Clinical Study Protocol

Drug Substance	dapagliflozin
Study Code	D1693C00005
Edition Number	1

A 24-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled, International Phase III Study with a 28-week Extension Period to Evaluate the Safety and Efficacy of Dapagliflozin 10mg once daily in Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on a background combination of Metformin and Sulfonylurea

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

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

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

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

AstraZeneca

PROTOCOL SYNOPSIS

A 24-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled, International Phase III Study with a 28-week Extension Period to Evaluate the Safety and Efficacy of Dapagliflozin 10 mg once daily in Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on a background combination of Metformin and Sulfonylurea

International Co-ordinating Investigator or Principal Investigator or National Co-ordinating Investigator

Study centre(s) and number of patients planned

This international study will be conducted at approximately 50 study centres. A target of 216 patients will be randomised with estimated enrolment period of 9 months.

Study period		Phase of development
Estimated date of first patient enrolled	Q4 2011	IIIb
Estimated date of last patient completed	Q3 2013	

Objectives

Primary Objective

The primary objective of this study is to compare the change from baseline in haemoglobin A1c (HbA1c) to week 24 between dapagliflozin 10 mg in combination with metformin and sulfonylurea and placebo in combination with metformin and sulfonylurea.

Key Secondary Objectives

- To compare the change from baseline in fasting plasma glucose (FPG) to week 24 between dapagliflozin and placebo.
- To compare the change from baseline in total body weight to week 24 between dapagliflozin and placebo.

- To compare the proportion of patients achieving a therapeutic glycaemic response, defined as HbA1c <7.0%, at week 24 between dapagliflozin and placebo.

- To compare the change from baseline in seated systolic blood pressure (SBP) to week 8 between dapagliflozin and placebo.

Other Secondary Objectives

Efficacy

- To compare dapagliflozin and placebo on the following additional variables: glycaemic control, blood pressure, weight, waist circumference, lipid metabolism, insulin metabolism and patient reported outcomes over 24 weeks of treatment.

Exploratory objectives

- To compare the effects of dapagliflozin and placebo on weight related quality of life as measured by SHIELD-WQ-9 at week 24.

- To compare the effects of dapagliflozin and placebo on weight related quality of life as measured by IWQOL-Lite at week 24.

Safety objectives

- To evaluate the safety and tolerability of dapagliflozin by assessment of Adverse Events (AE), including adjudication of CV events, laboratory values, electrocardiogram, pulse, blood pressure, hypoglycaemic events and physical examination findings.

Genetics objectives

- To collect and store DNA for future exploratory research into genes that may influence response, eg, distribution, safety, tolerability and efficacy of treatment and genetic factors that may influence susceptibility to type 2 diabetes and/or associated conditions. The purpose of the genetic research is to enable future exploratory pharmacogenetic research studies.

Objectives of the 28-week site- and patient-blinded extension period

- To assess the safety and tolerability of dapagliflozin over 52 weeks of treatment.

- To assess the maintenance of efficacy of dapagliflozin versus placebo over 52 weeks of treatment.

- To compare scores of change in treatment satisfaction, individual satisfaction and perceived frequency of hyper/hypoglycaemia using the Diabetes Treatment Satisfaction Questionnaire change (DTSQc) observed with dapagliflozin versus placebo at week 52.

- To assess HRQL- (EQ-5D-3L), weight related quality of life (SHIELD-WQ-9, IWQOL-Lite) and treatment satisfaction (DTSQc and DTSQs) over 52 weeks of treatment.

Study design

This is a 24-week randomised, double-blind, placebo-controlled, 2-arm, parallel-group, multicentre study with an 8-week placebo lead-in period, and a 28-week site- and patient-blinded extension period.

Target patient population

Men and women with type 2 diabetes who:

- are ≥18 years old, the upper age limit should be based on local metformin label restrictions
- have inadequate glycaemic control, defined as:
  - HbA1c of ≥7.7 to ≤11.0% at enrolment
  - HbA1c of ≥7.0 to ≤10.5% at randomisation

are on a stable dose combination therapy of metformin ≥1500mg/day and maximum tolerated dose which must be at least half maximum dose of sulfonylurea for at least 8 weeks prior to enrolment.

Investigational product, dosage and mode of administration

Dapagliflozin 10 mg tablets, administered orally once daily for the 24-week double-blind treatment period and the 28-week site- and patient-blinded extension period.

Comparator, dosage and mode of administration

Matching placebo for dapagliflozin 10 mg administered orally once daily for the 8-week placebo lead-in period, the 24-week double-blind treatment period and the 28-week site- and patient-blinded extension period.

Additional drug, dosage and mode of administration

Throughout the course of the study patients will remain on their background anti-hyperglycaemic medications, which will be a stable dose combination therapy of metformin ≥1500mg/day and maximum tolerated dose, which must be at least half maximum dose of sulfonylurea. Therapy is given according to the approved product label.

Open-label rescue therapy with Dipeptidyl-Peptidase-4 Inhibitor (DPP-4 inhibitor) as first line therapy or insulin as second line therapy in case that after 6 months of DPP-4 inhibitors treatment the glycaemic control is still inadequate or DPP-4 inhibitors are poorly tolerated or contraindicated. Insulin should also be used in case that DPP-4 inhibitors are not available on

the market in the particular country or that its usage is not accordance to local practice, or in the opinion of the Investigator, insulin treatment will be more beneficial to the patient.

Rescue therapy will be given according to local standards of care, the approved product label in the applicable countries and according to national and international diabetes guidelines. Rescue therapy will be prescribed by the Investigator.

Duration of treatment

Following initial screening and the 1-week enrolment period, patients will enter the 8-week placebo lead-in period. Then they will be randomised to the 24-week double-blind treatment period followed by the 28-week site- and patient-blinded extension period. After either completion of the randomised treatment periods or discontinuation from treatment, patients will enter a 3-week follow-up period.

The total planned study duration including the follow-up period will be 64 weeks.

Outcome variable(s):

Efficacy

Primary outcome variable:

- Change in HbA1c from baseline to week 24.

Key secondary outcome variables:

- Change in fasting plasma glucose (FPG) from baseline to week 24.
- Change in total body weight from baseline to week 24.
- Proportion of patients achieving a therapeutic glycaemic response, defined as HbA1c <7.0% at week 24.
- Change in seated systolic blood pressure (SBP) from baseline to week 8.

Other secondary outcome variables:

- Proportion of patients discontinued for lack of efficacy or rescued for failing to maintain FPG below pre-specified rescue criteria at weeks 4, 8, 16 and 24.
- Change in HbA1c in patients with baseline HbA1c ≥8.0% from baseline to week 24.
- Change in HbA1c in patients with baseline HbA1c ≥9.0% from baseline to week 24.
- Change in FPG from baseline to week 8.
- Change in seated SBP from baseline to week 24.

- Proportion of patients with seated blood pressure of <130/80 mmHg at week 24 in patients with baseline elevated blood pressure (baseline SBP ≥130 mmHg and/or baseline diastolic blood pressure (DBP) ≥80 mmHg).

- Percent change in fasting lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides) from baseline to week 24.

- Change in HOMA-2, HOMA-IR from baseline to week 24.

- Change in insulin, proinsulin and C-peptide values from baseline to week 24.

- Change in waist circumference from baseline to week 24.

- Effect of dapagliflozin versus placebo from baseline to week 24 on health-related quality of life (HRQL) as measured by Euro quality of life 5 Dimensions 3 levels (EQ-5D-3L).

- Scores of treatment satisfaction, individual satisfaction and perceived frequency of hyper/hypoglycaemia as measured by Diabetes Treatment Satisfaction Questionnaire status (DTSQs) at baseline, week 24 and at week 52.

- Scores of change of treatment satisfaction, individual satisfaction and perceived frequency of hyper/hypoglycaemia using the Diabetes Treatment Satisfaction Questionnaire change (DTSQc) observed with dapagliflozin versus placebo at week 52.

- To assess HRQL- (EQ-5D-3L), weight related quality of life (SHIELD-WQ-9, IWQOL-Lite) and treatment satisfaction (DTSQc and DTSQs) over 52 weeks of treatment.

Exploratory

- Effects of dapagliflozin and placebo on weight related quality of life as measured by SHIELD-WQ-9.

- Effects of dapagliflozin and placebo on weight related quality of life as measured by IWQOL-Lite.

Safety

- AEs, including adjudication of CV events, laboratory values, electrocardiogram, pulse, blood pressure, hypoglycaemic events and physical examination findings.

Statistical methods

The primary objective of this study is to assess the efficacy of dapagliflozin versus placebo in terms of the primary efficacy variable change in HbA1c from baseline to week 24. The

primary efficacy variable, change in HbA1c from baseline to week 24, will be analysed by an analysis of covariance (ANCOVA) model, including terms for treatment group and baseline covariate. The ANCOVA model will be used to derive a least squares estimate of the treatment difference with 95% confidence interval and corresponding two-sided p-value. Further, two-sided 95% confidence intervals for the mean change within each treatment group will be calculated. For subjects who discontinue prior to week 24 or start rescue medication during, or prior to, week 24, the last post-baseline measurement prior to or on the date of the first dose of rescue medication will be used for calculating efficacy endpoints. Comparisons of the dapagliflozin treatment groups versus placebo in proportions will be performed using the methodology of Zhang, Tsiatis and Davidian and Tsiatis, Davidian, Zhang and Lu with adjustment for baseline value.

A hierarchical closed testing procedure will be used to control the Type I error rate across the primary and key secondary objectives. If the primary endpoint is statistically significant, key secondary variables will be tested in the order presented within this protocol. For all other variables, nominal p-values will be reported without significance testing.

Efficacy will be evaluated using the full analysis set. The safety analysis set will be used in all summaries of safety data.

To detect a difference of 0.5% between dapagliflozin versus placebo for change in HbA1c from baseline to week 24, assuming a standard deviation =1.1%, 103 evaluable patients (full analysis set) for each treatment group would provide 90% power at a significance level =0.050. Assuming that 5% of the patients will not be evaluable in the full analysis set, 108 patients per treatment group (216 patients total) are planned for randomisation.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ADA	American Diabetes Association
AE	Adverse Event (see definition in Section 6.4.1)
ANCOVA	Analysis of Covariance
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body Mass Index
CDC	Centres for Disease Control and Prevention
CEC	Clinical Event Committee
CK	Creatine Kinase
CV	Cardiovascular
DAE	Discontinuation of Investigational Product due to Adverse Event
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
DPP-4	Dipeptidyl-peptidase-4
DTSQs	Diabetes Treatment Satisfaction Questionnaire status
DTSQc	Diabetes Treatment Satisfaction Questionnaire change
ECG	Electrocardiogram
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EQ-5D-3L	EuroQol 5 Dimension questionnaire 3 levels
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
HbA1c	Glycosylated haemoglobin A1c
HCG	Human Chorionic Gonadotropin
HOMA	Homeostatic Model Assessment
HRQL	Health-Related Quality of Life
IATA	The Air Transport Association

Abbreviation or special term	Explanation
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.
IP	Investigational Product
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
IWQOL-Lite	Impact of Weight on Quality of Life Questionnaire-Lite
LOCF	Last Observation Carried Forward
LSLV	Last Subject Last Visit
MDRD	Modification of Diet in Renal Disease equation
MODY	Maturity-onset diabetes of Young
NYHA	New York Heart Association (NYHA) Classification
OAE	Other Significant Adverse Event (see definition in Section 11.2.2)
PGx	Pharmacogenetic research
PRO	Patient reported outcome
QD	Once Daily
SAE	Serious Adverse Event (see definition in Section 6.4.2).
SBP	Systolic blood pressure
SHIELD-WQ-9	Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes Weight Questionnaire 9
SU	Sulphonylureas
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
ULN	Upper limit of normal
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background

Type 2 diabetes mellitus (T2DM) is characterised by beta-cell dysfunction and peripheral insulin resistance leading to hyperglycaemia (Matthaei et al 2000, Meier and Butler 2005). Chronic hyperglycaemia is associated with the development of both macrovascular (myocardial infarction, stroke, peripheral arterial disease), and microvascular (nephropathy, retinopathy, neuropathy) complications (UKPDS group 1998). Current treatment regimens aiming to reduce glucose levels in patients with type 2 diabetes have focused on the stimulation of insulin secretion (eg, sulphonylureas, glinides, GLP-1 analogs, DPP-4 inhibitors), improvement in insulin sensitivity (eg, metformin, thiazolidinediones), inhibition of intestinal glucose absorption (eg, alpha-glucosidase inhibitor), or the replacement of insulin. However, the limited efficacy of currently available anti-hyperglycaemic agents, as well as associated side effects (eg, hypoglycaemia, oedema, weight gain, etc.) clearly underline the need for novel anti-hyperglycaemic treatment strategies (ACCORD 2008, ADA 2009, Koro et al 2004). In addition, the majority of patients with type 2 diabetes require more than one anti-hyperglycaemic agent to achieve glycaemic targets (Nathan 2006).

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

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

Dapagliflozin has been designed as a potent and selective inhibitor of SGLT2. This compound is being developed as an oral 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 orally once daily. In this study, dapagliflozin treatment led to significant and clinically relevant reductions in fasting plasma glucose (FPG), postprandial glucose (PPG), and haemoglobin A1c (HbA1c) levels throughout the entire dose range, and was associated with weight loss. Overall, these findings supported the further development of dapagliflozin and the implementation of pivotal studies of sufficient duration to more fully characterize the safety and efficacy of the 2.5, 5, and 10 mg doses. The Phase III program is meanwhile completed and the file is submitted for approval and under review at the moment.

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

1.2 Research hypothesis

After 24 weeks of treatment, there will be a greater mean reduction from baseline in HbA1c achieved with dapagliflozin 10 mg compared with placebo in patients with T2DM who have inadequate glycaemic control on metformin and sulfonylurea.

1.3 Rationale for conducting this study

This is a Phase IIIb study that will be performed as part of the clinical development program for dapagliflozin for the treatment of type 2 diabetes. This study intends to compare dapagliflozin with placebo in patients with type 2 diabetes, who are inadequately controlled on metformin and sulfonylurea.

Metformin is a biguanide; its major effect is to decrease hepatic glucose output and lower fasting glucose. It is recommended as the initial pharmacological therapy in both the US and the EU because of its glycaemic efficacy, weight neutrality, low risk of hypoglycaemia, good tolerability and relatively low cost (Nathan et al 2008).

Sulfonylureas (SU) are quite commonly used as second line therapy in patients inadequately controlled with metformin. Sulfonylurea therapy is however associated with side effects such as increased incidence of hypoglycaemia and weight gain.

Since many patients with type 2 diabetes do not reach glycaemic goals with dual agent therapy, many will require an additional agent with an alternate mechanism of action.

A usual next step would be the initiation of insulin treatment. 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 anti-hyperglycaemic treatment, by increasing cardiovascular risk and reducing the ability to exercise.

Dapagliflozin when added to ongoing metformin or sulfonylurea monotherapy showed improvement in glycaemic parameters as well as weight reduction.

Dapagliflozin might provide additional improvement of metabolic control of type 2 diabetes and potentially attenuate SU-related weight gain or produce weight loss when added to ongoing SU therapy.

1.4 Benefit/risk and ethical assessment

Risk category

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

Potential risks

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

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

In a pooled analysis of all phase 2b and 3 studies in the dapagliflozin development program there was an imbalance in the frequency of subjects who had an SAE of breast cancer or bladder cancer. The significance of these findings is not clear at present; however a causal relationship with the use of dapagliflozin seems unlikely.

Overall there were no imbalances of liver function test parameters in Phase III studies. One subject on dapagliflozin 5 mg had an SAE reported as drug-induced acute hepatitis and was later also diagnosed with probable autoimmune hepatitis.

Due to the diuretic effect of dapagliflozin, volume depletion (dehydration, hypovolaemia and/or hypotension) is a potential concern. In the clinical program, from which subjects who in the judgment of investigator may be at risk of dehydration or volume depletion were excluded, very few serious events related to volume depletion were reported and they were equally distributed between dapagliflozin and placebo groups. In the limited experience in subjects with T2DM on concomitant loop diuretics, events related to volume depletion were more common in the dapagliflozin groups compared with the placebo group. Temporary interruption of dapagliflozin should be considered for subjects who develop volume depletion.

In addition, all patients in this study will continue taking metformin and sulfonylurea as background medications. These drugs are a widely used anti-hyperglycaemic treatment and will be prescribed according to the approved label.

Thus, the benefits and risks associated with the background medication and comparator treatment are well established and presented in their respective approved prescribing information. No study procedure will put patients at a risk beyond those ordinarily encountered during the performance of routine medical examinations or routine tests.

Protection against risks

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

Potential benefits to patients

All patients will continue taking their active background anti-hyperglycaemic therapy; however, a direct benefit from randomised treatment cannot be assured as one half of patients will receive placebo, and the efficacy of dapagliflozin in this clinical setting is assumed but has yet to be established. In this study, the dose of dapagliflozin 10 mg once daily (QD) was chosen to provide efficacy in reducing hyperglycaemia while mitigating the potential for AEs, based on previous clinical experience. In addition, dapagliflozin is expected to help decrease body weight (or prevent weight gain) as well as help lower blood pressure especially in patients with elevated baseline blood pressure. Patients are also expected to receive some benefit in the form of increased medical care/attention when participating in study procedures, which includes at least 12 clinic visits with at least 11 physical examinations over the 64-week study. Patients will also receive counselling on dietary and life-style modifications. It is commonly observed that even patients receiving placebo in diabetes studies show some

improvement in glycaemic control, likely due to their increased compliance to dietary and life-style counselling while they are participating in a clinical study.

Informed consent and alternatives to participation

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

Conclusion

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

For additional details on benefits and risk, please see the Investigator's Brochure.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to compare the change from baseline in haemoglobin A1c (HbA1c) to week 24 between dapagliflozin 10 mg in combination with metformin and sulfonylurea and placebo in combination with metformin and sulfonylurea.

2.2 Secondary objectives

2.2.1 Key Secondary Objectives

- To compare the change from baseline in fasting plasma glucose (FPG) to week 24 between dapagliflozin and placebo.
- To compare the change from baseline in total body weight to week 24 between dapagliflozin and placebo.
- To compare the proportion of patients achieving a therapeutic glycaemic response, defined as HbA1c <7.0%, at week 24 between dapagliflozin and placebo.
- To compare the change from baseline in seated systolic blood pressure (SBP) to week 8 between dapagliflozin and placebo.

2.2.2 Other Secondary Objectives

- To compare the proportion of patients discontinued for lack of efficacy or rescued for failing to maintain FPG below pre-specified rescue criteria at weeks 4, 8, 16 and 24 between dapagliflozin and placebo.
- To compare the change from baseline in HbA1c to week 24 between dapagliflozin and placebo in patients with baseline HbA1c ≥8.0 %.
- To compare the change from baseline in HbA1c to week 24 between dapagliflozin and placebo in patients with baseline HbA1c ≥9.0%.
- To compare the change from baseline in FPG to week 8 between dapagliflozin and placebo.
- To compare the change from baseline in seated SBP to week 24 between dapagliflozin and placebo.
- To compare the proportion of patients who achieve seated BP of <130/80 mmHg at week 24 in patients with baseline elevated blood pressure (BP) (baseline SBP ≥130 mmHg and/or baseline diastolic blood pressure (DBP) ≥80mmHg).
- To compare the percent change from baseline in fasting lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides) to week 24 between dapagliflozin and placebo.
- To compare the change from baseline in HOMA-2, HOMA-IR to week 24 between dapagliflozin and placebo.
- To compare the change from baseline in insulin, proinsulin and C-peptide values to week 24 between dapagliflozin and placebo.
- To compare the change from baseline in waist circumference to week 24 between dapagliflozin and placebo.
- To compare the effect of dapagliflozin versus placebo from baseline to week 24 on health-related quality of life (HRQL) as measured by Euro quality of life 5 Dimensions 3 Levels (EQ-5D-3L).
- To compare scores of treatment satisfaction, individual satisfaction and perceived frequency of hyper/hypoglycaemia as measured by Diabetes Treatment Satisfaction Questionnaire status (DTSQs) observed with dapagliflozin versus placebo from baseline to week 24 and week 52.

2.2.3 Exploratory objective

- To compare the effects of dapagliflozin and placebo on weight related quality of life as measured by SHIELD-WQ-9 at week 24.

- To compare the effects of dapagliflozin and placebo on weight related quality of life as measured by IWQOL-Lite at week 24.

2.3 Safety objective

To evaluate the safety and tolerability of dapagliflozin by assessment of adverse events (AE), including CV events, laboratory values, electrocardiogram, pulse, blood pressure, hypoglycaemic events and physical examination findings.

2.4 Pharmacogenetic Objective

To collect and store DNA for future exploratory research into genes that may influence response, eg, distribution, safety, tolerability and efficacy of treatment and genetic factors that may influence susceptibility to type 2 diabetes and/or associated conditions. The purpose of the genetic research is to enable future exploratory pharmacogenetic research studies.

2.5 Objectives for the 28-week site- and patient-blinded extension period

- To assess the safety and tolerability of dapagliflozin over 52 weeks of treatment.

- To assess the maintenance of efficacy of dapagliflozin versus placebo over 52 weeks of treatment.

- To compare scores of change in treatment satisfaction, individual satisfaction and perceived frequency of hyper/hypoglycaemia using the Diabetes Treatment Satisfaction Questionnaire change (DTSQc) observed with dapagliflozin versus placebo at week 52.

- To assess HRQL- (EQ-5D-3L), weight related quality of life (SHIELD-WQ-9, IWQOL-Lite) and treatment satisfaction (DTSQc and DTSQs) over 52 weeks of treatment.

3. STUDY PLAN AND PROCEDURES

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

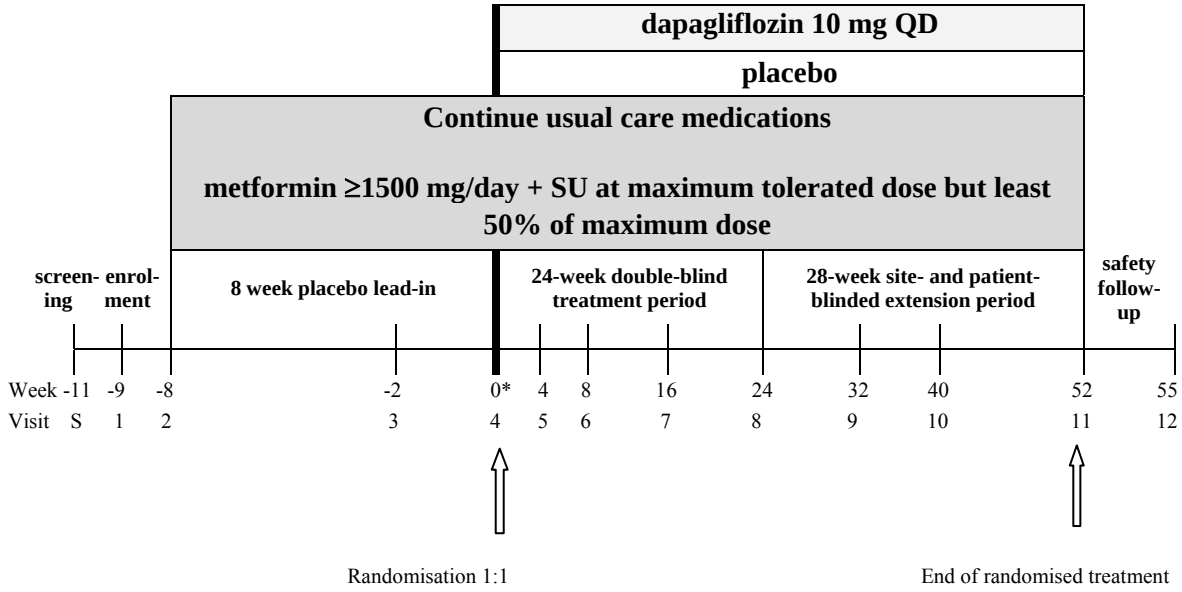
3.1 Overall study design and flow chart

This is a 24-week, international, multicentre, randomised, double-blind, parallel-group, placebo-controlled, Phase IIIb study with a 28-week site- and patient- blinded extension

period to evaluate the efficacy and safety of dapagliflozin 10 mg daily in patients with type 2 diabetes. Dapagliflozin or placebo will be added to the therapy of patients who have inadequate glycaemic control on combination of metformin and sulfonylurea.

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

Figure 1 Study flow chart



* "Week 0" means first day of randomised treatment period and should be used as reference point for calculation of dates for the next visits

Before entry into the study, patients will be screened for an HbA1c level. Patients who meet the HbA1c inclusion criterion will be enrolled and examined for all inclusion and exclusion criteria. Patients will continue to take their anti-hyperglycaemic medications and on next visit will be re-examined for inclusion and exclusion criteria and will enter a 8-week placebo lead-in period. During the lead-in period, laboratory test results will be obtained, patient compliance will be evaluated, and concomitant anti-hypertensive medication adjusted if needed. Patients will then be randomised to the 24-week double-blind treatment period followed by the 28-week site-and patient-blinded extension period. After either completion of the treatment periods or discontinuation from treatment, patients will enter the 3-week follow-up period. The follow-up visit provides the opportunity to further evaluate changes in physical signs, symptoms or laboratory parameters that may be related to dapagliflozin. The total planned study duration from Visit 1 to the safety follow-up (Visit 12) will be 64 weeks.

This international study will be conducted at approximately 50 study centres. A target of 216 patients will be randomised with estimated enrolment period of 9 months. Recruitment will be competitive between sites and countries. Enrolment will be stopped once enough patients are screened to provide the globally projected number of randomised patients. Centres may be discontinued from the study if recruitment rates are poor and new centres may be added if necessary to achieve recruitment goals.

Study Periods

3.1.1 Screening Visit (Visit S)

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

Potentially eligible patients must perform a screening visit (Visit S) within 14 days prior to Visit 1. A Screening Informed Consent Form will be provided by AstraZeneca to all the centres, and implemented locally based on all applicable regulatory requirements and laws. The written screening informed consent must be obtained prior to conducting screening activities.

Patients will be allowed to proceed to Visit 1 only if they meet HbA1c inclusion criteria (Inclusion criterion 5, Section 4.1).

Patients are not allowed to be re-screened.

All patients who are screened should be listed on a patient screening log. See also Section 6.1.

3.1.2 Enrolment Visit (Visit 1, week –9)

Eligible patients will provide informed consent, undergo assessment of all applicable inclusion and exclusion criteria, and submit laboratory samples. Patients will continue their current oral anti-hyperglycaemic therapy during this time. Diet and lifestyle advice will be given according to clinical practice.

Successfully screened patients may not be enrolled if sufficient number of patients has been enrolled in the study.

3.1.3 Placebo lead-in period (Visit 2 to 4, week -8 to week 0)

Visit 2 can be performed as a telephone visit if it is clear before the scheduled visit that a patient is not eligible based on the laboratory results from Visit 1 (see criteria in Section 4) and that his or her participation in the study should be terminated.

At Visit 2 (week –8) patients will undergo re-assessment of inclusion/exclusion criteria. The eligible patients will be given placebo in a single-blind fashion (blind to the patient only). At Visit 3 (week –2) central laboratory results from samples collected at Visit 2 will be checked to confirm patient's eligibility.

The doses of metformin and sulfonylurea will remain stable throughout the study, with exception described in Section 3.1.4 and 3.1.7.

A glucometer and a patient diary will also be provided to patients and they will be instructed to monitor their fasting plasma glucose (FPG) at least every second day and to enter the results into the patient diary. Investigators may instruct patients to monitor their FPG more

often, according to their local treatment guidelines or clinical judgement. For FPG monitoring procedures and assessment of hypoglycaemic events please refer to Section 6.4.9.1.

Diet and lifestyle advice will be reinforced at each visit according to clinical practice.

Adjustment of anti-hypertensive medication

During the placebo lead-in period, concomitant anti-hypertensive medications should be adjusted in patients with seated systolic BP ≥160 mmHg or seated diastolic BP ≥100 mmHg, without adding new anti-hypertensive agents to the patient's regimen. Only those patients with seated systolic BP <160 mmHg and diastolic BP <100 mmHg at the end of placebo lead-in period will be randomised.

3.1.4 Randomisation and 24-week Double-blind Treatment Period (Visits 4-8, week 0 to week 24)

Randomisation visit (Visit 4)

Eligible patients will be randomised at Visit 4 (week 0, baseline) in a 1:1 ratio to receive either dapagliflozin 10 mg or placebo. Laboratory results from V3 will be used to assess patient's eligibility.

24-week Double-blind Treatment Period (Visits 4-8)

After the randomisation visit, patients will have study visits at four- to eight-week intervals until the end of the 24-week double-blind treatment period (Visit 8, week 24).

Patients will continue to monitor their FPG levels at least every second day and will continue to enter the results into the patient diary. Investigators may instruct patients to monitor their FPG more often, according to their local treatment guidelines or clinical judgement. Hypoglycaemic events should also be entered into the patient diary. For FPG monitoring procedures and assessment of hypoglycaemic events please refer to Section 6.4.9.1.

Diet and lifestyle advice will be reinforced at each visit during the double-blind treatment period, according to clinical practice.

The need for initiation of rescue therapy during 24-week double-blind treatment period will be assessed based on criteria in Table 1. Procedures for rescue are described in Section 3.1.7.

Table 1 Criteria for initiation of rescue therapy during the 24-week double-blind treatment period

Period	Central Laboratory FPG
From week 4 (Visit 5) to week 16 (Visit 7) including day of Visit 5 and Visit 7	FPG >240 mg/dL (13.2 mmol/l)
From week 16 (Visit 7) to week 24 (Visit 8) excluding day of Visit 7 including day of Visit 8	FPG >200 mg/dL (11.1 mmol/l)

Adjustment of background anti-hyperglycaemic medication

Metformin cannot be down titrated during the treatment period.

Sulfonylurea can be down titrated only once during the treatment period to mitigate recurrent hypoglycaemic events at the discretion of the investigator.

No up-titration of metformin and sulfonylurea during the treatment period is allowed.

Adjustment of anti-hypertensive medication

Background anti-hypertensive medications should not be increased or decreased between weeks 0-8 (Visits 4, 5 and 6). Exceptions to this rule are:

- Patients with confirmed SBP ≥160 mmHg or DBP ≥100 mmHg on or after week 4 should return for a follow-up visit within 1 week. If the BP is still elevated, changes in background blood pressure medication should be made.
- Blood pressure medication may be decreased if in the investigator's judgement the patient has symptomatic hypotension or has documented orthostatic hypotension during a study visit.

After week 8, changes in anti-hypertensive medication may be made as needed for appropriate blood pressure management. All medication changes, including dose modifications, should be recorded in the Medication module of the eCRF.

3.1.5 28-week site- and patient-blinded Extension period (Visits 8-11, week 24 to week 52)

After the 24-week randomised treatment period, patients will continue the treatment to which they were randomised and enter the 28-week site-and patient-blinded extension period. Patients will return for study visits every 8-12 weeks during this period.

Patients will monitor their FPG levels at least once a week and will continue to enter the results into the patient diary. For FPG monitoring procedures and assessment of hypoglycaemic events please refer to Section 6.4.9.1.

Diet and lifestyle advice will be reinforced at each visit during this period, according to clinical practice.

The need for initiation of rescue therapy during 28-week site- and patient-blinded extension treatment period will be assessed based on criteria in Table 2. Procedures for rescue are described in Section 3.1.7.

Table 2 Criteria for initiation of rescue therapy during the 28-week site - and patient - blinded extension period

Period	Central Laboratory HbA1c
From week 24 (Visit 8) to week 52 (Visit 11) excluding day of Visit 8 and Visit 11	HbA1c >8.0%

Patients will discontinue investigational product at the end of this treatment period (Visit 11, week 52).

Visit 11 (End of Treatment Visit, week 52)

At week 52 patients will come to the centre for the End of Treatment Visit. The last intake of investigational product will be in the morning on day before the End of Treatment Visit.

Patients who prematurely discontinue study treatment should return and complete the procedures described for the End of Treatment Visit as soon as possible after the last intake of investigational product.

3.1.6 Follow-up period (Visit 12, week 55)

Patients who complete the scheduled study treatment and those who prematurely discontinued study treatment will have the Follow-up Visit (Visit 12) 3 weeks after the last intake of investigational product. During this time patients can be treated as necessary without any further protocol restrictions.

3.1.7 Rescue therapy

Patients with inadequate glycaemic control based on progressively stricter glycaemic criteria will remain in the study but will receive open-label rescue therapy in addition to their randomised double-blind investigational product. To determine if rescue therapy is required, glycaemic parameters will be assessed at the central laboratory at each visit from Visit 5 to Visit 10.

If patient's self-monitored glucose is above the upper limit:

- defined for each period between Visit 5 and Visit 8 in Table 1,
- after Visit 8 above 200mg/dL (11.1 mmol/l),

the patient should repeat the self-measurement on the same day. If the second result is also above the limit the patient should return to the study site within 1 week to have the FPG or HbA1c (depending on study period) measured in the central laboratory.

Criteria for initiation of rescue therapy are specified

- in Table 1 for the period between visits 5 to 8,
- in Table 2 for the period between visits 8 to 11.

When Investigator receives central laboratory FPG result exceeding limits mentioned above from samples taken at:

- Visit 5 to Visit 8:
  - when FPG entries in patient's diary collected between study visits do not confirm excided levels of fasting plasma glucose, it is Investigator's decision either to invite patient for retest (within 5 working days) or schedule a Rescue Visit
  - when FPG entries in patient's diary collected between study visits confirm high levels of fasting plasma glucose patient should be scheduled directly for a Rescue Visit

When a laboratory result indicates that a patient meets the rescue criteria, a Rescue Visit should be scheduled within 5 workdays. Tests and examinations to be performed at a Rescue Visit are shown in Table 3. Patients will continue their study medication as before and will receive open-label rescue therapy in addition to their randomised double-blind investigational product.

- Open label DPP4-inibitor should be considered as first choice rescue therapy. The dosing should be in accordance with the manufacturer's recommendations and clinical practise.
- Open label insulin should be considered in case that after 6 months of DPP4-inibitors treatment the glycaemia control is still inadequate or DPP4-inhibitors are poorly tolerated. Insulin should also be used in case that DPP4-inibitors are not available on the market in the particular country or its usage is not accordance to local practice or in the opinion of the Investigator Insulin treatment will be more beneficial to the patient.
- The regimen and dosing should be in accordance with the manufacturer's recommendations and clinical practise.

All Rescue therapy will be prescribed by the investigator in accordance with local standards of care and the approved product label in the applicable country.

Investigators are blinded to patients' FPG and HbA1c results after randomisation. Once the patient meets rescue criteria, the exact value is reported by central laboratory to the study site. The central laboratory FPG and HbA1c values measured after the initiation of the rescue medication will be reported to the investigator to ensure proper follow-up of the rescued patient.

Rescued patients will be instructed to monitor their FPG daily, especially in case of insulin addition, and to enter the results into the patient diary. Investigators may instruct patients to monitor their FPG more often, according to their local treatment guidelines or clinical judgement. The patients should be encouraged to always self-monitor plasma glucose in case of symptoms suggestive of hypoglycaemia and to register any signs of hypoglycaemia in the supplied diary.

Patients who receive oral anti-hyperglycaemic rescue therapy only and have a central laboratory HbA1c >8% for 6 months despite a maximum tolerated dose of oral anti-hyperglycaemic rescue therapy and the possibility of insulin treatment has been evaluated will be discontinued from the study. For patients receiving insulin as rescue medication an up-titration step should be considered instead of study discontinuation.

Insulin as rescue therapy can be up-titrated by the investigator as needed to obtain glycaemic control. Up-titration of the insulin dose is recommended if central laboratory HbA1c >8%. Change in insulin dose is not a reason for discontinuation from the study.

Table 3 Study Plan

	Screening	Enrolment	Placebo lead-in		24-week double-blind treatment period					28-week site- and patient-blinded extension period			Follow-up	Rescue
Visit	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**[c)]	**12 FU**	**R**
Week	**-11**	**-9**	**-8**	**-2**	**0**	**4**	**8**	**16**	**24**	**32**	**40**	**52**	**55**	
Visit window (days) [a)]		(0)[b)]	(±3)	(±3)	(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(+7)	
Screening informed consent and blood sample for HbA1c	X													
Informed consent		X												
Demography and medical history		X												
Inclusion / Exclusion criteria		X	X [d)]	X [d)]	X									
Randomisation					X									
Brief physical examination			X			X	X	X		X	X			
Complete physical examination		X			X				X			X	X	X

	Screening	Enrolment	Placebo lead-in		24-week double-blind treatment period					28-week site- and patient-blinded extension period			Follow-up	Rescue
Visit	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**[c]	**12 FU**	**R**
Week	**-11**	**-9**	**-8**	**-2**	**0**	**4**	**8**	**16**	**24**	**32**	**40**	**52**	**55**	
Vital signs (BP, pulse)		X	X	X	X	X	X	X	X	X	X	X	X	X
Orthostatic BP, pulse					X	X	X	X	X			X	X	X
Weight		X	X	X	X	X	X	X	X	X	X	X	X	X
Height		X												
Waist circumference		X			X				X			X		X
12-lead ECG		X			X				X			X	X	X
Concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments [e]		X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test [f]		X	X	X	X	X	X	X	X	X	X	X	X	X
SAEs		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
Dispense investigational product via IWRS/IVRS			X		X	X	X	X	X	X	X			

	Screening	Enrolment	Placebo lead-in		24-week double-blind treatment period					28-week site- and patient-blinded extension period			Follow-up	Rescue
Visit	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**[c)]	**12 FU**	**R**
Week	**-11**	**-9**	**-8**	**-2**	**0**	**4**	**8**	**16**	**24**	**32**	**40**	**52**	**55**	
Drug accountability				X	X	X	X	X	X	X	X	X		
Diet and lifestyle advice		X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense glucometer and/or supplies; provide instructions			X	X	X	X	X	X	X	X	X			X
Dispense patient diary			X	X	X	X	X	X	X	X	X			X
Patient diary review for glucometer values/ hypoglycaemic events [g)]				X	X	X	X	X	X	X	X	X		X
PRO - EQ-5D-3L					X				X			X		
PRO-SHIELD-WQ-9					X [i)]				X			X		
PRO IWQOL-Lite					X				X			X		

	Screening	Enrolment	Placebo lead-in		24-week double-blind treatment period					28-week site- and patient-blinded extension period			Follow-up	Rescue
Visit	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**[c)]	**12 FU**	**R**
Week	**-11**	**-9**	**-8**	**-2**	**0**	**4**	**8**	**16**	**24**	**32**	**40**	**52**	**55**	
PRO - DTSQs					X				X			X		
PRO - DTSQc												X[j)]		
Informed consent, blood sample for genetics [h)]					(X)	(X)	(X)	(X)	(X)					

[a)] Once a patient is randomised, all visits should be scheduled relative to Visit 4. Any slippage in time from one visit must not accumulate to affect other visits.
[b)] Enrolment visit should be performed within 14 days after screening visit, when laboratory results from Visit S are available.
[c)] End of Treatment Visit.
[d)] Only laboratory results from previous visits should be assessed for patient's eligibility.
[e)] Specifications of laboratory parameters are shown in Table 7 and Table 8.
[f)] Pregnancy test will be done on all female patients who are not postmenopausal or hysterectomised (for definition see section 4.1, point 6).
[g)] Patients should be instructed to contact the investigator by phone if a hypoglycaemic event occurs, in cases specified in the patient diary.
[h)] Genetic informed consent must be obtained before genetic blood sample is taken. Blood sample donation is optional and can be taken only once at any time from Visit 4 (ie, randomisation) to Visit 8.
[i).] PRO-SHIELD WQ-9, version baseline should be used.
[j).] For patient who completes the study as planned standard PRO-DTSQc will be used, for early terminated patient Early Termination PRO-DTSQc must be used.

3.2 Rationale for study design, doses and control groups

3.2.1 Study design and regulatory requirement

The current study is designed to demonstrate the efficacy and safety of dapagliflozin versus placebo in patients with inadequate glycaemic control while continuing background therapy on metformin and sulfonylurea. The study has standard design features for a confirmatory Phase III diabetes study (eg, multi-center, randomised, double-blind, parallel group) and incorporates the relevant features of the Committee for Proprietary Medicinal Products' guidance for investigations of diabetes (CPMP 2002) with regard to duration of treatment, choice of study population, and choice of outcome variables.

3.2.2 Study doses and control groups

Control group

This is a placebo-controlled study.

Dapagliflozin

Results of pre-clinical pharmacokinetic and toxicology studies support the safety of conducting a Phase III clinical development program for dapagliflozin. In Phase I clinical pharmacology studies (single ascending-dose and 2-week multiple ascending-dose studies in healthy volunteers and patients with type 2 diabetes), dapagliflozin was safe and well tolerated with a favourable pharmacokinetic and pharmacodynamic profile. A Phase IIb study in patients with type 2 diabetes demonstrated good glycaemic efficacy and an acceptable safety profile over a wide range of doses. Based on considerations of efficacy, pharmacodynamic, and safety data from the Phase I and II programs, daily doses up to 10 mg of dapagliflozin have been chosen for the Phase III studies. The 10 mg dose was chosen for this study as it has been extensively studied in Phase III trials and is the dose expected to deliver the most favourable benefit:risk profile. The Phase III program is meanwhile completed and the file is submitted for approval and under review at the moment.

3.2.3 Choice of outcome variables

HbA1c is the variable of choice for assessment of glycaemic control and was therefore chosen as the primary outcome variable. Because of its novel, complementary mechanism of action, dapagliflozin may have additive or synergistic HbA1c-lowering effects when given in combination with other anti-hyperglycaemic agents. Additionally, as beneficial effects on FPG, SBP and weight have been observed in other dapagliflozin studies, these variables have been chosen as key secondary objectives (see Table 4).

Table 4 Efficacy variables with related objectives and rationale

Efficacy variable	Related objective	Rationale
HbA1c	Change from baseline in HbA1c to week 24 Proportion of patients achieving a therapeutic glycaemic response, defined as HbA1c <7.0%, at week 24. Change from baseline in HbA1c to week 24 in patients with baseline HbA1c ≥8.0%. Change from baseline in HbA1c to week 24 in patients with baseline HbA1c ≥9.0%	HbA1c is the clinical and regulatory parameter used to estimate glycaemic efficacy in patients with type 2 diabetes (CPMP 2002). HbA1c targets for patients with type 2 diabetes range from <6.5% (IDF 2005, AACE 2011) to <7% (ADA 2011). The degree of change in HbA1c in patients with type 2 diabetes is related to the baseline HbA1c level; patients with higher HbA1c at baseline tend to have greater reductions in HbA1c when treated with any anti-hyperglycaemic agent (Bloomgarden 2006).
Fasting Plasma Glucose	Change from baseline in FPG to week 8 and 24. Proportion of patients discontinued for lack of efficacy or rescued for failing to maintain FPG on pre-specified rescue criteria at weeks 4, 8, 16, and 24.	Fasting plasma glucose is well-established measures of glycaemic efficacy, and are considered by the CHMP to be acceptable secondary endpoints (CPMP 2002).
Total Body Weight	Change from baseline in total body weight to week 24.	More than 85% of patients with type 2 diabetes are overweight (BMI ≥27 kg/m2) or obese (BMI ≥30 kg/m2) (CDC 2004). Weight loss is a fundamental goal for the majority of patients with type 2 diabetes since it has been shown to improve comorbid conditions such as hypertension, dyslipidemia, heart disease, osteoarthritis, and sleep apnea (NHLBI 1998).

Efficacy variable	Related objective	Rationale
Blood pressure	Change from baseline in seated SBP to week 8. Change from baseline in seated SBP to week 24. Proportion of patients who achieve a seated blood pressure of <130/80 mmHg at week 24 in patients with baseline blood pressure (SBP ≥130 mmHg and/or baseline diastolic blood pressure (DBP) ≥80 mmHg).	The American Diabetes Association and the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 2004) guidelines recommend a blood pressure target of <130/80 in patients with diabetes (ADA 2011, JNC 2004). Lowering blood pressure in patients with diabetes has been shown to reduce the risk of coronary heart disease events, stroke, retinopathy and nephropathy (JNC 2004).
Fasting lipids	Percent change from baseline in fasting lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides) to week 24.	Patients with type 2 diabetes have an increased prevalence of lipid abnormalities, which contributes to their high risk of cardiovascular disease (ADA 2011). For this reason, it is important to evaluate the lipid effects of anti-hyperglycaemic agents.
HOMA-2, HOMA-IR	Change from baseline in the following parameters to week 24: - β-cell function (as measured by Homeostasis Model Assessment 2 [HOMA-2]) - Insulin resistance (as measured by HOMA-IR) - Insulin, c-peptide, proinsulin	β-cell dysfunction and insulin resistance contribute to the pathogenesis of type 2 diabetes; improvements in these parameters may be observed with improved glycaemic control (Poitout et al 2008).
Waist circumference	Change from baseline in waist circumference to week 24.	The presence of excess fat in the abdomen out of proportion to total body fat is an independent predictor of risk factors and morbidity. Waist circumference is positively correlated with abdominal fat content (NHLBI 1998).

3.2.4 Choice of study population

Age

The upper age limit will be based on local metformin prescribing guidelines.

HbA1c

The HbA1c inclusion criterion at randomisation was selected to include patients with a wide range of glycaemic control. The lower bound of this interval (ie, 7%) reflects the most recent American Diabetes Association treatment guidelines (ADA 2011). Although other guidelines recommend treatment to lower HbA1c targets, the results of some studies suggest that these stricter targets may not be appropriate for all patients (ACCORD 2008, ADA 2011). The upper limit of this interval (ie, 10.5%) was chosen because insulin is generally the treatment of choice for patients with HbA1c values above this level (ADA 2011).

Pregnancy or breastfeeding

Dapagliflozin has not been tested in pregnant women and the risks to embryo, foetus, and infant are unknown. For this reason, women who are pregnant or breastfeeding are excluded and women of childbearing age are instructed to take precautions to avoid becoming pregnant during the study. Based on pre-clinical studies dapagliflozin must not be used in the second and third trimesters of pregnancy. For more information relating to dapagliflozin exposure and pregnancy, please refer to the IB.

Other

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

4. PATIENT SELECTION CRITERIA

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

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

4.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria.

The following criteria apply to the enrolment, placebo lead-in and randomisation visits (Visits 1, 2, 3, and 4).

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

2. Diagnosis of type 2 diabetes mellitus.

3. Men or women age ≥18 years old, the upper age limit should be based on local metformin label restrictions.

4. Stable dose combination therapy of metformin ≥1500mg/day and maximum tolerated dose which must be at least half maximum dose of sulfonylurea for at least 8 weeks prior to enrolment.

5. HbA1c inclusion criteria:

   - At enrolment (Visit 1) – laboratory values from screening visit:

     ≥7.7% and ≤11.0%.

   - At the randomisation visit (Visit 4) – laboratory values from visit 3:

     ≥7.0% and ≤10.5%.

6. For women only: Women not of childbearing potential, or women of childbearing potential who comply with the following:

   - Use a highly effective method of birth control (see below) to avoid pregnancy throughout the study and for up to 4 weeks after the study.

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

Definitions:

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

Women NOT of Childbearing Potential - Women who are permanently or surgically sterilized or postmenopausal. Permanent sterilisation includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion. Tubal occlusion is considered a highly effective method of birth control but does not absolutely

exclude possibility of pregnancy. (The term occlusion refers to both occluding and ligating techniques that do not physically remove the oviducts).

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

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

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

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

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

1. Provision of informed consent for genetic research.

If a patient declines to participate in the optional genetic research, there will be no penalty or loss of benefit to the patient. The patients will not be excluded from other aspects of the study described in this Clinical Study Protocol.

4.2 Exclusion criteria

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

The following criteria apply to the enrolment, placebo lead-in and randomisation visits (Visits 1, 2, 3, and 4).

Endocrine and metabolic disorders

1. Diagnosis of Type 1 diabetes mellitus, known diagnosis of MODY or secondary diabetes mellitus.

2. History of diabetic ketoacidosis.

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

4. FPG >270 mg/dL (>15 mmol/L) – assessed based on laboratory results from Visits 1, 2 and 3.

5. BMI >45 kg/m^2

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

7. Diabetes insipidus.

8. Thyroid-stimulating hormone (TSH) and free T4 values outside normal range; an abnormal TSH value needs to be followed up with a free T4 test. Patients with abnormal free T4 values will be excluded.

Cardiovascular disorders

9. Recent Cardiovascular Events in a patient:

   - Acute Coronary Syndrome (ACS) within 2 months prior to enrolment.
   - Hospitalization for unstable angina or acute myocardial infarction within 2 months prior to enrolment.
   - Acute Stroke or TIA within 2 months prior to enrolment.
   - Less than 2 months post coronary artery revascularization prior to enrolment.

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

11. Blood pressure:

   - At enrolment (Visit 1):
     Systolic BP ≥170 mmHg and/or diastolic BP ≥110 mmHg.
   - At randomisation (Visit 4):
     Systolic BP ≥160 mmHg and/or diastolic BP ≥100 mmHg.

Kidney or urological disorders

12. Measured serum creatinine value of ≥1.5 mg/dL (133 μmol/L) for male patients and ≥1.4 mg/dL (124 μmol/L) for female patients or renal function that would preclude treatment with metformin according to local guidance.

13. History of unstable or rapidly progressing renal disease.

14. Familial renal glucosuria. This condition is diagnosed as glucosuria (>1.0 mmol/L urine) in the presence of normoglycaemia in patients without the diagnosis of diabetes mellitus.

15. History of unexplained microscopic or gross hematuria, or microscopic hematuria at Visit 1, confirmed by a follow-up sample at next scheduled visit, where according to the investigator a satisfactory evaluation of hematuria has not been conducted based on guidance in Section 6.4.9.3.

Hepatic disorders

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

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

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

19. History of drug-induced liver enzyme elevations.

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

Hematologic/oncologic disorders/conditions

21. Haemoglobin <10 g/dL (<100 g/L) or 6.2 mmol/L for men; haemoglobin <9.0 g/dL (<90 g/L) or 5.9 mmol/L for women.

22. History of chronic haemolytic anaemia or haemoglobinopathies (for example, sickle cell anaemia, thalassemia, sideroblastic anaemia). Mild haemolysis due to artificial heart valves or due to sickle cell trait is not an exclusion criterion except when haemoglobin levels are too low (as defined in haemoglobin criteria above).

23. Iron deficiency anaemia with iron therapy started in the past 12 weeks prior to enrolment visit, or a recent diagnosis of iron deficiency anaemia that requires therapeutic management within the next 24 weeks in the judgement of the investigator.

24. Donation or transfusion of blood, plasma, or platelets within the past 12 weeks prior to enrolment.

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

Infectious disease/immunologic disorders

26. Known immunocompromised status, including patients who underwent organ transplantation.

Musculoskeletal disorders

27. Creatine Kinase (CK) >3x ULN.

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

Reproductive status

29. Pregnant or breastfeeding patients.

Prohibited medications

30. Use of any anti-hyperglycaemic medications other than metformin or sulfonylurea during the 10 weeks prior to enrolment.

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

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

Other standard criteria

33. Intolerance, contraindication or potential allergy or hypersensitivity to dapagliflozin, metformin, sulfonylurea, sulphonamides, DPP-4 inhibitors, placebo, or formulation excipients.

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

35. Volume depleted patients. Patients at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics should have careful monitoring of their volume status.

36. Acute or chronic metabolic acidosis.

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

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

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

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

41. Participation in another clinical study with an investigational product during the last 4 weeks prior to enrolment.

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

42. Previous bone marrow transplant.

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

Procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

Note: Patient's eligibility will be assessed based on values provided by central laboratory.

5. STUDY CONDUCT

5.1 Restrictions during the study

- All patients will visit the clinic fasting in the morning, before 11 a.m. if possible.
- Patients will be instructed to abstain from all food and beverages for 12 hours prior to each clinic visit (drinking water is allowed).
- On the morning of the clinic visit, investigational product and all other medications including anti-hypertensive, lipid lowering and anti-platelet agents, oral anti-hyperglycaemic drugs should not be taken at home. Patients should bring all their medications and investigational product to the site.

  Anti-hypertensive medication can be taken with a glass of water immediately after completion of blood pressure and body weight measurements.

  After blood and urine sample collection has been completed, patients can take their medications including oral anti-hyperglycaemic drugs, lipid-lowering and anti-platelet agents. Anti-hyperglycaemic drugs should be taken during the meal.

  Antiepileptic drugs and antibiotics shall be taken as required.
- Patients should not drink alcohol within 24 hours prior to each visit and should not use tobacco/nicotine within 12 hours prior to each visit.

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

As up to approximately 124 mL of blood will be drawn from each patient during the entire duration of the clinical study (excluding optional genetic blood sample and extra blood samples taken at unscheduled, specialized liver/liver discontinuation visits), patients should be instructed to abstain from donating any blood during the clinical study and for 12 weeks following their last study visit.

Prohibited and restricted concomitant medications are listed in Section 5.6.3.

5.2 Patient enrolment and randomisation

The Principal Investigator or delegate will:

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

2. Assign potential patient a unique enrolment number, beginning with 'E' using Interactive Web Response System (IWRS) or Interactive Voice Response System (IVRS) at Visit 1 (Enrolment Visit).

3. At Visits 1, 2, 3, and 4 determine patient eligibility. See Sections 4.1 and 4.2

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

Randomisation codes will be assigned at Visit 4, after all inclusion/exclusion criteria have been evaluated.

If patients have been withdrawn from participation in the study they cannot re-enter into the study.

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

5.2.1 Procedures for randomisation

Randomisation to study treatment will be done via Interactive Web Response System (IWRS) or Interactive Voice Response System (IVRS) at Visit 4. The global randomisation administrator at AstraZeneca will prepare a central randomisation list using balanced blocks to ensure approximately equal numbers of subjects across the treatment groups. The IWRS/IVRS will allocate a block of randomization numbers for each centre as they randomize their first subjects in sequential order. For a centre, the IWRS/IVRS will continue to randomise subjects sequentially within the block until the block is exhausted. Once a block is exhausted, the next available block will be allocated to a centre upon their next randomization. The IWRS/IVRS will provide the randomisation number and the appropriate bottle numbers from Investigational Product Supply available at the study centre. Randomisation numbers and associated kit numbers will not be sequential within a centre. Forced randomisation is not allowed.

The patient should always be provided medication with the bottle number allocated by the IWRS/IVRS. If a patient is dispensed with a wrong drug supply, the centre must immediately notify the AstraZeneca representative and IWRS contact. Corrections for the patient and the IWRS/IVRS will be made as required. Until resolution, the patient should continue taking study medication, but at the latest until the next scheduled visit.

5.3 Procedures for handling patients incorrectly enrolled or randomised

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

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

Where patients that do not meet the inclusion criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post-initiation, the investigator should inform the AstraZeneca Study Physician immediately. The AstraZeneca Study Physician is to ensure all such contacts are appropriately documented.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The study will be conducted in a double blind fashion. The dapagliflozin 10 mg tablet and its matching placebo will be identical in size, colour, smell, taste, packaging and labelling.

Until the completion of the 24-week randomised treatment period, no member of the extended study team at AstraZeneca or Bristol-Myers Squibb, at the investigational centres or any Contract Research Organization handling data will have access to the randomisation scheme, with the exception of relevant persons at Pharmaceutical Development Supply Chain at AstraZeneca or their designee, where the information is needed to package study medication, and the drug safety departments at Bristol-Myers Squibb and AstraZeneca. Patients and investigators will remain blinded past the 24-week randomised treatment period.

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

5.4.2 Methods for unblinding the study

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

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

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

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

5.5 Treatments

5.5.1 Identity of Investigational Product

Table 5 Identity of Investigational Product

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

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

Dapagliflozin and its matching placebo will be packed in bottles containing 35 tablets. The tablets may contain lactose, which may cause discomfort in lactose-intolerant individuals.

5.5.2 Doses and treatment regimens

Duration of dosing:

- Dapagliflozin 10 mg tablets, administered orally once daily for the 24-week double-blind treatment period and the 28-week site-and patient- blinded extension period.
- Matching placebo for dapagliflozin 10 mg administered orally once daily for the 8-week placebo lead-in period, the 24-week double-blind treatment period and the 28-week site-and patient- blinded extension period.

The investigational product dapagliflozin and matching placebo will be taken orally. The investigational product should be taken once daily in the morning and at approximately the same time of the day during the study period. Nevertheless prior to each clinical visit patients should be instructed not to take any medication at morning and to abstain from all food and beverages for 12 hours; however, drinking water is allowed. In the day of study visit investigational product and other concomitant medications will be taken in the morning, after completion of certain required study procedures.

At the randomisation visit, investigational product will be ingested as a witnessed dose after completing the BP measurements and all other visit procedures.

Table 6 Drug Dispensing Scheme

Visit ID	No. of bottles to dispense of dapagliflozin 10 mg or matching placebo[a]
Visit 1	N/A
Visit 2	2 bottles (Lead-in)
Visit 3	N/A
Visit 4	1 bottle
Visit 5	1 bottle
Visit 6	2 bottles
Visit 7	2 bottles
Visit 8	2 bottles
Visit 9	2 bottles
Visit 10	3 bottles
Visit 11	N/A
Visit 12	N/A

[a] Each bottle contains 35 tablets.

5.5.3 Additional study drug

DPP-4 inhibitors or insulin will be used as rescue therapy and commercial packs will be supplied locally or prescribed by local investigator.

5.5.4 Labelling

Labelling of the investigational product will be carried out by AstraZeneca or their designee in accordance with current Good Manufacturing Practice (GMP). The labels will be translated into local languages and in accordance with local regulations for each participating country. The labels will fulfil GMP Annex 13 requirements and/or local regulatory.

The label will include at least the following information:

- Name of sponsor (AstraZeneca)
- Study drug(s) dosage form, route of administration, and quantity of dosage units
- Study code
- Order number (to identify the contents and packaging operation)
- Enrolment code (will be added by the investigator when investigational product is dispensed)
- Kit ID

- Visit number (will be added by the investigator when investigational product is dispensed)
- Directions for use (For oral use)
- The name of the investigator, if applicable (will be added by the investigator when investigational product is dispensed)
- The period of use, eg, expiry date
- Storage conditions
- "for clinical trial use only"
- "keep out of reach of children"

5.5.5 Storage

The investigational product should be kept in a secure place under appropriate storage conditions. The labels on the investigational product specify the appropriate storage.

5.6 Concomitant and post-study treatment(s)

5.6.1 Before randomisation

Restrictions on changes of anti-hypertensive therapy before randomisation are described in Section 3.1.3.

No other restrictions are applicable.

5.6.2 Randomised treatment period

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

Background anti-hypertensive medications should not be increased between weeks 1-8 unless the patient has a confirmed SBP ≥160 mmHg or DBP ≥100 mmHg. Concomitant anti-hypertensive medications should not be decreased between weeks 1-8 unless in the investigator's judgement the patient has symptomatic hypotension or has documented orthostatic hypotension during a study visit. After week 8, changes in anti-hypertensive medication may be made as needed for appropriate blood pressure management.

The administration of all medication must be recorded in the appropriate sections of the electronic Case Report Form (eCRF). The specific medication, the indication for use, and the dates of usage should also be reported. Trade name of the medication should be recorded in the eCRF. Generic name can be used if trade name is unknown. Additionally, the total daily

dose of the following medications should be reported: metformin, sulfonylurea, diuretics, anti-hypertensive agents, and HMG-CoA reductase inhibitors (statins).

Other medications considered necessary for the patient's safety and well-being may be given at the discretion of the investigator. For prohibited and restricted medication, see Section 5.6.3.

5.6.3 Prohibited medications during study

1. Anti-hyperglycaemic medications other than metformin or sulfonylurea (unless patient requires rescue therapy)

2. Weight loss medication, including but not limited to sibutramine, phentermine, orlistat, rimonabant, benzphetamine, diethylproprion, methamphetamine, and/or phendimetrazine

3. Treatment with glucocorticoids equivalent to oral prednisolone ≥10 mg/day (betamethasone ≥1.2 mg, dexamethasone ≥1.5 mg, hydrocortisone ≥40 mg), (two temporary periods of higher daily doses for no longer than 7 days each are allowed; topical or inhaled corticosteroids are allowed)

5.6.4 Treatment after the study

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

5.7 Treatment compliance

The administration of all investigational product should be recorded in the appropriate sections of the eCRF.

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

5.7.1 Accountability

The Investigational Product (IP) provided for this study will be used only as directed in the study protocol.

The study personnel will account for investigational product received at the site and dispensed to and returned from the patient.

The investigator is responsible for making sure:

- That the investigational product is handled and stored safely and properly (see Section 5.5.5).
- That the investigational product is only dispensed to study patients in accordance with this protocol.

Patients should return all unused investigational product and empty containers to the investigator.

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

5.8 Discontinuation of Investigational Product

Patients may be discontinued from investigational product in the following situations:

General discontinuation criteria:

1. Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
2. Adverse Events, ie, any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the patient.
3. Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca.
4. Risk to patients as judged by the investigator and /or AstraZeneca.
5. Incorrectly enrolled patients (see Section 5.3).
6. Patient lost to follow-up (see Section 5.9.3).
7. Withdrawal of informed consent to the use of biological samples collected as an integral part of the study, see Section 7.5.

Study-specific discontinuation criteria:

8. Use of (need for) any anti-hyperglycaemic medication other than investigational product or background metformin or sulfonylurea or rescue therapy allowed by protocol. However, insulin use is permitted in the following situations:

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

   (b) For up to 14 days in total during the study and up to 7 continuous days if there is a documented illness or infection that requires additional therapy for maintaining glycaemic control.

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

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

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

10. Treatment with weight loss medication, including but not limited to sibutramine, phentermine, orlistat, rimonabant, benzphetamine, diethylproprion, methamphetamine, and/or phendimetrazine

11. Major and/or frequent hypoglycaemic events, defined as ≥1 major event or recurring minor events (see Section 6.4.9.1 for definition of minor and major). This definition should be applied after possible contributing factors (eg, excessive physical activity) have been excluded by the investigator.

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

13. Patients who receive oral anti-hyperglycaemic rescue therapy only and have a central laboratory HbA1c >8% for 6 months despite the maximum tolerated dose of rescue therapy and the possibility of insulin treatment has been evaluated. (**NB**: for patients receiving insulin as rescue medication an up-titration step should be considered instead of study discontinuation).

14. An increase in serum creatinine of ≥0.5 mg/dL above the baseline value confirmed by a repeated measurement within one week or a decrease in renal function that would preclude continued treatment with metformin according to local guidance (Please see Appendix J for further guidance).

15. Patients with an increased CK >10xULN confirmed at a repeated measurement preferably within 24 hours, but not exceeding 72 hours, see Section 5.8.1.

16. Patients with a central laboratory ALT and/or AST >3xULN will be scheduled for a follow-up visit within 3 days following the receipt of the result (See Appendix I 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 >3xULN and total bilirubin (TB)>1.5xULN,

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

    – ALT and/or AST are >8xULN.

17. Serum Sodium ≤125 mmol/L with or without symptoms (See Appendix H for further guidance).

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

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

5.8.1 Procedures for discontinuation of a patient from Investigational Product

A patient that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any Adverse Events. If possible, the patient will undergo procedures of Visit 11 (End of Treatment Visit) as soon as possible after last intake of investigational product and will have a Follow-up Visit (Visit 12) 3 weeks after last intake of investigational product (see Table 3). Adverse Events will be followed up (See Sections 6.4.3 and 6.4.4). Patient's diaries and all investigational products should be returned by the patient.

Stop of investigational product will lead to withdrawal from the study after completion of the Follow up Visit (Visit 12).

Patients with an increased CK >10x ULN will have their investigational product temporarily stopped and undergo a repeated CK test preferably within 24 hours, but not exceeding 72 hours. If repeated CK is confirmed >10x ULN the patient should permanently discontinue study medication (in which case an Adverse Event must be reported). Otherwise investigational product may be resumed unless otherwise contraindicated.

Patients with increased liver function tests as defined in Section 5.8 under listing 16 will have repeat liver function tests within 3 days. If repeat liver function tests still are increased as outlined in Section 5.8 under listing 16, the patient should immediately permanently

discontinue study medication (in which case an Adverse Event must be reported). If repeat liver function tests still are increased but not meet criteria outlined in Section 5.8 under listing 16, the patient should continue study medications unless otherwise contraindicated.

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

5.9 Withdrawal from study

Patients are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any Adverse Events. If possible, they will be seen and assessed by an investigator. Adverse Events will be followed up (see Sections 6.4.3 and 6.4.4); patient diaries and investigational products should be returned by the patient.

Pregnant patients confirmed by pregnancy test or otherwise verified will be withdrawn from the study (also see Section 13.3).

5.9.1 Pre-randomisation

A patient who withdraws from study during pre-randomisation will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator to terminate participation in the study. AEs will be followed up (see Sections 6.4.3 and 6.4.4); patient diaries should be returned by the patient.

5.9.2 Randomised patients

Randomised patients who have withdrawn their consent for study treatment before week 52 should return and complete procedures of Visit 11 (End of Treatment Visit) (see Table 3) as soon as possible after last intake of investigational product. These patients should also be scheduled for a Follow-up Visit (Visit 12) if they do not refuse to take part at this study visit. A Follow-up Visit (Visit 12) will be performed 3 weeks after last intake of investigational product (the allowed visit window is + 7 days), see Table 3 for further details.

In addition, patients who discontinue the study due to an AE including a laboratory abnormality should be followed by the investigator until the event has been resolved or stabilised.

Patients withdrawn after randomisation will not be replaced.

5.9.3 Patients lost to follow-up

Patient lost to follow-up is defined by the inability to reach the patient after:

- three attempts of either phone calls, faxes or emails,
- having sent one registered letter/certified mail

- or one unsuccessful effort to check the vital status of the patient using public available sources, if allowed by national regulations.

All attempts and contacts should be documented in the patient's medical records. Patients lost to follow up will be withdrawn from the study.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

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

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement.

Data must be entered into the WBDC system at the investigational centre within 72 hours after the performed 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 provided by AstraZeneca.

When data have been entered, reviewed⁄queried, edited and Source Data Verification (SDV) has been performed by an AstraZeneca representative, the data will be frozen to prevent further editing.

The Principle Investigator or his/her deputy is responsible for signing the completed eCRF. A copy of the completed eCRF will be archived at the study site.

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

The patients will record results of self-monitored FPG and information about hypoglycaemic events in paper diaries.

PROs will be completed in paper. Data will be entered on the eCRF by trained study personnel.

Data collected at Screening Visit will not be recorded in eCRF, but in central laboratory database only. A Screening number (S code) will be created for all patients by the investigator. This S-code will identify screening laboratory results together with date of birth and gender.

6.2 Data collection at enrolment and follow-up

6.2.1 Data collection at enrolment

At enrolment the following data will be collected and recorded in the appropriate sections of the eCRF:

- Date of birth, sex, race and ethnicity
- Other characteristics – weight, height, waist circumference, information about smoking and alcohol
- Medical history, specific disease history and family history on coronary heart disease
- NYHA class for patients with Congestive Heart Failure
- Physical examination including pulse and blood pressure measurements
- ECG examination
- Blood samples for laboratory variables listed in Table 7 and Table 8.
- Pregnancy test, if applicable

Procedures to be done during Enrolment Visit are listed in Table 3.

6.2.2 Follow-up procedures

A Follow-up visit (Visit 12) will be performed 3 weeks + 7 days after the end of the double-blind treatment period, see Table 3 for further details.

6.3 Efficacy

6.3.1 Efficacy laboratory variables

Table 7 Efficacy Laboratory Variables

Visit	S	1	2	3	4	5	6	7	8	9	10	11	12	R
Study Week	**-11**	**-9**	**-8**	**-2**	**0**	**4**	**8**	**16**	**24**	**32**	**40**	**52**	**55**	
HbA1c	X	X		X	X	X	X	X	X	X	X	X	X	X
FPG [a)]		X	X	X	X	X	X	X	X	X	X	X	X	X
Insulin [a)]					X				X			X		X
Proinsulin					X				X			X		X
C-peptide					X				X			X		X
HOMA-2, HOMA-IR					X				X			X		X
Total cholesterol[a)]		X			X				X			X		X
LDL-C [a)]		X			X				X			X		X
HDL-C [a)]		X			X				X			X		X
TG [a)]		X			X				X			X		X

[a)] fasting

The laboratory parameters that will be measured to assess efficacy are displayed in Table 4 by visit. These variables will be assessed at the central laboratory. For information on methods of collection, assessment, labelling, storage and shipment of samples, see the Laboratory Manual.

Due to the fasting laboratory assessments, all patients will visit the clinic on a fasting stomach in the morning, before 11 a.m. Patients will be instructed not to eat or drink anything for 12 hours before visiting the clinic (drinking water is allowed).

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

In addition, patients will be instructed not to take investigational product and any other concomitant medications in the morning before visiting the clinic.

The results from baseline and onwards will not be reported to the investigator unless the values meet the defined discontinuation criteria in Section 5.8, except for TC, HDL-C, LDL C and TG which will be reported. In addition, if rescue medication is initiated, the central laboratory FPG and HbA1c values will be reported to the investigator to ensure proper follow-up of the rescued patient.

6.3.2 HbA1c

HbA1c will be analysed by a central laboratory according to the procedures described in the Laboratory Manual which will be distributed to each study site.

6.3.3 Blood pressure

Systolic and diastolic blood pressure are both efficacy and safety variables in this study, measurement of BP is described in Sections 6.4.8.1 and 6.4.8.2.

A standard mercury sphygmomanometer with a standardised cuff adapted to the size of the patient's arm is recommended. Oscillometric devices (such as Dynamap) may be used at sites where:

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

The devices must be calibrated with a frequency according to local regulations.

6.3.4 Total Body Weight

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

6.3.5 Waist circumference

The patient's waist circumference will be recorded in centimetres (cm) to one decimal place. The waist circumference should be measured in 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-supplied measuring tape.

6.3.6 HOMA-2, HOMA-IR

HOMA-2 and HOMA-IR are methods for assessing β-cell function and insulin resistance from glucose and insulin or C-peptide concentrations. These will be calculated by AstraZeneca.

6.3.7 Patient reported outcomes (PRO)

PROs will be assessed at baseline, week 24 and week 52 by EQ-5D-3L for generic health status, DTSQs and DTSQc for treatment satisfaction and two questions on HRQL in relation to self-perceived weight change: the SHIELD-WQ-9 and IWQOL-Lite (see Section 6.5). The instruments/questions will be self-administered using paper and pencil questionnaires. The staff at the clinic should never help the subject to choose an answer and must be neutral in their response to the subject's questions. The staff at the clinic is not allowed to interpret or

rephrase the questions for the subject. After the subject has completed the questionnaire, the study personnel will review the questionnaire for completeness only.

6.4 Safety

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

6.4.1 Definition of Adverse Events

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

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

6.4.2 Definitions of Serious Adverse Event

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

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

Any event of cancer, drug dependency/abuse, laboratory abnormalities fulfilling the Hy's law definition (ALT/AST>3xULN and total bilirubin >2xULN) or overdose (defined as the accidental or intentional ingestion of any dose of the investigational product that is considered both excessive and medically important) should be reported as an SAE using the most relevant SAE criteria, as judged by the Investigator.

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

6.4.3 Recording of Adverse Events

Time period for collection of Adverse Events

All AEs will be collected from the start of the lead-in period (Visit 2) throughout the treatment period and including the follow-up period (Visit 12).

SAEs will be recorded from the time of informed consent until the end of the study (Visit 12).

Follow-up of unresolved Adverse Events

Any AEs that are unresolved at the patient's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary. The requirement to follow-up is not intended to delay database lock or production of the clinical study report. Both these activities should proceed as planned with ongoing AEs if necessary.

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

Variables

The following variables will be collected for each AE;

- AE (verbatim)
- Date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- Outcome.

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation

- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Causality assessment in relation to Additional Study Drug
- Description of AE.

Maximum intensity will be graded according to the following rating scale:

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities)
- very severe (debilitating, significantly incapacitates patient despite symptomatic therapy).

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

Causality collection

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

For SAEs causal relationship will also be assessed for other medication, additional study drugs and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as ‘yes’.

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

Adverse Events based on signs and symptoms

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

Adverse Events based on examinations and tests

The results from protocol mandated laboratory test and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs will only be reported as AEs if they are clinically significant, fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product, or require the patient to receive specific corrective therapy.

If a deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated measurements will be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination or ECG evaluation as compared with the baseline assessment will be reported as an AE.

Hypoglycaemic events

A separate section in the eCRF will be used to document all reported episodes of hypoglycaemia (see Section 6.4.9.1). Hypoglycaemic episodes should only be reported on the AE eCRF page if the event fulfils protocol criteria for a Serious Adverse Event (see Section 6.4.2). In this case, an SAE must be reported in addition to the hypoglycaemia eCRF pages for hypoglycaemia.

Cardiovascular events

Cardiovascular (CV) events will be monitored in the study population and an independent CV adjudication committee will review events (see Section 6.4.15). CV events will be analyzed in conjunction with CV events observed in other Phase II and Phase III dapagliflozin studies and reported separately.

Hepatic events

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

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

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

6.4.4 Reporting of Serious Adverse Events

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

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

An automated email alert will be sent to the designated AstraZeneca representative, when the page with SAE information is saved in WBDC system by the Investigators or other site personnel. If the WBDC system is not available, then the Investigator or other study site personnel reports by fax an SAE to the appropriate AstraZeneca representative. A paper back-up SAE report is used for this purpose. The same reporting time frames still apply. The investigator is responsible for completing the eCRF as soon as the system becomes available again. The AstraZeneca representative will forward all information relevant to the SAE to Bristol-Myers Squibb Pharmacovigilance via fax or email.

6.4.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology, coagulation and urinalysis will be taken at the times indicated in the Study Plan (see Table 3).

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.

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

For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.4.3.

The following laboratory variables will be measured:

Table 8 Safety laboratory variables

Visit	1	2	3	4	5	6	7	8	9	10	11	12	R
Study Week	**-9**	**-8**	**-2**	**0**	**4**	**8**	**16**	**24**	**32**	**40**	**52**	**55**	
Haematology													
Haemoglobin	X			X	X	X	X	X	X	X	X	X	X
Haematocrit	X			X	X	X	X	X	X	X	X	X	X
Red blood cell count	X			X		X		X			X	X	X
White blood cell count and differential	X			X		X		X			X	X	X
Platelet count	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
Alanine Aminotransferase (ALT, SGPT)	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
Creatine Kinase (CK)	X			X	X	X	X	X	X	X	X	X	X
Total Bilirubin (TB) [a)]	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

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**R**
Study Week	**-9**	**-8**	**-2**	**0**	**4**	**8**	**16**	**24**	**32**	**40**	**52**	**55**	
Electrolytes:	X			X	X	X	X	X	X	X	X	X	X
(- Sodium - Bicarbonate - Potassium - Chloride - Calcium - Magnesium - Phosphorus)													
Total protein	X			X		X		X			X	X	X
Albumin	X			X		X		X			X	X	X
Uric acid	X			X	X	X	X	X	X	X	X	X	X
Serum Creatinine (SCr)	X			X	X	X	X	X	X	X	X	X	X
Calculated creatinine clearance (Cockroft-Gault formula) [b)]	X			X	X	X	X	X	X	X	X	X	X
Estimated Glomerular Filtration Rate (MDRD formula)	X			X	X	X	X	X	X	X	X	X	X
Serum Bone Metabolism Marker (Parathyroid Hormone (PTH) and 25 hydroxy-vitamin D)				X				X			X	X	X
FSH	X												
TSH, Free T4 [c)]	X												
Hepatitis Screen Panel [d)]	X												

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**R**
Study Week	**-9**	**-8**	**-2**	**0**	**4**	**8**	**16**	**24**	**32**	**40**	**52**	**55**	
Urinalysis													
Glucose [e)]	X			X	X	X	X	X	X	X	X	X	X
Blood by dipstick [f)]	X			X	X	X	X	X	X	X	X	X	X
Albumin	X			X	X	X	X	X	X	X	X	X	X
Creatinine	X			X	X	X	X	X	X	X	X	X	X
Pregnancy test [g)]	X	X	X	X	X	X	X	X	X	X	X	X	X

a) Both direct and indirect bilirubin will be reported if Total Bilirubin >1.5 X ULN.
b) Creatinine clearance will be calculated by the method of Cockcroft and Gault.
c) Free T4 will be measured only if TSH is outside of normal range.
d) Includes Hepatitis B viral antibody IgM, Hepatitis B surface antigen and Hepatitis C virus antibody.
e) Results will be blinded.
f) Microscopy if dipstick positive for blood
g) Urine HCG pregnancy test for women of childbearing potential (HCG minimum sensitivity of 25 IU/L) (dipstick analyzed at the study centre).

For blood volume see Section 7.1

6.4.6 Physical examination

A physical examination should be done according to schedule shown in Study Plan (Table 3).

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

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

Baseline data is collected at Visit 4 and any new or aggravated findings discovered on subsequent physical examinations should be recorded as AE if clinically relevant (see Section 6.4.3).

6.4.7 ECG

A 12-lead ECG will be taken (supine position, standard ECG with a recommended paper speed of 50 mm/second covering at least 6 sequential beats) after the patient has been lying down resting for at least 5 minutes. Heart rate, will be recorded from standard lead of the computerised ECG and will be entered in the eCRF. The ECG will be evaluated by the investigator and entered as 'Normal' or 'Abnormal' in the eCRF. If the ECG is evaluated as "Abnormal" the investigator should document the specific abnormality and report AE if clinically relevant (see Section 6.4.3).

Each original ECG print out signed and dated by Investigator will be kept in the medical records as a source document.

6.4.8 Vital signs

6.4.8.1 Pulse and blood pressure

One 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 three blood pressure (BP) measurements separated by 2 minutes each. All three BP readings should be recorded. At Visit 1 the seated BP will be recorded three times in both the left and the right arms. All three measurements should be made in one arm before transferring the cuff to the other arm. The arm with the highest mean seated BP readings will be the one used for all subsequent readings. The average of the three BP readings will be used for study analyses. BP readings should be taken while the patient is in a comfortable seated position with the arm supported at the level of the heart. All readings should be recorded. Ideally, blood pressure should be measured with the same machine, at the same time of day, and by the same personnel at each visit.

6.4.8.2 Orthostatic blood pressure

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

Supine BP and pulse

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

Standing BP and pulse

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

If a new occurrence of previously absent orthostatic hypotension is demonstrated, it should be recorded as AE in the eCRF. The investigator may consider to reduce concomitant anti-hypertensive medication to alleviate signs and symptoms of orthostatic hypotension.

6.4.9 Other safety assessments

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

6.4.9.1 Fasting plasma glucose concentrations and hypoglycaemic events

Patient self-monitoring of FPG is performed in order to reduce the risks associated with prolonged hyperglycaemia and to confirm symptoms of hypoglycaemia. Patients will be asked to perform self-monitoring of FPG using glucometers provided by AstraZeneca. The patients will receive instructions for the use of the glucometer according to the manufacturer's instructions.

FPG should be self-monitored at least every second day between visits 2 and 8 and at least once a week between visits 8 and 11. The results should be recorded in the patient diary, which will be collected and reviewed by the study personnel at each visit starting with Visit 3; a print-out will be stored in the investigator study file. A new diary will be dispensed to the patient at each of these visits.

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

If self-monitored FPG is
above 240 mg/dL (13.2 mmol/L) from week 4 (Visit 5) to week 16 (Visit 7),
or above 200 mg/dL (11.1 mmol/L) from week 16 (Visit 7) to week 52 (Visit 11),
the patient should repeat the FPG on the same day.

If the second FPG value is above 240 mg/dL (13.2 mmol/L) or 200 mg/dL (11.1 mmol/L), respectively, the patient should contact the study centre and be scheduled for a central laboratory FPG (or HbA1c after Visit 8) measurement within one week.

If central laboratory values are similar, the patient should receive rescue therapy.

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

A hypoglycaemic event can be either:

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

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

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

For the evaluation of hypoglycaemic events, this study will use the definitions provided in the CPMP guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus (CPMP 2002), 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 episode with a capillary or plasma glucose measurement <63 mg/dL (<3.5 mmol/L) regardless of need for external assistance or an asymptomatic capillary or plasma glucose measurement below 63 mg/dL (3.5 mmol/L), that does not qualify as a major episode

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

Data to be collected for each hypoglycaemic event:

- Date and time of episode (start and stop)
- Whether the patient was sleeping at the time of the event
- Whether symptoms were present, and list of symptoms
- Possible contributing factors
- Whether a finger stick value was obtained, and if so, the plasma glucose value
- Whether intervention was needed for recovery
- How the episode was treated
- Whether recovery was prompt after treatment
- Time of last anti-hyperglycaemic drug administration
- Time of last meal and its contents

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

6.4.9.2 Urinary and Genital Infections

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

Urinary Tract Infections

At every scheduled visit starting from the randomisation visit, the investigator will question patients about symptoms of urinary tract infections, including but not limited to pain or burning or uncomfortable pressure in the lower abdomen/pelvic area while passing urine, blood in the urine, and symptoms of urinary urgency (a strong and uncontrolled urge to pass urine). If based on the response to these questions or other suggestive signs or symptoms (dysuria, urgency or frequency of urination, suprapubic or perineal discomfort, flank, back, or abdominal pain, costovertebral angle tenderness, nausea, vomiting, fever, chills, or sepsis) the investigator believes that a urinary tract infection may be present, urine cultures (in a local laboratory) should be obtained to confirm a presumptive diagnosis of cystitis, urinary tract infection, pyelonephritis, or prostatitis. Mid-stream clean catch urine collections are recommended. Clinical judgement and local standards of care should apply to decisions concerning therapy. It is strongly recommended that a diagnosis of a recurrent urinary tract infection, defined either as two infections in a 6-month period or three infections in a 12-month period, should result in referral to a gynecologist (women) or urologist (men) for further diagnosis and treatment. Any treatment needs to be documented in the eCRF.

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

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

Genital Infections

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

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

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

Asymptomatic bacteriuria

During enrolment, treatment and follow up of patients in this trial, the investigator may discover a patient with asymptomatic bacteriuria. Asymptomatic bacteriuria is defined as the presence of $\geq 10^5$ colony forming units/mL of bacteria, in a properly collected voided urine specimen, without signs or symptoms typically attributed to urinary tract infection. Asymptomatic bacteriuria is prevalent among diabetic women, and is associated with pyuria in 70% of cases. Neither guidelines from the US (Nicolle et al 2005, USPST 2004) nor Europe (European Association of Urology 2008) recommend screening for, or treatment of, asymptomatic bacteriuria in non-pregnant diabetic patients. In this study, the central laboratory will report urinary dipstick test results for hemoglobin but will not routinely report the results of urinary dipstick tests for leukocyte esterase as a screening test for pyuria in surveillance urine examinations.

6.4.9.3 Microscopic Hematuria

In the event that hematuria is observed during a subject’s participation, the sponsors recommend standard of care in diagnosing the cause of the hematuria. This section presents references and an example of standard of care evaluation of microscopic hematuria. Local standards of care should be followed.

Patients with repeated reports of microscopic hematuria in 2 or more properly collected urine samples need to have follow-up for this result according to standard of care. The American Urological Association defines microscopic hematuria as three or more red blood cells per high-power microscopic field in urinary sediment from two or more properly collected urinalysis specimens (American Urological Association (AUA) website, 2011;Grossfeld et al, 2001). These Best Practice guidelines have been evaluated by Jung 2011 in a study of 772,000 patients.

Patients who show microscopic hematuria that is accompanied by significant proteinuria, red blood cell casts, or dysmorphic red blood cells in the sediment should be evaluated for the presence of primary renal disease and need to be referred to a nephrologist (American Urological Association (AUA) website, 2011; Grossfeld et al, 2001).

Patients who lack other explanation for their hematuria, or who have risk factors for significant urologic disease, will need a urological evaluation and should be referred to an urologist. Risk factors for significant urological disease include unexplained microscopic hematuria as well as smoking history, occupational exposure to dyes or chemicals (such as benzenes or aromatic amines), visible hematuria, age >40 years, previous urologic history, history of irritative voiding symptoms, history of urinary tract infection, analgesics or phenacetin abuse, history of pelvic irradiation, or cyclophosphamide use (American Urological Association (AUA) website, 2011, Grossfeld et al, 2001). Results from any procedure or investigations should be reported on the eCRF.

6.4.10 Volume depletion

Dapagliflozin has a modest diuretic effect. The risk of volume depletion is enhanced when two diuretics are used in combination and in patients that otherwise are at risk for volume depletion. Therefore, caution should be exercised when administering to patients at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics. These patients should be carefully monitored for of volume status, electrolytes, and renal function.

6.4.11 Change in kidney function

Please see Appendix J for further guidance.

6.4.12 Hyponatremia

Please see Appendix H for further guidance.

6.4.13 CK abnormalities

Please see Section 5.8.1 “Procedures for discontinuation of a patient from investigational product.”

6.4.14 Liver function test abnormalities

Please see Section 5.8.1 “Procedures for discontinuation of a patient from investigational product” and Appendix I.

6.4.15 Independent Adjudication Committee

6.4.15.1 Adjudication of cardiovascular events

A Clinical Event Committee (CEC), blinded to the treatment of the patients, will independently adjudicate certain cardiovascular Adverse Events, and they will operate in accordance with a dedicated Clinical Event Committee Charter/Manual of Operations: Dapagliflozin Program. Events related to the following will be sent to the CEC for adjudication:

Death including:

1. Cardiovascular Death

2. Non-cardiovascular Death

Myocardial Infarction (MI) including:

1. ECG and /or cardiac enzymes confirmed MI

2. Sudden death

3. Percutaneous coronary intervention-related MI

4. Coronary artery bypass graft-related MI

5. MI diagnosed via pathologic criteria

6. Silent MI

Fatal and Non-fatal Stroke including:

1. Ischaemic Stroke

2. Haemorrhagic Stroke

Serious Adverse Events of the following:

1. Heart failure

2. Cardiac arrhythmia

3. Unstable angina

4. Unplanned arterial revascularization (coronary, carotid and peripheral)

5. Cardiac arrest with successful resuscitation

6. Deep Vein Thrombosis and Pulmonary Emboli

7. Systemic non-stroke arterial embolism/thrombosis including systemic arterial occlusion

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

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

6.4.15.2 Adjudication of hepatic events

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

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

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

6.5 Patient reported outcomes (PRO)

The PROs questionnaires/questions used in this study are the EQ-5D-3L, DTSQ status, DTSQ change, SHIELD-WQ-9 and IWQOL-Lite. The methods for collection the PRO data are presented below.

6.5.1 EQ-5D-3L

The EQ-5D-3L is a generic, preference-based utility questionnaire and consists of two parts, the EQ VAS and the EQ-5D-3L index (Kind 1996). The EQ VAS is a visual analogue scale ranging from 0 = worst possible health to 100 = best possible health. The EQ-5D-3L index is a five dimension questionnaire. The dimensions consist of mobility, self-care, usual activity, pain/discomfort and anxiety/depression. Each item has three levels: no problems, some problems and severe problems.

The translations of the EQ-5D-3L into local languages have been performed according to a linguistic validation process.

The questions will be assessed at baseline, after 24 weeks and after 52 weeks. The questions (VAS and five dimensions) will take approximately 5 minutes to answer. The patients need to be able to read and to be fluent in the local language to be able to answer the questions.

6.5.2 DTSQs and DTSQc

The DTSQ has been developed to assess patient´s satisfaction with treatment and perception of change in hyper- and hypoglycaemia (Bradley 1994). The DTSQ has 2 versions, the DTSQ status version (DTSQs) and the DTSQ change version (DTSQc) (see Appendix G). Both versions have 8 items, with a small difference in item 7. The DTSQc instructions and response options differ from those of the DTSQs, as the relative change in satisfaction will be assessed

instead of a measure of absolute satisfaction. The DTSQs will be used at baseline, week 24 and at week 52 and the DTSQc at week 52 (end of treatment).

For clarity regarding satisfaction among patients that discontinue an Early Termination DTSQc will be used for those patients, only difference is information to patient regarding recall time.

The Early Termination DTSQc has a recall time of "For the past few weeks/months…" This is to establish if the dropout is due to problems/dissatisfaction or some other reason. The patient may leave the study, for example if they move, yet still be satisfied with treatment. This information needs to be captured. Both the DTSQs and the Early Termination DTSQc should be used for early-terminated patients.

Translations of the DTSQs and DTSQc into local languages have or will be performed according to a linguistic validation process.

6.5.3 SHIELD-WQ-9

The SHIELD-WQ-9 measures HRQL in response to self-perceived weight change. It consists of two questions where question 1 asks the patient if she/he has gained, lost weight or stayed at the same and question 2 is based on response to question 1 and asks about effects (nine dimensions) due to change or lack of change in body weight using four response options: worsen, improved, stayed the same and not applicable.

The questions have been used in the observational study SHIELD - Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (Bays et al 2007a, Bays et al 2007b). It is included for exploratory purposes and the questions will be assessed at baseline, after 24 weeks and after 52 weeks.

Translations of the questions into local languages have or will be performed according to a linguistic validation process.

6.5.4 IWQOL-Lite

The IWQOL-Lite is a 31-item measure that assesses quality of life in overweight/obese individuals. The measure consists of scores on five dimensions-physical function (11 items), self-esteem (7 items), sexual life (4 items), public distress (5 items) and work (4 items), in addition there is a global score (sum of scale scores). Participants are asked to rate items with respect to the past week on this instrument (from never true to always true). Scores on the IWQOL-Lite (domains and global score) range from 0-100. Higher scores indicate poorer quality of life (Kolotkin et al 2002).The IWQOL-Lite has demonstrated excellent psychometric properties in overweight persons seeking treatment, in a community setting and in persons with and without diabetes (Kolotkin et al 2003). IWQOL-Lite is included for exploratory purposes and the questions will be assessed at baseline, after 24 weeks and after 52 weeks.

Translations of the questions into local languages have or will be performed according to a linguistic validation process.

6.5.5 Administration of PRO questionnaires

The instruments/questions will be self-administered using paper and pencil questionnaires. It is important to administer the questionnaire and questions according to recommendation for standardized administration. The patient should be informed about how important his/her participation is. The patients should complete the questionnaire/questions before any other study related procedures take place and before any communication with the study personnel.

The questionnaire/questions should be completed in a quiet place without influence from study personnel or accompanied family or friend. The staff at the clinic should never help the patient to choose an answer and must be neutral in their response to the patient's questions. The staff at the clinic is not allowed to interpret or rephrase the questions for the patient. After the patient has completed the questionnaire and questions, the study personnel will review the questionnaire/questions for completeness only.

6.6 Pharmacokinetics (Not applicable)

6.7 Pharmacodynamics (Not applicable)

6.8 Pharmacogenetics

6.8.1 Collection of pharmacogenetic samples

The 10 mL blood sample for genetic research will be obtained from the patients at randomisation, at Visit 4. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an Adverse Event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 4, it may be taken at any visit until Visit 8. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Please see Appendix D for further guidance.

6.9 Health economics (Not applicable)

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

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

Table 9 Volume of blood to be drawn from each patient

Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
HbA1c	2	2	4
Haematology (including HbA1c)	3	11	33
FPG	2	13	26
Other safety and efficacy assessments (see Table 7, Table 8)	3.5	13	45.5
Other safety and efficacy assessments (see Table 7, Table 8)	5	3	15
Pharmacogenetics [a]	10.0	1	10.0
Total			123.5 (133.5)[b]

a) Genetic blood sample donation is optional.
b) The total blood volume stated within brackets includes the optional genetic blood sample. Extra blood samples in case of unscheduled, specialized liver/liver discontinuation visits are not included. Rescue visits are included.

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed after analyses. Pharmacogentic samples will be retained for further use as described in Appendix D.

7.3 Labelling and shipment of biohazard samples

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

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

7.4 Chain of custody of biological samples

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

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

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

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

Samples retained for further use is registered in AstraZeneca bio bank system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca and/or Bristol-Myers Squibb are not obliged to destroy the results of this research.

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

Note: As collection of the pharmacogenetic samples is not an integral part of the study, any patient withdrawing consent for donated pharmacogenetic sample will be not withdrawn from further study participation.

The Principal Investigator:

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

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

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

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

8.2 Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

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

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

8.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients

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

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

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

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

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

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

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

8.4 Informed consent

A screening and enrolment Informed Consent Form will be provided to all the sites, and implemented locally, when possible, based on all applicable regulatory requirements and laws.

The Principal Investigator(s) at each centre will:

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

The genetic research is optional and the patient may participate in the main study without participating in the genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for the main study (non-genetic components of the study) and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The

principal investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue the genetic aspect of the study at any time.

8.5 Changes to the protocol and informed consent form

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

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

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

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

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

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

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

8.6 Audits and inspections

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

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

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

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

9.2 Training of study site personnel

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

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

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

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

9.3 Monitoring of the study

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

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in

accordance with the Laboratory Manual and that investigational products accountability checks are being performed

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

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

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

9.3.1 Source data

Refer to Clinical Study Agreement for location of source data.

9.4 Study agreements

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

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

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.5 Study timetable and end of study

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

The study is expected to start in Q4 2011 and to end by Q3 2013.

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

10. DATA MANAGEMENT BY COGNIZANT

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

Data will be entered in the Web Based Data Capture (WBDC) system at the study site. Trained study personnel will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the eCRF Instructions. The eCRF Instructions will also guide the study site in performing data entry. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. The data will then be Source Data Verified (SDV), reviewed/ queried and updated as needed. Principal Investigator is responsible for signing the eCRF and this can be delegated to a trained Investigator. The eCRF is signed electronically as per the eCRF instructions.

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

The data will be frozen and then locked to prevent further editing. When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked. Copy of the database will be provided to the study centre for archiving.

The study Data Management Plan will describe in greater detail the methods used to collect, check, and process clinical data. It will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process. Prior to breaking the treatment codes, all decisions on the evaluability of the data from each individual patient must have been made and documented. Following database lock, required amendments to the database due to critical errors will only be allowed with the appropriate supporting documentation. Non-critical errors will not result in amendments to the database but will be captured by study team via the appropriate documentation in Study Master File.

Management of external data

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

Dictionary coding

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

Management of genotype data

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

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

Data associated with biological samples

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

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

11.1 Calculation or derivation of efficacy variable(s)

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

11.1.1 Change and percent change from baseline

Change from baseline will be calculated as absolute difference between the value measured at or derived for a specific time point after baseline minus baseline value. Baseline is defined as the last value collected on/or prior to Visit 4 (randomisation).

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

11.1.2 Last observation carried forward (LOCF)

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

11.2 Calculation or derivation of safety variable(s)

11.2.1 Other safety variables

The safety evaluations will include analyses of AEs, laboratory parameters, ECG, vital signs (pulse and BP), orthostatic BP, hypoglycaemic events, cardiovascular events and physical examination. The analysis of safety will be based on the safety analysis set. Safety data gained during the 24-week double-blind treatment period, the 28-week extension period and the 3-week safety follow-up period will be evaluated. Safety variables will be summarized descriptively.

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

Males:

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

Females:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \; x \; (140 - \text{Age})}{72 \; x \; \text{serum creatinine (mg/dL)}} \; x 0.85$$

The MDRD equation will be used to calculate eGFR.

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

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

11.2.2 Other significant Adverse Events (OAE)

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

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

11.3 Calculation or derivation of patient reported outcome variables

11.3.1 EuroQol (EQ-5D-3L)

The respondent rates his/her current health state on the EQ VAS by drawing a line from the box marked "your health state today" to the appropriate point on the EQ VAS. A three-digit number between 000 and 100 is read off the thermometer, from the exact point where the line crosses the scale, for example, 046 or 098. This is the EQ VAS score. In order to achieve comparable results, it is necessary to adhere to the standard text and instructions and layout of EQ VAS.

The EQ-5D-3L index includes five dimensions and each dimension has three levels: no problem, some problem and severe problem. A utility weight, elicited from the general

population, is assigned to each health state. In this study the EQ-5D-3L index values will be calculated using the European VAS value set (Greiner 2003).

11.3.2 DTSQs and DTSQc

The scoring of the DTSQs are presented below and include measures of satisfaction:

- Treatment Satisfaction: The following items will produce a Treatment Satisfaction core: Items 1, 4, 5, 6, 7 and 8 (range 0-36). The higher the score, the greater the satisfaction with treatment.

- Individual satisfaction with treatment items (1, 4, 5, 6, 7 and 8). All rated: 6 (very satisfied, convenient, flexible etc) to 0 (very dissatisfied, inconvenient, inflexible etc.) The higher the score, the greater the satisfaction with each aspect of treatment.

- 'Perceived frequency of hyperglycaemia' (item 2) and 'Perceived frequency of hypoglycaemia' (item 3). Both rated: 6 (most of the time) to 0 (none of the time). Lower scores indicate levels closer to the ideal and higher indicate problems.

The scores from the DTSQs assessed at baseline will be presented using the calculations above.

The scoring of the DTSQc are presented below and include measures of relative change in satisfaction:

- Treatment Satisfaction (change): items 1, 4, 5, 6, 7 and 8 are summed to produce a Treatment Satisfaction (change) score (range +18 to –18). The higher (lower) the score, the greater the improvement (deterioration) in satisfaction with treatment. A score of 0 represents no change.

- Individual satisfaction with treatment change items (1, 4, 5, 6, 7 and 8), range +3 to –3. The higher (lower) the score, the greater the improvement (deterioration) in satisfaction of each aspect of treatment.

- Perceived frequency of hyperglycaemia' (item 2) and 'Perceived frequency of hypoglycaemia' (item 3) range +3 ('much more of the time now') to –3 ('much less of the time now'): Negative scores indicate fewer problems with blood glucose levels. Positive scores indicate more problems than before.

The scores from the DTSQc assessed at week 52 will be presented using the calculations above.

11.3.3 SHIELD-WQ-9

The response options from the two questions will be presented as number and percent of patients on scores predetermined on each response option. The response options are '1-3' on Question 1 and '1-4' on Question 2.

11.3.4 IWQOL-Lite

Raw scores for each domain are computed for each of the five domains only if a minimum of 50% of the items are answered, and for the total score only if 75% of the answers are completed. When scoring a domain with missing items, pro-rate scores on individual domain (or on total score) using average score of other items on that scale (or on total score).

Raw scores are calculated for each domain and total score as follows:

1. Compute the average for the valid responses to items for that domain (5=always true, 4=usually true, 3=sometimes true, 2=rarely true, 1=never true).

2. Multiply that average by the total number of items for that domain (Physical function=11, Self-esteem=7, Sexual=4, Public distress=5, Work=4, Total=31).

3. Round to the nearest whole integer.

Transformed scores (0-100 format similar to SF36) are calculated as follows:

1. Subtract the raw score (as calculated above) from the maximum score for each domain (Physical function=55, Self-esteem=35, Sexual=20, Public distress=25, Work=20, Total=155).

2. Divide that difference by the range of each domain (Physical function=44, Self esteem=28, Sexual=16, Public distress=20, Work=16, Total=124).

3. Multiply that total by 100.

11.4 Calculation or derivation of pharmacokinetic variables (Not applicable)

11.5 Calculation or derivation of pharmacodynamic variable(s) (Not applicable)

11.6 Calculation or derivation of pharmacogenetic variables

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

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

12.1 Description of analysis sets

The evaluation of efficacy will be performed for the full analysis set as outlined below. The primary efficacy variable and selected secondary variables may be reanalyzed using the per-protocol analysis set if more than 10% of the patients in any treatment group in the full analysis set are excluded from the per-protocol analysis set.

The primary analysis will be based on the full analysis set using the last observation carried forward approach (LOCF).

The analysis of safety will be based on the safety analysis set.

A detailed description of analysis sets is given below. The decision to include or exclude patients from each analysis set will be based on relevant protocol deviations and will be performed in a blind data review prior to unblinding. A summary of the number of patients per analysis set will be given and reasons for exclusion of patients from an analysis set will be listed.

12.1.1 Full analysis set

The full analysis set will include all randomised patients (as randomised) who received at least one dose of study medication during the 24-week double-blind short-term treatment period who have a non-missing baseline value and at least one post-baseline value for at least one efficacy variable to be analyzed at week 24. The intention-to-treat principle will be preserved despite the exclusion of patients who took no study medication, as the decision of whether or not to begin treatment during the randomised treatment period could not be influenced by knowledge of the assigned treatment. Where appropriate, missing data will be replaced using the last observation carried forward (LOCF) approach.

12.1.2 Per-protocol analysis set

The per-protocol analysis set is a subset of the full analysis set consisting of patients who do not violate the terms of the protocol, which may affect the primary efficacy endpoint significantly. All decisions to exclude patients from the full analysis set to create the per-protocol analysis set will be made prior to the unblinding of the study.

12.1.3 Safety analysis set

The safety analysis set will include all randomised patients who received at least one dose of study medication and who provide any safety records. Patients who were dispensed the wrong randomised treatment (ie those randomised to dapagliflozin 10 mg but actually given placebo, or vice versa) for the duration of the first 24 weeks will be counted in the treatment group for which they received medication. Where appropriate, missing data will be replaced using the last observation carried forward (LOCF) approach.

12.2 Methods of statistical analyses

12.2.1 Analysis of the 24-week double-blind short-term treatment period

The primary objective of this study is to show superiority of dapagliflozin versus placebo in terms of the primary efficacy variable change in HbA1c from baseline to week 24.

The following null hypothesis H_0 will be tested against the alternative hypothesis H_A (α=0.050, two-sided):

H_0: $\mu_T - \mu_P = 0$,

H_A: $\mu_T - \mu_P \neq 0$,

where μ_T denotes the mean absolute change in HbA1c from baseline to week 24 in the group of patients treated with dapagliflozin as add-on therapy to on a combination of a sulfonylurea and metformin (test medication, T) and μ_P the mean absolute change in HbA1c from baseline to week 24 in the group of patients treated with placebo as add-on therapy to a combination of a sulfonylurea and metformin (placebo, P).

Four key secondary variables have been identified:

- Change in fasting plasma glucose (FPG) from baseline to 24 weeks.
- Change in total body weight from baseline to week 24.
- Proportion of patients achieving a therapeutic glycaemic response, defined as HbA1c <7.0%, 24 weeks.
- Change in seated systolic blood pressure (SBP) from baseline to week 8.

A hierarchical closed testing procedure will be used to control the Type I error rate across the primary and key secondary objectives. If the primary endpoint is statistically significant, key secondary variables will be tested in the order presented within this protocol. Treatment comparisons will be individually tested at a two-sided significance level of 0.050. For all other variables, nominal p-values will be reported without significance testing.

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

The primary and secondary efficacy analyses will be based on the full analysis set. The primary efficacy variable and selected secondary variables may be reanalyzed using the per-protocol analysis set if more than 10% of the patients in any treatment group in the full analysis set are excluded from the per-protocol analysis set.

The LOCF approach means that for all changes (or percent changes) from baseline to a specific time point post-baseline, analyses will be based on measurements available at that time point or the last post-baseline measurement prior to the time point, if no measurement is

available at that time point. Unless otherwise specified, if a patient initiates rescue medication, the last value taken on or before the first rescue dose will be used for analysis.

The primary efficacy variable, change in HbA1c from baseline to week 24, will be analyzed by an analysis of covariance (ANCOVA) model including terms for treatment group and baseline covariate. The ANCOVA model will be used to derive a least squares estimate of the treatment difference with 95% confidence interval and corresponding two-sided p-value. Further, two-sided 95% confidence intervals for the mean change within each treatment group will be calculated. The same method will be applied for analyzing other continuous efficacy variables.

The proportion of patients achieving a therapeutic glycaemic response, defined as HbA1c <7.0%, at week 24, will be analyzed using the methodology of Zhang, Tsiatis and Davidian and Tsiatis, Davidian, Zhang and Lu when there are at least 5 responders on average by treatment group. For proportion of responders, estimates, confidence intervals, and tests will be obtained using this methodology with adjustment for baseline HbA1c. For each treatment group, the probability of response is first modeled using a logistic regression model with baseline HbA1c as a term. Treatment group estimates of response rate are then obtained by integrating each group's modeled probability of response over the observed distribution of baseline covariate). The difference in response rate between dapagliflozin and placebo will be displayed along with the 95% confidence intervals. P-values will be calculated (when applicable). When there are less than 5 responders on average by treatment group, the unadjusted proportions and difference between unadjusted proportions, exact 95% confidence interval, and p-values from the Fisher's exact test (when applicable) will be provided. The same method will be applied for analyzing other proportions of patients achieving a pre-defined response.

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

The time course of 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 change (absolute or percent) from baseline to each scheduled measuring time point after baseline and the last individual measuring time point.

Due to the large number of centres and the expected low number of patients per centre it will not be appropriate to explore centre effects. Tables by region will be provided in order to explore regional effects. Regional effects will be included in the statistical model in additional exploratory analyses if appropriate. Any pooling of regions with few patients in geographical clusters will be specified in the Statistical Analysis Plan (SAP) before breaking the blind.

12.2.2 Analysis after the 28-week site- and patient-blinded extension period

All variables to be analyzed after the 24 weeks of double-blind treatment will be re-examined at the week 52 time point. In general, the data from this period will be summarized descriptively using point estimates and 95% confidence intervals. Details of the planned analyses will be provided in a separate Statistical Analysis Plan (SAP) specific to this period. The results from the extension period will be reported separately.

12.2.3 Analysis of safety

The safety evaluations will include analyses of AEs, laboratory values, ECG, vital signs (pulse and blood pressure), hypoglycaemic events, calculated creatinine clearance, estimated glomerular filtration rate and physical examination findings.

The analysis of safety will be based on the safety analysis set. Safety data gained during the 24-week double-blind treatment period, the 28-week site- and patient-blinded extension period as well as during the 3-week safety follow-up period will be evaluated. Safety data will be summarized descriptively and presented by treatment group. The primary safety analyses include all data regardless of rescue. For data such as hypoglycaemia, sensitivity analyses may be performed on data collected prior to rescue by replacing missing data using the LOCF approach.

12.2.4 Analysis of pharmacogenetic variables

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. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated.

12.2.5 Interim analyses

The study will declare database lock after the first 24 weeks of randomised double-blind treatment are completed in order to perform the confirmatory efficacy and safety analyses. Additional analyses for data up to 52 weeks of randomised treatment are considered to be supplemental.

12.3 Determination of sample size

The sample size for this study was selected to demonstrate a difference in the mean change in HbA1c from baseline to week 24 between dapagliflozin and placebo in patients on a combination of metformin and sulfonylurea.

To detect a difference of 0.5% between dapagliflozin versus placebo for change in HbA1c from baseline to week 24, assuming a standard deviation (SD) =1.1%, 103 evaluable patients (full analysis set) for each treatment group would provide 90% power at a significance level = 0.050. Assuming that 5% of the patients will not be evaluable in the full analysis set, 108 patients per treatment group (216 patients total) are planned for randomisation.

In 6-month dapagliflozin studies, a SD of 1.1% was selected based upon the Phase II dapagliflozin study as well as historical data from other diabetes programs.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

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

In the case of a medical emergency the investigator may contact the Study Leader. If the Study Leader is not available, contact the Study Physician at the AstraZeneca Marketing Company site shown below.

Name	Role in the study	Address & telephone number
	Study Leader responsible for the protocol	
	Study Physician responsible for the protocol at MC site	

13.2 Overdose

Overdose is defined as the accidental or intentional ingestion of any dose of investigational product that is considered both excessive and medically important. Dapagliflozin has been well tolerated at doses of up to 500 mg/day in single dose testing in healthy volunteers and up to 100 mg/day in repeat dose testing for 14 days in healthy volunteers and patients with type 2 diabetes. Once an investigator decides that a particular occurrence is an overdose, it must be reported as a Serious Adverse Event. If an overdose is suspected, monitoring of vital functions as well as treatment as appropriate should be performed.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

Pregnancy itself is not regarded as an Adverse Event unless there is a suspicion that the investigational product under study and/or metformin and/or sulfonylurea may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions

without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

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

The PREGREP module in the CRF is used to report the pregnancy. This module in the eCRF should be completed by the investigator and the AstraZeneca representative will forward the information to Bristol Myers Squibb using the same procedure as for SAE reporting. An AstraZeneca paper Pregnancy Outcome Report, part 2, is used to report the outcome of the pregnancy.

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AstraZeneca

Clinical Study Protocol Appendix A

Drug Substance	dapagliflozin
Study Code	D1693C00005
Edition Number	1
Protocol Dated	

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A 24-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled, International Phase III Study with a 28-week Extension Period to Evaluate the Safety and Efficacy of Dapagliflozin 10mg once daily in Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on a background combination of Metformin and Sulfonylurea

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

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

AstraZeneca Research and Development site representative

ASTRAZENECA SIGNATURE(S)

A 24-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled, International Phase III Study with a 28-week Extension Period to Evaluate the Safety and Efficacy of Dapagliflozin 10mg once daily in Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on a background combination of Metformin and Sulfonylurea

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

AstraZeneca Research and Development site representative

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A 24-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled, International Phase III Study with a 28-week Extension Period to Evaluate the Safety and Efficacy of Dapagliflozin 10mg once daily in Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on a background combination of Metformin and Sulfonylurea

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

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice and local regulations, and I ensure that all relevant site staff follows the instructions given in the latest version of the Laboratory Manual for Investigators.

Centre No.:

Signature:

Clinical Study Protocol Appendix B

Drug Substance	dapagliflozin
Study Code	D1693C00005
Edition Number	1

Appendix B
Additional Safety Information

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

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous 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	D1693C00005
Edition Number	1

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

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

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

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

Clinical Study Protocol Appendix D

Drug Substance	dapagliflozin
Study Code	D1693C00005
Appendix Edition Number	1
Appendix	

Appendix D
Pharmacogenetics Research

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
DNA	Deoxyribonucleic acid
EDTA	Ethylenediamine tetra-acetic acid
ICH	International Conference on Harmonisation
LIMS	Laboratory information management system
PGx	Pharmacogenetics

1. BACKGROUND AND RATIONALE

AstraZeneca and Bristol-Myers Squibb intend to perform genetic research in the dapagliflozin clinical development programme to explore how genetic variations may affect the clinical parameters associated with dapagliflozin where appropriate. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Future research may suggest genes or gene categories as candidates for influencing not only response to dapagliflozin in background combination of metformin and SU, but also susceptibility to Type 2 Diabetes for which dapagliflozin may be evaluated. Thus, this genetic research may involve study of un-named genes or gene categories, but only as related to Type 2 Diabetes susceptibility and drug action.

2. GENETIC RESEARCH OBJECTIVES

The objective of this research is to collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) and/or susceptibility to Type 2 Diabetes to dapagliflozin and agents used in combination or as comparators.

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Selection of genetic research population

3.1.1 Study selection record

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

3.1.2 Inclusion criteria

For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

3.1.3 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
- Whole blood transfusion in 120 days of genetic sample collection

3.1.4 Discontinuation of subjects from this genetic research

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

- Withdrawal of consent for genetic research: Subjects 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 Collection of samples for genetic research

The blood sample for genetic research will be obtained from the subjects at Visit 4. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 4, it may be taken at any visit until the Visit 8. Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume, see Section 7.1 of the Clinical Study Protocol.

3.3 Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

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 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.

4. ETHICS

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 8 of the main Clinical Study Protocol.

4.1 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 must be 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.

4.2 Subject data protection

AstraZeneca will not provide individual genotype results to subjects, 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 subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

5. DATA MANAGEMENT

Any genotype data generated in this study will be in the Bristol-Myers Squibb or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyze the samples.

The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

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.

Clinical Study Protocol Appendix E

Drug Substance	dapagliflozin
Study Code	D1693C00005
Edition Number	1

Appendix E
Visit to Visit Guide

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LIST OF TABLES

1. BACKGROUND

The purpose of this appendix is to provide a detailed visit to visit guide. Procedures are listed in the sequence in which they should be performed. However, if site staff organises visits differently, the following rules must be obeyed:

1. At randomisation visit all examinations, measurements and samplings must be done before first dose of investigational product is taken.

2. Blood pressure measurements must be taken before blood samples are taken.

3. At each visit blood and urine samples must be taken and body weight must be measured before taking medications at clinic.

4. Patient Reported Outcome questionnaires must be completed by patient at Visits 4, 8 and 11 before any other procedures are done.

2. VISIT TO VISIT GUIDE

Table 1 Visit windows

Visit	Time	Time window (days)
Screening Visit	-11 weeks	≤14 days prior to Enrolment
Visit 1 (Enrolment)	-9 weeks	up to 14 days from Screening
Visit 2	-8 weeks	±3 days
Visit 3	-2 weeks	±3 days
Visit 4 (Randomisation)	0	±3 days
Visit 5	4 weeks	±3 days
Visit 6	8 weeks	±3 days
Visit 7	16 weeks	±7 days
Visit 8	24 weeks	±7 days
Visit 9	32 weeks	±7 days
Visit 10	40 weeks	±7 days
Visit 11 (End of Treatment)	52 weeks	±7 days
Visit 12 (Follow-up)	55 weeks	±7 days

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

2.1 Screening Visit

Investigator will screen only patients who are potentially eligible for the study, in terms of medical conditions and existing therapies.

After obtaining written informed consent for screening, site staff will take blood sample for HbA1c test. Subjects with result of 7.7% ≤HbA1c ≤11.0% will be scheduled for an enrolment visit within 14 days.

Patient should be fasting at the next visit.

2.2 Visit 1 – Enrolment (week –9)

The following procedures should be done in the order shown:

- Obtain written informed consent (ICF) before any other study associated procedures are done. Document process in source documentation.
- Inform the patient of the optional genetic section of the study
- Document patient demographics data (date of birth, gender, race and ethnic group)
- Document medical history
- Document concomitant medications; for metformin, sulfonylurea, anti-hypertensive agents, diuretics and statins daily dose should be recorded in eCRF
- Assess inclusion and exclusion criteria (see Section 4.1 and 4.2 in the Clinical Study Protocol)
- Allocate a unique Enrolment code (E-code) to the patient through IWRS/IVRS
- Perform complete physical examination (including general appearance, head, eyes, ears, nose, throat, neck, cardiovascular system, lungs, abdomen, lymph nodes, extremities, neurological system, skin, and musculoskeletal system). The patient should always be evaluated for the presence of oedema.
- Measure blood pressure and pulse (see Section 6.4.8.1 in the Clinical Study Protocol)
- Obtain 12-lead Electrocardiogram (ECG) (see Section 6.4.7 in the Clinical Study Protocol)
- Draw a blood samples including Hepatitis Screen Panel and send to the central lab
- Take urine sample from the patient and send to central laboratory

- Perform a urine pregnancy test (only applicable to women of childbearing potential)
- Measure patient's weight and height
- Measure patient's waist circumference
- SAEs are collected from the time point of signing the ICF
- Give diet and lifestyle advice
- Explain patient the use of concomitant medications on the day of the visits
- Schedule Visit 2 one week after Visit 1, ask patient to be fasting at the next visit
- Complete electronic Case Report Form (eCRF) within 72 hours.

2.3 Visit 2 – start of Placebo lead-in period (week –8)

Visit 2 will occur 1 week after Visit 1.

Visit 2 can be performed by telephone if the patient is not eligible based on the laboratory results from Visit 1 and the patient can be terminated.

If laboratory values from Visit 1 confirm patient eligibility, the following procedures should be done in the order shown:

- Measure blood pressure and pulse
- Draw a blood sample and send to the central laboratory
- Perform a urine pregnancy test (only applicable to women of childbearing potential)
- Measure patient's weight
- Document concomitant medications: for metformin, sulfonylurea, anti-hypertensive agents, diuretics and statins daily dose should be recorded in eCRF
- Collect and document SAEs and fill in event forms when applicable
- Perform brief physical examination (including checking the cardiovascular system, lungs, abdomen, and extremities, and any organ system pertinent to the patient's signs, symptoms, or AEs). The patient should always be evaluated for the presence of oedema.
- Assign 2 bottles of Investigational Product via IWRS (patient should not be informed that she/he receives placebo), verify kit in IWRS and dispense IP

- Dispense glucometer, explain the use of the device and provide supplies and instructions
- Dispense patient diary
- Give diet and lifestyle advice
- Schedule Visit 3 seven weeks after Visit 1, ask the patient to be fasting and give instructions what concomitant and background medications are NOT allowed to take in the morning of the next visit
- Complete eCRF within 72 hours.

2.4 Visit 3 (week –2)

Visit 3 will occur 7 weeks after Visit 1.

The following procedures should be done in the order shown:

- Assess laboratory results from Visit 2 for inclusion and exclusion criteria
- Measure blood pressure and pulse
- Draw a blood sample for HbA1c (to be used for evaluation on inclusion criterion at Randomisation) and send to the central laboratory
- Draw a blood sample and send to the central laboratory
- Perform a urine pregnancy test (only applicable to women of childbearing potential)
- Measure patient's weight
- After blood pressure measurement, and blood and urine sampling, patient should take investigational product along with other medications.
- Check returned investigational product and complete drug accountability
- Review patient's diary for glucometer values/hypoglycaemic events and dispense new diary
- If applicable, provide supplies and instructions for the glucometer
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications: for metformin, sulfonylurea, anti-hypertensive agents, diuretics and statins daily dose should be recorded in eCRF

- Give diet and lifestyle advice
- Schedule Visit 4 nine weeks after Visit 1, ask the patient to be fasting and give instructions what concomitant and background medications are NOT allowed to take in the morning of the next visit
- Complete eCRF within 72 hours.

2.5 Visit 4 – Randomisation (week 0)

Randomisation Visit will be scheduled 9 weeks after Enrolment Visit.

The following procedures should be done in the order shown:

- Ask patient to complete questionnaires in following sequence: EQ-5D-3L, SHIELD-WQ-9 baseline, IWQOL-Lite and DTSQs
- Assess inclusion and exclusion criteria
- Measure blood pressure and pulse
- Measure orthostatic blood pressure and pulse
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Perform a urine pregnancy test (only applicable to women of childbearing potential)
- Measure patient's weight
- Measure patient's waist circumference
- Obtain 12-lead Electrocardiogram (ECG)
- After obtaining written informed consent for genetic sub-study, draw blood sample for genetics and send to central laboratory (This sample can be obtained at any further visit till Visit 8)
- Check returned investigational product and complete drug accountability
- Review patient's diary for glucometer values/hypoglycaemic events and dispense new diary
- If applicable, provide supplies and instructions for the glucometer
- Perform a complete physical examination

- Randomise subject via IWRS/IVRS
- Allocate, verify and dispense Investigational Product kit via IWRS/IVRS (dapagliflozin/placebo)
- First dose of investigational product should be witnessed. After blood pressure and weight measurements, and blood and urine sampling, patient should take investigational product along with other medications.
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications: for metformin, sulfonylurea, anti-hypertensive agents, diuretics and statins daily dose should be recorded in eCRF
- Give diet and lifestyle advice
- Schedule Visit 5 four weeks after Visit 4, ask the patient to be fasting and give instructions what concomitant and background medications are NOT allowed to take in the morning of the next visit
- Complete eCRF within 72 hours.

2.6 Visit 5 (week 4)

Visit 5 will occur 4 weeks after Visit 4.

The following procedures should be done in the order shown:

- Measure blood pressure and pulse
- Measure orthostatic blood pressure and pulse
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Perform a urine pregnancy test (only applicable to women of childbearing potential)
- Measure patient's weight
- After blood pressure and weight measurements, and blood and urine sampling, patient should take investigational product along with other medications.
- Check drug accountability. Collect from patient all used and unused bottles with investigational product.

- Review patient's diary for glucometer values/hypoglycaemic events and dispense new diary
- If applicable, provide supplies and instructions for the glucometer
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications; for metformin, sulfonylurea, anti-hypertensive agents, diuretics and statins daily dose should be recorded in eCRF
- Perform brief physical examination (see details at Visit 2)
- Allocate, verify and dispense Investigational Product kit via IWRS/IVRS (dapagliflozin/placebo)
- Give diet and lifestyle advice
- Schedule Visit 6 eight weeks after Visit 4, ask the patient to be fasting and give instructions what concomitant and background medications are NOT allowed to take in the morning of the next visit
- Complete eCRF within 72 hours.

2.7 Visit 6 (week 8)

Visit 6 will occur 8 weeks after Visit 4.

The following procedures should be done in the order shown:

- Measure blood pressure and pulse
- Measure orthostatic blood pressure and pulse
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Perform a urine pregnancy test (only applicable to women of childbearing potential)
- Measure patient's weight
- After blood pressure and weight measurements, and blood and urine sampling, patient should take investigational product along with other medications
- Review patient's diary for glucometer values/hypoglycaemic events and dispense new diary

- If applicable, provide supplies and instructions for the glucometer
- Check drug accountability. Collect from patient all used and unused bottles with investigational product.
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications: for metformin, sulfonylurea, anti-hypertensive agents, diuretics and statins daily dose should be recorded in eCRF
- Perform brief physical examination (see details at Visit 2)
- Allocate, verify and dispense Investigational Product kits via IWRS/IVRS (dapagliflozin/placebo)
- Give diet and lifestyle advice
- Schedule Visit 7 sixteen weeks after Visit 4, ask the patient to be fasting and give instructions what concomitant medications are allowed to take in the morning of the next visit
- Complete eCRF within 72 hours.

2.8 Visit 7 (week 16)

Visit 7 will occur 16 weeks after Visit 4.

The following procedures should be done in the order shown:

- Measure blood pressure and pulse
- Measure orthostatic blood pressure and pulse
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Perform a urine pregnancy test (only applicable to women of childbearing potential)
- Measure patient's weight
- After blood pressure and weight measurements, and blood and urine sampling, patient should take investigational product along with other medications.
- Review patient's diary for glucometer values/hypoglycaemic events and dispense new diary

- If applicable, provide supplies and instructions for the glucometer
- Check drug accountability. Collect from patient all used and unused bottles with investigational product.
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications: for metformin, sulfonylurea, anti-hypertensive agents, diuretics and statins daily dose should be recorded in eCRF
- Perform brief physical examination (see details at Visit 2)
- Allocate, verify and dispense Investigational Product kits via IWRS/IVRS (dapagliflozin/placebo)
- Give diet and lifestyle advice
- Schedule Visit 8 twenty four weeks after Visit 4, ask the patient to be fasting and give instructions what concomitant medications are allowed to take in the morning of the next visit
- Complete eCRF within 72 hours.

2.9 Visit 8 (week 24)

Visit 8 will occur 24 weeks after Visit 4.

The following procedures should be done in the order shown:

- Ask patient to complete questionnaires in following sequence: EQ-5D-3L, SHIELD-WQ-9, IWQOL-Lite and DTSQs
- Measure blood pressure and pulse
- Measure orthostatic blood pressure and pulse
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Perform a urine pregnancy test (only applicable to women of childbearing potential)
- Measure patient’s weight
- Measure patient’s waist circumference
- Obtain 12-lead Electrocardiogram (ECG)

- After blood pressure and weight measurements, and blood and urine sampling, patient should take investigational product along with other medications
- Review patient's diary for glucometer values/hypoglycaemic events and dispense new diary
- If applicable, provide supplies and instructions for the glucometer
- Check drug accountability. Collect from patient all used and unused bottles with investigational product.
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications: for metformin, sulfonylurea, anti-hypertensive agents, diuretics and statins daily dose should be recorded in eCRF
- Perform a complete physical examination
- Allocate, verify and dispense Investigational Product kits via IWRS/IVRS (dapagliflozin/placebo)
- Give diet and lifestyle advice
- Schedule Visit 9 thirty two weeks after Visit 4, ask the patient to be fasting and give instructions what concomitant and background medications are NOT allowed to take in the morning of the next visit
- Complete eCRF within 72 hours.

2.10 Visit 9 (week 32)

Visit 9 will occur 32 weeks after Visit 4.

The following procedures should be done in the order shown:

- Measure blood pressure and pulse
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Perform a urine pregnancy test (only applicable to women of childbearing potential)
- Measure patient's weight
- After blood pressure and weight measurements, and blood and urine sampling, patient should take investigational product along with other medications.

- Review patient's diary for glucometer values/hypoglycaemic events and dispense new diary
- If applicable, provide supplies and instructions for the glucometer
- Check drug accountability. Collect from patient all used and unused bottles with investigational product.
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications: for metformin, sulfonylurea, anti-hypertensive agents, diuretics and statins daily dose should be recorded in eCRF
- Perform brief physical examination (see details at Visit 2)
- Allocate, verify and dispense Investigational Product kits via IWRS/IVRS (dapagliflozin/placebo)
- Give diet and lifestyle advice
- Schedule Visit 10 forty weeks after Visit 4, ask the patient to be fasting and give instructions what concomitant and background medications are NOT allowed to take in the morning of the next visit
- Complete eCRF within 72 hours.

2.11 Visit 10 (week 40)

Visit 10 will occur 40 weeks after Visit 4.

The following procedures should be done in the order shown:

- Measure blood pressure and pulse
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Perform a urine pregnancy test (only applicable to women of childbearing potential)
- Measure patient's weight
- After blood pressure and weight measurements, and blood and urine sampling, patient should take investigational product along with other medications
- Review patient's diary for glucometer values/hypoglycaemic events and dispense new diary

- If applicable, provide supplies and instructions for the glucometer
- Check drug accountability. Collect from patient all used and unused bottles with investigational product.
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications: for metformin, sulfonylurea, anti-hypertensive agents, diuretics and statins daily dose should be recorded in eCRF
- Perform brief physical examination (see details at Visit 2)
- Allocate, verify and dispense Investigational Product kits via IWRS/IVRS (dapagliflozin/placebo)
- Give diet and lifestyle advice
- Schedule Visit 11 fifty two weeks after Visit 4, ask the patient to be fasting and give instructions what concomitant and background medications are NOT allowed to take in the morning of the next visit
- Complete eCRF within 72 hours.

2.12 Visit 11 – End of Treatment Visit (week 52)

Visit 11 will occur 52 week after Visit 4.

Patients who prematurely discontinue study treatment permanently should return and complete procedures described for End of Treatment Visit as soon as possible after last intake of Investigational Product.

The following procedures should be done in the order shown:

- Ask patient to complete questionnaires in following sequence: EQ-5D-3L, SHIELD-WQ-9, IWQOL-Lite, DTSQs and DTSQc
- Measure blood pressure and pulse
- Measure orthostatic blood pressure and pulse
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Perform a urine pregnancy test (only applicable to women of childbearing potential)
- Measure patient’s weight

- Measure patient's waist circumference
- Obtain 12-lead Electrocardiogram (ECG)
- After blood pressure and weight measurements, and blood and urine sampling, patient should take investigational product along with other medications
- Review patient's diary for glucometer values/hypoglycaemic events
- Check drug accountability. Collect from patient all used and unused bottles with investigational product.
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications: for metformin, sulfonylurea, anti-hypertensive agents, diuretics and statins daily dose should be recorded in eCRF
- Perform a complete physical examination
- Give diet and lifestyle advice
- Schedule Visit 12 three weeks after Visit 11
- Complete eCRF within 72 hours.

2.13 Visit 12 – Follow-up Visit (3 weeks after last intake of investigational product)

Visit 12 will occur 3 weeks after last intake of investigational product, both for patients who completed study treatment according to study schedule and for patients who prematurely discontinued study treatment.

The following procedures should be done in the order shown:

- Measure blood pressure and pulse
- Measure orthostatic blood pressure and pulse
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Perform a urine pregnancy test (only applicable to women of childbearing potential)
- Measure patient's weight
- Obtain 12-lead Electrocardiogram (ECG)

- After blood pressure and weight measurements, and blood and urine sampling, patient should take their medications.
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications: for metformin, sulfonylurea, anti-hypertensive agents, diuretics and statins daily dose should be recorded in eCRF
- Perform a complete physical examination
- Give diet and lifestyle advice
- Complete eCRF within 72 hours.

2.14 Rescue Visit

Rescue criteria for initiation of rescue therapy are in Section 3.1.7 of the Clinical Study Protocol.

The following procedures should be done in the order shown:

- Measure blood pressure and pulse
- Measure orthostatic blood pressure and pulse
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Perform a urine pregnancy test (only applicable to women of childbearing potential)
- Measure patient's weight
- Measure patient's waist circumference
- Obtain 12-lead Electrocardiogram (ECG) (see Section 6.4.7 in the Clinical Study Protocol)
- After blood pressure and weight measurements, and blood and urine sampling, patient should take investigational product along with other medications.
- Review patient's diary for glucometer values/hypoglycaemic events and dispense new diary
- If applicable, provide supplies and instructions for the glucometer
- Collect and document AEs and SAEs and fill in event forms when applicable

- Document concomitant medications: for metformin, sulfonylurea, anti-hypertensive agents, diuretics and statins daily dose should be recorded in eCRF
- Perform a complete physical examination
- Give diet and lifestyle advice
- Complete eCRF within 72 hours.

Appendix F
New York Heart Association (NYHA) Classification

NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION

The NYHA classification will be based on the following definitions:

Class I No limitation:

Ordinary physical exercise does not cause undue fatigue, dyspnoea or palpitations.

Class II Slight limitation of physical activity:

Comfortable at rest but ordinary activity results in fatigue, palpitations, dyspnoea.

Class III Marked limitation of physical activity:

Comfortable at rest but less than ordinary activity results in symptoms.

Class IV Unable to carry out any physical activity without discomfort:

Symptoms of congestive heart failure are present even at rest with increased discomfort with any physical activity.

Clinical Study Protocol Appendix G

Drug Substance	dapagliflozin
Study Code	D1693C00005
Edition Number	1

Appendix G
Patient Reported Outcomes

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Euro-Qol (EQ-5D)

Health Questionnaire

English version for the UK

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

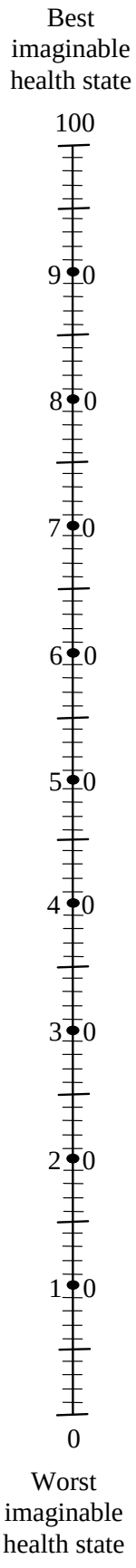
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



SHIELD-WQ-9: Baseline

Questions on weight and health related quality of life

1. **Compared to 3 months ago, have you…** (tick one box)

❑ Gained weight ❑ Lost weight ❑ Stayed the same

2. **Based on your response to question 1 above how did your body weight change(s) or lack of body change affect you in the following areas?**
(tick one box for each statement)

My change or lack of change in body weight had the following effects…	Worsen	Improved	Stayed the same	Not Applicable
How I feel physically – physical health	1 ☐	2 ☐	3 ☐	4 ☐
My interactions with family	1 ☐	2 ☐	3 ☐	4 ☐
My work performance	1 ☐	2 ☐	3 ☐	4 ☐
My interactions with co-workers or friends	1 ☐	2 ☐	3 ☐	4 ☐
My social activities	1 ☐	2 ☐	3 ☐	4 ☐
My daily activities	1 ☐	2 ☐	3 ☐	4 ☐
My self-esteem	1 ☐	2 ☐	3 ☐	4 ☐
How I feel emotionally - emotional health	1 ☐	2 ☐	3 ☐	4 ☐
My overall quality of life	1 ☐	2 ☐	3 ☐	4 ☐

SHIELD-WQ-9

SHIELD-WQ-9: Week 24 and Week 52

Questions on weight and health related quality of life

1. **Since your last visit, have you…** (tick one box)

❑ Gained weight ❑ Lost weight ❑ Stayed the same

2. **Based on your response to question 1 above how did your body weight change(s) or lack of body change affect you in the following areas?**
(tick one box for each statement)

My change or lack of change in body weight had the following effects…	Worsen	Improved	Stayed the same	Not Applicable
How I feel physically – physical health	1 ☐	2 ☐	3 ☐	4 ☐
My interactions with family	1 ☐	2 ☐	3 ☐	4 ☐
My work performance	1 ☐	2 ☐	3 ☐	4 ☐
My interactions with co-workers or friends	1 ☐	2 ☐	3 ☐	4 ☐
My social activities	1 ☐	2 ☐	3 ☐	4 ☐
My daily activities	1 ☐	2 ☐	3 ☐	4 ☐
My self-esteem	1 ☐	2 ☐	3 ☐	4 ☐
How I feel emotionally - emotional health	1 ☐	2 ☐	3 ☐	4 ☐
My overall quality of life	1 ☐	2 ☐	3 ☐	4 ☐

SHIELD-WQ-9

Impact of Weight on Quality of Life Questionnaire—Lite Version (IWQOL-Lite)

Please answer the following statements by circling the number that best applies to you in the past week. Be as open as possible. There are no right or wrong answers.

Physical Function		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I have trouble picking up objects.	5	4	3	2	1
2.	Because of my weight I have trouble tying my shoes.	5	4	3	2	1
3.	Because of my weight I have difficulty getting up from chairs.	5	4	3	2	1
4.	Because of my weight I have trouble using stairs.	5	4	3	2	1
5.	Because of my weight I have difficulty putting on or taking off my clothing.	5	4	3	2	1
6.	Because of my weight I have trouble with mobility.	5	4	3	2	1
7.	Because of my weight I have trouble crossing my legs.	5	4	3	2	1
8.	I feel short of breath with only mild exertion.	5	4	3	2	1
9.	I am troubled by painful or stiff joints.	5	4	3	2	1
10.	My ankles and lower legs are swollen at the end of the day.	5	4	3	2	1
11.	I am worried about my health.	5	4	3	2	1
Self-esteem		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I am self-conscious.	5	4	3	2	1
2.	Because of my weight my self-esteem is not what it could be.	5	4	3	2	1
3.	Because of my weight I feel unsure of myself.	5	4	3	2	1
4.	Because of my weight I don't like myself.	5	4	3	2	1
5.	Because of my weight I am afraid of being rejected.	5	4	3	2	1
6.	Because of my weight I avoid looking in mirrors or seeing myself in photographs.	5	4	3	2	1
7.	Because of my weight I am embarrassed to be seen in public places.	5	4	3	2	1

Sexual Life		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I do not enjoy sexual activity.	5	4	3	2	1
2.	Because of my weight I have little or no sexual desire.	5	4	3	2	1
3.	Because of my weight I have difficulty with sexual performance.	5	4	3	2	1
4.	Because of my weight I avoid sexual encounters whenever possible.	5	4	3	2	1

Public Distress		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I experience ridicule, teasing, or unwanted attention.	5	4	3	2	1
2.	Because of my weight I worry about fitting into seats in public places (e.g. theaters, restaurants, cars, or airplanes).	5	4	3	2	1
3.	Because of my weight I worry about fitting through aisles or turnstiles.	5	4	3	2	1
4.	Because of my weight I worry about finding chairs that are strong enough to hold my weight.	5	4	3	2	1
5.	Because of my weight I experience discrimination by others.	5	4	3	2	1
Work (Note: For homemakers and retirees, answer with respect to your daily activities.)		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I have trouble getting things accomplished or meeting my responsibilities.	5	4	3	2	1
2.	Because of my weight I am less productive than I could be.	5	4	3	2	1
3.	Because of my weight I don't receive appropriate raises, promotions or recognition at work.	5	4	3	2	1
4.	Because of my weight I am afraid to go on job interviews.	5	4	3	2	1

IWQOL-Lite – English (US).

Diabetes Treatment Satisfaction Questionnaire: DTSQs

The following questions are concerned with the treatment for your diabetes (including insulin, tablets and/or diet) and your experience over the past few weeks. Please answer each question by circling a number on each of the scales.

1. How satisfied are you with your current treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

2. How often have you felt that your blood sugars have been unacceptably high recently?

most of the time	6	5	4	3	2	1	0	none of the time

3. How often have you felt that your blood sugars have been unacceptably low recently?

most of the time	6	5	4	3	2	1	0	none of the time

4. How convenient have you been finding your treatment to be recently?

very convenient	6	5	4	3	2	1	0	very inconvenient

5. How flexible have you been finding your treatment to be recently?

very flexible	6	5	4	3	2	1	0	very inflexible

6. How satisfied are you with your understanding of your diabetes?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

7. Would you recommend this form of treatment to someone else with your kind of diabetes?

Yes, I would definitely recommend the treatment	6	5	4	3	2	1	0	No, I would definitely not recommend the treatment

8. How satisfied would you be to continue with your present form of treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

Please make sure that you have circled one number on each of the scales.

Health Psychology Research, Dept of Psychology, Royal Holloway, University of London, Egham, Survey, TW20 0EX, UK

Diabetes Treatment Satisfaction Questionnaire (change): DTSQc

For the past 12 months you have been taking part in a diabetes treatment study. At the start of the stud you may have had a change of treatment. Today we would like to know how your experience of your current treatment (including medication and diet) has changed from your experience of treatment before the study began. Please answer each question by circling a number on each of the scales to indicate the extent to which you have experienced changes. If you have experienced no change, please circle '0'.

1. How satisfied are you with your current treatment?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

2. How often have you felt that your blood sugars have been unacceptably high recently?

much more of the time now	3	2	1	0	-1	-2	-3	much less of the time now

3. How often have you felt that your blood sugars have been unacceptably low recently?

much more of the time now	3	2	1	0	-1	-2	-3	much less of the time now

4. How convenient have you been finding your treatment to be recently?

much more convenient now	3	2	1	0	-1	-2	-3	much less convenient now

5. How flexible have you been finding your treatment to be recently?

much more flexible now	3	2	1	0	-1	-2	-3	much less flexible now

6. How satisfied are you with your understanding of your diabetes?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

7. How likely would you be to recommend your present treatment to someone else with your kind of diabetes?

much more likely to recommend the treatment now	3	2	1	0	-1	-2	-3	much less likely to recommend the treatment now

8. How satisfied would you be to continue with your present form of treatment?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

Please make sure that you have circled one number on each of the scales.

Diabetes Treatment Satisfaction Questionnaire (change): DTSQc – Early Termination

For the past few weeks/months you have been taking part in a diabetes treatment study. At the start of the stud you may have had a change of treatment. Today we would like to know how your experience of your current treatment (including medication and diet) has changed from your experience of treatment before the study began. Please answer each question by circling a number on each of the scales to indicate the extent to which you have experienced changes. If you have experienced no change, please circle '0'.

1. How satisfied are you with your current treatment?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

2. How often have you felt that your blood sugars have been unacceptably high recently?

much more of the time now	3	2	1	0	-1	-2	-3	much less of the time now

3. How often have you felt that your blood sugars have been unacceptably low recently?

much more of the time now	3	2	1	0	-1	-2	-3	much less of the time now

4. How convenient have you been finding your treatment to be recently?

much more convenient now	3	2	1	0	-1	-2	-3	much less convenient now

5. How flexible have you been finding your treatment to be recently?

much more flexible now	3	2	1	0	-1	-2	-3	much less flexible now

6. How satisfied are you with your understanding of your diabetes?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

7. How likely would you be to recommend your present treatment to someone else with your kind of diabetes?

much more likely to recommend the treatment now	3	2	1	0	-1	-2	-3	much less likely to recommend the treatment now

8. How satisfied would you be to continue with your present form of treatment?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

Please make sure that you have circled one number on each of the scales.

Clinical Study Protocol Appendix H

Drug Substance	dapagliflozin
Study Code	D1693C00005
Edition Number	1

Appendix H
Algorithm on Management of Hyponatraemia

ALGORITHM ON MANAGEMENT OF HYPONATRAEMIA

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

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

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

  – If the repeat sodium concentration within 7 days of restarting the investigational product is <130 mmol/L, investigational product will be discontinued. Patients will have an end of treatment visit and a follow-up visit three weeks after discontinuation of investigational product as specified in section 5.8.1 in the CSP.

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

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

  If there is **no** suspected new, temporary, and reversible cause of hyponatraemia based on clinical assessment (other than investigational product), investigational product will be discontinued. Patients will have an end of treatment visit and a follow-up visit three weeks after discontinuation of investigational product as specified in section 5.8.1 in the CSP.

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

  – If the repeat sodium concentration within 7 days is <130 mmol/L, investigational product will be discontinued. Patients will have an end of treatment visit and a follow-up visit three weeks after discontinuation of investigational product as specified in section 5.8.1 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 to 129 mmol/L, the investigator's clinical judgment should apply concerning whether such patients should be entered into this algorithm.

AstraZeneca

Clinical Study Protocol Appendix I

Drug Substance	dapagliflozin
Study Code	D1693C00005
Edition Number	1

Appendix I
Algorithm on Management of Sustained Elevated Liver Safety Abnormalities

ALGORITHM ON MANAGEMENT OF SUSTAINED ELEVATED LIVER SAFETY ABNORMALITIES

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

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

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

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

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

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

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

- ALT and/or AST are >8 x ULN

In each of these situations, study medication will be discontinued, the Sponsor notified and the End of Treatment Visit performed within 3 days of the confirmed laboratory results (see Section 5.8.1). At the End of Treatment Visit, medical history including details of risk factors for liver diseases (if not previously assessed) will be requested and additional blood sampling performed (**Specialized Liver Panel** and **Liver Discontinuation Panel**, see detailed below). Patient should also be scheduled for a Follow-up Visit (ie, procedures of Visit 14) 3 weeks

after discontinuation of investigational product. A referral consultation to a hepatologist or gastroenterologist (specializing in liver abnormalities) should be obtained.

Any additional tests and/or examinations should be carried out at the discretion of the Investigator. Any further investigations and laboratory results for patients with abnormal laboratory values at the Follow-up Visit should be made available to the Sponsor upon request.

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

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

Guidance on Assessment of Hepatic Laboratory Abnormalities

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

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

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

Specialized Liver Panel

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

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

Liver Discontinuation Panel

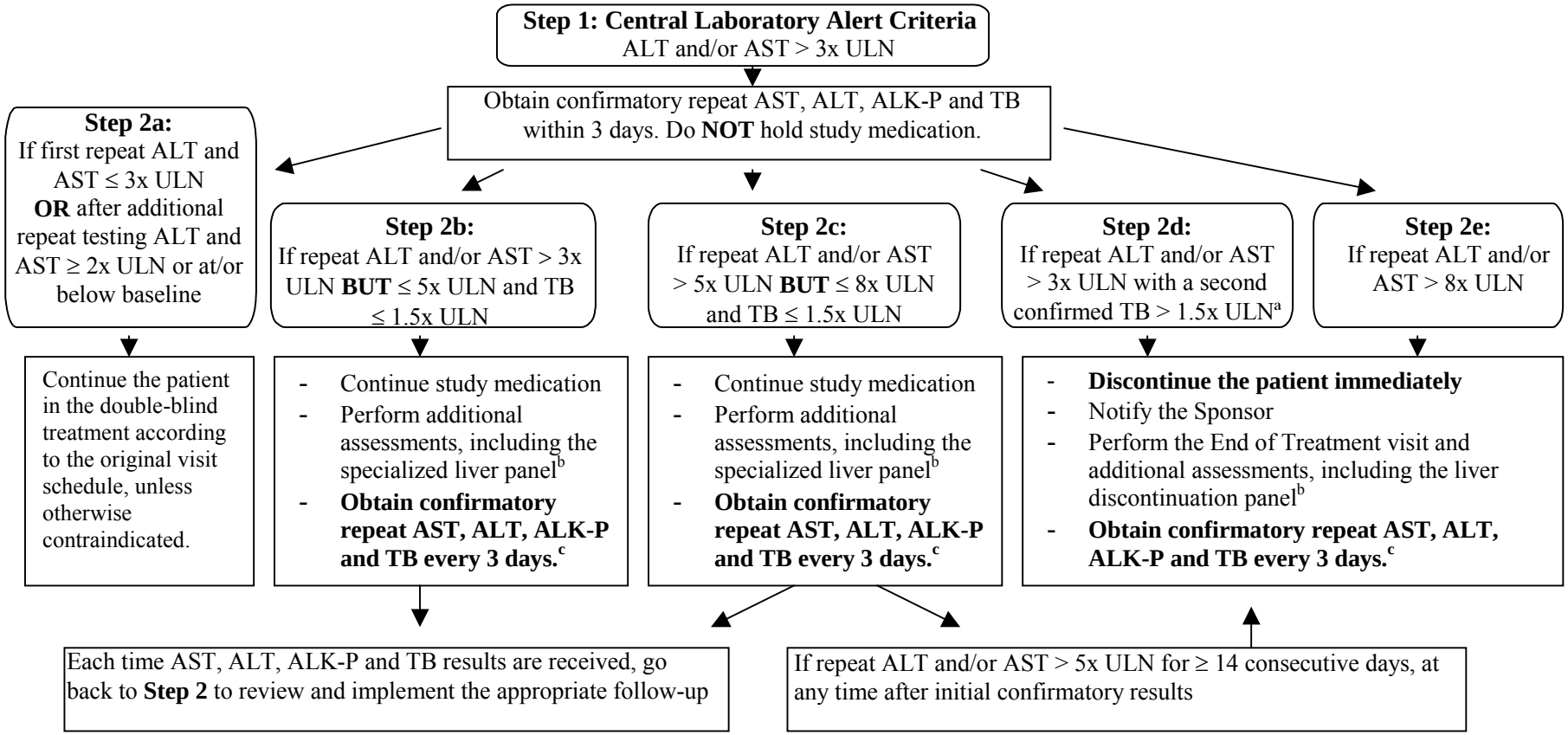
For patients who are discontinued from the study as a result of sustained elevated liver safety abnormalities, additional central laboratory tests will be performed at the time of End of Treatment Visit. Similar to the Specialized Liver Panel, these laboratory tests will study the possible causes of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

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

- Ceruloplasmin
- Toxoplasmosis
- Alpha-1 antitrypsin

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

Figure 1 Sustained elevated liver safety abnormalities flow chart



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

[b] Please see text above in the Appendix for details on additional assessments to be performed (AE assessment, PE, review of current medical history including focused review of current medical history including focused review of risk factors for liver diseases and collection of blood samples [specialized liver panel or liver discontinuation panel]).

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