **(Heine et al 2005**, **Groop et al 1986**). However as type II diabetes is a progressive disease, over time, in spite of high doses of antihyperglycaemic therapy, glucose control may deteriorate. In a multicentre, controlled trial of more than 4.000 patients with type II diabetes followed for more than 9 years **(Turner R, Cull C, Holman** R. 1996), even insulin therapy did not achieve the therapeutic goal of normoglycaemia, particularly in patients with severe hyperglycemia. Further, weight gain, fluid retention and the risk of hypoglycemia are common problems of insulin therapy and present a major concern for many patients. Excessive weight gain may negatively interact with antidiabetic treatment, by increasing cardiovascular risk and reducing the ability to exercise. Patients with inadequate glycaemic control on at least 30 units of insulin per day may benefit from the addition of an oral antidiabetic drug (dapagliflozin) with an insulin independent mechanism of action that is expected to complement the antihyperglycaemic action of insulin while at the same time help mitigate the excessive weight gain or even cause weight loss.

Change in HbA1c is the primary endpoint in the study, since CPMP guidelines suggest that therapeutic confirmatory studies in patients with Type 2 diabetes should demonstrate the superiority in favourable evolution of HbA1c. Other key secondary endpoints of interest in this study of patients on daily injectable insulin therapy are change in insulin dose and change in body weight.

The first 24+24-weeks in this Phase III clinical study is therefore designed to investigate the safety and efficacy of dapagliflozin 2.5, 5 and 10 mg as add-on therapy to insulin compared to placebo in improving glycaemic control in subjects with type 2 diabetes who have inadequate glycaemic control defined as HbA1c ≥7.5% and ≤10.5% on ≥30 IU injectable insulin dose for at least 8 weeks prior to enrolment. This study is required to demonstrate that dapagliflozin is more effective as add-on therapy to insulin in the treatment of type 2 diabetes than placebo in patients inadequately controlled with insulin therapy alone.

The Division of Metabolism and Endocrinology Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration has recommended that additional long-term evidence is needed for products seeking an indication to treat diabetes mellitus (US Department of Health and Human Services- Food and Drug Administration, Center for Drug Evaluation and Research 2008). To establish the safety of any new anti-diabetic drug to treat type 2 diabetes based on HbA1c measurements, there is a need to demonstrate that this therapy will not result in an unacceptable increase in cardiovascular risk. To comply with these requirements, released after the start of the study, a second long-term extension period was added.

This second extension period (56 weeks) is designed to investigate the overall safety and efficacy of dapagliflozin 2.5 mg and 10 mg as add-on therapy to insulin compared to placebo in patients, who are still on active study treatment after the first 48 weeks of double-blind treatment, have not developed any reason for study discontinuation and are willing to participate in the second extension. Subjects randomized to placebo, dapagliflozin 2.5 or 10 mg will continue their randomized double-blind treatment. Subjects randomized to dapagliflozin 5 mg will be switched to dapagliflozin 10 mg. The switch of middle dose to the highest one is to gain more experience and further evaluate the efficacy and safety of the higher dose (10 mg) of dapagliflozin.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to assess the efficacy of 2.5 mg, 5 mg and 10 mg dapagliflozin compared to placebo as add-on therapy to insulin in improving glycaemic control in subjects with type 2 diabetes who have inadequate glycaemic control on ≥ 30 IU injectable insulin daily for at least 8 weeks prior to enrolment., as determined by the change in HbA1c levels from baseline to Week 24.

2.2 Secondary objectives

Key secondary objectives

Four key secondary objectives are identified a priori for special consideration in this study, in addition to the primary objective (superiority for HbA1c). A hierarchical closed testing procedure will be applied in order to control the type I error rate to support secondary superiority claims of dapagliflozin plus insulin treatment over placebo plus insulin treatment for the following key secondary objectives, for each dose of dapagliflozin:

- to examine whether treatment with dapagliflozin in combination with insulin is superior in reducing body weight or causing less weight gain as compared to placebo added to insulin treatment after 24 weeks of treatment.
- to examine whether treatment with dapagliflozin in combination with insulin leads to a lower absolute calculated mean daily insulin dose as compared to placebo added to insulin treatment alone, from baseline to week 24.
- to examine whether treatment with dapagliflozin in combination with insulin leads to higher percentage of patients with calculated mean daily insulin dose reduction from baseline to week 24 as compared to placebo added to insulin treatment
- to examine whether treatment with dapagliflozin in combination with insulin is superior in reducing Fasting Plasma Glucose (FPG) as compared to placebo added to insulin treatment after 24 weeks of treatment.

Other secondary objectives

Efficacy

To compare the effects of each dose of dapagliflozin versus placebo given as add-on therapy to insulin on additional weight and glycaemic outcome variables as well as changes in blood pressure and lipid values:

- Percentage change of calculated mean daily insulin dose from baseline to week 24
- Mean change in HbA1c from baseline to week 24 in patients with baseline HbA1c ≥9%
- Proportion of patients achieving a therapeutic glycaemic response defined as HbA1c < 7% at week 24
- Mean change in HbA1c from baseline to week 24in patients with HbA1c ≥ 7.5% and < 9% at baseline.
- Mean change in HbA1c from baseline to week 24 in patients with BMI ≥27 kg/m^2 at baseline.

- Mean change in HbA1c from baseline to week 24 in patients with BMI ≥30 kg/m^2 at baseline.
- Mean change in body weight from baseline to week 24 in patients with a baseline BMI ≥30 kg/m^2
- Mean change in body weight from baseline to week 24 in patients with a baseline BMI ≥27 kg/m^2
- Mean change in waist circumference from baseline to week 24
- Mean change of FPG after 1 week of treatment
- Mean change in seated systolic BP and seated diastolic BP from baseline to week 24
- Mean change in seated systolic BP and seated diastolic BP from baseline to week 24 in patients with baseline seated systolic BP>140 mmHg
- Percentage change in total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG) and free fatty acids (FFA) from baseline to week 24

Safety

- To evaluate the safety and tolerability by assessment of adverse events (AE) laboratory values, electrocardiogram (ECG), pulse, blood pressure (BP),
- hypoglycaemic events, creatinine clearance, estimated glomerular filtration rate (eGFR), total protein/creatinine ratio (mg/g) calculated and physical examination findings (e.g. oedema).

Pharmacokinetic objectives

- To explore the relationships between exposure measures and efficacy endpoints such as reduction in HbA1c from baseline

Objectives of the 24-week extension period I

- To assess the safety and tolerability parameters over 48 weeks of treatment
- To assess the maintenance of efficacy of each dose of dapagliflozin plus insulin over 48 weeks of treatment

Objectives of the 56-week extension period II

- To assess the safety and tolerability of dapagliflozin 2.5 mg and 10 mg compared with placebo as add on therapy to insulin over 104 weeks of treatment

- To assess the maintenance of efficacy of dapagliflozin 2.5 mg and 10 mg compared with placebo as add on therapy to insulin over 104 weeks of treatment

- To assess the influence of switching dapagliflozin 5 mg to 10 mg on the safety and efficacy parameters compared with placebo as a add on therapy to insulin over 56 weeks of treatment

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

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

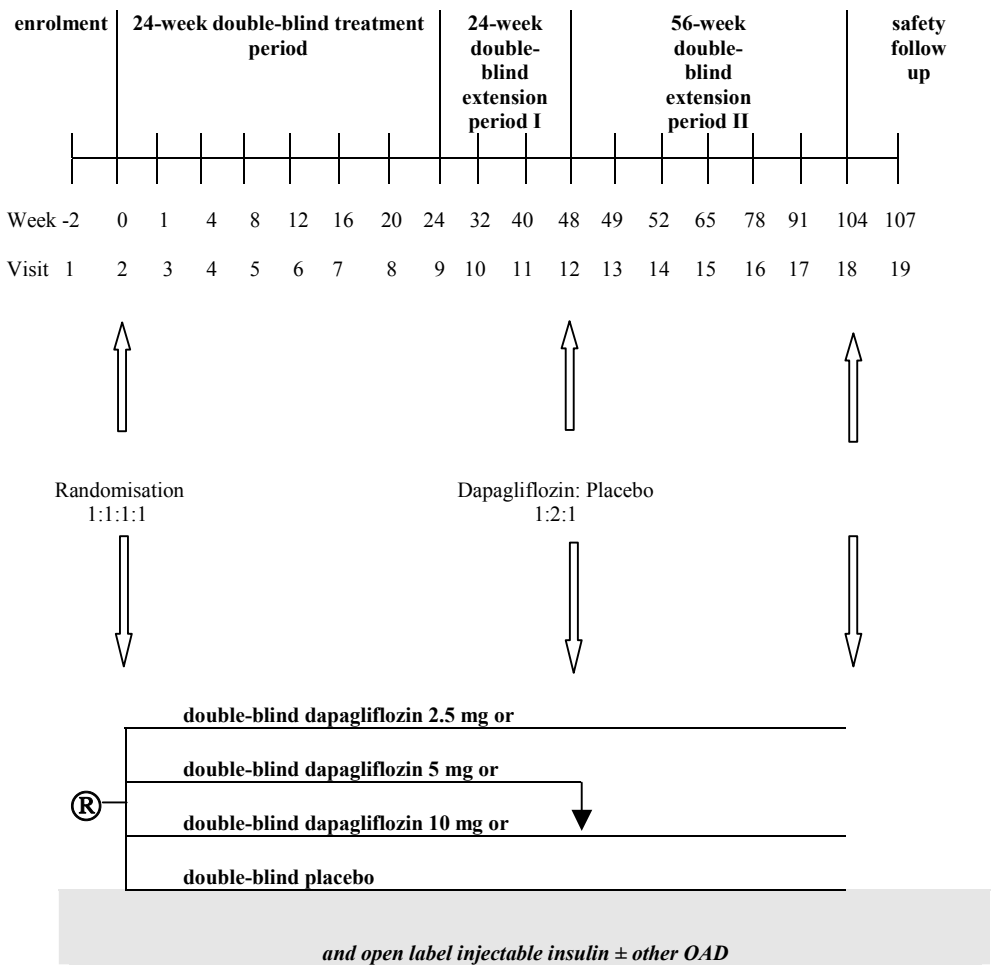
This is a 24-week, international, randomized, parallel-group, double-blind, placebo-controlled Phase III study with a 24-week double -blind extension period I to evaluate the efficacy and safety of dapagliflozin 2.5 mg, 5 mg and 10 mg as add-on therapy and a 56-week double blind-extension period II that includes a switch of dapagliflozin 5 mg or matching placebo to 10 mg or matching placebo (for patients initially randomised to placebo) to evaluate the efficacy and safety of dapagliflozin as add-on therapy in adult patients with type 2 diabetes who have inadequate glycaemic control (HbA1c ≥7.5% and ≤10.5%) on ≥ 30 IU injectable insulin daily for at least 8 weeks prior to enrolment, with or without OADs.

This study will be conducted at approximately 150 centres world-wide. Approximately 1610 patients will be enrolled to randomize 644 patients. It is expected that approximately 4-5 patients will be randomized per centre. Centres may be discontinued from the study if recruitment rates are poor and new centres may be added if necessary to achieve recruitment goals. Recruitment will be competitive across countries and centres. Centres will stop enrolment once enough patients are screened to provide the globally projected number randomized.

Patients with type 2 diabetes and inadequate glycaemic control (HbA1c ≥7.5% and ≤10.5%) on ≥30 IU mean daily injectable insulin dose for at least 8 weeks prior to enrolment with or without additional OADs will be eligible to enter the study. Patients will be stratified according to whether their treatment regimen includes OADs or not. No more than 60% of enrolled patients can be taking insulin plus OADs. Enrolment in the strata with OADs may be stopped to ensure adequate numbers of patients who are not taking any OADs. Patients should be instructed to abstain from all food and beverages for 12 hours prior to each clinical visit, however, drinking water after midnight is allowed. Patients should not take any insulin or OAD medication on the morning of the study visits. In the morning prior to each visit, acceptable concomitant medications can be taken with water only. At visit 2, on the day of randomization, the calculated mean daily insulin dose which is an average of the total daily insulin dose used over the last seven documented days between visits 1 and 2 will be recorded as the baseline insulin dose. Eligible patients with at least 30 IU calculated mean daily insulin dose will be randomized if the daily insulin requirements over the past seven days with insulin

dose documentation (between visits 1 and 2) does not vary more than 10% of the calculated mean daily insulin dose on more than one occasion. (For example for a patient whose calculated mean daily insulin dose is 50 IU, daily doses may not be <45 and >55 IU on more than one occasion within the past seven days with insulin dose documentation).

Figure 1 Study flow chart



The actual study will consist of the following 5 parts:

Enrolment period (Visit 1, week –2 to week 0)

Patients with type 2 diabetes on at least 30 IU of insulin per day for at least 8 weeks prior to enrolment, with or without OADs with known HbA1c values ≥7,5 % and ≤10.5% will provide informed consent and submit laboratory samples. Patients on metformin therapy should be on at least 1500 mg/day of metformin or at the maximum tolerable dose for a period of at least 8 weeks prior to enrolment. Patients on other OAD medications should be on at least half maximum daily recommended dose of the OAD for a period of at least 8 weeks prior to enrolment. Patient will be provided with a glucometer and a patient diary and be instructed to record their daily SMBG as well as insulin use during the next two weeks. Patients will be instructed to continue their current insulin and if applicable any ongoing OAD therapy at the same dose level during enrolment period.

24-week double-blind treatment period (Visit 2–9; week 0 to week 24)

If all lab inclusion criteria for V1 are met, Visit 2 should occur two weeks after visit 1. All further applicable inclusion and exclusion criteria will be checked and the mean daily insulin dose will be calculated by the investigator. The calculated mean daily insulin dose is an average total daily insulin dose used over the last seven documented days. Eligible patients with at least 30 IU calculated mean daily insulin dose will be randomized if the daily insulin requirements over the past seven days with insulin dose documentation does not vary more than 10% of the calculated mean daily insulin dose on more than one occasion. (For example for a patient whose calculated mean daily insulin dose is 50 IU, daily doses may not be <45 and >55 IU on more than one occasion within the past seven days with insulin dose documentation).

Eligible patients will be randomized in a 1:1:1:1 ratio to receive either dapagliflozin at 2.5 mg, 5 mg, 10 mg or placebo once daily. Patients will return for visits 1 week after start of treatment and then approximately every 4 weeks to assess efficacy and safety of the treatment. The patients will be instructed to record their fasting SMBG as well as insulin use daily. The patients will further be instructed to always self-monitor plasma glucose in case of symptoms suggestive of hypoglycaemia and to register any signs of hypoglycaemia in the supplied diary. During the study treatment the patients will be instructed to keep their insulin (and if applicable OAD) dose unchanged.

The determination of FPG at the study centre will be made using the HemoCue™ glucometer provided by AstraZeneca.

The evaluation at each of the study visits should take into account both the plasma glucose measurements made by the patients prior to visits and the investigator's measurements at the visits.

Up-titration is defined as an increase in mean daily insulin dose that meets both of the following criteria:

1. the increase in insulin dose is more than 5 IU (i.e. 6 IU or greater)

and

2. the increase in insulin dose is greater that 10% of the baseline insulin dose (baseline insulin dose is calculated daily mean isnulin dose documented at visit 2, week 0).

Any insulin dose changes (even if more than 5 IU/ day or more than 10% of the mean daily insulin dose at baseline) during hospitalisation is not considered as an up-titration as long the insulin dose change is not for a period of more than 10 days and the primary reason for hospitalisation is not management of the patient's glycaemic control. Similarly, if insulin requirement has increased temporarily, e.g. due to an infection, it will not be considered an up-titration even if the insulin dose increase is more than 5 IU or more than 10 % of the baseline mean daily insulin dose as long as such an increase is for a period of not more than 10 days and the insulin dose is expected to return to the baseline level once the precipitating condition has resolved.

Up-titration of the insulin dose during the 24-week double-blind treatment period shall be considered by the investigator under the following circumstances:

From Visit 3 to Visit 6:

- if the FPG measurement taken at the site visits 3 (week 1), visits 4 (week 4), 5 (week 8), or 6 (week 12) exceeds 240 mg/dl (13.3 mmol/l) and this FPG result is confirmed by both the central laboratory and a repeat FPG measurement at the site at a return visit within 72 hours

or

- if at least 3 fasting SMBG diary measurements from the past 7 days exceed 240 mg/dl (13.3 mmol/l). Diary fasting SMBG values that meet these criteria should be recorded in the eCRF.

From Visit 6 to Visit 9:

- if the FPG measurement taken at the site visits 7 (week 16), 8 (week 20) **or** 9 (week 24) exceeds 220 mg/dl (12.2 mmol/l) and this FPG result is confirmed by both the central laboratory and a repeat FPG measurement at the site at a return visit within 72 hours

or

- if at least 3 fasting SMBG diary measurements from the past 7 days exceed 220 mg/dl (12.2 mmol/l). Diary fasting SMBG values that meet these criteria should be recorded in the eCRF.

The last HbA1c and FPG values measured by central laboratory prior to the up-titration of insulin dose will be carried forward for the efficacy analyses at week 24 (visit 9).

Reduction of daily insulin dose shall be ordered by the investigator under the following circumstances:

Within the first 7 days of active randomized treatment:

- if the patient reports two or more readings of plasma glucose value ≤80 mg/dl (≤4.4 mmol/l).

After the first 7 days of active randomized treatment:

- if the patient reports two of more readings of plasma glucose value ≤70 mg/dl (≤3.8 mmol/l).

Patients should be encouraged to contact the investigator in such a case to allow the reduction of insulin dose.

Background OAD therapy may only be decreased if a concern of hypoglycaemia arises in a patient that has already been completely taken off of insulin.

Background OAD therapy may not be increased at any time during the study

Patients will be discontinued from the study if they have had complete withdrawal of both insulin and if applicable other OAD, they subsequently experience more than one event of major hypoglycaemia, and the investigator decides that current treatment puts the patient at risk of either repeated hypoglycaemic events or major hypoglycaemia. Major hypoglycaemia is defined as a symptomatic event requiring external assistance due to severe impairment in consciousness or behaviour with a capillary or plasma glucose value <3 mmol/l (<54 mg/dl) and prompt recovery after glucose or glucagon administration.

Randomized patients who discontinue early should complete the procedures described for visit 18 (end of treatment period) immediately following discontinuation of study drug. Thereafter patients should return for the 3 week follow up visit so that visit 19 procedures can be completed.

Long-term, double-blind extension period I (Visits 10–12, Weeks 25-48)

After 24 weeks of double-blind treatment, patients will continue in the randomized double-blind extension period with the same treatment given as at the end of the 24-week double-blind treatment period. Patients will return for visits approximately every 8 weeks to assess efficacy and safety of the treatment. The patients will be instructed to record their fasting SMBG as well as insulin use daily. The patients will further be instructed to always self-monitor plasma glucose in case of symptoms suggestive of hypoglycaemia and to register any signs of hypoglycaemia in the supplied diary. During the study treatment the patients will be instructed to keep their insulin (and if applicable OAD) dosage unchanged.

Up-titration is defined as an increase in mean daily insulin dose that meets both of the following criteria:

1. the increase in insulin dose is more than 5 IU (i.e. 6 IU or greater)

and

2. the increase in insulin dose is greater that 10% of the baseline insulin dose.

Any insulin dose changes (even if more than 5 IU/ day or more than 10% of the mean daily insulin dose at baseline) during hospitalisation is not considered as an up-titration as long the insulin dose change is not for a period of more than 10 days and the primary reason for hospitalisation is not management of the patient's glycaemic control. Similarly, if insulin requirement has increased temporarily, e.g. due to an infection, it will not be considered an up-titration even if the insulin dose increase is more than 5 IU or more than 10 % of the baseline mean daily insulin dose as long as such an increase is for a period of not more than 10 days and the insulin dose is expected to return to the baseline level once the precipitating condition has resolved.

Up-titration of the insulin dose during the 24-week double-blind extension period shall be considered by the investigator under the following circumstances:

- if HbA1c measured by central laboratory exceeds 8% at any point of the 24 weeks double-blind extension period

or

- if the FPG measurement taken at the site visits exceeds 180 mg/dl (9.9 mmol/l) and this FPG result is confirmed by both the central laboratory and a repeat FPG measurement at the site at a return visit within 72 hours

or

- if at least 3 fasting SMBG diary measurements from the past 7 days exceed 180 mg/dl (9.9 mmol/l). Diary fasting SMBG values that meet these criteria should be recorded in the eCRF.

Insulin dose should not be uptitrated if both the following scenarios are met:

1. A patient has experienced unexpected hypoglycemic event/s

   and

2. An uptitration of insulin may put the patient at an increased risk of hypoglycaemia in the clinical opinion of the investigator.

An unexpected hypoglycemic event is an hypoglycemic event that cannot be explained by circumstances such as missing a meal, or extensive physical exertion.

If a patient experiences an unexpected hypoglycemic event in spite of high FPG or HbA1c levels, the investigator should consider a change in timing of the insulin dose and/or a change of the insulin regimen, rather than considering uptitration of the insulin dose.

The last HbA1c and FPG values measured by central lab prior to the up-titration of the insulin dose will be carried forward for the efficacy analyses at week 48.

Reduction of insulin dose shall be ordered by the investigator if the patient reports two of more readings of plasma glucose value ≤70 mg/dl (≤3.8 mmol/l). In addition, the investigator may consider an insulin dose adjustment (dose reduction or change in timing of insulin dose) in patients who report symptoms suggestive of hypoglycaemia without confirmatory glucose measurements if, in the opinion of the investigator, the patient is at increased risk of further hypoglycemic episodes without such insulin dose adjustments.

Patients should be encouraged to contact the investigator in such a case to allow the reduction of insulin dose.

Background OAD therapy may only be decreased if a concern of hypoglycaemia arises in a patient that has already been completely taken off of insulin.

Background OAD therapy may not be increased at any time during the study.

Patients will be discontinued from the study if after they have had complete withdrawal of both insulin and if applicable other OAD, they subsequently experience more than one event of major hypoglycaemia, and the investigator decides that current treatment poses the patient at risk of either repeated hypoglycaemic events or major hypoglycaemia. Major hypoglycaemia is defined as a symptomatic event requiring external assistance due to severe impairment in consciousness or behaviour with a capillary or plasma glucose value <3 mmol/l (<54 mg/dl) and prompt recovery after glucose or glucagon administration.

Randomized patients who discontinue early should complete the procedures described for visit 18 (end of treatment period) immediately following discontinuation of study drug. Thereafter patients should return for the 3 week follow up visit so that visit 19 procedures can be completed.

Long-term, double-blind extension period II (Visits 13–18, Weeks 49-104)

After the long term double blind extension period I patients, who

- are still on active study treatment
- and have not developed any reason for study discontinuation

will be asked if they would like to continue the study for another 56 weeks and will sign an informed consent form. All patients randomised to placebo, dapagliflozin 2.5 mg or 10 mg treatment at visit 2 will continue the double-blind extension period II with the same treatment. All patients randomised to dapagliflozin 5 mg will be switched to 10 mg dapagliflozin without breaking the blind.

The patients will be instructed to record their fasting SMBG as well as insulin use daily. The patients will further be instructed to always self-monitor plasma glucose in case of symptoms suggestive of hypoglycaemia and to register any signs of hypoglycaemia in the supplied diary. During the study treatment the patients will be instructed to keep their insulin (and if applicable OAD) dosage unchanged. Patients will contact the investigator 1 week after visit 12 for a telephone visit. During this phone call the investigator will discuss whether the current insulin dose is still adequate and whether there have been any changes in AEs and concomitant medication. The patient will then come in 3 weeks later for the next regular site visit (visit 14). After that patients will return for visits every 13 weeks to assess efficacy and safety of the treatment..

Up-titration of the insulin dose during the long-term, double-blind extension period II should be considered by the investigator under the following circumstances:

- >7.5% at V14,V15
- >7,0% at V16,V17,V18

Insulin dose should not be uptitrated if both the following scenarios are met:

1. A patient has experienced unexpected hypoglycemic event/s

<u>and</u>

2. An uptitration of insulin may put the patient at an increased risk of hypoglycaemia in the clinical opinion of the investigator.

An unexpected hypoglycemic event is an hypoglycemic event that cannot be explained by circumstances such as missing a meal, or extensive physical exertion.

If a patient experiences an unexpected hypoglycemic event in spite of high FPG or HbA1c levels, the investigator should consider a change in timing of the insulin dose and/or a change of the insulin regimen, rather than considering uptitration of the insulin dose.

The last HbA1c and FPG values measured by central lab prior to the up-titration of the insulin dose will be carried forward for the efficacy analyses at week 104.

Reduction of insulin dose shall be ordered by the investigator if the patient reports two or more readings of plasma glucose value ≤70 mg/dl (≤3.8 mmol/l). In addition, the investigator may consider an insulin dose adjustment (dose reduction or change in timing of insulin dose) in patients who report symptoms suggestive of hypoglycaemia without confirmatory glucose measurements if, in the opinion of the investigator, the patient is at increased risk of further hypoglycemic episodes without such insulin dose adjustments.

Patients should be encouraged to contact the investigator in such a case to allow the reduction of insulin dose.

Background OAD therapy may only be decreased if a concern of hypoglycaemia arises in a patient that has already been completely taken off of insulin. If background OAD therapy needs to be reduced, the last HbA1c and FPG values measured by the central laboratory prior to the reduction in other OAD dose will be carried forward for the efficacy analyses at week 104.

Background OAD therapy may not be increased at any time during the study.

Patients will be discontinued from the study if after they have had complete withdrawal of both insulin and if applicable other OAD, they subsequently experience more than one event of major hypoglycaemia, and the investigator decides that current treatment poses the patient at risk of either repeated hypoglycaemic events or major hypoglycaemia. Major hypoglycaemia is defined as a symptomatic event requiring external assistance due to severe impairment in consciousness or behaviour with a capillary or plasma glucose value <3 mmol/l (<54 mg/dl) and prompt recovery after glucose or glucagon administration.

Randomized patients who discontinue early should complete the procedures described for visit 18 (end of treatment period) immediately following discontinuation of study drug. Thereafter patients should return for the 3 week follow up visit so that visit 19 procedures can be completed.

The patients will stop taking investigational product at the end of treatment visit 18 (Week 104).

Follow-up period (Visit 19, Week 105-107)

Patients will stop taking the investigational products at Visit 18 (end of treatment period) and thereafter be followed for 3 weeks. During this time patients can be treated as appropriate without any restrictions by the protocol.

Table 1 Study plan

	Enrol-ment	**24-week double-blind treatment period**							**24-week double-blind extension period I**				**56-week double-blind extension period II**						**Follow up**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Study week	**-2**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48**	**49**	**52**	**65**	**78**	**91**	**104**	**107**
Informed consent	x											x[h]							
Demography and Medical history		x																	
Inclusion/exclusion criteria	x[e]	x[c]										x[j]							
Randomization		x																	
Brief Physical examination			x	x	x	x	x	x		x	x			x	x		x		x
Complete Physical Examination		x							x			x				x		x	
Vital signs		x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Orthostatic BP measurement		x	x	x		x			x		x	x		x		x		x	x
Weight		x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Height		x																	
BMI		x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Waist circumference		x							x			x				x		x	
12-lead ECG		x							x			x				x		x	
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x[i]	x	x	x	x	x	x

Table 1 Study plan

	Enrol-ment	24-week double-blind treatment period							24-week double-blind extension period I				56-week double-blind extension period II						Follow up
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Study week	**-2**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48**	**49**	**52**	**65**	**78**	**91**	**104**	**107**
Laboratory assessments	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Pregnancy test[a]	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Collection of Pharmacokinetic blood samples [g]					x			x											
Local FPG (HemoCue)		x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
AEs		x	x	x	x	x	x	x	x	x	x	x	x[i]	x	x	x	x	x	x[f]
Serious adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x[i]	x	x	x	x	x	x[f]
Dispense investigational product		x		x	x	x	x	x	x	x	x	x		x	x	x	x		
Drug accountability of investigational product				x	x	x	x	x	x	x	x	x		x	x	x	x	x	
Diet / life-style advice	x	x	x	x	x	x	x	x	x	x	x	x	x[i]	x	x	x	x	x	x
Dispense of glucometer and/or supplies/ provide instruction	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	
Dispense patient diary	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	

Table 1 Study plan

	Enrol-ment	24-week double-blind treatment period							24-week double-blind extension period I				56-week double-blind extension period II						Follow up
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Study week	**-2**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48**	**49**	**52**	**65**	**78**	**91**	**104**	**107**
Patient diary review for insulin use / glucometer values / hypoglycaemic events[b]		x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]
Informed consent and blood sample for genetic research[d]	x																		

a Pregnancy test will be done on all female patients who are not post menopausal or hysterectomized

b Patients should be instructed to contact investigator in case of an hypoglycaemic event immediately by phone

c The mean daily insulin dose will be calculated by investigator. The calculated mean daily insulin dose is an average daily insulin use over the last 7 documented days.

d Genetic informed consent (IC) must be obtained before genetic blood sample is taken, when patient eligibility for the study has been confirmed. Blood sample donation is optional and can be done from randomization Visit 2 to Visit 9

e Inclusion criteria checked at V1: age, consent, diagnosis, HbA1c

f 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.

g samples will be taken pre dose, 60 min post dose and 180 min post dose.

h patients still on active study treatment who have not developed any reason for study discontinuation will be asked to continue the study for another 56 weeks

i information will be obtained during a telephone call with the patient

j Inclusion / exclusion criteria checked at visit 12: written informed consent for extension period II provided, any patient with discontinuation criteria present at V12 to be excluded

Table 2 Visit design and visit windows

Visit ID	Visit description		Visit Window*
Visit 1	Enrolment		-2 weeks
Visit 2	Randomization / Start of Treatment		0 weeks (±3 days)
Visit 3	Treatment		1 weeks (±1 days)
Visit 4	Treatment		4 weeks (±5 days)
Visit 5	Treatment	24 week double blind treatment	8 weeks (±5 days)
Visit 6	Treatment		12 weeks (±5 days)
Visit 7	Treatment		16 weeks (±5 days)
Visit 8	Treatment		20 weeks (±5 days)
Visit 9	Treatment		24 weeks (±5 days)
Visit 10	Treatment		32 weeks (±7 days)
Visit 11	Treatment	24 week double blind extension period I	40 weeks (±7 days)
Visit 12	Treatment		48 weeks (±7 days)
Visit 13	Treatment		49 weeks (±1 days)
Visit 14	Treatment		52 weeks (±10 days)
Visit 15	Treatment	56 week double blind extension period II	65 weeks (±10 days)
Visit 16	Treatment		78 weeks (±10 days)
Visit 17	Treatment		91 weeks (±10 days)
Visit 18	Treatment		104 weeks (±10 days)
Visit 19	Follow - up Period		107 weeks (±14 days)

* to be calculated after randomisation from baseline Visit 2

3.2 Rationale and risk/benefit assessment

3.2.1 Rationale for study design, doses and control groups

3.2.1.1 Study design and regulatory requirement

The current trial is designed to demonstrate the efficacy and safety of dapagliflozin when used as add-on therapy to insulin in patients with type 2 diabetes inadequately controlled with insulin alone for at least 8 weeks prior to enrolment. Specifically, this study will investigate if treatment with dapagliflozin as add-on to insulin is beneficial for patients with type 2 diabetes as compared to placebo as add-on therapy to insulin. A superiority comparison will be applied for this randomized, double-blind, placebo-controlled study. This protocol incorporates the relevant features of the Committee for Proprietary Medicinal Products' guidance for investigations of diabetes **(CPMP 2002)** with regard to control group, duration of treatment, choice of study population, and choice of outcome variables.

Short term clinical studies of up to 12 weeks duration have been completed using all three doses of dapagliflozin as a starting dose in patients with type 2 diabetes. The clinical experience gained to date in these short term studies demonstrates that a titration regimen is not necessary for the clinical use of dapagliflozin. In addition, the three doses of dapagliflozin are being tested independently as starting doses in other ongoing long term phase III studies of up to two years in duration.

3.2.1.2 Study doses and control groups

Patients must be on a stable treatment of at least 30 IU of insulin per day, with or without OADs for 8 weeks to be eligible for enrolment in this trial. Patients on metformin therapy should be on at least 1500 mg/day of metformin or at the maximum tolerable dose for a period of at least 8 weeks prior to enrolment. Patients on other OAD medications should be on at least half maximum daily recommended dose of the OAD for a period of at least 8 weeks prior to enrolment. Patients with at least 30 IU calculated mean daily insulin dose will be randomized at visit 2 if the daily insulin requirements over the past seven days with insulin use documentation does not vary more than 10% of the calculated mean daily insulin dose. To ensure approximate balance across treatment groups within each stratum (patients with additional OADs and patients without additional OADs) the randomisation will be performed in two strata: one for patients with OADs and one for patients without OADs. Eligible patients will be randomized in a 1:1:1:1 ratio to receive either dapagliflozin at 2.5 mg, 5 mg, 10 mg or placebo once daily. During the study treatment the patients will be instructed to keep their insulin (and if applicable OAD) dose unchanged. Patient will be instructed to record their fasting SMBG and insulin use daily. Patient will further be instructed to always self-monitor plasma glucose in case of symptoms suggestive of hypoglycaemia and to register any signs of hypoglycaemia in the supplied diary. The dapagliflozin doses 2.5 mg, 5 mg, and 10 mg/day were chosen for the Phase III program based on efficacy, pharmacodynamic, and safety data from the Phase I and Phase II programs. This dose range is supported by the following assessments:

- In the Phase I and IIa program, maximal glucosuria was seen at the 10 to 20 mg dose level. Doses ≥20 mg only increased the duration of glucosuria. In the Phase IIb study (MB102008), glucosuria appeared related to dose, with maximal glucosuria seen at the 20 and 50 mg doses.

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

- In the Phase IIb study (MB102008), weight loss was seen at all doses, with an apparent relationship to dose.

- In the Phase IIb study (MB102008) genitourinary infections were more common in the 20 and 50 mg dose groups.

- In the Phase IIb study (MB102008) an increase in haematocrit was seen at all doses, with an apparent relationship to dose, and a step-up seen at doses greater than 10 mg.

- In the Phase IIb study (MB102008) the incidence of the marked laboratory abnormality of hyperphosphataemia was higher than for placebo at doses of 20 and 50 mg dapagliflozin.

Based on the data from the Phase IIb trial, doses greater than 10 mg increase the potential risks of fluid losses, increased hematocrit and hyperphosphatemia, without the promise of substantially greater glycaemic efficacy.

3.2.1.3 Choice of outcome variables

In the regulatory guidelines for type 2 diabetes **(CPMP 2002)**, HbA1c is the variable of choice for determination of glycaemic control and was therefore chosen as the primary variable. Dapagliflozin as an agent that inhibits renal tubular glucose re-absorption may have an additive glucose lowering effect when given in combination with another anti-diabetic drug. Positive effect on HbA1c, weight and Fasting Plasma Glucose as well as reduction in insulin dose may be expected. The reduction of HbA1c is therefore chosen as a primary efficacy endpoint whereas reduction of body weight, mean daily insulin dose reduction and FPG are chosen as important secondary efficacy endpoints in part to characterise the dapagliflozin therapy.

Other measures are assessed in this protocol to better understand the mechanistic and pharmacodynamic effects of dapagliflozin. In particular, these include other secondary efficacy outcome variables of change in glycaemic parameters, seated systolic and diastolic blood pressure, and lipids.

3.2.1.4 Choice of study population

The study population was selected to balance demands on representation of the future patient population and limit bias caused by confounding factors. The prevalence of type 2 diabetes increases with age and therefore the study will include also elderly patients up to 80 years of age. Women are not allowed to be or to become pregnant or breast feeding since dapagliflozin has not been tested in pregnant or breast feeding women and the risk to the embryo, foetus, or infant are unknown.

The HbA1c entry criterion was selected to permit patients with a wide range of glycaemic levels. The HbA1c interval of ≥7.5 % and≤10.5 % reflects inaedaquate glyaemic control and is chosen in order to exclude patients who could easily be treated to normoglyceamia by slightly optimising insulin dose. Continuously evolving treatment guidelines such as the International Diabetes Federation Global Guideline for type 2 diabetes 2005 (**International Diabetes Federation 2005**), The National Institute for Clinical Excellence Guideline Management of type 2 diabetes – Management of Blood Glucose (**National Institute for Clinical Excellence** 2002), American Diabetes Association Position Statement on Standard of Medical Care in Diabetes 2006 (**American Diabetes Association 2006**), and the American Association of Clinical Endocrinologist Medical guidelines for the management of diabetes mellitus (**American Association of Clinical Endocrinologists** 2007) suggest HbA1c level <6.5% for optimal gylcaemic control. Although individual guidelines recommend treatment to normal HbA1c levels (e.g. <6.1%), the risk of hypoglycaemia may limit the possibility to achieve this in clinical practice. The purpose of the remaining inclusion and exclusion criteria is to limit confounding factors that would complicate the interpretation of the results (eg corticosteroid-induced type 2 diabetes, haemoglobinopathies that would interfere with the HbA1c analyses) or to exclude patients whose safety could be compromised by participation in the study.

3.2.2 Risk/benefit and ethical assessment

In a Phase 2b study all doses of dapagliflozin were associated with a statistically significant and clinically relevant improvement in glycemic control and relatively minor AE's and effects upon fluid/electrolyte status. The safety data collected to date from clinical studies in healthy volunteers and subjects with T2DM indicate that the clinical safety profile of dapagliflozin supports proceeding with Phase 3 studies at doses of 2.5 mg, 5 mg and 10 mg per day. Evaluation of the clinical safety and clinical efficacy data accumulated so far indicate an acceptable risk/benefit profile at these planned doses. The long-term safety profile of dapagliflozin is not currently known.

For further information please refer to Clinical Study Protocol Appendix I - Overall Benefit and Risk Assessment.

The planned switch of patients randomised to the dapagliflozin 5 mg treatment arm to dapagliflozin 10 mg during long term extension period II will have no influence on the above risk-benefit assessment.

3.3 Selection of study population

3.3.1 Study selection record

Investigator(s) must keep a record of subjects who were considered for enrolment but were never enrolled eg subject screening log. This information is necessary to establish that the subject population was selected without bias.

3.3.2 Inclusion criteria

For inclusion in the study subjects must fulfil all of the following criteria:

Inclusion criteria at enrolment (visit 1):

1. Provision of a written informed consent

2. Men and women diagnosed with type 2 diabetes

3. Age ≥18 - ≤80 years at time of consenting

4. Patients with inadequate glycaemic control, defined as HbA1c ≥7.5% and ≤10.5%, and who, according to investigators judgement, are on a stable insulin regimen, with a mean dose of at least 30 IU of injectable insulin per day, for a period of at least 8 weeks prior to enrolment. Patients may also be treated with maximally two OADs under the approved prescribing information. OAD treatment should be at a stable dose for a period of at least 8 weeks.

Patients on metformin therapy should be on at least 1500 mg/day of metformin or at the maximum tolerable dose for a period of at least 8 weeks prior to enrolment. Patients on other OAD medications should be on at least half maximum daily recommended dose of the OAD for a period of at least 8 weeks prior to enrolment.

Inclusion criteria before randomisation (visit 2):

1. Patients with HbA1c ≥7.5% and ≤10.5% according central laboratory values measured from sample taken at visit 1 and who are on a stable insulin regimen with a mean insulin dose of least 30 IU of injectable insulin per day either without any other OADs or with a stable dose of OADs that have been approved in combination with insulin.

2. Daily insulin requirements over the past seven days with insulin dose documentation that does not vary more than 10% on more than one occasion of the calculated mean daily insulin dose at visit two (For example for patient whose calculated mean daily insulin dose at visit 2 is 50 IU, daily doses in the preceding seven days with insulin dose documentation may not be <45 and >55 IU on more than one occasion).

3. Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 4 weeks after the study in such manner that the risk of pregnancy is minimized and must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of study medication. WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥12 consecutive months; or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level >35mIU/mL).Even women who are using oral, implanted or injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where the partner is sterile (eg vasectomy), should be considered to be of child bearing potential.

4. Body Mass Index (BMI) ≤ 45 kg/m^2

For inclusion in the optional genetic research, subjects must fulfil the following criterion:

5. Provision of informed consent for genetic research

If a subject declines to participate in the genetic research, there will be no penalty or loss of benefit to the subject. The subject will not be excluded from other aspects of the study described in this Clinical Study Protocol, so long as they consent.

Inclusion criteria before entering long-term, double-blind extension period II (visit 12):

1. Provision of a written informed consent for the participation in the long-term, double-blind extension period II.

3.3.3 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

Exclusion criteria at randomization visit (visit 2):

1. Clinical diagnosis of type 1 diabetes, MODY or secondary diabetes mellitus (eg chronic pancreatitis, partial pancreatectomy).

2. Symptoms of poorly controlled diabetes that in judgement of the investigator would preclude participation in this trial including, but not limited to, marked polyuria and polydipsia with greater than 10% weight loss during the 3 months prior to enrolment.

3. Treatment with more than two additional OADs

4. History of diabetes insipidus

5. Use of inhaled insulin or injectable GLP-1 receptor agonists or DPP-4 inhibitors within 8 weeks of enrolment visit

6. Calculated Creatinine Clearance <50 ml/min/1.73m2 (calculated by Cockcroft-Gault formula) or a measured serum creatinine value of >2mg/dl (177 µmol/l). Patients on concomitant metformin therapy will be excluded if serum creatinine ≥1.5 mg/dl (133 µmol/l) for male subjects and ≥1.4 mg/dl (124 µmol/l) for female subjects

7. Known condition of congenital renal glucosuria

8. Total bilirubin >34.2 µmol/l, >2.0 mg/dl

9. Creatine kinase ≥3xULN

10. Hemoglobin ≤10.0 g/dl (≤100 g/l) for men; hemoglobin ≤9.5 g/dl (≤95 g/l) for women

11. Thyroid-stimulating hormone (TSH) values outside normal range confirmed by abnormal T4 values

12. Positive serologic evidence of current infectious liver disease including patients being positive for Hepatitis B viral antibody IgM, Hepatitis B surface antigen and Hepatitis C virus antibody.

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

14. Significant cardiovascular history within the past 6 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

15. Pregnant or breastfeeding patients

16. Treatment with glucocorticoids equivalent to oral prednisolone >10 mg (betametasone >1.2 mg/dexametasone >1.5 mg/hydrocortisone >40 mg)/day within 30 days prior to enrolment; topical or inhaled corticosteroids are allowed

17. History of bariatric surgery

18. Administration of weight loss medication, including but not limited to sibutramine, phentermine, orlistat, rimonabant, benzphetamine, diethylpropion, methamphetamine, and/or phendimetrazine, within 30 days prior to enrolment

19. Treatment for Human immunodeficiency virus (HIV)/use of antiviral drugs (delavirdine, indinavir, nelfinavir, ritonavir, saquinavir) and/or known immunocompromised status, including patients who have undergone organ transplantation

20. Intolerance, contraindication or potential allergy to dapagliflozin or placebo or formulation recipients

21. Congestive heart failure defined as New York Heart Association (NYHA) class III or IV (see Appendix D), and/or left ventricular ejection fraction of ≤40%

22. Severe respiratory failure or severe emphysema

23. Severe uncontrolled hypertension defined as systolic BP ≥180 mm Hg and/or diastolic BP ≥110 mm Hg

24. Patients who, in the judgment of the investigator, may be at risk for dehydration

25. History of chronic hemolytic anemia or hemoglobinopathies (sickle cell anemia or thalassemias, sideroblatic anemia)

26. History of alcohol abuse or illegal drug abuse within the past 12 months

27. History of malignancy within the last 5 years, excluding successful treatment of basal or squamous cell skin carcinoma

28. Involvement in the planning and conduct of the study (applies to both AZ and BMS staff or staff at the study centre)

29. Previous enrolment or randomization to treatment in the present study

30. Received an investigational agent within 30 days prior to receiving study medication

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

32. Suspected or confirmed poor protocol or medication compliance as judged by the investigator

33. Severe hepatic insufficiency and/or significant abnormal liver function defined as Aspartate aminotransferase (AST) >3 x upper limit of normal (ULN) and/or Alanine aminotransferase (ALT) >3 x ULN

34. Urine albumin:creatinine ratio (UACR) >1800 mg/g (>203.4 mg/mmol/Cr)

For the participation in the optional genetic research, patients must not

1. Have had previous bone marrow transplant

2. Received blood transfusion in the 120 days preceding the date of genetic sampling collection.

If either of these 2 exclusion criteria is present, the patient cannot participate in the optional blood sample donation.

Exclusion criteria before entering long-term, double-blind extension period II (visit 12):

1. Safety reasons as judged by the investigator, AstraZeneca and/or Bristol-Myers Squibb Pharmacovigilance

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

3. Any clinical adverse event , laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject

4. Development of study specific discontinuation criteria listed below. These criteria include one or more of the following parameters:

   (a) Treatment with glucocorticoids equivalent to oral prednisolone >10 mg/day (two temporary periods of higher daily doses but no longer than 7 days each are allowed)

   (b) Severe hypoglycaemic events, defined as ≥1 major hypoglycemia in spite of complete withdrawal of insulin and if applicable other OAD and the investigator decides that current treatment poses the patient at risk of either repeated hypoglycemic events or major hypoglycaemia.

   (c) Pregnancy identified by positive pregnancy test or otherwise verified

   (d) Confirmed increase in serum creatinine of ≥0.5 mg/dl (44 µmol/L) for patients with baseline creatinine of < 1.4 mg/dl (123 µmol/L) or confirmed increase in serum creatinine of ≥1 mg/dl (88 µmol/L) for patients with baseline creatinine of ≥ 1.4 mg/dl (123 µmol/L). Patients with serum creatinine above these values will have their study medication held and a repeated serum creatinine test within 7 days. If serum creatinine is still elevated as specified above (≥0.5 mg/dl or ≥1.0 mg/dl above baseline), the patient should discontinue the clinical study medication. Otherwise study medication may be resumed unless otherwise contraindicated. For further details please see Appendix G of this protocol.

   (e) CK >10 x ULN confirmed at a repeated measurement within 24 hours.

(f) Patients with a central laboratory ALT and/or AST >3x ULN will be scheduled for a follow-up visit within 3 calendar days following the receipt of the result. See Appendix H for further guidance.

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

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

(g) No longer applicable.

(h) Serum sodium ≤125 mmol/l with or without symptoms: dosing of blinded study medication will be interrupted. For further detail please follow instructions stated in Appendix E.

(i) Haemoglobin ≤9.0 g/dl (90 g/l)

3.3.4 Restrictions

After visit 1 all patients will visit the clinic on a fasting stomach 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 visit at the clinic (drinking water is allowed). Allowed medications can be taken with water only.

The patients should refrain from alcohol intake 24 hours prior to each visit and are recommended not to use tobacco/nicotine within 12 hours prior to each visit.

If a patient comes to a visit without having followed the above instructions, then the patient will be re-scheduled for the entire visit (if possible within allowed time-window, see Table 2).

As up to approximately 378 ml of blood will be drawn from the patients during the entire duration of the Clinical Study, patients should be instructed to abstain from donating any blood during the Clinical Study and for 3 months following their last study visit.

Restricted concomitant medications are listed in section 3.7, and fasting prior to laboratory assessments are detailed in section **4.7.2.1**.

3.3.5 Discontinuation of subjects from treatment or assessment

3.3.5.1 Criteria for discontinuation

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.

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

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. Safety reasons as judged by the investigator, AstraZeneca and/or Bristol-Myers Squibb Pharmacovigilance

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

4. Incorrect enrolment i.e., the patient does not to meet the required inclusion/exclusion criteria for the study

5. Any clinical adverse event , laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.

6. Patient lost to follow-up (as defined by the inability to reach the patient after 3 documented phone calls, fax, email, or attempts to contact him/her through patient locator agencies (if allowed per national regulation) and having sent one letter by registered/certified mail; all should be documented in the patients medical records).

7. Development of study specific discontinuation criteria listed below. These criteria include one or more of the following parameters:

   (a) Treatment with glucocorticoids equivalent to oral prednisolone >10 mg/day (two temporary periods of higher daily doses but no longer than 7 days each are allowed)

   (b) Severe hypoglycaemic events, defined as ≥1 major hypoglycemia in spite of complete withdrawal of insulin and if applicable other OAD and the investigator decides that current treatment poses the patient at risk of either repeated hypoglycemic events or major hypoglycaemia.

   (c) Pregnancy identified by positive pregnancy test or otherwise verified

(d) Confirmed increase in serum creatinine of ≥0.5 mg/dl (44 µmol/L) for patients with baseline creatinine of < 1.4 mg/dl (123 µmol/L) or confirmed increase in serum creatinine of ≥1 mg/dl (88 µmol/L) for patients with baseline creatinine of ≥ 1.4 mg/dl (123 µmol/L). Patients with serum creatinine above these values will have their study medication held and a repeated serum creatinine test within 7 days. If serum creatinine is still elevated as specified above (≥0.5 mg/dl or ≥1.0 mg/dl above baseline), the patient should discontinue the clinical study medication. Otherwise study medication may be resumed unless otherwise contraindicated. For further details please see Appendix G of this protocol.

(e) CK >10 x ULN confirmed at a repeated measurement within 24 hours.

(f) Patients with a central laboratory ALT and/or AST >3x ULN will be scheduled for a follow-up visit within 3 calendar days following the receipt of the result. See Appendix H for further guidance.

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

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

(g) No longer applicable

(h) Serum sodium ≤125 mmol/l with or without symptoms: dosing of blinded study medication will be interrupted. For further detail please follow instructions stated in Appendix E.

(i) Haemoglobin ≤9.0 g/dl (90 g/l).

3.3.5.2 Procedures for discontinuation

Patients who discontinue should always be asked about the reason(s) for their discontinuation and the presence of any adverse events. If possible, they should be seen and assessed by an investigator(s). Adverse events should be followed up; diary cards and investigational products should be returned by the patient.

Patients with an increased CK >10 x ULN will have their study medication held and repeated CK test within 24 hours. If repeated CK is still >10 x ULN the patient should discontinue the study medication. Otherwise study medication may be resumed unless otherwise contraindicated.

Patients with increased liver function tests as defined in section 3.3.5.1 under listings 7(f), will be scheduled for a follow-up visit within 3 calendar days following the receipt of the result. Patients should remain on study medication until the confirmatory results are obtained unless otherwise contraindicated. See CSP Appendix H - Algorithm on Management of Sustained Elevated Liver Safety Abnormalities for further guidance. If repeated liver function tests still are increased as outlined in section 3.3.5.1 under listings 7(f), the patient should permanently discontinue all study medication and be withdrawn from the study (see CSP Appendix H - Algorithm on Management of Sustained Elevated Liver Safety Abnormalities for further guidance).

Randomized patients who discontinue before week 104 should complete the procedures described for Visit 18 as soon as possible but at the latest 7 days after discontinuation. These patients should also be scheduled for a follow-up visit (i.e. procedures of Visit 19) 3 weeks after discontinuation of investigational product.

3.3.5.3 Procedures for treatment interruption

In case study treatment was interrupted for more than 7 consecutive days and the restart of study therapy is considered, the investigator must contact the AstraZeneca study team physician to discuss further procedures before restarting study medication.

3.3.5.4 Procedures for handling incorrect enrolled subjects

Patients not meeting the inclusion/exclusion criteria for the study should, under no circumstances, be randomized into the study. If a patient not meeting the study criteria is randomized in error, the patient should complete the study unless there are safety concerns or if the patient withdraws the consent. Data collected for patients randomized in error will be included in the analyses.

3.3.5.5 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 but these will not be used in any subsequent analyses.

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.

3.4 Treatments

3.4.1 Identity of investigational product and comparators

The following investigational products and placebo will be manufactured by Bristol-Myers Squibb Pharmaceutical Research Institute or their designee and distributed by AstraZeneca. The tablets may contain lactose, which may cause discomfort in lactose-intolerant individuals.

Table 3 Investigational product and additional drug

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

3.4.2 Doses and treatment regimens

- Dapagliflozin tablets, 2.5 mg, 5 mg and 10 mg, and matching placebos administered orally for the 24-week double-blind treatment period and the 24-week long-term double-blind extension period I. of the study.

- Dapagliflozin tablets, 2.5 mg and 10 mg, and matching placebos administered orally for the 56-week double-blind treatment period II of the study.

Due to different size of tablet, each patients must take 2 tablets once daily to ensure dose blindness. The investigational product dapagliflozin and a matching placebo should be taken once daily as directed by the investigator. The investigational product should be taken at approximately the same time of the day 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 after midnight is allowed.

3.4.3 Insulin and other background OAD treatment

Patients will be instructed not to take any insulin or OAD medication on the morning of the study visit. In the morning prior to each visit, acceptable concomitant medications can be taken with water only. For further information on insulin- and background OAD treatment please refer to section 3.1.

3.4.4 Labelling

Primary packing of the investigational product will be carried out by Bristol-Myers Squibb or their designee in accordance with current Good Manufacturing Practice (GMP). Labelling of the investigational product will be carried out by AstraZeneca or a Contract Research Organization (CRO) in accordance with current GMP. The labels will be translated into local languages and in accordance with local regulations for each participating country.

All investigational products will be packed in bottles. Each bottle will contain 35 tablets**.** The labels or booklets for bottles will be translated into local languages. The labels /booklets will fulfil GMP Annex 13 requirements and local regulatory guidelines.

3.4.5 Storage

All investigational products and placebo must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage conditions is specified on the investigational product labels, carton labels, and in the Investigator's Brochure.

3.4.6 Accountability

Investigational products and placebo will only be delivered to the centre when the required regulatory approvals have been obtained. It is the investigator´s and/or institution's responsibility to establish a system for handling study treatments 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 placebo. This record is in addition to any drug accountability information recorded in the electronic Case Report Forms (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 should be signed by the investigator or a designated person.

The investigator is responsible for making sure that:

- the investigational products and placebo are handled and stored safely and properly (see section 3.4.5)
- the investigational products and placebo are only dispensed to study patients in accordance with this protocol

The investigational products and placebo are to be prescribed only by the investigator. Under no circumstances will the investigator allow the investigational product and placebo to be used other than as directed by the protocol.

Patients must return all unused investigational products and placebo and empty containers to the investigator. The investigator will retain all returned investigational products and placebo, along with any investigational products and placebo not dispensed. At the termination of the Clinical Study or at the request of AstraZeneca, the investigator will either return any unused investigational products and placebo to AstraZeneca, or investigational products and placebo may be destroyed at the study centre depending on local regulations. The return and/or destruction will be documented on a form supplied by AstraZeneca or its designee

3.5 Method of assigning subjects to treatment groups

After written informed consent has been obtained the patient will be assigned a E-code (country, centre, and patient specific). The E-code will be used to identify the patient throughout study participation. Patient eligibility will be established before treatment randomization.

A computer generated, stratified, block randomization schedule, containing stratum, randomization code and treatment, will be provided by AstraZeneca. The randomisation w**ill** be performed in two strata, one for patients with OADs and one for patients without OADs to ensure approximately equal numbers of patients across the treatment groups within each stratum. The randomization for both strata will be done within balanced blocks. The study medication will be packed according to this schedule.

Subject eligibility will be established before treatment randomization. Randomization to study treatment will be done on Visit 2, in OAD and non OAD strata. Subjects will be randomized strictly sequentially within each stratum, as subjects are eligible for randomization. If a subject discontinues from the study, the subject number will not be reused, and the subject will not be allowed to re-enter the study.

The number and size of tablets will be identical for the investigational products for the 4 treatment arms (applicable until week 12) and for the 3 treatment arms during long term extension period II starting after visit 12. Forced randomization is not allowed. If a patient is dispensed with a wrong drug supply, AstraZeneca must be immediately notified. Corrections for the patient will be made as required. Until resolution, the patient should continue taking study medication, but at the latest until the next scheduled visit.

3.6 Blinding and procedures for unblinding the study

3.6.1 Methods for ensuring blinding

This study will be conducted in a double-blind fashion. All investigational products (dapagliflozin 2.5 mg, 5 mg and matching dapagliflozin 2.5 / 5 mg placebo as well as dapagliflozin 10 mg and matching dapagliflozin 10 mg placebo) are identical in appearance, smell and taste. They will also be packaged into identical bottles. AstraZeneca will provide individual treatment codes, indicating the treatment allocation for each randomized patient.

Until the completion of the 24-week double-blind treatment period, no member of the extended study delivery team at AstraZeneca or Bristol-Myers Squibb, at the investigational centres or any CRO handling data will have access to the randomization scheme, with the exception of the patient safety department and IPS at Bristol-Myers Squibb and AstraZeneca and individual unblinded persons at the central laboratories (Quintiles and Atlanbio). See Section 3.6.2. for further details.

During the long term-double-blind extension period I and II, investigators, patients, and study monitors will continue to be blinded until completion of week 104 without any knowledge of the treatment codes, except for cases of medical emergencies. The treatment codes and knowledge of any results will be strictly kept 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.

3.6.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the investigator(s) or pharmacists at the study centre.

The treatment code must not be broken except in medical emergencies when the appropriate management of the patient necessitates knowledge of the treatment randomization. The investigator(s) must document and report to AstraZeneca any breaking of the treatment code. Bristol-Myers Squibb retains the right to break the code for SAEs suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

Patient for whom the treatment code has been broken by the investigator must be withdrawn from the Clinical Study, complete the procedures described for end of treatment and scheduled to complete the follow-up visit.

Patient's treatment in the study can be unblinded through envelopes to be found in the investigator's file.

The first 24 weeks of double-blind treatment comprise the confirmatory portion of this study. AstraZeneca plans to analyze the efficacy and safety data from the first 24-week double-blind treatment period after the last patient has completed the 24-week double-blind period of the study. The treatment codes will be unblinded only after all data for this period have been collected, cleaned, and locked and after all decisions for the evaluability of the data from each individual have been made and documented. Unblinding the data will allow AstraZeneca and Bristol-Myers Squibb personnel to complete the planned analyses for registration purposes. Analyses of the long term double-blind extension period I and II are supplemental.

3.7 Pre-study, concomitant and post-study treatment(s)

3.7.1 General medication

Other medication than described in Exclusion Criteria section 3.3.3 and Discontinuation Criteria section 3.3.5.1which is considered necessary for the patient's safety and well-being (e.g., to treat illnesses or complaints that occur during the study), may be given at the discretion of the Investigator(s). The administration of all medication (including investigational product and placebo and other medication in use within 30 days prior to the day of enrolment and during the course of the study) must be recorded in the appropriate sections of the Electronic case report form (eCRF). The specific type of medication (trade or generic name), the indication for use, and the dates of usage should be reported. The calculated total daily dose of injectable insulin and used other OAD should also be recorded.

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

3.7.2 Prohibited and restricted medication and herbal/over-the-counter therapy

For prohibited and restricted medication, see Exclusion Criteria section 3.3.3 and Discontinuation Criteria section 3.3.5.1.

3.8 Treatment compliance

Patients will be asked to return all unused investigational products and empty packages to the clinic at each visit. The patient's compliance will be discussed at each study visit and assessed based on returned tablet counts and on records in patient diaries. Tablet counts will be recorded in the eCRF. Patients judged to be non-compliant (non-compliance is defined as patients taking less than 80% or more than 120% of their prescribed dose of investigational product), may continue in the study, but should be counselled on the importance of taking their study medication as prescribed.

4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

4.1 Primary variable

HbA1c is the primary assessment for determination of efficacy accepted by the FDA and defined in the CPMP Note for guidance on clinical investigations of medicinal products in the treatment of diabetes mellitus. The primary outcome variable is the absolute change in HbA1c from baseline to week 24 of the double-blind treatment period.

4.2 Screening and demographic measurements

In addition to what is specified in Table 1 for enrolment, the following data will be collected on the appropriate eCRF:

- Date of birth, sex, race and ethnicity
- Information about smoking, alcohol, medical history, and specific disease history

4.3 Patient-Reported Outcomes (PROs) (Not applicable)

4.4 Health Economic measurements and variables (Not applicable)

4.5 Pharmacokinetic measurements and variables

Plasma samples for analysis of dapagliflozin will be obtained at the Week 8 and Week 20 visits immediately prior to dosing, 60 minutes post-dose and 180 minutes post dose.

4.6 Efficacy and pharmacodynamic measurement and variables

The relationship between primary and secondary objectives and variables is show in Table 4.

Table 4 Relationship between objectives and variables

Objective	Variable
Primary objective	
The primary objective of this study is to assess the efficacy of 2.5 mg, 5 mg and 10 mg dapagliflozin compared to placebo as add-on therapy to insulin in improving glycaemic control in subjects with type 2 diabetes who have inadequate glycaemic control on ≥ 30 IU injectable insulin daily for at least 8 weeks prior to enrolment, as determined by the change in HbA1c levels from baseline to Week 24.	Change in HbA1c from baseline to week 24
Key secondary objectives	
To examine whether treatment with dapagliflozin in combination with insulin is superior in reducing body weight or causing less weight gain as compared to placebo added to insulin treatment after 24 weeks of treatment.	Change in body weight from baseline to week 24
To examine whether treatment with dapagliflozin in combination with insulin leads to a lower absolute calculated mean daily insulin dose as compared to placebo added to insulin treatment alone, from baseline to week 24.	Absolute change in calculated mean daily insulin dose reduction from baseline to week 24
To examine whether treatment with dapagliflozin in combination with insulin leads to higher percentage of patients with calculated mean daily insulin dose reduction from baseline to week 24 as compared to placebo added to insulin treatment.	Proportion of patients with calculated mean daily insulin dose reduction from baseline to week 24
To examine whether treatment with dapagliflozin in combination with insulin is superior in reducing Fasting Plasma Glucose (FPG) as compared to placebo added to insulin treatment after 24 weeks of treatment.	Change in FPG from baseline to week 24
Other secondary objectives	
To compare the effects of each dose of dapagliflozin versus placebo given as add-on therapy to insulin on additional weight and glycaemic outcome variables.	Percent change of calculated mean daily insulin dose from baseline to week 24

Objective	Variable
	Change in HbA1c from baseline to week 24 in patients with a HbA1c of ≥9% at baseline
	Proportion of patients achieving HbA1c <7% at week 24
	Mean change in HbA1c from baseline to week 24 in patients with a HbA1c of ≥7.5% and <9% at baseline
	Mean change in HbA1c from baseline to week 24 in patients with BMI ≥27 kg/m^2 at baseline
	Mean change in HbA1c from baseline to week 24 in patients with BMI ≥30 kg/m^2 at baseline
	Mean Change in FPG from baseline to week 1
	Absolute change in body weight from baseline to week 24 in patients with a baseline Body Mass Index (BMI) ≥27 kg/m^2
	Mean change in body weight from baseline to week 24 in patients with a baseline BMI ≥30 kg/m^2
	Mean change in waist circumference from baseline to week 24
To compare the effects of each dose of dapagliflozin versus placebo given as add-on therapy to insulin on systolic and diastolic blood pressure (BP).	Mean change in seated systolic BP and seated diastolic BP from baseline to week 24
	Mean change in seated systolic BP and seated diastolic BP from baseline to week 24 in patients with baseline seated systolic BP > 140 mmHg
To compare the effects of each dose of dapagliflozin versus placebo given as add-on therapy to insulin on lipoprotein levels and free fatty acids.	Percent change in TC, LDL-C, HDL-C, TG and FFA from baseline to week 24
Safety objectives	
To evaluate the safety and tolerability by assessment of adverse events (AE), laboratory values, electrocardiogram (ECG), pulse, blood pressure (BP), hypoglycaemic events, calculated creatinine clearance, estimated glomerular filtration rate (eGFR), total protein/creatinine ratio (mg/g) and physical examination findings	AEs, laboratory values, ECG, pulse, BP, hypoglycaemic events, calculated creatinine clearance, eGFR, total protein/creatinine ratio (mg/g) and physical examination findings

Objective	Variable
Pharmacokinetic objectives	
To explore the relationships between exposure measures and efficacy endpoints such as reduction in A1C from baseline	Relationships between exposure measures (e.g. AUC) and efficacy endpoints (e.g. changes from baseline in HbA1c)
Objectives for the long-term double-blind extension period I	
To assess the same safety and tolerability parameters as for the first 24 weeks, over 48 weeks of treatment	AEs, laboratory values, ECG, pulse, BP, hypoglycaemic events, calculated creatinine clearance, eGFR, total protein/creatinine ratio (mg/g) and physical examination findings (e.g. oedema) from baseline to week 48
To assess the maintenance of efficacy of dapagliflozin plus insulin over 48 weeks of treatment	Change in HbA1c from week 24 to week 48
	Change in HbA1c from baseline to week 48 .
	Change in FPG from baseline to week 48 .
	Change in body weight from baseline to week 48
	Proportion of patients with calculated mean daily insulin dose reduction from baseline to week 48
	Change in calculated mean daily insulin dose from baseline to week 48
	Percent change of calculated mean daily insulin dose from baseline to week 48
	Change in HbA1c from baseline to week 48 in patients with a HbA1c of ≥9% at baseline
	Proportion of patients achieving HbA1c <7% at week 48
	Change in HbA1c from baseline to week 48 in patients with a HbA1c of ≥7.5% and <9% at baseline
	Change in HbA1c from baseline to week 48 in patients with BMI ≥27 kg/m^2 at baseline
	Change in HbA1c from baseline to week 48 in patients with BMI ≥30 kg/m^2 at baseline
	Change in body weight from baseline to week 48 in patients with a baseline BMI ≥30 kg/m^2

Objective	Variable
	Change in body weight from baseline to week 48 in patients with a baseline Body Mass Index (BMI) ≥27 kg/m^2
	Change in waist circumference from baseline to week 48
	Change in seated systolic BP and seated diastolic BP from baseline to week 48
	Change in seated systolic BP and seated diastolic BP from baseline to week 48 in patients with baseline seated systolic BP > 140 mmHg
	Percent change in TC, LDL-C, HDL-C, TG and FFA from baseline to week 48
Objectives for the long-term double-blind extension period II	
To assess the same safety and tolerability parameters as for the first 24 weeks, over 104 weeks of treatment	AEs, laboratory values, ECG, pulse, BP, hypoglycaemic events, calculated creatinine clearance, eGFR, total protein/creatinine ratio (mg/g) and physical examination findings (e.g. oedema) from baseline to week 104, and from week 48 to week 104
To assess the maintenance of efficacy of dapagliflozin plus insulin over 104 weeks of treatment	Change in HbA1c from baseline to week 104.
	Change in HbA1c from week 24 to week 104
	Change in HbA1c from week 48 to week 104
	Change in FPG from baseline to week 104, and from week 48 to week 104
	Change in body weight from baseline to week 104, and from week 48 to week 104
	Proportion of patients with calculated mean daily insulin dose reduction from baseline to week 104, and from week 48 to week 104
	Mean change and percentage change in calculated mean daily insulin dose from baseline to week 104.
	Mean change and percentage change of calculated mean daily insulin dose from week 48 to week 104

Objective	Variable
	Change in HbA1c from baseline to week 104, and from week 48 to week 104 in patients with a HbA1c of ≥9% at baseline
	Proportion of patients achieving HbA1c <7% at week 104 and from week 48 to week 104
	Change in HbA1c from baseline to week 104, and from week 48 to week 104 in patients with a HbA1c of ≥7.5% and <9% at baseline
	Change in HbA1c from baseline to week 104, and from week 48 to week 104 in patients with BMI ≥27 kg/m^2 at baseline
	Change in HbA1c from baseline to week 104, and from week 48 to week 104 in patients with BMI ≥30 kg/m^2 at baseline
	Change in body weight from baseline to week 104, and from week 48 to week 104 in patients with a baseline BMI ≥30 kg/m^2
	Change in body weight from baseline to week 104, and from week 48 to week 104 in patients with a baseline Body Mass Index (BMI) ≥27 kg/m^2
	Change in waist circumference from baseline to week 104, and from week 48 to week 104
	Change in seated systolic BP and seated diastolic BP from baseline to week 104, and from week 48 to week 104
	Change in seated systolic BP and seated diastolic BP from baseline to week 104, and from week 48 to week 104 in patients with baseline seated systolic BP > 140 mmHg
	Percent change in TC, LDL-C, HDL-C, TG and FFA from baseline to week 104, and from week 48 to week 104

Baseline is defined as the assessment performed at the randomization visit (Visit 2). The laboratory parameters that will be measured to assess efficacy are displayed in Table 5 by visit. The results from baseline and onwards will not be reported to the investigator unless the values meet the defined insulin titration criteria see section 3.4.2 except for total cholesterol, HDL-C, LDL-C, TG and FFA which will be reported.

Table 5 **Efficacy laboratory variables for Enrolment, 24-Week Double-Blind Treatment Period and 80-Week long term Double-Blind Extension Period I and II**

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Study Week	**-2**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48**	**49**	**52**	**65**	**78**	**91**	**104**	**107**
HbA1C	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
FPG		x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Total cholesterol		x							x			x				x		x	x
LDL-C		x							x			x				x		x	x
HDL-C		x							x			x				x		x	x
TG		x							x			x				x		x	x
FFA		x							x			x				x		x	x

4.6.1 Blood and urine samples

4.6.1.1 Methods of assessment

Clinical laboratory

Blood samples for clinical laboratory tests will be obtained by standardized techniques and assessed by the central laboratory.

Sample collection

The central laboratory will provide the centres with all the appropriate materials for specimen collection and sample processing, packaging, and shipping. A laboratory manual for investigators giving detailed instructions will be provided to each centre prior to the start of the Clinical Study. The investigator should follow the procedures defined in this manual.

When blood is taken for analysis, patients should have been sitting for at least 5 minutes prior to sampling. A tourniquet may be applied but for no longer than 2 minutes and it should be removed prior to the collection of blood.

Sample labeling

All samples will be labelled with a bar code containing a number which references the study code, centre number, E-code and visit number. These labels will be prepared and supplied by the central laboratory for all tubes and containers which are used to collect, treat, store or ship aliquots of the samples to the central laboratory. The centre staff will record the patient information on the label, as instructed in the laboratory manual.

Sample shipment

Shipment of samples will be carried out according to the manual provided by the central laboratory.

Pharmacokinetics

Venous blood samples for determination of dapagliflozin and if needed BMS-801576 in plasma will be taken at the times presented in the study plan (Table 1). Blood samples will be collected, labelled and shipped as detailed below. The date and time of the collection will be recorded. Venous blood samples (3mL) will be collected into 3 mL K2EDTA tubes. After the sample is collected, the tubes will be gently inverted 8-10 times and placed in on chipped wet ice. Within 60 minutes of collection, the samples will be centrifuged for 15 minutes at 4°C at a relative centrifugal force of 1000g. Using a fresh pipette, the plasma will be transferred to a clean 1.8 mL polypropylene tube and immediately frozen upright at -20°C or below in a frost-free freezer. The samples will be kept frozen at this temperature before shipment on dry ice to the designated laboratory.

4.7 Safety measurements and variables

The methods for collecting safety data are described below.

4.7.1 Adverse events

4.7.1.1 Definitions

The definitions of adverse events (AEs) and serious adverse events (SAEs) are given below. It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The principal investigator is responsible for ensuring this.

Adverse event

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 (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., 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.

Serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up) and at any dose of the investigational product, comparator, or placebo 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 patient or may require medical intervention to prevent one of the outcomes listed above.
- Cancer
- Overdose (defined as the accidental or intentional ingestion of any dose of the investigational product that is considered both excessive and medically important)

A causality assessment (i.e., their relationship to study treatment) will be assessed by the investigator(s) and must be recorded for all SAEs and AEs. The eCRF asks the question, "In your medical judgement, is there a reasonable possibility that the event may have been caused by the investigational product?" If there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then this should be answered "yes". Otherwise, if no valid reason exists for suggesting a possible relationship, then this should be answered "no". If more than one AE is identified, a causality assessment must be made for each AE. For SAEs the causality will also be assessed with regard to concomitant medication. For further guidance on the definition of an SAE and a guide to the interpretation of the causality question, see Appendix B to the Clinical Study Protocol.

Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as "yes".

4.7.1.2 Recording of adverse events

AEs will be collected and recorded in the eCRF from the start of the randomization period (Visit 2) until the end of the study (Visit 19). SAEs will be collected from the time at which informed consent is obtained until the end of the study (Visit 19).

Variables

The following variables will be recorded in the eCRF for each AE: verbatim, 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.

The causality of non-serious AEs to the investigational products will be assessed in the same way as for SAEs. See section 4.7.1.1 and Appendix B for further guidance.

Maximum intensity will be graded according to the following definitions:

- mild (awareness of event but easily tolerated)
- moderate (discomfort enough to cause some interference with usual activity)
- severe (inability to carry out usual activity)
- very severe (debilitating, significantly incapacitates patient despite symptomatic therapy)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in section 4.7.1.1. 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.

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 eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. In instances of well-recognized symptoms, they can be recorded as the commonly used diagnosis (e.g., fever, runny nose, and cough can be recorded as "flu"). 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 should be recorded separately.

Adverse Events based on examinations and tests

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, and other safety variables should only be reported as AEs if they are clinically significant, fulfil any of the SAE criteria, are the reason for discontinuation or interruption 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 should be reported as an AE, and the associated laboratory result/vital sign should be considered as additional information. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment should be reported as an AE.

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting Investigator (e.g., anaemia versus low haemoglobin value).

Hypoglycaemic events

Signs and symptoms of hypoglycaemia, hypoglycaemia episode 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 4.7.1), in which case an SAE must be reported in addition to the hypoglycaemia eCRF pages for hypoglycaemia. Instead a separate section in the eCRF will be used to document all reported episodes of hypoglycaemia. 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 deemed by the Investigator to meet the definition of hypoglycaemia should be reported on the hypoglycaemia eCRF pages (see section 4.7.4.1).

Overdose

An overdose is defined as the accidental or intentional ingestion of any dose of an investigational product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see section 4.7.1.3).

Pregnancy

Should a pregnancy occur, it must be reported in accordance with the procedures described in section 9.4, Procedures in case of pregnancy. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

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 data base lock will be reported to AstraZeneca, who will notify the appropriate Bristol-Myers Squibb Pharmacovigilance contact.

AEs reported after end of treatment

All AEs will be collected up to and including the final visit. Only unsolicited SAEs will be collected for a period of up to 30 days after the last dose of investigational product. All SAEs and associated concomitant medications will be recorded in the appropriate sections of the eCRF and reported to the Bristol-Mayer Squibb Pharmacovigilance as described in section 4.7.1.3.

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.

4.7.1.3 Reporting of serious adverse events

Investigators and other centre personnel must inform appropriate AstraZeneca representatives via the web based data capture (WBDC) system of any SAE that occurs in the course of the study within 1 calendar day (i.e., immediately but no later than the end of the next business day) of when he or she becomes aware of it. Follow-up information on SAEs must also be reported by the Investigator within the same time frame.

The AstraZeneca representative will work with the investigator to compile all the necessary information and ensure that 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). SAE information will be entered and submitted into the WBDC system on the relevant eCRF modules. If the system is unavailable, the Investigator should fax a paper back-up SAE report to the AstraZeneca representative immediately, recognising that the same reporting time frames still apply. The Investigator is responsible for completing the eCRF as soon as the system becomes available again. The AstraZeneca representative will forward all information relevant to the SAE to Bristol-Myers Squibb Pharmacovigilance via fax or email.

AstraZeneca or the Investigator is responsible for informing the Ethics Committees of the SAE as per local requirements. Reporting of SAEs to Regulatory Authorities is the responsibility of Bristol-Myers Squibb.

4.7.2 Laboratory safety measurements and variables

4.7.2.1 Methods of 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 on a fasting stomach in the morning, before 11 a.m..The patients will be instructed not to have ingested any food or beverages 12 hours before visiting the clinic (however, drinking water is allowed). Also, the patients will be instructed not to take the investigational product, insulin or other OADs in the morning before visiting the clinic. Allowed concomitant medication can be taken with water only.

All samples should be taken by adequately trained study personnel and handled in accordance with given 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 the available results with regard to clinically significant abnormalities. The laboratory reports should be signed and dated and retained at centre as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see section 4.7.1.2

The complete list of safety laboratory tests is displayed in Table 6 below. The laboratory tests are conducted following the assessment schedule outlined in section 4.7.2.1. In case a patient experiences sustained elevated liver safety abnormalities additional blood sampling needs to be performed. For further guidance please refer to CSP Appendix H - Algorithm on Management of Sustained Elevated Liver Safety Abnormalities.

Table 6 Safety laboratory variables for Enrolment, 24-Week Double-Blind Treatment Period and 80-Week long term Double-Blind Extension Period I and II

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Study Week	**-2**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48**	**49**	**52**	**65**	**78**	**91**	**104**	**107**
Haema-tology																			
Haemo-globin	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Haematocrit	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Red blood cell count	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Erythrocyte mean corpuscle volume	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Erythrocyte mean corpuscle haemoglobin concentration	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Reticulo-cytes	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
White blood cell count and differential	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Platelet count	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Clinical chemistry (serum)																			
Aspartate Aminotransferase (AST, SGOT)	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Alanine Aminotransferase (ALT, SGPT)	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Alkaline Phosphatase (AP)	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Creatine Kinase (CK)	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Total Bilirubin (TB)	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Blood Urea Nitrogen (BUN)	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Electrolytes [g]	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Total protein	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Albumin	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Study Week	**-2**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48**	**49**	**52**	**65**	**78**	**91**	**104**	**107**
Uric acid	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Serum Creatinine (SCr), calculated creatinine clearance (Cockroft-Gault formula)[a]	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Serum Cystatin C		x							x			x				x		x	x
Serum Bone Metabolism Marker (Parathyroid Hormone (PTH) and 25-hydroxy vitamin D)		x							x			x				x		x	x
Follicle Stimulating Hormone (FSH)	x																		
TSH[e]	x																		
Hepatitis Screen Panel[f]	x																		
Urinalysis																			
Glucose[b]	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Blood by dipstick[c]	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Albumin	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Total protein	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Creatinine	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Calculated Urinary albumine: creatinine ratio (UACR)	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Calculated total protein : creatinine ratio	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Pregnancy test[d]	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x

a Creatinine clearance will be calculated by the method of Cockcroft and Gault.

b Results will be blinded.

c Microscopy if dipstick positive for blood.

d Urine or serum pregnancy test (see section 4.7.1.2)

e If abnormal, measure free T4.

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

g Sodium, Bicarbonate, Potassium, Chloride, Calcium, Magnesium, Phosphorus

h Total Bilirubin (mg/dL, mmol/L) Reflex testing of Direct (Conjugated) and Indirect (Unconjugated) Bilirubin if TB > 1.5X ULN.

4.7.2.2 Derivation or calculation of outcome variables

Creatinine clearance will be calculated by the method of Cockcroft and Gault.

4.7.3 Vital signs, ECG and physical examination

Vital signs (pulse and BP), ECG, weight, height and physical examination results will be obtained. For the timing of individual measurements, see Table 1and Table 2

4.7.3.1 Methods of assessment

Pulse and blood pressure

Pulse measurement will be taken after the patient has been sitting and resting for at least 5 minutes and before blood samples are taken. The pulse measurement will be followed by 3 BP measurements obtained at least 1 min apart on the reference arm, using a standardized cuff adapted to the size of the patient's arm. All 3 readings have to be recorded. For analysis the average of the 3 BP readings will be used. BP readings will be taken with the patients comfortably in a seated position with the arms raised to the level of the heart and in a supported position. All readings should be recorded as accurately as possible and the same BP measurement device should be used for all assessments for a given patient. The reference arm, is defined as the arm with has been used for systolic BP measurements at the baseline visit. The reference arm should be used for all BP measurements through the entire study

Orthostatic blood pressure

At selected visits where orthostatic BP is measured, measurements should be obtained following completion of seated blood pressure.

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

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

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. 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 has to further specify the abnormality that was detected.

One original ECG print-out, signed and dated by the investigator, will be kept in the medical records, ensuring a copy is maintained in the source documents for the study.

Weight and height

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

Waist circumference

The waist should be measured in the standing position at the natural waist (smallest waist circumference). If there is no natural waist, the measurement should be made at the level of the umbilicus. Measurements should be made at the end of normal inspiration with a centrally measuring tape supplied by AZ.

Physical examinations

- A brief physical examination should include cardiovascular, lungs, abdomen, and extremities; and any organ systems pertinent to the patient's signs, symptoms, or adverse events. Presence of oedema should always be checked.

- A complete physical examination should include general appearance, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdomen, lymph nodes, extremities, neurological, skin, and musculoskeletal. Presence of oedema should always be checked.

Baseline data is collected at visit 2, and new findings at the following physical examinations are recorded as change from baseline.

4.7.3.2 Derivation or calculation of outcome variables

BMI will be computed by AstraZeneca.

BMI = weight / height^2 (where weight is measured in kg, and height in metres).

The mean BP measurements (of 3 measurements) will be computed by AstraZeneca for each patient at each visit.

4.7.4 Other safety measurements and variables - SMBG and UTI / GI

Values from self-monitoring of fasting plasma glucose will be monitored daily through the entire study. SMBG values and data regarding hypoglycaemic events as well as daily insulin use will be collected in a patient diary.

4.7.4.1 Methods of assessment

Self-monitoring of fasting plasma glucose should be done in order to reduce risk of prolonged periods of undetected hyperglycaemia or to confirm hypoglycaemia. Patients will be asked to do self-monitoring of fasting plasma glucose using glucometers provided by AstraZeneca. The patients will receive instructions how to use the glucometer, according to the manufacturer's instruction.

The memory of the glucometer should be reviewed to compare with the patient's diary, as applicable. The glucose values should be reviewed by the site to identify any unusual high or low values, to confirm that the values (from the glucometer's memory and/or from the patient's diary) were obtained for the patient and to calculate the mean insulin dose. If finger stick glucose values are discordant from glycaemic control assessed by the central laboratory or with clinical symptoms, the patient's glucometer should be tested and the procedure for using it reviewed with the patient.

Fasting plasma glucose concentrations

Fasting plasma glucose should be self-monitored. The glucometer will be calibrated to show plasma glucose levels. The patient diary will be reviewed and collected from visit 1 on and kept in the investigator study file. A new diary for the next period will be dispensed to patients continuing in the study.

If at least 3 fasting SMBG diary measurements from the past 7 days exceed

240 mg/dl (13,3 mmol/l) at V3, V4, V5, V6

220 mg/dl (12.2 mmol/l) at V7, V8, V9

180mg/dl (9.9 mmol/l) at V10, V11, V12

the investigator should consider up-titration of insulin. In this case the corresponding SMBG values should be recorded in the eCRF.

Up-titration of the insulin dose during the long-term, double-blind extension period II should be considered by the investigator if HbA1c measured by central laboratory is

- >7.5 % at V14, V15,
- >7.0 % at V16, V17, V18

Insulin dose should not be uptitrated if both the following scenarios are met:

1. A patient has experienced unexpected hypoglycemic event/s

and

2. An uptitration of insulin may put the patient at an increased risk of hypoglycaemia in the clinical opinion of the investigator.

   An unexpected hypoglycemic event is an hypoglycemic event that cannot be explained by circumstances such as missing a meal, or extensive physical exertion.

If a patient experiences an unexpected hypoglycemic event in spite of high FPG or HbA1c levels, the investigator should consider a change in timing of the insulin dose and/or a change of the insulin regimen, rather than considering uptitration of the insulin dose.

The last HbA1c and FPG values measured by central laboratory prior to the increase in insulin dose will be carried forward for the efficacy analyses at week 24 (visit 9).

Reduction of daily insulin dose will not be allowed except for reasons of patient safety under the following circumstances:

Reduction of insulin dose shall be ordered by the investigator if the patient reports two of more readings of plasma glucose value ≤70 mg/dl (≤3.8 mmol/l). In addition, the investigator may consider an insulin dose adjustment (dose reduction or change in timing of insulin dose) in patients who report symptoms suggestive of hypoglycaemia without confirmatory glucose measurements if, in the opinion of the investigator, the patient is at increased risk of further hypoglycemic episodes without such insulin dose adjustments.

Diary fasting SMBG values that meet these criteria should be recorded in the eCRF.

Hypoglycaemic events

The patient will be asked to always self-monitor fasting plasma glucose in case of symptoms suggestive of hypoglycaemia and to register any signs of hypoglycaemia in the supplied diary.

- A hypoglycaemic event can be either
- An episode with symptoms and confirmed low glucose.
- An episode with low glucose.
- An episode with symptoms suggestive of hypoglycaemia when glucose was not measured.

For the evaluation of hypoglycaemic events special attention will be given to hypoglycaemia as defined in accordance with 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 <54 mg/dL (<3.0 mmol/L), and prompt recovery after glucose or glucagon administration.

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

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

Data to be collected for each hypoglycaemic event:

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

- If symptoms are present or not and which symptoms

- If fingerstick value obtained and the plasma glucose value

- Intervention needed for recovery and possible contributing factors

- Time of last drug administration

- Time of last meal

The patient diary will be reviewed and data regarding hypoglycaemic events 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 occurs, or more than one minor event since last visit, the patient should contact the investigator. For recording of hypoglycaemic events/symptoms suggestive of hypoglycaemic events as AEs, see section 4.7.1.1and 4.7.1.2.

Reduction of insulin dose shall be ordered by the investigator under the following circumstances:

Within the first 7 days of active randomized treatment:

- if the patient report two or more readings of plasma glucose value ≤80 mg/dl (≤4.4 mmol/l).

After the first 7 days of active randomized treatment:

- if the patient report two of more readings of plasma glucose value ≤70 mg/dl (≤3.8 mmol/l).

Patients should be encouraged to contact the investigator in such a case to allow the reduction of insulin dose.

Background OAD therapy may only be decreased if a concern of hypoglycaemia arises in a patient that has already been completely taken off of insulin. If background OAD therapy needs to be reduced, the last HbA1c and FPG values measured prior to the reduction in other OAD dose will be carried forward for the efficacy analyses at week 24.

Background OAD therapy may not be increased at any time during the study

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:

Asymptomatic bacteriuria is defined as the presence of ≥105 colony forming units/mL of bacteria, in a properly collected voided urine specimen, without signs or symptoms typically attributed to urinary tract infection. Asymptomatic bacteriuria is prevalent among diabetic women, and is associated with pyuria in 70% of cases. Neither the Infectious Diseases Society of America nor the U.S. Preventive Services Task Force recommends screening for, or treatment of, asymptomatic bacteriuria in non-pregnant diabetic patients (Nicolle LE et al 2005, US Preventive Services Task Force 2004). In this study, the central laboratory will not routinely report the results of urinary dipstick tests for leukocyte esterase as a screening test for pyuria in surveillance urine examinations.

At every scheduled visit starting from the randomization visit, the investigator will question subjects about symptoms of urinary tract infections, including but not limited to pain or burning or uncomfortable pressure in the lower abdomen/pelvic area while passing urine, blood in the urine, and symptoms of urinary urgency (a strong and uncontrolled urge to pass urine). If based on the response to these questions or other suggestive signs or symptoms (dysuria, urgency or frequency of urination, suprapubic or perineal discomfort, flank, back, or abdominal pain, costovertebral angle tenderness, nausea, vomiting, fever, chills, or sepsis) the investigator believes that a urinary tract infection may be present, urine cultures (in a local laboratory) should be obtained to confirm a presumptive diagnosis of cystitis, urinary tract infection, pyelonephritis, or prostatitis. Mid-stream clean catch urine collections are recommended. Clinical judgment and local standards of care should apply to decisions concerning therapy.

Study drug should be held in subjects with clinical evidence of upper tract UTI (e.g. pyelonephritis) or presumed urosepsis until the course of treatment of the infection has been completed and clinical recovery has occurred. It is recommended that a follow-up urine culture is obtained within 7 days of clinical recovery from a documented urinary tract infection. Whether additional therapy is prescribed because of culture results should be determined by Investigator judgment, after consultation with the Study Team Physician.

In addition, at every scheduled study visit starting from the randomization visit, the investigator will question subjects about symptoms of genital infections including but not limited to itching, soreness or redness in the genital area and a change or increase in genital discharge. The diagnosis of vaginitis, vulvovaginitis, vulvitis or balanitis can be made based on physical examinations, culture of secretions or a therapeutic response to treatment of fungal or other vaginal pathogens. A urine culture is not required for diagnosis of genital infections 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 judgment and subject's medical history, related adverse events as defined in Section 4.7.1 Additional information, including but not limited to completion of supplemental eCRFs may be requested for certain adverse events and/or laboratory abnormalities which are reported/identified during the course of the study.

4.7.5 Independent Adjudication Committee

4.7.5.1 Cardiovascular Clinical Event Committee (CCEC)

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

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

Death including:

(a) Cardiovascular Death

(b) Non-cardiovascular Death

Myocardial Infarction (MI) including:

(a) ECG and /or cardiac enzymes confirmed MI

(b) Sudden death

(c) PCI-related myocardial infarction

(d) CABG-related myocardial infarction

(e) MI diagnosed via pathologic criteria

(f) Silent MI

Fatal and Non-fatal Stroke including:

(a) Ischemic stroke

(b) Hemorrhagic stroke

Serious Adverse Events of the following:

(a) Heart failure

(b) Cardiac arrhythmia

(c) Unstable angina

(d) Unplanned arterial revascularization (coronary, carotid and peripheral)

(e) Cardiac arrest with successful resuscitation

(f) Deep Vein Thrombosis and Pulmonary Emboli

(g) Systemic non-stroke arterial embolism/thrombosis including systemic arterial occlusion

(h) Non-traumatic amputation of the lower limb. Only events above the ankle will be considered for adjudication.

In order to provide the independent CCEC 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.

4.7.5.2 Hepatic Adjudication Committee

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

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

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

4.8 Volume of blood sampling and handling of biological samples

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

Table 7 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	15	18	270
	Haematology	5	18	90
Pharmacokinetic		3	6	18
Total		23	24	378
Genotyping		9	1	9

4.8.1 Analysis of biological samples

4.8.1.1 Clinical chemistry samples

The analytic stability limits defined by the contracted central clinical laboratory will be applied to all analyses performed on behalf of AstraZeneca. The central laboratory will not analyse samples that fall outside these stability limits. Analytical data will not be reported if found to have been derived from a sample that fell outside these stability limits. The standards of procedure followed by the central laboratory may be amended in accordance with its Standard Operating Procedures. The central laboratory will inform AstraZeneca of the stability limits relevant to this study before the first patient gives informed consent to take part in the study.

If the contracted central clinical laboratory chooses to sub-contract the analytical work to another laboratory, the contracted central clinical laboratory must assure itself and provide assurance to AstraZeneca that the other laboratory will apply defined stability limits to all analyses performed on behalf of AstraZeneca. Samples falling outside these limits must not be analysed or data reported. The other laboratory will inform AstraZeneca of the stability limits relevant to this study before the first patient gives informed consent to take part in the study.

4.9 Genetic measurements and co-variables

Patients who provide written informed consent related to genetic research will provide a blood sample according to the Study Plan, see Table 1. Individual patients will not be identified. Samples and data will be kept confidential and stored separately. For more information, see Appendix F.

5. DATA MANAGEMENT

Data must be entered into the WBDC system at the investigational centre within 2 business days 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. Data entered in the WBDC system will immediately be saved at a central database and changes tracked to provide an audit trail. When data have been entered, reviewed, edited and Source Data Verification (SDV) performed, the Investigator will electronically sign the eCRF and the data will be locked to prevent further editing. An electronic copy (disc or equivalent) of the eCRF will be provided to the investigational centre after the study database has been locked for archiving at the investigational centre.

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. If loaded to WBDC efficacy variables will be blinded to investigator according to section 4.6.

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. Prior to breaking the treatment codes, all decisions on the evaluability of the data from each individual patient must have been made and documented. The Study Delivery Team at AstraZeneca will document the date of clean file and database lock.

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.

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. An electronic copy (disc or equivalent) of the eCRF will be made available to the Investigator centre after the study database has been locked.

Concomitant medications will be coded using the Bristol-Myers Squibb Drug Dictionary. Adverse events will be coded using MedDRA.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Statistical evaluation – general aspects

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

The first 24 weeks of double-blind treatment represent the confirmatory part of the study. Efficacy and safety data of the first 24-week treatment period will be analyzed after completion of this treatment period. Efficacy and safety analyses for the long-term double-blind extension period I and II will be performed for exploratory purposes and will provide supportive data. All investigators, patients and staff of Bristol-Myers Squibb and AstraZeneca except drug safety department and IPS will be blinded until completion of the 24-week treatment period (see Sections 3.6.1and 3.6.2). During the long-term double-blind extension period I and II, all investigators, patients, and study monitors will remain blinded.

6.2 Description of outcome variables in relation to objectives and hypotheses

The primary objective of the study is to assess the efficacy of 2.5 mg, 5 mg and 10 mg dapagliflozin compared to placebo as add-on therapy to insulin in improving glycaemic control in subjects with type 2 diabetes who have inadequate glycaemic control on ≥ 30 IU injectable insulin daily for at least 8 weeks prior to enrolment, as determined by the change in HbA1c levels from baseline to week 24. The objective will be statistically analyzed using Dunnett's method (overall type I error rate for the primary endpoint 0.05). The significance level for each pair-wise group comparison of dapagliflozin versus placebo will be approximately 0.019.

Key secondary objectives are to compare the effects of each dose of dapagliflozin versus placebo given as add-on therapy to insulin after a 24-week double-blind treatment period by evaluation of:

1. The change in body weight from baseline to week 24

2. The absolute change in calculated mean daily insulin dose from baseline to week 24

3. The proportion of subjects with calculated mean daily insulin dose reduction from baseline to week 24

4. The change in FPG from baseline to week 24

The statistical testing of the primary and key secondary outcome variables will proceed in a sequential manner, to control the type I error rate within each dapagliflozin group at the 0.05 level. Specifically, the significance or non-significance of the treatment comparisons for the primary outcome variable will determine which, if any, statistical inferences are made for the key secondary outcome variables. Only those dapagliflozin groups significantly superior to placebo for the primary outcome variable will have statistical inference versus placebo for the first key secondary outcome variable, (1). Then, the testing for the other key secondary outcome variables will proceed so that

- the significance or non-significance of the treatment comparisons for (1) will determine which, if any, statistical inferences are made in treatment comparisons for (2), and
- the significance or non-significance of the treatment comparisons for (2) will determine which, if any, statistical inferences are made in treatment comparisons for (3), and
- the significance or non-significance of the treatment comparisons for (3) will determine which, if any, statistical inferences are made in treatment comparisons for (4).

If at least one of the primary comparisons between a dapagliflozin treatment group and the placebo treatment group is significant at the 0.019 level for the primary outcome variable, all statistical tests for the four key secondary outcome 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 secondary outcome variable will be done using a step-wise procedure.

Other secondary outcome variables shall provide supportive efficacy and safety information regarding the differences between the treatment groups.

6.3 Description of analysis sets

Two analysis sets are specified for efficacy, the full analysis set and the per-protocol analysis set. The primary efficacy variable of change from baseline in HbA1c will be reanalyzed 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. Otherwise, efficacy analysis will be restricted to the full analysis set. These analysis sets and the safety analysis set are described as follows.

6.3.1 Full analysis set

The full analysis set will include all randomized subjects (as randomized) who received at least one dose of study medication during the 24-week double-blind treatment period, who have a non-missing baseline value and at least one post-baseline efficacy value for at least one efficacy variable during the 24-week double-blind treatment period. 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 randomized treatment period could not be influenced by knowledge of the assigned treatment. Missing values will be replaced by the last observation carried forward (LOCF) approach.

6.3.2 Per protocol analysis set

The per-protocol analysis set is 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 endpoint significantly. All decisions to exclude subjects from the primary data set will be made prior to the unblinding of the study.

6.3.3 Safety analysis set

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

6.4 Method of statistical analysis

6.4.1 Analysis of primary and secondary efficacy for the 24-week treatment period

The primary and secondary efficacy analyses will be based on the full analysis set. The primary endpoint may also be analyzed with the per-protocol analysis set. Treatment effects will be determined through pair-wise treatment group comparisons: each dapagliflozin treatment group versus placebo. No statistical comparisons will be made amongst the dapagliflozin groups.

For endpoints not examining insulin dose, the last post-baseline measurement prior to the first up-titration will be used for subjects whose insulin dose is up-titrated (i.e., patients are censored at the time of up-titration). Endpoints examining insulin dose will also use LOC, but without censoring at the time of titration. To directly assess the relationship between changes in insulin dose and HbA1c, changes in HbA1c will also be summarized using the observations from the same time points as analyzed for insulin dose as a supportive analysis.

The change from baseline to week 24 in HbA1c will be analyzed using an analysis of covariance model (ANCOVA) with factors for treatment group and use of other OADs as fixed effects, and covariate for baseline HbA1c. The model will be used to derive least squares estimates of the treatment differences (each dapagliflozin dose group versus placebo) in mean change with corresponding p-value and two-sided 95% confidence interval. Further, two-sided 95% confidence intervals for the mean change within each treatment group will be calculated.

To preserve the Type I error rate ≤ 0.050 (two-sided) across the primary and within each dose group for the four key secondary endpoints, a hierarchical step-wise procedure will be used to interpret the statistical significance of these treatment comparisons. The details of the step-wise procedure are provided in Section 6.2.

Continuous secondary efficacy variables will be analyzed by means of an ANCOVA for change from baseline using treatment group and use of other OADs as fixed effects and baseline value as a covariate. By analogy to the primary efficacy variable, the model will be used to derive point estimates and two-sided 95% confidence intervals for the mean change within each treatment group as well as for the difference in mean change between the dapagliflozin and placebo groups. Nominal p-values for the difference between the treatment groups will be provided.

When examining secondary endpoints defined within a subgroup (e.g., change in HbA1c in subjects with baseline HbA1c ≥9 %, change in HbA1c in subjects with baseline HbA1c ≥7.5 % and <9%, change in HbA1c in subjects with baseline BMI ≥27 kg/m2, change in HbA1c in subjects with baseline BMI ≥30 kg/m2, absolute change in body weight in subjects with baseline BMI ≥27 kg/m2, absolute change in body weight in subjects with baseline BMI ≥30 kg/m2, absolute change in seated systolic BP and seated diastolic BP in subjects with baseline seated systolic BP >140 mmHg), the same methods will be used.

Treatment effects on the primary endpoint will also be summarized within different subgroups to examine the robustness of the results across various categories of baseline characteristics. The two strata (with OADs and without OADs) will be considered subgroups. For this particular subgroup analysis, the interaction term between treatment and strata will be added to the ANCOVA model and tested for significance. Additionally, 95% confidence intervals of the treatment differences between each dapagliflozin group and placebo within each stratum will be provided. Other subgroups and their analyses will be outlined in the SAP.

The time course of all continuous variables will be presented using standard descriptive summary statistics calculated at each scheduled measuring time point and the last individual measuring time point. Moreover, standard descriptive summary statistics will be calculated for the absolute change from baseline to each scheduled measuring time point after baseline and the last individual measuring time point.

Discrete variables will be summarized by counts, proportions, and corresponding 95% confidence intervals. Comparisons between the treatment groups will be analyzed using two-sided Fisher's exact tests.

6.4.2 Analysis of efficacy during the long-term, double-blind extension period I and II

All variables to be analyzed at week 24 will be re-examined at the week 48 and 104 time point. Further, changes from week 48 to week 104 will be analyzed (see Section 4.6). In addition, the change in HbA1c levels from week 24 to week 48 and 104, and from week 48 to week 104 will be evaluated (see Section 4.6). In general, the same statistical methodology as described for the 24-week treatment period will be used for data in the long term double-blind extension period I and II. Summaries will be limited to point estimates and 95% confidence intervals.

For extension period II, summaries will be provided by the original, randomized treatment groups although selected analyses will also provide results for the pooled group of all patients who received 10 mg during this period

6.4.3 Analysis of Pharmacokinetics

The dapagliflozin plasma concentrations obtained by sampling of individual subjects will be used to build a population pharmacokinetic model to estimate pharmacokinetic parameters (e.g. CL/F, Vd/F and ka). Possible covariate effects on PK parameters (e.g. gender effect on CL/F) may be identified and quantified. The estimated pharmacokinetic parameters will be used to compute individual exposure measures (e.g. AUC, Cmin). Relationships between these exposure measures and efficacy endpoints (e.g. changes from baseline in HbA1c) will be explored. Similar exploratory analyses may be performed for other efficacy and safety measures. The pharmacokinetic data and efficacy endpoint responses derived from this study may be pooled with similar data from other studies to refine the modelled exposure-response relationship. Listings and summary statistics will be reported for pharmacokinetic parameters and exposure measures. The pharmacokinetic analysis will be described in a separate report

6.4.4 Analysis of safety

The safety evaluations will include analyses of AEs, laboratory parameters, ECG, vital signs, hypoglycaemic events, calculated creatinine clearance, eGFR, total protein/creatinine ratio (mg/g) oedema and physical examination. The analysis of safety will be based on the safety analysis set. Safety data gained during the 24-week treatment period, the long term double-blind extension period I and II as well as during the 3-week follow-up period will be evaluated. Safety variables will be summarized descriptively.

For extension period II, summaries will be provided by the original, randomized treatment groups although selected analyses will also provide results for the pooled group of all patients who received 10 mg during this period.

6.5 Determination of sample size

Each pairwise treatment group comparison will be tested at a significance level of approximately 0.019, according to Dunnett's method, in order to maintain an overall type I error rate < 0.050 for the primary objective. To detect a difference of 0.5% between each dapagliflozin group versus placebo for changes from baseline to week 24 in HbA1c, assuming a SD = 1.2%, and at a two-sided significance level of 0.019, 153 evaluable subjects are needed in each treatment group to provide 90% power. Assuming that 5% of the subjects will not be evaluable in the full analysis set, 161 subjects per treatment group (644 subjects total) are planned for randomization.

Approximately 700 patients will be offered to enter the long-term extension period II. This estimate is based on the number of actually randomised patients (808) and the assumption that approximately 14 % of the randomised patients will have been withdrawn at week 48 (visit 12).

6.6 Interim analyses

Summaries of long-term safety data may be produced during the long-term double-blind extension period II to support regulatory submissions if the study is not yet completed. These summaries will be conducted on safety data collected until a pre-specified cut-off date, regardless of observation time of each subject. The summaries will be descriptive. No formal statistical hypothesis testing will be performed and efficacy data will not be analysed.

Investigators, patients, and study monitors will continue to be blinded until completion of the study without any knowledge of the treatment codes, except for cases of medical emergencies.

Safety parameters to be analysed, will have the following rules applied.:

For summary at a time point using observed values (e.g. safety labs at week 65) to be presented, there should be at least 10 subjects with non-missing observations in at least one treatment group.

6.7 Data monitoring board

Not applicable.

7. STUDY MANAGEMENT

7.1 Monitoring

Before first patient enrolled into the study, a representative of AstraZeneca will 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)

During the study, a monitor from AstraZeneca or company representing AstraZeneca 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 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). This will require direct access to all original records for each patient (e.g. 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.

The monitor or another AstraZeneca representative will be available between visits if the investigator(s) or other staff at the centre need information and advice.

7.2 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, an Ethics Committee may visit the centre to perform audits or inspections, including source data verification. The purpose of an AstraZeneca audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator should contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at his or her centre.

7.3 Training of staff

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 to the study the appropriate investigational staff will be trained by AstraZeneca personnel or delegates on how to use the WBDC system, laboratory related issues and all other necessary means which will be used in this study.

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

7.4 Changes to the protocol

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

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol must be notified to or approved by each Ethics Committee, and if applicable, also the local regulatory authority, before implementation. Local requirements must be followed.

If an administrative change is required, such a change must be must be notified to or approved by each Ethics Committee according to local requirements.

If a protocol amendment requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the centre's Ethics Committee must be notified. Approval of the revised Informed Consent Form by AstraZeneca and by the Ethics Committee is required before the revised form is used.

AstraZeneca will distribute amendments and new versions of the protocol to each principal investigator(s), who in turn is responsible for the distribution of these documents to, and to the staff at his or her centre. The distribution of these documents to Ethics Committee and the regulatory authority will be handled according to local practice.

7.5 Study agreements

The principal investigator at each 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.

7.6 Study timetable and end of study

Before a patient's enrolment in the study and any study-related procedures are undertaken the following should be fulfilled:

- Signed Clinical Study Protocol and other agreements between AstraZeneca and the Principal Investigator/Study Site.
- Approval of the study by the Ethics Committee
- Approval of the study, if applicable, by the regulatory authority.

The planned overall timetable for the study is as follows:

First Patient In	Q2 2008
Last Patient In	Q1 2009

24-weeks double-blind treatment period:

Last Patient Last Visit	Q2 2009

Long term double-blind extension period I:

Last Patient Last Visit	Q4 2009
Data base lock	Q1 2010

Long term double-blind extension period II

Last Patient Last Visit	Q1 2011
Data base lock	Q1 2011

End of study is defined as database lock, which is the time point after which no patients will be exposed to study related activities.

8. ETHICS

8.1 Ethics review

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

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favourable opinion in writing by an Ethics Committee as appropriate. The investigator must submit written approval to AstraZeneca before he or she can enrol any patient into the study.

The Principal Investigator is responsible for informing the Ethics Committee of any amendment to the protocol in accordance with local requirements. In addition, the Ethics Committee must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the Ethics Committee annually, as local regulations require.

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

Where there is a genetic research, 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

8.2 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

For studies including genetic analysis special precautions are taken as described in appendix F.

8.3 Informed consent

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. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be 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

The patient's signed and dated informed consent for study prolongation must be obtained before extending the active study treatment at visit 12.

The principal investigator(s) must store the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

8.4 Subject data protection

The Master 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.

All data protection and confidentiality principles, described in the main study protocol, are applicable to this genetic research.

Reference to participation in this 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, 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, however, it must be recognised that there are exceptional circumstances where individuals may see both genetic data and a patient's personal identifier, for example in the case of a medical emergency, when AstraZeneca Physicians and investigators might know the patients' identity and might have access to the genetic data, or during regulatory audit where designated authorities must be permitted access to the relevant files.

9. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

9.1 AstraZeneca emergency contact procedure

In the case of a medical emergency you may contact the Drug Safety Representative. If the Drug Safety Representative is not available, contact the Study Delivery Team Physician or Study Delivery Tam Leader at the AstraZeneca Research and Development site shown below.

Role in the study	Name	Address & telephone number
Study Delivery Team Leader		
Study Delivery Team Physician		
Patient Safety Representative		

The address, telephone and fax number of other parties involved in the study e.g., Central Laboratory as well as the local AstraZeneca representative can be found in the 'Supplement A Study Delivery Team Contacts in the Event of Emergency'

9.2 Procedures in case of medical emergency

The principal investigator(s) 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 should be reported as such, see section 4.7.1.1.

The treatment code may not be broken unless in an emergency situation when the appropriate management of the patient necessitates knowledge of the treatment allocation. In such an emergency, the Investigator will, if time and circumstances permit, contact the local AstraZeneca representative prior to breaking the treatment code. If the treatment code is broken, the date, time, and reason should be recorded and the Investigator should sign the record, see also section 3.6.2.

9.3 Procedures in case of overdose

An overdose is defined as the accidental or intentional ingestion of any dose of an investigational product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see section 4.7.1.3). If an overdose is suspected, monitoring of vital functions as well as treatment as appropriate should be performed.

9.4 Procedures in case of pregnancy

If a patient becomes pregnant, the investigational product should be stopped and the AstraZeneca representative should be informed. The pregnancy report module in the eCRF should be completed by the investigator and the AstraZeneca representative will forward the information to BMS using the same procedure as for SAE reporting. The outcome of each pregnancy will also be collected once this information is available.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. However, 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.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All pregnancies must be reported on the pregnancy module in the eCRF. All outcomes of pregnancy must be reported to AstraZeneca on the pregnancy outcomes report that will be available in the Investigator Study File

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Clinical Study Protocol: Appendix B

Drug Substance	Dapagliflozin
Study Code	D1690C00006
Appendix Edition Number	1.0
Appendix Date	

Appendix B
Additional Safety Information

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

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

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

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

Clinical Study Protocol: Appendix C

Drug Substance	Dapagliflozin
Study Code	D1690C00006
Appendix Edition Number	1.0
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Appendix C
WHO Risk Categories

Risk group	Shipping Requirement	Pathogen	Risk to individuals	Risk to the community	Examples of Pathogens and their Risk groups
1	Standard Diagnostic (IATA PI650)	A micro-organism that is unlikely to cause human disease.	NONE OR VERY LOW	NONE OR VERY LOW	Most bacteria, fungi and viruses
2	Standard Diagnostic (IATA PI650)	A pathogen that can cause human or animal disease but is unlikely to be a serious hazard to laboratory workers, the community, livestock or the environment. Laboratory exposures may cause serious infection, but effective treatment and preventive measures are available and the risk of spread of infection is limited.	MODERATE	LOW	Legionella pneumophila E. Coli 0157
3	Standard Diagnostic (IATA PI650)	A pathogen that usually causes serious human or animal disease but does not ordinarily spread from one infected individual to another. Effective treatment and preventive measures are available.	HIGH	LOW	HIV Hepatitis B Hepatitis C
4	High risk(IATA PI602)	A pathogen that usually causes serious human or animal disease and that can be readily transmitted from one individual to another, directly or indirectly. Effective treatment and preventive measures are not usually available.	HIGH	HIGH	Lassa Fever Ebola Virus

If a subject is being withdrawn due to a suspected infection in WHO risk categories 2, 3 and 4 no biological samples from this subject are allowed to be sent to the laboratory. Samples will be destroyed according to normal routines at the study site.

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Clinical Study Protocol Appendix D	
Drug Substance	Dapagliflozin
Study Code	D1690C00006
Appendix Edition Number	1.0
Appendix Date	

Appendix D
New York Heart Association (NYHA) Classification

1. NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION

The NYHA classification will be based on the following definitions:

Class I — No limitation:
Ordinary physical exercise does not cause undue fatigue, dyspnoea or palpitations.

Class II — Slight limitation of physical activity:
Comfortable at rest but ordinary activity results in fatigue, palpitations, dyspnoea.

Class III — Marked limitation of physical activity:
Comfortable at rest but less than ordinary activity results in symptoms.

Class IV — Unable to carry out any physical activity without discomfort:
Symptoms of congestive heart failure are present even at rest with increased discomfort with any physical activity.

Clinical Study Protocol: Appendix E	
Drug Substance	Dapagliflozin
Study Code	D1690C00006
Appendix Edition Number	1.0
Appendix Date	

Appendix E
Algorithm on Management of Hyponatraemia

1. ALGORITHM ON MANAGEMENT OF HYPONATRAEMIA HEADING

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

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

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

  – If the repeat sodium concentration within 7 days of restarting the investigational product is <130 mmol/L, investigational product will be discontinued. Patients will have an end of treatment visit and a follow-up visit three weeks after discontinuation of investigational product as specified in section 3.3.5.2 in the CSP.

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

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

  – If there is no suspected new, temporary, and reversible cause of hyponatraemia based on clinical assessment (other than investigational product), investigational product will be discontinued. Patients will have an end of treatment visit and a follow-up visit three weeks after discontinuation of investigational product as specified in section 3.3.5.2 in the CSP.

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

    If the repeat sodium concentration within 7 days is <130 mmol/L, investigational product will be discontinued. Patients will have an end of treatment visit and a follow-up visit three weeks after discontinuation of investigational product as specified in section 3.3.5.2 in the CSP.

    If the repeat sodium level concentration within 7 days is ≥130 mmol/L investigational product may be restarted unless otherwise contraindicated. Serum sodium will be rechecked in 7 days after restarting the

investigational product, and further management should be based on composite of sodium concentration, clinical assessment of the patient and an evaluation of underlying cause of hyponatraemia.

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

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Clinical Study Protocol Appendix F	
Drug Substance	Dapagliflozin
Study Code	D1690C00006
Appendix Edition Number	2.0
Appendix Date	

Appendix F
Optional Genetic Research

GENETICS RESEARCH SYNOPSIS

A 24-week international, randomized, parallel-group, double-blind, placebo-controlled Phase III study with a 24-week extension period to evaluate the efficacy and safety of dapagliflozin therapy when added to the therapy of patients with type 2 diabetes with inadequate glycaemic control on insulin.

The genetic research activities described in this appendix (including the collection and storage of genetic samples), are optional for study centres as well as for individual patients. These research activities will hereafter be referred to as "this genetic research." The clinical study protocol to which this document is appended will be referred to as "the main study." The term "genetic sample" means a blood sample collected for genetic research and/or deoxyribonucleic acid (DNA) prepared from it.

This genetic research will be performed only after the appropriate Ethics Committee has approved it. Informed consent will be obtained using a form separate from that used for the main study. All sections of the protocol for the main study also apply to this genetic research. This appendix details additional procedures and considerations for inclusion of patients in the genetic component of the clinical study.

Study centre(s) and number of patients who may be enrolled in this genetic research

The main study will be conducted in 644 randomised patients recruited from approximately 150 centres.

Since the pharmacogenetic component of this clinical study is optional the number of patients who will agree to participate in the genetic component of the clinical study is unknown.

Objectives

The purpose of the genetic research is to enable future exploratory pharmacogenetic research studies. DNA obtained from the blood sample and health information collected from the main clinical study may be used to study the causes and progression of type 2 diabetes and other metabolic diseases and response to study treatments. Samples from this and other clinical studies may also be used in conjunction to accomplish this objective.

Study design

This is a 24-week, international, randomized, parallel-group, double-blind, placebo-controlled Phase III study with a 24-week double-blind extension period to evaluate the efficacy and safety of dapagliflozin 2.5, 5 and 10 mg as add-on therapy in adult patients with type 2 diabetes who have inadequate glycaemic control (HbA1c $\geq$7.5% and $\leq$10.5%) on $\geq$ 30 IU injectable insulin daily for at least 8 weeks prior to enrolment, with or without OADs. A 9 ml

(approximately) optional blood sample for genetic research can be collected at a single visit from Visit 2 (randomization visit) to Visit 9.

Target patient population

Men or women who are ≥18 years of age at the enrolment visit (Visit 1) diagnosed with type 2 diabetes, who fulfil the inclusion criteria for the main study, and who give informed consent for this genetic research.

Co-variables

Those genes putatively important in determining the response to study treatments (where response is defined broadly to include drug disposition, safety, efficacy and tolerability). This includes those genes coding for the drug targets as well as pathways and accessory pathway genes required for drug activity. Genes coding for proteins associated with the absorption, distribution, metabolism, and excretion of study drugs from the body eg, specific drug transporters and drug metabolising enzymes. Genes that may influence progression and prognosis of type 2 diabetes and related metabolic, nutritional and endocrine disorders under study within the dapagliflozin programme (ie, those diseases and disorders falling into international classification of diseases and related health problems (ICD)-9 multilevel clinical classification software, category 3 –"Endocrine, nutritional and metabolic diseases and immunity disorders"), or genes related to any other outcomes followed up on as part of the clinical study.

Statistical methods

The number of patients who will agree to participate in this genetic research is unknown. It is therefore not possible to establish whether sufficient data will be generated. A statistical analysis plan will be prepared where appropriate.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
eCRF	electronic Case report form
DNA	Deoxyribonucleic acid
EDTA	Ethylenediamine tetra-acetic acid
ICH	International conference on harmonisation
mL	Millilitre

1. BACKGROUND

AstraZeneca and Bristol-Myers Squibb plan to include investigations into genetic variations and their effect on drug response as part of the drug development program for all projects where it is considered to be appropriate. By using this information, the aim is to better understand the impact of genetic variation and how it can be utilised to bring better drugs to the market.

To achieve this goal a systematic collection of deoxyribonucleic acid (DNA) for genetic analysis (derived from blood samples taken from consenting study patients) will be implemented across a broad range of relevant clinical studies. The ability to acquire appropriate consent to collect blood samples to establish a DNA archive to allow future meta-analysis of data derived from a number of studies for dapagliflozin is of the utmost importance. This genetic research forms part of this strategy.

1.1 Rationale for genetic research

AstraZeneca and Bristol-Myers Squibb intends to perform genetic research in the dapagliflozin clinical development programme to explore how genetic variations may affect the clinical parameters associated with dapagliflozin where appropriate.

The benefits of being able to explore associations between genes and clinical outcomes within the dapagliflozin programme are potentially many and include:

- Examination of drug response
- Efficacy
- Safety
- Toxicity
- Overall survival

2. GENETIC RESEARCH OBJECTIVES

Genes that may be investigated include:

- genes encoding drug targets (of study drug(s))
- genes encoding proteins which function in drug transport and metabolism
- genes encoding products that may play a role in response to therapy

In addition to the above, it is likely that additional information on other genes important for this drug and for type 2 diabetes and other metabolic diseases for which the investigational product is being developed will become available in the future. It is therefore important to retain the possibility of investigating additional genes in the context of this dapagliflozin clinical study.

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Genetic research plan

This appendix to the Clinical Study Protocol has been subjected to peer review according to AstraZeneca standard procedures.

The patient will be asked to participate in this genetic research at Visit 2. If the patient agrees to participate, a single blood sample will be taken for genetic research at Visit 2. If the sample isn't drawn at visit 2, it may be drawn at any other scheduled visit until Visit 9.

3.2 Selection of genetic research population

3.2.1 Study selection record

All patients will be asked to participate in this genetic research. Participation is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

3.2.2 Inclusion criteria

For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the study protocol and:

- Provide informed consent for the genetic sampling and analyses.

3.2.3 Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous bone marrow transplant.
- Received blood transfusion in the 120 days preceding the date of genetic sampling collection.

If either of these two exclusion criteria is present, the patient cannot participate in the optional blood sample donation.

3.2.4 Discontinuation of patients from this genetic research

3.2.4.1 Criteria for discontinuation

Specific reasons for discontinuing a patient from this genetic research are:

- Withdrawal of consent for genetic research. Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment.

3.2.4.2 Procedures for discontinuation

Patients who discontinue from the main study should always be asked specifically whether they are withdrawing or continuing their consent for this 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 so 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 but these will not be used in any subsequent analyses.

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.

4. GENETIC MEASUREMENTS AND CO-VARIABLES

4.1 Summary of genetics objectives and analysis

The purpose of this genetic research is to generate a resource for future exploratory pharmacogenetic research studies. DNA obtained from the blood sample and health information collected from the main clinical study may be used to investigate the effects of DNA variation on response to study treatments and study the causes and further progression of type 2 diabetes and other metabolic diseases. Samples from this and other clinical studies may also be used in conjunction to accomplish this objective.

The joint exploratory data analysis may be performed in the future by Statistical Genetics and Biomarkers in Exploratory Development, Global Biostatistics and Programming and the department of Pharmacogenomics in Clinical Discovery at Bristol-Myers Squibb and/or the

AstraZeneca equivalent (including approved external service providers) to investigate if genetic variants (genotypes) are associated with clinical outcomes (phenotypes) such as, but not limited to, drug response, efficacy, safety, toxicity, and overall survival. The following potential analyses may be performed as appropriate:

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

4.2 Collection of samples for genetic research

Patients will provide a blood sample as per the inclusion criteria and visit schedule.

A single venous blood sample (approximately 9 mL) will be collected into a vacutainer or similar blood collection tube containing ethylenediamine tetra-acetic acid (EDTA) and gently inverted a minimum of five times to mix thoroughly. Tubes will be labelled with the protocol study number, centre number, enrolment code and/or randomisation number and date of sample collection. No personal identifiers (patient name, initials, or date of birth) will be placed on the tube or accompanying documentation. A record of the date of the patient consent to the genetic research and the date of the blood sample collection will be recorded in the appropriate section of the electronic Case Report Form (eCRF).

Genotype is a stable parameter; therefore, if for any reason the blood sample is not drawn at Visit 2, it may be drawn at any other scheduled visit after Visit 2 until Visit 8. The genetic blood sample should ideally be drawn through the same cannula used to draw blood samples required for the main study.

4.2.1 Sample processing and shipping

Samples will be transported in ambient temperature from the centre to the central laboratory where they will be split into two aliquots and stored frozen.

Where possible, blood samples should be shipped daily with other ambient samples and shipment should be coordinated with the receiving centre to ensure arrival within working hours. A requisition sheet, detailing the protocol study number, centre number, enrolment code and/or randomisation number and date of sample collection, should accompany the shipment.

4.2.2 Storage and coding of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality.

The samples and data for genetic analysis in this study will be de-identified. This will require each blood sample to be double coded and labelled with a second unique identifier. The sample and data will not be labelled with a personal identifier. The study number and patient number will be linked to this second unique identifier. The investigator will not be able to link the blood sample to the patient. The link between the clinical study/patient number and the unique second number is maintained by the Bristol-Myers Squibb Sample Bank, but unknown to the investigator.

Once DNA is extracted from the de-identified blood sample it is given another unique identifier. The DNA number will be used to identify the sample and corresponding data at the designated contract laboratory. No personal details identifying the individual donor will be available to any AstraZeneca or Bristol-Myers Squibb employee or external provider working with the DNA. A link between the blood sample and the DNA extracted from the sample will be maintained in a confidential link file.

All genetic samples will be stored under secure conditions with restricted access at Bristol-Myers Squibb and/or AstraZeneca. The blood 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 sample collection date or according to local legislation. Samples may be destroyed prior to this timeframe if the patient has withdrawn consent.

5. MANAGEMENT OF GENETIC RESEARCH DATA

In the case of genotypic data, only the date the patient gave consent to participation in the genetic research and the date the blood sample was taken from the patient will be recorded in the eCRF and database. The genotypic data will not be merged with the entire clinical dataset collected from the patient population for statistical analysis. However, relevant subsets of clinical data may be replicated for genotype-phenotype analysis.

Genotypic data will be stored in the Bristol-Myers Squibb Sample Bank or another secure database, separate from that used for the main study. Some or all of the dataset from the main study may be duplicated within the Bristol-Myers Squibb Sample Bank to facilitate exploratory genetic analyses.

5.1 Reporting of genotypic results

Any results from this genetic research will be reported separately from the clinical study report for the main study. AstraZeneca and Bristol-Myers Squibb will not provide individual genotype results to patients, their family members, any insurance company, an employer, clinical study investigator, general physician or any other third party, unless required to do so by law. The patient's DNA will not be used for any purpose other than those described in the study protocol.

Individual patients will not be identified in any report or publication resulting from this work. The data and results of this study may be reviewed with collaborators and published, but neither the patient's name nor any other personal identifiers will appear in any publication or report. De-identification will be done after the genotypic data and clinical data sets have been merged.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of patients who will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether a statistically relevant number of patients will consent to provide sufficient data to 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.

7. STUDY MANAGEMENT

7.1 Monitoring

Before first patient entry into the study, a representative of AstraZeneca will visit the investigational study centre. In addition to the requirements described in the main study, this genetic research will be discussed.

During the study, a representative of AstraZeneca will have regular contacts with the investigational centre. One of the purposes of these visits will be to perform source verification of the genetic consent of participating patients and to ensure that the investigational team are adhering to the specific requirements of this genetic research.

7.2 Training of staff

Before the first patient is entered into the study the investigational staff will have an opportunity to discuss the procedures associated with the collection of blood samples, extraction of DNA and genetic research with a representative of AstraZeneca. The ethical considerations specific to genotyping and the importance of the informed consent process will be made clear. The requirements for the collections of the patients' sample will also be made clear.

7.3 Changes to the protocol

Any changes to the genetic research will comply with the principles described in Section 7.4 of the main body of the protocol.

7.4 Study agreements

The principal investigator at each 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. Specific reference to requirements relating to this genetic research will be included in the study agreement(s).

8. ETHICS

8.1 Ethics review

In addition to documenting Ethics Committee approval of the main study, approval must be obtained for this genetic research and the associated genetic informed consent from the relevant 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 patients participates in this genetic research.

8.2 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

For studies including genetic analysis special precautions are taken as described in section 4.2.2 of this Appendix.

8.3 Informed consent

The genetic component of this study is optional and the patient may participate in other components of the 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 patients understand that they may freely discontinue from the genetic aspect of the study at any time.

8.4 Patient data protection

All data protection and confidentiality principles, described in the main study protocol, are applicable to this genetic research.

Reference to participation in this genetic research should not be recorded into the patients' general medical records, unless required by local regulations. Instead, all notes should be kept within the clinical study records.

Due to the exploratory nature of this genetic research, there will be no routine communication of results to patients. Bristol-Myers Squibb or AstraZeneca will not provide individual genotype results to patient, 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 to prevent genetic data from being linked to the identity of the patient. However, it must be recognised that there are exceptional circumstances where individuals may see both genetic data and a patients personal identifier, for example in the case of a medical emergency, when AstraZeneca Physicians and investigators might know the patient's identity and might have access to the genetic data, or during regulatory audit where designated authorities must be permitted access to the relevant files.

With respect to optional blood sample donation, the only information that will be recorded in the eCRF and clinical database will be information related to the provision of informed consent for genetic research and sample collection information. No genotypic data derived from samples collected in this study will be stored in the main clinical database. Genotypic data will be stored in the Bristol-Myers Squibb secure database or another secure database, separate from that used for the main study. Some or all of the dataset from the main study may be duplicated within the Bristol-Myers Squibb secure database to facilitate exploratory genetic analyses.

9. REFERENCES - NOT APPLICABLE

AstraZeneca

Clinical Study Protocol Appendix G	
Drug Substance	Dapagliflozin
Study Code	D1690C00006
Appendix Edition Number	2
Appendix Date	

Appendix G
Case Identification and Management of Decreased Renal Function

1. CASE IDENTIFICATION AND MANAGEMENT OF DECREASED RENAL FUNCTION

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

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

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

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

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

Patients should return for repeat central laboratory testing as soon as possible, no later than 7 days after the abnormal result. Study drug should be interrupted pending the results of repeat testing. If after interruption the serum creatinine value remains above the increase limit described above (³0.5 mg/dl or ³1.0 mg/dl above baseline), the patient should permanently discontinue the medication and be withdrawn from the study (in which case an Adverse Event must be reported).

If after study drug interruption the serum creatinine value has decreased to below the increase limit (<0.5 mg/dl or <1.0 mg/dl above baseline), study drug can be re-started if appropriate in the investigator's judgment and after consultation with the study delivery team physician. If study drug is re-started, the patient should return for a follow-up central lab serum creatinine 7-14 days after re-start, although more frequent assessments may be done at investigator discretion. If the patient restarts study drug and the serum creatinine value increases again to the increase limit (³0.5 mg/dl or ³1.0 mg/dl above baseline), the patient should permanently discontinue the medication and be withdrawn from the study (in which case an Adverse Event must be reported).

AstraZeneca

Clinical Study Protocol Appendix H	
Drug Substance	Dapagliflozin
Study Code	D1690C00006
Edition Number	3
Date	

Appendix H

Algorithm on Management of Sustained Elevated Liver Safety Abnormalities

1. ALGORITHM ON MANAGEMENT OF SUSTAINED ELEVATED LIVER SAFETY ABNORMALITIES

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

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

- **If the repeat ALT and AST are ≤ 3 ULN**, subject should continue in the double-blind treatment according to their original visit schedule unless otherwise contraindicated.

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

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

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

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

- **ALT and/or AST are >8 ULN**

Note: See below for discontinuation procedures.

Guidance on Assessment of Hepatic Laboratory Abnormalities

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

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

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

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

For patients who are discontinued from the study as a result of sustained elevated liver safety abnormalities as described above, study medication will be discontinued, the Sponsor notified and the early termination (End-of-Treatment) visit performed within 3 days of the confirmed laboratory results. Additional blood sampling must be done in conjunction with an early termination (End-of-Treatment) visit, in addition to the procedures noted above. A "Liver Discontinuation" visit laboratory kit, in addition to the Specialized Liver Panel kit as noted below, will need to be used to collect recommended blood samples. Additionally, supplemental (unscheduled) visit eCRF pages as well as supplemental eCRFs will need to be completed to collect "Liver Discontinuation" information. Patient should also be scheduled for a Follow-up visit (i.e. procedures of Visit 19) weeks after discontinuation of investigational product. A referral consultation to a hepatologist or gastroenterologist (specializing in liver abnormalities) should be obtained. Any additional tests and/or examinations should be carried out at the discretion of the Investigator. Any further investigations and laboratory results for patients with abnormal laboratory values at the safety follow-up visit should be made available to the Sponsor upon request.

Following the early termination (End-of-Treatment) visit, the Investigator should continue to monitor the subject's liver tests every 3 days following receipt of the prior laboratory results until the ALT and AST are ≤2 x ULN or until ALT and AST are at or below baseline levels. The frequency of retesting can decrease to once a week or less if abnormalities stabilize and the subject is asymptomatic.

Specialized Liver Panel

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

- Hepatitis A IgM
- Hepatitis BsAg
- Hepatitis B Core Ab IgM
- Hepatitis C virus RNA
- Hepatitis C Ab
- Hepatitis E IgM
- Epstein-Barr Virus (EBV) IgM Ab
- Lactate Dehydrogenase (LDH)
- Gamma-glutamyl-transpeptidase (GGT)

- Carbohydrate deficient transferrin (CDT)
- Prothrombin time (PT/INR)
- Iron Panel - iron, ferritin, total iron binding capacity (TIBC)
- Immunology Panel including Antinuclear Antibody (ANA), Anti-Smooth Muscle Antibody (SMA) and Anti-Liver/Kidney Microsomal Antibody (Anti-LKM)
- Anti-tissue Transglutaminase Antibody

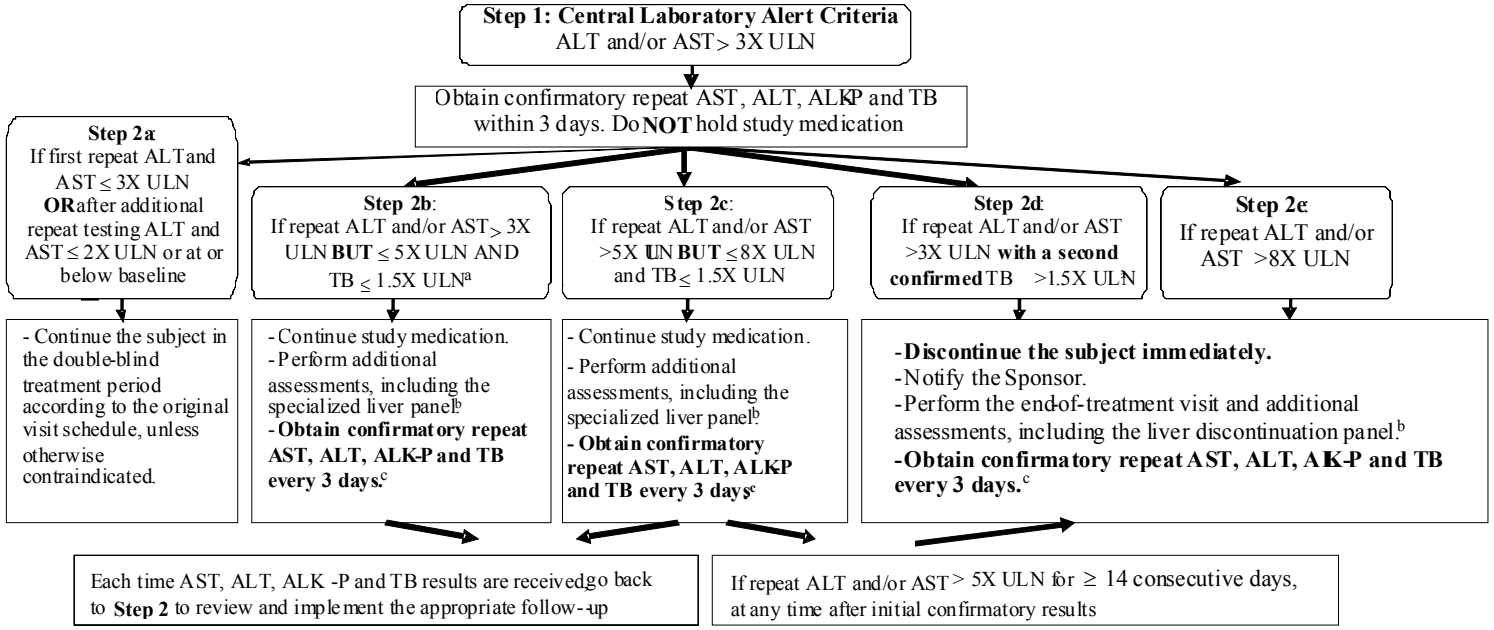
Liver Discontinuation Panel

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

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

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

Figure 1 Sustained elevated liver safety abnormalities flow chart



[a] In subjects with repeat ALT or AST >3XULN, only subjects with TB ≤ 1,5XULN at Step 1 should be followed according to Step 2b. Subjects with an initial TB and confirmatory repeat TB > 1,5 X ULN should be followed according to Step 2d.

[b] See above for details on additional assessments to be performed (AE assessment, PE, review of current medical history including focused review of risk factors for liver diseases and collection of blood samples **[specialized liver panel for Step 2b and c; specialized liver panel and liver discontinuation panel for Step 2d and e])**

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

AstraZeneca

Clinical Study Protocol Appendix I	
Drug Substance	Dapagliflozin
Study Code	D1690C00006
Edition Number	1
Date	

Appendix I
Overall Risk Benefit Assessment

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1. SUMMARY OF RISKS

Six clinical pharmacology studies have been completed in the dapagliflozin program. In these studies, 116 healthy subjects and 38 subjects with type 2 diabetes mellitus (T2DM) have received at least 1 single oral dose (2.5 – 500 mg and 5 – 100 mg, respectively) of dapagliflozin. Forty subjects (24 healthy volunteers [range of mean duration of exposure: 1-14 days] and 16 subjects with T2DM [mean duration of exposure: 13 days]) have received doses ≥ 100 mg of apagliflozin. Multiple daily doses of dapagliflozin were given to 30 healthy subjects (2.5 – 100 mg) and 39 subjects with T2DM (5 – 100 mg) for up to 14 days.

In a Phase 2b clinical study 279 subjects received 1 of 5 doses of dapagliflozin (2.5 mg, 5 mg, 10 mg, 20 mg or 50 mg) for 12 weeks. A second Phase 2b study is ongoing. Data from approximately 514 subjects who have been exposed to dapagliflozin indicate that it is generally safe and well tolerated at doses up to 50 mg for 12 weeks or in single doses up to 500mg.

Due to the mechanism of action of dapagliflozin, clinical and nonclinical findings, the following important identified and potential risks are discussed here.

1.1 Identified Risk

1.1.1 Vaginal/Vulvovaginal Infections

Dapagliflozin increases the urinary excretion of glucose. Increased glucose levels in genital tissues potentially enhance yeast adhesion and growth. Vaginal and Vulvovaginal infections were reported in the Phase 2b study in the dapagliflozin arms, but not the metformin or placebo arms, and did not appear to be dose related. Vulvovaginal mycotic infection was reported as an AE for 5 subjects (1.8%) and vaginal infection was reported for 3 subjects (1.1%) in patients treated with dapagliflozin. In the phase 2a study, vulvovaginal mycotic infection was reported as an AE in 2 subjects with T2DM; both were treated with Dapagliflozin (1 subject received 100 mg dapagliflozin plus 500 mg metformin and 1 subject received 25 mg dapagliflozin).

Targeted questioning related to symptoms of genital infections will be done by investigators in the phase III program at all scheduled visits. In addition, all adverse events related to genital and urinary tract infections during phase III program will be captured in specialized case report forms that will collect additional information related to these events

1.2 Potential Risks

1.2.1 Urinary Tract Infections

Dapagliflozin increases the urinary excretion of glucose, a potential substrate for urinary and vaginal pathogens. In the phase IIb study, the adverse events of urinary tract infections were comparable between dapagliflozin arms (7.5%) ant the metformin arm (7.1%). Fewer subjects reported an adverse event of urinary tract infection in placebo arm.

In the phase 3 program targeted questioning related to symptoms of urinary tract infections will be done by investigators at all scheduled visits. In addition, all events of genitourinary tract infections will be captured on specialized case report forms which will gather additional information on these events. Also the occurrence of urinary tract infections and genital infections will be monitored. To reduce overlap between urinary and genital tract adverse event reporting, specific guidelines will be included to assist better classification and management of these events.

1.2.2 Hypoglycemia

In the Phase 2b study there were no confirmed hypoglycaemic events, defined as a documented blood glucose of ≤50 mg/dL. The reported incidence of unconfirmed hypoglycaemic events were higher in the dapagliflozin treatment groups compared with the placebo group, but similar to that in the metformin treatment group. The incidence varied within the dapagliflozin arms without relationship to dose. One unconfirmed event of moderate intensity required third party assistance.

In the Phase 2a study one patient treated with dapagliflozin and metformin had a confirmed hypoglycaemic event.

In the Phase 3 program, dapagliflozin will be combined with other anti-diabetic agents, which might increase the risk of hypoglycemic events. In addition to close monitoring of plasma glucose, glucometers will be supplied to each subject. Instructions will be provided to promptly report to the site any plasma glucose values and/or signs and symptoms suggestive of hypoglycemia. Guidelines for discontinuation due to hypoglycemia are included in the phase III protocols.

1.2.3 Dehydration/Hypovolemia/Hypotension

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 hypovolemia or dehydration. In the Phase 2b study, no events of dehydration, hypovolemia or marked abnormality of BUN ≥ 60 mg/dL were reported. However, symptoms that could be related to dehydration and hypovolemia, such as hypotension, orthostatic hypotension, dizziness, blurred vision and presyncope, were reported. With mean baseline ratios of serum BUN to creatinine of 17-19, dapagliflozin-treated subjects exhibited minor increases in this ratio in contrast with a decrease in subjects treated with placebo. In addition to an increase in BUN/CR ratio there was a slight increase in fractional excretion of sodium and a dose-dependent increase in mean 24- hour urine volume in the dapagliflozin arms.

In the Phase 2b study, MB102008, there was a decrease from baseline in mean standing systolic blood pressure by 4-5 mmHg in the 10-50 mg dapagliflozin treatment arms, and by 2-3 mmHg at the lower doses.

In the phase 3 program, any symptoms, adverse events, vital signs and laboratory parameters indicative of dehydration/hypovolemia will be closely monitored. As a precaution, subjects at risk for hypovolemia or electrolyte disturbance should not receive dapagliflozin until more

clinical information is available from human studies. In phase III if subjects already receiving dapagliflozin were to develop conditions that may cause hypovolemia or electrolyte imbalance, decisions to interrupt or discontinue dapagliflozin therapy and management of subjects should be based on clinical judgment as would apply to the use of diuretic drugs. In addition, blood pressure will be measured frequently during the phase 3 program and orthostatic blood pressure will be measured at selected visits throughout the program.

1.2.4 Serum electrolyte abnormalities

Adverse events of hypokalemia and hyponatremia were each reported in one subject receiving dapagliflozin. Seven subjects receiving dapagliflozin had serum sodium concentrations ≤ 130 mEq/l. The marked abnormality of hypokalemia (serum potassium ≤ 2.5 mEq/L) was seen in 2 subjects receiving the 50 mg dose and in no subjects in any other arm. Dapagliflozin was associated with increased prevalence compared to placebo of the marked abnormality of hyperphosphatemia (serum phosphorus ≥5.0 mg/dL). Mean serum phosphorus compared to baseline increased by 0.2 mg/dL at the 20 mg and 50 mg doses; 0.1 mg/dL at the 5 mg and 10 mg doses as well as placebo; and was unchanged at the 2.5 mg dose. Mean serum magnesium concentrations increased by up to 0.2 mEq/L at all doses, however, no magnesium values for any subject reached predefined levels of marked laboratory abnormality.

In the phase 3 program, serum electrolytes will be monitored at each study visit. In addition, appropriate criteria for discontinuation of patients due to electrolyte abnormalities including an algorithm on the management of hyponatremia will be implemented.

1.2.5 Renal impairment

In clinical studies, there were no reports of renal impairment, renal failure or marked abnormality of serum creatinine ≥ 2.5 mg/dL. In the phase IIb study, measured 24-hour urinary creatinine clearance decreased slightly, with the smallest decrease in the dapagliflozin 2.5 mg group and the largest decrease in the dapagliflozin 50 mg group (by 16.3 ml/min from baseline), with no change in the placebo group. There were no changes in the mean or median serum creatinine values at week 12 when compared to baseline in the dapagliflozin treatment arms. Increased serum creatinine was reported in one subject in dapagliflozin arm and in no subjects receiving placebo or metformin.

In addition to serum creatinine, Cystatin C, considered to be a better indicator of changes in glomerular filtration rate (GFR) will also be measured in the Phase 3 Program. Also, a study to evaluate the safety of dapagliflozin treatment over 12 months in T2DM patients with moderate renal impairment will also be conducted in parallel to the phase 3 program.

1.2.6 Bone Fracture

To date, bone metabolism disorders, including bone fractures, have not been reported in clinical trials. However, an increase in serum markers of bone metabolism was noted in subjects treated with dapagliflozin in the Phase 2b study. There were small increments in mean serum parathyroid hormone concentration, without apparent relationship to dose. A small increase in the parathyroid hormone level was noted in the placebo arm as well.

In the Phase 3 program we plan to implement a bone safety monitoring plan through a combination of close monitoring of electrolytes and hormones involved in bone metabolism in all studies and the monitoring of serum biomarkers of bone metabolism in selected studies.

Also, in a Phase III study of 24-month duration, dual-energy x-ray absorptiometry (DEXA) scan will be obtained periodically to evaluate bone density.

1.2.7 Increased hematocrit

In the Phase 2 study a dose dependent mean increase in hematocrit was seen in the dapagliflozin arms after 12 weeks of treatment. There was a slight decrease in the metformin arm and no apparent change in the placebo arm.

Reductions in plasma volume due to diuresis or stimulation of erythropoietin secretion may potentially contribute towards an increase in hematocrit level. In the Phase 3 program hematocrit will be measured regularly at study visits.

1.2.8 Increased creatine phosphokinase

In the phase 2b study, MB102008, the adverse event of an increase in blood creatine phosphokinase (CPK) was reported in seven subjects (2.5%) treated with dapagliflozin, and was not reported in subjects who received either placebo or metformin. Changes in mean serum CPK compared to baseline were small, and inconsistent, in all treatment arms. The maximum increment in mean serum creatine phosphokinase was 25 U/L, seen in the 10 mg dapagliflozin treatment arm at two weeks. There were no marked abnormalities defined as CPK ≥ 10X ULN reported in this study. In clinical studies no cases of acute renal failure, myopathy, and/or rhabdomyolysis were reported. There were no apparent drug related effects with respect to AST, ALT, or bilirubin.

In phase 3 program, CPK criteria for exclusion and discontinuation from the study will be implemented. CPK levels will also be measured at regular intervals in the phase 3 studies.

1.2.9 Non clinical Toxicology findings

Non-reversible bone remodeling changes characterized by an increased thickness of the primary trabeculae and tissue mineralization associated with hypercalcemia were noted only in rats at very high exposure multiples (1945 - 2846x) relative to the human area under the curve (AUC) at a clinical dose of 10 mg. Data from an investigative study in rats suggests that dysregulation of calcium homeostasis and concomitant high dose tissue mineralization is likely a consequence of off-target SGLT-1 inhibition ultimately leading to increased absorption of calcium from the GI tract.

Dapagliflozin has an approximately eight fold greater selectivity for SGLT-2 than SGLT-1 in humans (1 vs. 1600 nM) compared with rats (3 vs. 620 nM). No bone changes were noted in the 3-month mouse or in the 12-month dog studies at doses representing exposure (AUC) multiples of ≥ 982 and 3004 x, respectively. Bone changes were noted at only very high exposure multiples in rats (1945-2846x). Overall, the nonclinical data strongly suggests that

there is very low risk of these side effects occurring in humans at the doses selected for study in Phase 3.

Drug-related changes in numerous urinary parameters were noted in rats and dogs given dapagliflozin for up to 6 and 12 months, respectively. These findings were generally consistent with anticipated pharmacology and included dose-dependent increases in total urine glucose, calcium, phosphorus and volume in both species at all doses. Increases in urinary calcium and phosphorus are considered to be secondary to osmotic diuresis. Decreases in urine osmolality were also noted in both rats and dogs. Hypercalcemia was observed only in rats at very high exposure multiples (1945-2846x). Changes in serum phosphorus were observed in rats at exposure multiples of >318x. Most other findings were consistent with anticipated pharmacology and represent no safety concern for humans at the doses selected for study in Phase 3.

In the 6-month study in rats, cortical and medullary tubular dilatation, medullary tubular reactive hyperplasia with mineralization, and urothelial hyperplasia were observed in highdose male and female rats only (1945-2846x relative to the human AUC at a clinical dose of 10 mg). In addition, minimal to slight tubular cysts and exacerbated progressive murine nephropathy, an age-related spontaneous lesion commonly observed in Sprague-Dawley rats, were observed in high-dose female rats. Following a 3-month recovery period, no renal lesions, except exacerbation of chronic progressive nephropathy in the high-dose females were observed.

No renal histologic or clinical pathologic findings were noted in the 12-month dog study. Increases in total urinary protein were noted in both the 6-month rat (up to 5x) and 12-month dog studies (up to 7x) in the absence of drug-related renal histologic findings, except at the 150 mg/kg/day dose in female rats.

The repeat dose toxicology safety margins (exposure multiples) for male and female species respectively relative to the humans steady-state dapgliflozin exposure of 506 ng/mL*hr at the highest anticipated clinical dose of 10 mg QD can be summarized as under:

(a) 3 month mouse study- 601X and 972X

(b) 6 month rat study- 318X and 621X

(c) 12 month dog study- >3004X and 3044X (at highest dose tested: no target tissues identified)

The non clinical toxicology studies conducted support the continued clinical dosing of dapagliflozin in humans, including Phase 3 clinical studies of duration of up to at least 2 years in accordance with appropriate monitoring as highlighted in the individual risk sections.

2. SUMMARY OF BENEFITS

Many subjects with T2DM who receive pharmacological treatment are not reaching glycemic control goals. Currently available treatments for T2DM, including injectable insulin therapy and oral medications, have significant side effects such as hypoglycaemia and weight gain. There is, therefore, a need for better treatments for hyperglycemia and T2DM. Dapagliflozin, an inhibitor of sodium-glucose transporter 2, is a member of a new therapeutic class designed to treat hyperglycemia and T2DM. Dapagliflozen provides a novel mechanism of action for the treatment of T2DM that is not dependent on insulin secretion or insulin action to mediate its blood glucose lowering effect, making it potentially applicable to a wide spectrum of patients, and is expected to be compatible for use alone or in combination with other antidiabetic agents. In addition, this mechanism of action may have a lower risk of hypoglycemia than sulfonylureas, and will not likely be associated with weight gain.

The efficacy of dapagliflozin as an oral glucose-lowering agent was first demonstrated in a Phase 2a trial. Subjects with T2DM were treated with 5 mg, 25 mg, and 100 mg dapagliflozin for 14 days. There was a 2 to 4-fold greater percent mean change from baseline in serum glucose levels at all doses compared with placebo. In a Phase 2b trial, where dapagliflozin doses from 2.5 mg to 50 mg were tested, statistically significant differences in reduction of haemoglobin A1C (A1C) from baseline were achieved in all dapagliflozin treatment groups vs. placebo at week 12. The adjusted mean reduction from baseline in A1C in the dapagliflozin treatment groups were similar to the reduction seen in the metformin treatment group. The proportion of subjects achieving therapeutic glycemic response (A1C < 7%) at Week 12 was greater in the dapagliflozin treament groups compared with the placebo group. In patients with T2DM, better glycemic control as reflected by a lowering of HbA1c has been closely associated with a reduced risk of microvascular complications such as retinopathy, nephropathy and neuropathy. Along with changes in HbA1c, statistically significant differences in adjusted mean reduction in fasting plasma glucose (FPG) from baseline to Week 12 were achieved in the 5, 10, 20 and 50 mg dapagliflozin treatment groups vs. placebo.

Given that the mechanism of action of dapagliflozin results in gross glucose elimination, the end result of treatment should be a negative daily calorie balance (if all other energy parameters remain the same). This could be a great benefit to patients given that one of the major underlying factors in the epidemic rise in T2DM is a preponderance of obesity in modern societies. In the phase IIB study, decreases in percent change in body weight from baseline to Week 12 was seen in all treatment groups with greater mean percent reductions from baseline in the dapagliflozin treatment groups compared to either placebo or metformin

3. OVERALL BENEFITS AND RISKS ASSESSMENT

In a Phase 2b study all doses of dapagliflozin were associated with a statistically significant and clinically relevant improvement in glycemic control and relatively minor AE's and effects upon fluid/electrolyte status. The safety data collected to date from clinical studies in healthy volunteers and subjects with T2DM indicate that the clinical safety profile of dapagliflozin supports proceeding with Phase 3 studies at doses of 2.5 mg, 5 mg and 10 mg per day. Evaluation of the clinical safety and clinical efficacy data accumulated so far indicate an acceptable risk/benefit profile at these planned doses. The long-term safety profile of dapagliflozin is not currently known.

4. RECENTLY COMPLETED STUDIES

An additional phase 2b study (MB102009) has been completed and two Phase 3 studies (MB102013 and MB 102 014) short-term treatment periods have been concluded but not yet reported. Thus, the results from these studies are preliminary.

MB102009 was conducted in subjects who were not controlled on combination antihyperglycemic therapy with metformin and/or TZD and subcutaneous insulin. A total of 75 subjects were treated with dapagliflozin (10 or 20 mg) or placebo plus metformin and/or TZD and insulin for a treatment period of 12 weeks. The safety data from this recently completed study are in line with data from previously reported studies and indicate that the combination of dapagliflozin (in doses of 10 mg and 20 mg) and insulin is safe and well tolerated. Please note that 10 mg is the top dose of dapagliflozin being tested in phase III program.

Study MB102013 is a Phase III study evaluating the efficacy and safety of dapagliflozin compared to placebo in drug- naïve type 2 diabetic patients. The short-term treatment period was 24 weeks and is followed by an ongoing 78-week double-blind extension period. The main cohort of the study has 7 arms (placebo, 2.5, 5 and 10 mg dapagliflozin with morning (am) dosing and 2.5, 5 and 10 mg dapagliflozin with evening (pm) dosing), including patients with baseline HbA1c $\geq$ 7.0- $\leq$10.0%. A statistically significant effect of dapagliflozin on HbA1c after a 24-week treatment period was observed for the 5 and 10 mg dapagliflozin groups versus placebo. Overall, the safety profile was consistent with previous studies conducted with dapagliflozin. ALT elevations >3xULN were observed in 6/402 (1.5%) dapagliflozin patients including one subject with ALT >5xULN compared to 0/75 in the placebo group. All of these elevations were transient and none was associated with total bilirubin >1.5 X ULN or hepatic failure. The importance of this is unclear and requires further data to elucidate.

Study MB102014 is a Phase III study evaluating the efficacy and safety of dapagliflozin plus metformin compared to placebo plus metformin in type 2 diabetic patients with baseline HbA1c of 7-10%. The short-term period was 24 weeks followed by an ongoing 78-week double-blind extension period. The study includes 3 dapagliflozin + metformin treatment groups; 2.5, 5 and 10 mg. A statistically significant effect of dapagliflozin on HbA1c after a

24-week treatment period was observed for all dapagliflozin + metformin dose groups (2.5, 5 and 10 mg) versus placebo + metformin. Overall, the safety profile was consistent with previous studies conducted with dapagliflozin. ALT elevations >3xULN were observed in 3/405 (0.7%) dapagliflozin + metformin patients including one subject with ALT >5xULN compared to 0/136 in the placebo group. All of these elevations were transient and none was associated with total bilirubin >1.5 X ULN or hepatic failure. The importance of this is unclear and requires further data to elucidate. In the completed phase 1 and phase 2 diabetes studies to date, more than 350 healthy subjects have received at least 1 dose of dapagliflozin and more than 300 type 2 diabetic patients have received dapagliflozin for up to 3 months in completed studies. Additional 892 patients with type 2 diabetes have received dapagliflozin in the not yet reported studies MB 102013 and MB 102014 for up to 6 months

Thus, taking into account safety data from recently completed studies and two not yet reported studies, the overall evaluation of pharmacokinetics, efficacy and safety for dapagliflozin continues to support further clinical development of this product in patients.