AstraZeneca

Revised Clinical Study Protocol	
Drug Substance	dapagliflozin
Study Code	D1690C00018
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Date	

A 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled phase III study with an 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with type 2 diabetes, cardiovascular disease and hypertension, who exhibit inadequate glycaemic control on usual care.

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden.

AstraZeneca Research and Development site representative

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

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, age-stratified, placebo controlled phase III study with an 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with type 2 diabetes, cardiovascular disease and hypertension, who exhibit inadequate glycaemic control on usual care.

International Co-ordinating Investigator

Study centre(s) and number of patients planned

This international study will be conducted at approximately 150 study centres. It is estimated that 2500 patients will be screened to reach the target of 940 randomised patients during a recruitment period of approximately 8 months. It is expected that 5 to 40 patients will be randomised per centre.

All ongoing patients who are still on study drug (approximately 600) will be offered to enter the 52-week site- and patient-blinded extension period II.

Study period		Phase of development
Estimated date of first patient enrolled	Q1 2010	III
Estimated date of last patient completed	Q4 2012	

Objectives

There are 2 independent primary objectives of equal weight in this study:

- To compare the glycaemic efficacy of dapagliflozin 10 mg versus placebo when added to usual care in type 2 diabetes patients with cardiovascular disease and hypertension, measured as the mean change in haemoglobin A1c (HbA1c) from baseline to week 24, in the overall population and in the two predefined age subgroups (<65 years, ≥65 years).

- To compare the clinical benefit of dapagliflozin 10 mg versus placebo when added to usual care in type 2 diabetes patients with cardiovascular disease and hypertension at week 24, measured as the proportion of responders for a 3-item endpoint of clinical benefit, defined as:

  – an absolute drop of 0.5% or more from baseline HbA1c, and

  – a relative drop of 3% or more from baseline for total body weight, and

  – an absolute drop of 3 mmHg or more from baseline in seated systolic blood pressure,

  in the overall population and in the two predefined age subgroups (<65 years, ≥65 years).

Key secondary objectives:

- To compare the mean change in seated systolic blood pressure from baseline to week 8 between dapagliflozin 10 mg versus placebo, in the overall population and in the two predefined age subgroups (<65 years, ≥65 years).

- To compare the mean percent change in body weight from baseline to week 24 between dapagliflozin 10 mg versus placebo, in the overall population and in the two predefined age subgroups (<65 years, ≥65 years).

- To compare the mean change in seated systolic blood pressure from baseline to week 24 between dapagliflozin 10 mg versus placebo, in the overall population and in the two predefined age subgroups (<65 years, ≥65 years).

- To compare the proportion of patients with BMI baseline ≥27 kg/m^2 with a reduction from baseline of 5% or more in body weight with dapagliflozin 10 mg versus placebo from baseline to week 24, in the overall population and in the two predefined age subgroups (<65 years, ≥65 years).

Other Secondary Objectives:

Efficacy

- To assess the effects of dapagliflozin 10 mg versus placebo on other efficacy variables derived from measurements related to glycaemic control, blood pressure, body weight, fasting lipids and patient reported outcome (patient's health-related quality of life), in the overall population and in the two predefined age subgroups (<65 years, ≥65 years).

Safety

- To evaluate safety and tolerability of dapagliflozin by assessment of adverse events (including CV events), laboratory values, electrocardiogram, pulse, blood pressure,

hypoglycaemic events, calculated creatinine clearance, estimated glomerular filtration rate and physical examination findings.

Genetics

- To collect and store DNA for future exploratory research into genes that may influence response, eg, distribution, safety, tolerability and efficacy of dapagliflozin 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 extension period I:

- To assess the maintenance of efficacy of dapagliflozin 10 mg versus placebo over 52 weeks of treatment.

- To assess the safety and tolerability of dapagliflozin 10 mg over 52 weeks of treatment.

Objectives of the 52-week extension period II:

- To assess the maintenance of efficacy of dapagliflozin 10 mg versus placebo over 104 weeks of treatment.

- To assess the safety and tolerability of dapagliflozin 10 mg over 104 weeks of treatment.

Study design

This is a 24-week, randomised, double-blind, age-stratified, placebo-controlled, 2-arm, parallel-group, multicentre global Phase III study with a 4-week placebo lead in period and a 28-week extension period I and a 52-week extension period II site-and patient-blinded extension periods. Patients will be stratified according to three factors: age at enrolment (<65 years vs. ≥65 years), insulin use at randomisation (No vs. Yes), and time from most recent qualifying cardiovascular (CV) event (>1 year versus ≤1 year).

Target patient population

Male and female patients with type 2 diabetes, cardiovascular disease (coronary heart disease, stroke or peripheral artery disease) and hypertension, who have inadequate glycaemic control (HbA1c ≥7.0% and ≤10.0%) on existing therapies.

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 extension period I and the 52-week extension period II.

Comparator, dosage and mode of administration

Matching placebo for dapagliflozin 10 mg administered orally once daily for the 4-week placebo lead-in period, the 24-week double-blind treatment period and the 28-week extension period. I and the 52-week extension period II.

Duration of treatment

Within 14 days from initial screening patients will have an enrolment visit, then, after 7 days, patients will enter a 4-week placebo lead-in period (placebo will be given in a single-blind fashion, ie, blind to the patient only). Then they will be randomised to the 24-week double-blind treatment period followed by a 28-week site- and patient-blinded extension period I and a 52-week site- and patient-blinded extension period II. 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 112 weeks.

Outcome variable(s):

Efficacy

All efficacy variables will be evaluated in the overall population and in the two predefined age subgroups (<65years, ≥65years).

Primary outcome variables:

- Mean change in HbA1c from baseline to week 24
- Proportion of responders meeting all criteria of a 3-item endpoint of clinical benefit after 24 weeks of treatment, defined as:
  - an absolute drop of 0.5% or more from baseline HbA1c, and
  - a relative drop of 3% or more from baseline for total body weight, and
  - an absolute drop of 3 mmHg or more from baseline in seated systolic blood pressure.

Key secondary outcome variables:

- Mean change in seated systolic blood pressure from baseline to week 8
- Mean percent change in body weight from baseline to week 24
- Mean change in seated systolic blood pressure from baseline to week 24
- Proportion of patients with baseline BMI ≥27 kg/m^2 with a reduction from baseline of 5% or more in body weight from baseline to week 24

Other secondary outcome variables:

- Mean change in diastolic blood pressure from baseline to week 24
- Proportion of patients with seated systolic blood pressure <130 mmHg at week 24 in patients who had seated systolic blood pressure ≥130 mmHg at baseline
- Mean change in body weight from baseline to week 24
- Mean change in HbA1c in patients with baseline HbA1c ≥8.0% and HbA1c ≥9.0% from baseline to week 24
- Proportion of patients achieving a therapeutic glycaemic response defined as HbA1c <7.0% at week 24
- Mean change in fasting plasma glucose (FPG) from baseline to weeks 1 and 24
- Proportion of patients rescued for failing to maintain FPG below pre-specified rescue criteria at weeks 4, 8, 16, and 24
- Proportion of patients rescued for failing to maintain blood pressure (systolic and diastolic blood pressure) below pre-specified rescue criteria at weeks 8, 16 and 24
- Proportion of patients achieving a therapeutic response defined as a reduction in HbA1c of 0.5% or more at week 24
- Proportion of patients achieving a reduction from baseline of 3 mmHg or more and 5 mmHg or more in seated systolic blood pressure at week 24
- Mean percent change in fasting lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides and free fatty acids) from baseline to week 24.
- Mean change in calculated average daily insulin dose from baseline to week 24in patients treated with insulin at baseline.
- Mean change in health-related quality of life (HRQL) as assessed by the EuroQol-5D (EQ-5D) questionnaire from baseline to week 24

Safety

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

Statistical methods

The two primary objectives of this study are to show superiority of dapagliflozin 10 mg versus placebo in terms of (1) change in HbA1c from baseline to week 24 and (2) likelihood of meeting all criteria of the 3-item clinical benefit composite at week 24. These objectives will be assessed in the overall study population and separately for each of two strata: patients less than 65 years of age and patients 65 years of age or older.

The first primary efficacy variable, change in HbA1c from baseline to week 24, will be analyzed by an analysis of covariance (ANCOVA) model. When assessing the results overall, the model will include terms for treatment group, age-by-insulin use-by-time from most recent qualifying CV event group (8 levels) and baseline covariate. When assessing the results within each age stratum, the ANCOVA model will include terms for treatment group, insulin use-by-time from most recent qualifying CV event group (4 levels), 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 second primary efficacy variable, proportion of patients at week 24 who meet all criteria of a 3-item clinical benefit composite, will be analyzed by the Cochran-Mantel-Haenszel (CMH) method. When assessing the results overall, the CMH model will include age-by-insulin use-by-time from most recent qualifying CV event group as a strata variable. When assessing results within each age stratum, the CMH model will include insulin use-by-time from most recent qualifying CV event group as a strata variable. The difference in response rates between dapagliflozin and placebo will be displayed along with a 95% confidence interval derived from asymptotic theory. P-values will be calculated from a chi-square test using the appropriate CMH model described above. If there are less than 5 responders on average by treatment group, an exact 95% confidence interval will instead be calculated along with the p-value from Fisher's exact test.

A hierarchical testing procedure will be used to control the Type I error rate across the two primary and four key secondary endpoints, both in the overall population as well as within individual age strata. Initially, a Bonferroni multiplicity correction will be applied to the two tests associated with the primary efficacy variables in the overall study population so that each variable will be tested at α=0.025 (2-sided). For a given primary efficacy variable, if the test for the overall population is statistically significant, an additional Bonferroni correction will be applied so that each test within age strata will be performed at α=0.0125 (2-sided); however, no within-age strata tests will be performed if the test for the overall population is not statistically significant.

After performing all applicable tests for primary efficacy variables, testing of key secondary variables will be performed in a fixed order sequence. The testing sequence will be applied separately for the overall population and also for each of the two age strata. The alpha level used for each of the three testing streams will depend on the results of tests for the primary

variables in the corresponding population: α=0.05 (2-sided) if both primary variables are statistically significant; α=0.025 (2-sided) if only one of the primary variables is statistically significant; or no testing if the none of the primary variables are statistically significant. Thus, alpha levels may differ among the three populations for the key secondary variables. Within each population, inference for hypothesis testing will stop at the first occurrence of a failed test, regardless of how testing has progressed in the other two populations.

The primary analysis will be based on the full analysis set using the last observation carried forward approach (LOCF). If a patient initiates rescue for glycaemic or blood pressure control prior to week 24, the patient will be classified as not meeting the definition of the 3-item clinical benefit endpoint regardless of the actual Week 24 or LOCF values obtained.

With 470 randomized patients per age stratum (940 in total), the trial is designed to provide a minimum of 90% power to detect a difference of 25% versus 10% (Δ=15%) in the 3-item clinical benefit endpoint between treatment groups within each age stratum. With this same sample size, there is >99% power to detect a difference of 0.5% in mean change from baseline in HbA1c at week 24 between treatment groups within each age stratum.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.4.1)
ANCOVA	Analysis of covariance
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body Mass Index
CEC	Clinical Event Committee
CK	Creatine kinase
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of Investigational Product due to Adverse Event
CV	Cardiovascular
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
DPP-4	Dipeptidyl-peptidase-4
ECG	Electrocardiogram
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EMEA	European Medicines Agency
EQ-5D	EuroQol EQ-5D questionnaire
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GTI	Genital tract infection
HbA1c	Glycosylated haemoglobin A1c
HRQL	Health-related quality of life

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
LIMS	Laboratory Information Management System
LLOQ	Lower Limit of Quantification
LOCF	Last observation carried forward
LSLV	Last Subject Last Visit
MI	Myocardial infarction
MODY	Maturity-onset diabetes of young
OAD	Oral anti-diabetic medication
OAE	Other Significant Adverse Event (see definition in Section 11.2.1)
PAD	Peripheral Artery Disease
PGx	Pharmacogenetic(s)
PI	Principal Investigator
PPG	Postprandial glucose
PRO	Patient reported outcomes
QD	Daily
SAE	Serious adverse event (see definition in Section 6.4.2).
SBP	Systolic blood pressure
SAP	Statistical Analysis Plan
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
ULN	Upper limit of normal
UTI	Urinary tract infection
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background

Type 2 diabetes mellitus (T2DM) is characterized by β-cell dysfunction and peripheral insulin resistance leading to hyperglycaemia (Matthaei et al 2000; Meier et al 2005). Chronic hyperglycaemia has been associated with the development of both macrovascular (myocardial infarction, stroke), and microvascular (nephropathy, retinopathy) complications (UKPDS 1998a, UKPDS 1998b). Current treatment regimens aiming to reduce glucose levels in patients with T2DM have focused on the stimulation of insulin secretion (eg, sulphonylureas, glinides, DPP-4 inhibitors), the reduction of peripheral insulin resistance (eg, metformin, thiazolidinediones), the inhibition of intestinal glucose absorption (eg, acarbose), or the replacement of insulin. However, the limited efficacy of currently available anti-hyperglycaemic agents, as well as associated side effects (eg, hypoglycaemia, induction of edema, weight gain) clearly underline the need for novel anti-diabetic treatment strategies (Matthaei et al 2000; Koro et al 2004; Meier et al 2005; ADA 2009). In addition, the majority of patients with T2DM require more than one anti-hyperglycaemic agent to achieve glycaemic targets (Nathan et al 2006). Because less than 50% of patients with diabetes reach glycaemic control goals with current medical therapy (Koro et al 2004), there remains an unmet medical need for the treatment of T2DM. Furthermore, it has been documented that a large percentage of diabetes patients continues to be poorly controlled in terms of blood pressure and weight. Therefore, specifically in T2DM patients suffering from cardiovascular disease (CVD) and hypertension, who are considered to be at 'high risk' for new cardiovascular events, an unmet medical need exists to improve their diabetes treatment. The target population in this study will consist of T2DM patients with cardiovascular disease and hypertension, who exhibit inadequate glycaemic control on their existing therapies. The study population will include T2DM patients on insulin treatment, patients with some degree of renal impairment (creatinine clearance greater than 60 ml/min), and older patients age >65 years, in line with the recent FDA CV Guidance (FDA 2008).

Dapagliflozin is a rationally designed, potent, highly selective and orally active inhibitor of the human renal sodium-glucose cotransporter (SGLT2), the major transporter responsible for renal glucose reabsorption (List et al 2009). Dapagliflozin lowers plasma glucose by inhibiting the renal reabsorption of glucose and thereby by promoting its urinary excretion (Komoroski et al 2009a; Komoroski et al 2009b). Traditionally, the presence of glucose in the urine of diabetes patients has been seen as a sign of poor glycaemic control and thus something to be avoided. However, familial renal glucosuria in humans, due to genetic mutations that reduce the function of SGLT2, is associated with life-long glucosuria, which is generally asymptomatic (Santer et al 2003; Van den Heuvel et al 2002). Results from nonclinical studies and completed clinical studies suggest that dapagliflozin intentionally promotes the urinary excretion of glucose as a safe and effective method of reducing blood glucose levels. Chronic correction of hyperglycaemia by these agents has also been shown to improve overall glucose utilization and reduce hepatic glucose production in nonclinical models (Rosetti et al 1987; Dimitrakoudis et al 1992) suggesting that long-term treatment with

an SGLT2 inhibitor may effectively treat hyperglycaemia resulting from underlying defects in glucose homeostasis in patients with T2DM as well.

Dapagliflozin's novel mechanism of action, inhibition of SGLT2 and increased urinary glucose excretion, can result in lowering plasma glucose regardless of the patient's insulin sensitivity and β-cell functional secretory status (List et al 2009; Wilding et al 2009). Because the mechanism is independent of insulin secretion or insulin action, this approach to anti-diabetic activity provides an opportunity to achieve clinically important glycaemic efficacy with a relatively low risk of hypoglycaemia. This insulin independent mechanism also makes it potentially applicable to a broad spectrum of patients. In addition, the excretion of glucose may promote weight loss or prevent weight gain, a potential benefit for many patients with T2DM (List et al 2009; Wilding et al 2009). Furthermore, dapagliflozin may act as a diuretic because a moderate increase in urinary volume has been observed (Komoroski et al 2009b). A recent report (Wilding et al 2009) compared dapagliflozin with placebo as add-on therapy to insulin (after a 50% dose reduction) in insulin resistant patients with T2DM. Dapagliflozin was better in reducing HbA1c and produced better fasting plasma glucose (FPG) and postprandial glucose (PPG) levels and reduced body weight, compared with placebo.

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

1.2 Research hypothesis

Dapagliflozin treatment of patients with inadequately controlled type 2 diabetes mellitus and cardiovascular disease and hypertension on stable existing therapies results in better glycaemic control compared with placebo after 24 weeks of treatment.

Dapagliflozin treatment of patients with inadequately controlled type 2 diabetes mellitus and cardiovascular disease and hypertension on stable existing therapies results in greater clinical benefit, defined as a greater proportion of patients concurrently achieving a meaningful HbA1c reduction, body weight reduction, and systolic blood pressure reduction, than placebo after 24 weeks of treatment.

These hypotheses will be tested in the entire study population as well as independently within each age group (<65 years, ≥65 years).

1.3 Rationale for conducting this study

This study is one of the Phase III studies that will be performed as part of the clinical development programme for dapagliflozin for the treatment of type 2 diabetes. This study intends to compare efficacy and safety of dapagliflozin with placebo in patients with type 2 diabetes, cardiovascular disease and hypertension, as well as patients of older age and patients with mild to moderate impairment of renal function, who are inadequately controlled on existing anti-hyperglycaemic therapies. The stratum of age 65 or greater will allow for careful evaluation of efficacy and safety of dapagliflozin in such a 'high risk' population with T2DM, cardiovascular disease and hypertension. Cardiovascular safety will be monitored in the study

population and evaluated in conjunction with the CV safety observed in other dapagliflozin Phase II and Phase III studies.

An unmet medical need exists to improve the therapy of T2DM patients with such characteristics, who are considered to be at high risk of developing new complications of cardiovascular disease (Abbott et al 1998; Lehto et al 1997; Malmberg et al 2000; HOPE 2000). Dapagliflozin is a novel first-in-class drug that directly counters hyperglycaemia by inhibiting the extent of glucose reabsorption in the kidney proximal tubule with the result of increased glucose urinary excretion (Komoroski et al 2009a; Komoroski et al 2009b). Dapagliflozin has been shown in other studies in the Phase III programme to improve glycaemic control as measured by a reduced HbA1c level (List et al 2009; Wilding et al 2009). Increased urinary volume has also been observed suggesting that dapagliflozin may act as a diuretic and may lower blood pressure (Komoroski et al 2009b). Dapagliflozin has also been associated with decrease in body weight in some patients (Wilding et al 2009). Therefore, dapagliflozin potentially provides clinically meaningful benefits to T2DM patients such as improved glycaemic control, reduction of blood pressure and body weight reduction. The efficacy of dapagliflozin on these items of clinical benefit will be tested in this study as well. Dapagliflozin's mechanism of action is insulin independent and this suggests that the drug can be efficacious in patients with or without insulin treatment. Based on observations in the Phase III development programme, dapagliflozin can be safely added to other oral anti-diabetes drugs, for example metformin and insulin. This study has been extended by 52 weeks to a total of 80 weeks in order to obtain continued observations on long-term safety, tolerability and efficacy in the study population of high-risk patients.

1.4 Benefit/risk and ethical assessment

Risk category

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

Potential risks

The inhibition of SGLT2 results in increased urinary glucose concentrations, which may lead to an increased risk of developing urinary tract infections (UTIs) and mycotic infections. In clinical Phase-III studies, patients receiving dapagliflozin showed an increased frequency of UTIs and mycotic infections when compared to placebo.

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

In the unblinded Phase III studies, elevations in hepatic aminotransferases occurred in a greater proportion of dapagliflozin-treated patients compared with placebo-treated patients.

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. In addition, 24-week data from a recent Phase III study with a number of 'high risk' patients with similar characteristics as defined for the present study did not reveal any new safety concerns. Data from this study are summarised in the Investigator Brochure. 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.

None of the study procedures from the present study are likely to put patients at a risk beyond what is ordinarily encountered during the performance of routine medical examinations or 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 will conduct a real-time review of all safety information from all ongoing clinical dapagliflozin studies as they become available. Safety signal detection will include the integration of all available sources of safety information, including clinical study data, 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 programme 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), microscopic hematuria (Section 6.4.9.3)**,** hyponatraemia (Appendix I), decreased renal function (Appendix K) and liver function abnormalities (Appendix J).

Potential benefits to patients

All patients will continue to receive their existing background anti-hyperglycaemic therapy and the study protocol allows other existing therapies to be optimized before randomization to ensure that participants will receive optimal treatment according to country specific and/or regional guidelines. However, a direct benefit from randomised treatment cannot be assured as one half of patients are expected to receive placebo. The expectation, based on previous

Phase III studies, is that treatment with dapagliflozin is likely to improve glycaemic control (the extent however remains to be determined) because the effect does not seem to depend on age or CV risk factors as can be judged from previous data, and only moderate renal impairment is allowed. In this study, the dose of dapagliflozin (10 mg) has been chosen to provide efficacy in reducing hyperglycaemia while providing the best balance of benefit versus risk based on available information from previous studies. In addition, dapagliflozin is expected to decrease body weight (the extent of which needs to be determined) as well as lower blood pressure especially in patients with elevated baseline blood pressure. Furthermore, all patients including those who receive placebo treatment are expected to experience a benefit in the form of increased medical care/attention when participating in study procedures, which include at least 18 clinic visits with at least 17 physical examinations over the course of this 112-week study. Patients will also receive counselling for dietary and lifestyle 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 lifestyle counselling while they are participating in a clinical study. Rescue criteria for hyperglycaemia and hypertension have been defined according to guidelines in order to ensure adequate treatment for the participants.

Informed consent and alternatives to participation

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

Conclusion

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

2. STUDY OBJECTIVES

2.1 Primary objective

There are 2 independent primary objectives of equal weight in this study:

- To assess the glycaemic efficacy of dapagliflozin 10 mg versus placebo when added to usual care in type 2 diabetes patients with cardiovascular disease and hypertension, measured as the mean change in haemoglobin A1c (HbA1c) from baseline to week 24, in the overall population and in the two predefined age subgroups (<65 years, ≥65 years).

- To assess the clinical benefit of dapagliflozin 10 mg versus placebo when added to usual care in type 2 diabetes patients with cardiovascular disease and hypertension at week 24, measured as the proportion of responders for a 3-item endpoint of clinical benefit, defined as:

  – an absolute drop of 0.5% or more from baseline HbA1c, and

  – a relative drop of 3% or more from baseline for total body weight, and

  – an absolute drop of 3 mmHg or more from baseline in seated systolic blood pressure,

  in the overall population and in the two predefined age subgroups (<65 years, ≥65 years).

2.2 Secondary objectives

2.2.1 Key secondary objectives:

- To compare the mean change in seated systolic blood pressure from baseline to week 8 between dapagliflozin 10 mg versus placebo, in the overall population and in the two predefined age subgroups (<65 years, ≥65 years).

- To compare the mean percent change in body weight from baseline to week 24 between dapagliflozin 10 mg versus placebo, in the overall population and in the two predefined age subgroups (<65 years, ≥65 years).

- To compare the mean change in seated systolic blood pressure from baseline to week 24 between dapagliflozin 10 mg versus placebo, in the overall population and in the two predefined age subgroups (<65 years, ≥65 years).

- To compare the proportion of patients with baseline BMI ≥27 kg/m^2 with a reduction from baseline of 5% or more in body weight with dapagliflozin 10 mg versus placebo from baseline to week 24, in the overall population and in the two predefined age subgroups (<65 years, ≥65 years).

2.2.2 Other Secondary Objectives:

With respect to the overall study population and each of the two predefined age subgroups (<65 years, ≥65 years):

- To compare the mean change in seated diastolic blood pressure between dapagliflozin 10 mg versus placebo from baseline to week 24.

- To compare the proportion of patients with seated systolic blood pressure <130 mmHg treated with dapagliflozin 10 mg versus placebo at week 24 in patients who had seated systolic blood pressure ≥130 mm Hg at baseline.

- To compare the mean change in body weight between dapagliflozin 10 mg versus placebo from baseline to week 24.

- To compare the mean change in HbA1c in patients with baseline HbA1c ≥8.0% and HbA1c ≥9.0% between dapagliflozin 10 mg versus placebo from baseline to week 24.

- To compare the proportion of patients achieving a therapeutic glycaemic response defined as HbA1c <7.0% with dapagliflozin 10 mg versus placebo at week 24.

- To compare the mean change in fasting plasma glucose (FPG) between dapagliflozin 10 mg versus placebo from baseline to week 1 and 24.

- To compare the proportion of patients rescued for failing to maintain FPG below pre-specified rescue criteria with dapagliflozin 10 mg versus placebo at weeks 4, 8, 16, and 24.

- To compare the proportion of patients who were rescued for failing to maintain blood pressure (systolic and diastolic blood pressure) below pre-specified rescue criteria with dapagliflozin 10 mg versus placebo at weeks 8, 16 and 24.

- To compare the proportion of patients achieving a therapeutic response defined as a reduction in HbA1c of 0.5% or more with dapagliflozin 10 mg versus placebo at week 24.

- To compare the proportion of patients achieving a reduction from baseline of 3 mmHg or more and 5 mmHg or more in seated systolic blood pressure with dapagliflozin 10 mg versus placebo at week 24.

- To compare the mean percent change in fasting lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides and free fatty acids) between dapagliflozin 10 mg versus placebo from baseline to week 24.

- To compare the mean change in calculated average daily insulin dose in patients treated with insulin at baseline between dapagliflozin 10 mg versus placebo from baseline to week 24.

- To compare the mean change in health-related quality of life (HRQL) as assessed by the EuroQol-5D (EQ-5D) questionnaire, between dapagliflozin 10 mg versus placebo from baseline to week 24.

2.3 Safety objective

To evaluate safety and tolerability of dapagliflozin by assessment of adverse events (AE) including CV events, laboratory values, electrocardiogram (ECG), pulse, blood pressure (BP),

hypoglycaemic events, calculated creatinine clearance, estimated glomerular filtration rate (eGFR) 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 dapagliflozin 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 extension period I

- To assess the maintenance of efficacy of dapagliflozin 10 mg versus placebo over 52 weeks of treatment.
- To assess the safety and tolerability of dapagliflozin 10 mg over 52 weeks of treatment.

2.6 Objectives for the 52-week extension period II

- To assess the maintenance of efficacy of dapagliflozin 10 mg versus placebo over 104 weeks of treatment.
- To assess the safety and tolerability of dapagliflozin 10 mg over 104 weeks of treatment.

3. STUDY PLAN AND PROCEDURES

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

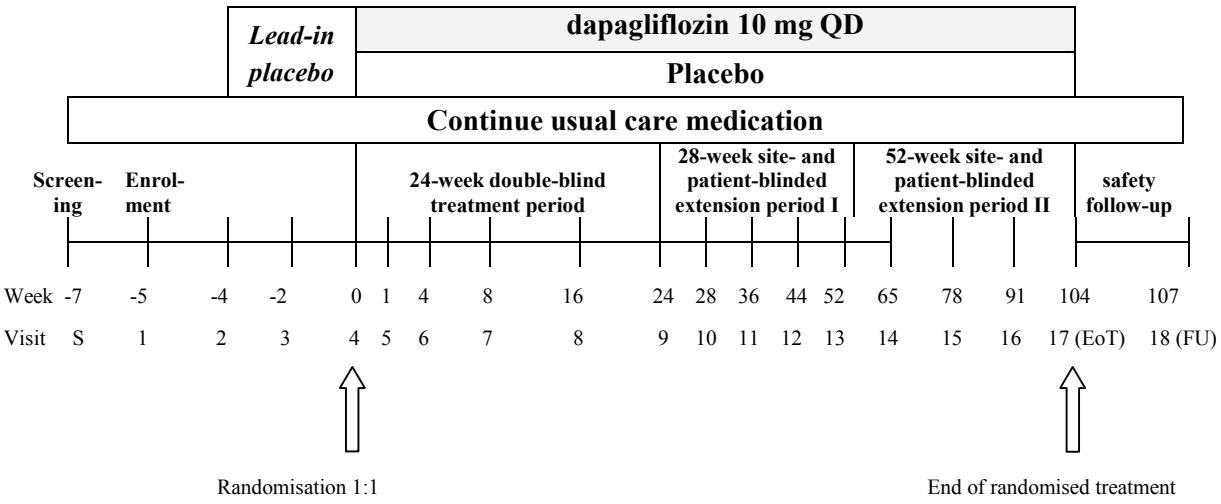
3.1 Overall study design and flow chart

Study design

This is a 24-week randomized, double-blind, placebo-controlled, 2-arm, parallel-group, multicentre global Phase III study with a 4-week placebo lead in period and a 28-week site- and patient-blinded extension period I and a 52-week site- and patient-blinded extension period II in patients with type 2 diabetes with cardiovascular disease and hypertension. Dapagliflozin 10 mg QD or matching placebo QD will be added to usual care of patients who have inadequate glycaemic control on their existing therapies.

This international study will be conducted at approximately 150 study centres in approximately 10 countries depending on local approval. It is estimated that 2500 patients will be screened to reach the target of 940 randomised patients during an enrolment period of approximately 8 months. It is expected that 5 to 40 patients will be randomised per centre.

Figure 1 Study flow chart



Before entry into the study, patients will be screened for an HbA1c level. Patients who meet the HbA1c inclusion criterion will be enrolled and examined for all inclusion and exclusion criteria. Patients will be re-examined for inclusion and exclusion criteria at Visit 2 (-4 weeks) and will enter a 4-week placebo lead-in period. During the lead-in period, laboratory test results will be obtained, patient compliance will be evaluated, and dosage of background therapy adjusted if needed (allowed changes are presented in Table 2). If applicable, at Visit 4 (Randomisation visit) the average daily insulin dose will be calculated, and on the same day the daily insulin dose will be reduced by 25%. (A recent publication (Wilding et al 2009) reports on the clinical experience in type 2 diabetes patients treated with placebo or dapagliflozin and a reduced insulin dose.) At Visit 4, patients who meet the inclusion and exclusion criteria, including HbA1c ≥7.0% and ≤10.0% (value from blood sample obtained at Visit 3) and a blood pressure less than 160/100 mmHg, will be randomised to the 24-week double-blind treatment period followed by a 28-week site-and patient-blinded extension period I and a 52-week site- and patient-blinded extension period II (see objectives of the extension period I in Section 2.5 and of the extension period II in Section 2.6). The 25%-reduced study dose of insulin and concomitant OADs, anti-hypertensive drugs, lipid lowering drugs and anti-platelet drugs should be kept constant throughout the entire 104-week treatment period. At randomisation, patients will be stratified according to age <65 years or ≥65 years, insulin use (No or Yes), and time from most recent qualifying CV event (more than 1 year versus 1 year or less (ie within 12 months) before enrolment) (see Section 4.1, Inclusion Criteria, item 6).

After either completion of the treatment periods or discontinuation from treatment, patients will enter a 3-week safety follow-up period without investigational product. The follow-up visit (Visit 18 (FU)) 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 18) will be 112 weeks.

3.1.1 Study Periods

A detailed overview of study periods, visit assessments and order of procedures is presented in Appendix E.

3.1.1.1 Screening Visit (Visit S, within 14 days prior to enrolment)

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

Potentially eligible patients, in terms of medical conditions and existing therapies, 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 the HbA1c inclusion criterion at enrolment, 7.2% ≤HbA1c ≤10.5% (sample will be taken at screening), (see Inclusion criterion 5, Section 4.1) Patients are not allowed to be re-screened. All patients who are screened should be listed on the patient screening log (see Section 6.2).

Anti-diabetic drugs except insulin cannot be changed. The dose of insulin can be changed by no more than a ten percent (10%) difference in the total daily insulin use (example: when 40 U of insulin is the daily dose, the allowed change is not more than 10%, or 4 U). Anti-hypertensive drugs, anti-platelet drugs and lipid lowering drugs can be added, withdrawn or dose changed.

3.1.1.2 Enrolment Visit (Visit 1, week –5)

Prior to this visit anti-hyperglycaemic treatment should have been uninterrupted on a daily basis for 8 weeks and stable for at least 4 weeks, consisting either of oral anti-diabetes drugs such as metformin, pioglitazone, sulfonylurea, acarbose, or a DPP-4 inhibitor (saxagliptin, sitagliptin, vildagliptin), as monotherapy or dual combination, or of existing therapy with insulin, either as monotherapy or in combination with oral anti-diabetes drugs. Use of rosiglitazone is not permitted.

Also, patients treated with anti-hypertensive drugs should be on existing anti-hypertensive therapy for at least 4 weeks prior to enrolment.

At the enrolment visit, Visit 1, patients will sign an informed consent form and undergo assessment of all inclusion/exclusion criteria. Eligible patients will submit laboratory samples and will receive diet and lifestyle advice.

Anti-diabetic drugs except insulin cannot be changed. The dose of insulin can be changed by no more than a ten percent (10%) difference in the total daily insulin use (example: when 40 U of insulin is the daily dose, the allowed change is not more than 10%, or 4 U). Anti-hypertensive drugs, anti-platelet drugs and lipid lowering drugs can be added, withdrawn or dose changed. For guidelines regarding changes to certain background medications at the Screening Visit and at Visits 1, 2 and 3 please see Table 2 in Section 3.1.2.

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

At the beginning of the placebo lead-in period (Visit 2, week –4) patients will undergo repeated assessment of all inclusion/exclusion criteria. At Visit 2, eligible patients will be given placebo in a single-blind fashion (blind to the patient only).

A glucometer and patient diary will be provided to patients who 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. FPG monitoring procedures and assessment of hypoglycaemic events are described in Section 6.4.9.1.

Anti-diabetic drugs except insulin cannot be changed. The dose of insulin can be changed by no more than a ten percent (10%) difference in the total daily insulin use (example: when 40 U of insulin is the daily dose, the allowed change is not more than 10%, or 4 U). The dose of anti-hypertensive drugs can be changed. Anti-platelet drugs and lipid lowering drugs can be added, withdrawn or dose changed.

Starting from Visit 2, throughout the entire duration of the study, patients treated with insulin will be asked to record their daily dose of insulin in their diary.

At **Visit 3** (week -2), patients will attend to assess the glycaemic control through the diary (FPG) and a blood sample for HbA1c. Also those patients who are on insulin therapy will be reminded to record their daily insulin dose into their diary. Concomitant medications and changes will be recorded. Allowed changes in background therapy are shown in Table 2. Patients will get dietary and lifestyle advice.

No changes are allowed in anti-diabetic drugs, anti-hypertensive drugs, anti-platelet drugs and lipid lowering drugs. The dose of insulin can be changed.

HbA1c measured from the sample taken at Visit 3 will be used for assessment of eligibility at Randomisation Visit (Visit 4).

3.1.1.4 Randomisation and Double-blind Treatment Period (Visits 4-9, week 0 to week 24)

Randomisation Visit (Visit 4)

Patients who continue to meet all inclusion and exclusion criteria (described in Sections 4.1 and 4.2) with an HbA1c ≥7.0% and ≤10.0% (data obtained at Visit 3) and a seated blood pressure <160/100 mmHg will be randomised. At Visit 4, the average daily insulin dose,

which is an average of the total daily insulin dose used on the days between Visit 3 and Visit 4 (including the day of visit 3) will be calculated and recorded. A minimum of 7 days of insulin dose records need to be available at visit 4.Subsequently, on the day of randomisation the average daily dose of insulin will be reduced by 25%. The insulin dose reduction will begin at breakfast, or any first occurrence of insulin administration. The 25% reduced insulin dose should be used as target value and will be kept constant throughout the study. Table 1 describes the steps involved in the 25% reduction of insulin dosing. Also refer to Section 5.6. with regard to changes in concomitant medication during the study treatment period.

Table 1 Insulin dose reduction by 25% in patients who are on insulin therapy prior to Visit 3

Algorithm for insulin dose reduction
At Visit 3 instruct patient that the insulin dose needs to be recorded daily and that the dose will be reduced by 25% at Visit 4.
1. At Visit 4, calculate and record the average daily insulin dose (short acting plus intermediate plus basal together) used on the days between Visit 3 and Visit 4 (including the day of visit 3).
2. Calculate the 25% proportion of the calculated average daily insulin dose for the patient [a)].
3. Record the 25% reduced daily insulin dose (after rounding up if needed) as the targeted dose. It will be the future study dose [b)].
4. Instruct patient to use the insulin study dose on the day of randomisation [c)] and during the study.
5. Ensure that treatment with the 25% reduced insulin dose begins at randomisation and will be the target insulin dose during the treatment period. The 25% reduced dose should be kept constant throughout the study.

a) Example: When 42 U is the average daily insulin dose (short acting plus intermediate plus bedtime or basal insulin), 25% of 42 U equals 10.5 U of insulin.

b) Example continued: In that patient, the 25% reduced insulin daily dose is 31.5 U of insulin and after rounding up, 32 U will be recorded as the target dose.

c) In patients
- on bedtime or long acting (basal) insulin only: investigators can reduce insulin dose by 25%.
- on short acting insulin, intermediate acting, and/or long acting insulin: investigators are advised to make the reduction in the short acting and intermediate acting insulin rather than making changes to the basal insulin (long acting insulin).
- on insulin pumps (continuous insulin administration): investigators are advised to make the reduction in the meal-related insulin (bolus insulin) rather than making changes to the basal insulin.

Diet and lifestyle modification will be reinforced at each visit.

At randomisation, patients will be randomly allocated to treatment with either dapagliflozin 10 mg QD or matching placebo QD in a 1:1 ratio. Patients will be stratified based on 3 factors:

Factor 1: Age

- Age Group 1 (Younger than age 65 at enrolment)
- Age Group 2 (Age 65 and older at enrolment)

Equal numbers of patients are planned to be enrolled into each age group (470 per each group); but at a minimum, each group must not be less than 40% of the anticipated study population. If the number of patients in one of the age groups reaches 60% of the total number of anticipated patients, further enrolment into the age group will be stopped.

Factor 2: Insulin Use

- Insulin Use Group 1 (No insulin used at randomisation)
- Insulin Use Group 2 (Insulin used at randomisation)

There is no restriction on numbers of patients enrolled within each insulin group, either within an age stratum or in the overall population.

Factor 3: Time from most recent qualifying CV event

- Time from Qualifying CV event Group 1 (more than 1 year before enrolment)
- Time from Qualifying CV event Group 2 (1 year or less (ie, within 12 months) before enrolment)

Qualifying CV events are defined in item 6, Section 4.1

There is no restriction on numbers of patients enrolled within each Time from Qualifying CV event group, either within an age stratum or in the overall population.

Therefore, 8 total strata will be formed for the purposes of randomisation by each combination of the three factors, with restrictions on the number in each age group but not on the number in each insulin use group nor Time from Qualifying CV event group. The IWRS will use information supplied at enrolment on age and time from most recent qualifying CV event and at randomization on insulin use to determine which of the 8 randomisation strata the patient is to be classified and randomized in a 1:1 allocation between treatment groups.

Visits 5-9

After the randomisation visit, patients will have follow-up visits at one- to eight-week intervals until the end of the randomised treatment period (Visit 9, 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. Glycaemic rescue criteria and relevant procedures are described in Section 5.6.2.

Diet and lifestyle modification will be reinforced at each visit during the double-blind treatment period.

3.1.1.5 Extension period I (Visits 9-13, week 24 to week 52)

Patients will return for follow-up visits at four- to eight-week intervals during the 28-week site-and patient-blinded extension period I.

Extension period II (Visits 13-17, week 52 to week 104)

After the extension period I all ongoing patients on study drug will be asked to continue the study for another 52 weeks and will sign an informed consent form for extension period II.

After Visit 13 patients who consent will continue in the site- and patient-blinded extension period II with the same treatment given as at the end of the extension period I.

Patients will return for follow-up visits at thirteen-week intervals during the 52-week site- and patient-blinded extension period II.

During the two extension periods 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. Glycaemic rescue criteria and relevant procedures are described in Section 5.6.2.

Diet and lifestyle modification will be reinforced at each visit during these periods.

Patients will discontinue investigational product at the end of this treatment period (Visit 17, End of Treatment Visit).

Visit 17 (End of Treatment Visit, week 104)

At week 104 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 permanently should return and complete the procedures described for the End of Treatment Visit as soon as possible after the last intake of investigational product.

Patients who complete the scheduled study treatment and who prematurely discontinued study treatment permanently will have the Follow-up Visit (Visit 18) 3 weeks after the last intake of investigational product.

3.1.1.6 Follow-up period (Visit 18, week 107)

Patients will be followed for 3 weeks after discontinuing investigational product. During this time patients can be treated as necessary without any further protocol restrictions.

3.1.1.7 Rescue Visit

A Rescue Visit will be scheduled in case glycaemic rescue criteria or hypertension rescue criteria are met (see Section 5.6.2).

3.1.2 Background therapy

Table 2 lists an overview of the allowed changes in background therapy before randomisation. Investigators will follow country or regional guidelines, when they make a decision about changes in background therapy. See Section 5.6.

Table 2 Allowed changes in background therapy before randomisation

	Visit S (screening)	Visit 1 (Enrolment)	Visit 2 (-4 weeks)	Visit 3 (-2 weeks)
Anti-diabetic drugs except insulin[a)]	No Change	No Change	No Change	No Change
Insulin[a, b, c)]	Only dose can be changed [c)]	Only dose can be changed [c)]	Only dose can be changed [c)]	No Change
Anti-hypertensive drugs[d)]	Drug can be added, withdrawn or dose changed	Drug can be added, withdrawn or dose changed	Only dose can be changed	No Change
Anti-platelet drugs	Drug can be added, withdrawn or dose changed	Drug can be added, withdrawn or dose changed	Drug can be added, withdrawn or dose changed	No Change
Lipid lowering drugs	Drug can be added, withdrawn or dose changed	Drug can be added, withdrawn or dose changed	Drug can be added, withdrawn or dose changed	No Change

a) Patients should be on uninterrupted anti-diabetic therapy for at least 8 weeks and on stable therapy for at least 4 weeks before enrolment
b) Insulin dose will be reduced by 25% on day of randomisation, Visit 4
c) The dose of insulin can be changed by no more than a ten percent (10%) difference in the total daily insulin use (example: when 40 U of insulin is the daily dose, the allowed change is not more than 10%, or 4 U
d) Patients on anti-hypertensive drugs should be on their therapy for at least 4 weeks before enrolment.

The dose of anti-hyperglycaemic medication(s) should not be increased or decreased between weeks 0-104 (Visits 4 and 17) unless rescue criteria (see Section 5.6.2) or a definition of hypoglycaemia (Section 5.6.2.3) are met. Patients who use insulin can qualify for rescue (ie, insulin uptitration; see Section 5.6.2.2) if criteria for glycaemic rescue are reached (see Section 5.6.2.1).

Anti-hypertensive medication(s) should not be changed between randomisation and week 104 (Visit 4 to 17) unless specific criteria are met. Rescue criteria have been defined (Section 5.6.2.4). Investigators can alter anti-hypertensive medication if in the patient's best

interest such as in case of angina, or symptomatic hypotension, or orthostatic hypotension (see Section 5.6.2.5).

Patients who need lipid lowering treatment and/or anti-platelet therapy shall be instructed to keep these therapies constant throughout the study (see Section 5.6.2.6).

A detailed overview of prohibited concomitant medications along with rules for administration of rescue therapy are presented in Section 5.6.5.

Section 5.6 describes how to record changes in concomitant medication including existing background therapies.

Table 3 Study Plan

	Screening	Enrolment	Placebo lead-in		24-week double-blind treatment period						28-week site- and patient-blinded extension period I				52-week site- and patient-blinded extension period II				Follow-up	Rescue
Visit	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17[c)]**	**18 FU**	**R[j)]**
Week	**-7**	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**65**	**78**	**91**	**104**	**107**	
Visit window (days) a)		**(0)[b)]**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±3)**	**(±3)**	
Screening informed consent and blood sample for HbA1c	**X**																			
Informed consent		X																		
Informed consent for the extension period II [k)]														X						
Patient reported outcome (EQ-5D)					X			X		X				X		X		X		
Demography and medical history		X																		

	Screening	Enrolment	Placebo lead-in		24-week double-blind treatment period						28-week site- and patient-blinded extension period I				52-week site- and patient-blinded extension period II				Follow-up	Rescue
Visit	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17[c)]**	**18 FU**	**R[j)]**
Week	**-7**	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**65**	**78**	**91**	**104**	**107**	
Visit window (days) a)		**(0)[b)]**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±3)**	**(±3)**	
In-/Exclusion criteria		X	X		X															
Randomisation					X															
Brief physical examination			X			X	X	X	X		X	X	X		X		X		X	
Complete physical examination		X			X					X				X		X		X		X
Vital signs (BP, pulse)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Orthostatic BP					X	X	X	X		X			X	X		X		X		
Weight		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height		X																		
12-lead ECG		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 I				52-week site- and patient-blinded extension period II				Follow-up	Rescue
Visit	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17[c)]**	**18 FU**	**R[j)]**
Week	**-7**	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**65**	**78**	**91**	**104**	**107**	
Visit window (days) a)		**(0)[b)]**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±3)**	**(±3)**	
Concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments d)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test e)		X	X	X	X	X	X	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	X	X	X	X	X	X
AEs			X	X	X	X	X	X	X	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	X	X	X	X	X			
Drug accountability					X		X	X	X	X	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 I				52-week site- and patient-blinded extension period II				Follow-up	Rescue
Visit	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17[c)]**	**18 FU**	**R[j)]**
Week	**-7**	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**65**	**78**	**91**	**104**	**107**	
Visit window (days) a)		**(0)[b)]**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±3)**	**(±3)**	
Diet and lifestyle advice		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense glucometer at V2; provide supplies, instructions			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Dispense patient diary			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Patient diary review for glucometer values/ hypoglycaemic events [f)]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Calculate average daily insulin dose					Xg)	Xh)	Xh)	Xh)	Xh)	Xh)	Xh)	Xh)	Xh)	Xh)	Xh)	Xh)	Xh)	Xh)		

	Screening	Enrolment	Placebo lead-in		24-week double-blind treatment period						28-week site- and patient-blinded extension period I				52-week site- and patient-blinded extension period II				Follow-up	Rescue
Visit	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17[c)]**	**18 FU**	**R[j)]**
Week	**-7**	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**65**	**78**	**91**	**104**	**107**	
Visit window (days) a)		**(0)[b)]**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±3)**	**(±3)**	
Informed consent, blood sample for genetic research [i)]					(X)	(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) Specifications of laboratory parameters are shown in Table 8 and Table 9.
e) Pregnancy test will be done on all female patients who are not postmenopausal or hysterectomised.
f) Patients should be instructed to contact the investigator by phone if a hypoglycaemic event occurs, in cases specified in the patient diary.
g) On the day of Visit 4 (Randomisation Visit), daily insulin dose will be reduced by 25% from the average daily dose between visits 3 and 4.
h) The mean daily insulin dose will be calculated by the investigator. On visits 5-17 the calculated mean daily insulin dose is the average daily insulin use over the last 7 documented days before the actual visit.
Genetic informed consent must be obtained before genetic blood sample is taken. Blood sample donation is optional and can be done any time from Visit 4 (ie, randomisation) to Visit 9.
j) Rescue refers to a Glycaemic Rescue Visit (Section 5.6.2.1). In case of a Rescue Visit due to hypertension (Section 5.6.2.4), it will be at the discretion of the investigator to decide if any laboratory assessments are needed.
k) Patients still on active study treatment who have not developed any reason for study discontinuation will be asked to continue the study for another 52 weeks.

3.2 Rationale for study design, doses and control groups

3.2.1 Study design and regulatory requirement

This is a 24-week randomized, double-blind, age-stratified, placebo-controlled, 2-arm, parallel-group, multicentre global Phase III study with a 4-week placebo lead-in period and a 28-week site-and patient-blinded extension period I and a 52-week site- and patient-blinded extension period II. Dapagliflozin 10 mg once daily (QD) or matching placebo QD will be added to the therapies of patients with T2DM who have inadequate glycaemic control on their existing therapies consisting of stable doses of either monotherapy or dual combination therapy with metformin, pioglitazone, sulfonylurea, or a DPP-4 inhibitor (saxagliptin, sitagliptin, vildagliptin) for at least 12 weeks at randomisation, or insulin monotherapy, or insulin therapy in combination with oral anti-diabetic therapy. Studies with an active arm and placebo arm both added to usual care are specifically mentioned in the EMEA Guidance (CPMP/EWP/1080/00, 30 May 2002) and the FDA Guidance on Diabetes Mellitus (Feb 2008) as examples of designs to study long-term glycaemic efficacy. To emphasize the importance of obtaining more efficacy and safety data in elderly patients, age ≥65 years has been chosen as a factor for stratification. In order to balance the risk of future cardiovascular events between treatment arms, patients will be stratified according to time from most recent qualifying CV event (1 year or less versus more than 1 year before enrolment).

3.2.2 Study doses and control groups

Control group

This is a placebo-controlled study. Placebo was chosen as comparator because no single oral active drug is available as comparator for the various therapeutic responses expected with dapagliflozin in this study.

Background therapy

Patients should have an HbA1c value of ≥7.2% and ≤10.5% at screening while on existing anti-diabetic therapy for at least 6 weeks and on stable therapy for at least 2 weeks at screening (to meet enrolment criteria, see Section 4.1), which indicates inadequate glycaemic control in spite of anti-hyperglycaemic therapy (Nathan et al 2009). Patients with a blood pressure higher than SBP ≥165 and DBP ≥100 mmHg at enrolment will not be enrolled in the study. Changes in anti-hyperglycaemic treatment will not be allowed at screening, at enrolment, placebo lead in period and during the entire 104 weeks treatment period. However, investigators will follow country or regional guidelines to optimize the treatment for blood pressure, plasma lipids and anti-platelet therapy according to the schedule in Table 2. Examples of guidelines are those published by the American Diabetes Association (ADA) (ADA 2009), National Institute for Health and Clinical Excellence (NICE) in the U.K. (NICE 2009), the Joint National Committee (JNC) (JNC7 2004) and European Society of Cardiology (ESC)(ESH/ESC 2007).

In the morning of the randomisation visit, the calculated average daily insulin dose, which is the average of the total daily insulin dose over the days between Visits 3 and Visit 4 (including day of visit 3) will be recorded. This dose, the average daily dose of insulin, will

be reduced by 25% (see Table 1 for calculation), but the dose of OAD(s) remains unchanged. Subsequently, the 25% reduced average insulin dose will be started on the day of randomisation with breakfast. The insulin dose administered on the day of randomisation will be the study baseline dose. Patients will be instructed to keep constant the 25% reduced insulin dose throughout the study treatment period.

Background OAD therapy should not be increased or decreased during the study treatment period, unless rescue criteria or definition of hypoglycaemia are met (see Section 5.6.2).

Investigators and patients should also keep constant the existing other therapies (anti-hypertensive drugs, lipid lowering drugs, anti-platelet drugs) while receiving investigational product during the entire 104-week study treatment period. (See Section 5.6).

Dapagliflozin

Results of pre-clinical pharmacokinetic and toxicology studies support the safety of conducting a Phase III clinical development programme 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 (List et al 2009). The dose of dapagliflozin 10 mg QD has been chosen because this daily dose has been shown to have good efficacy and a good safety profile in previous Phase II and Phase III studies. Dapagliflozin has been shown in a Phase III study to be efficacious when taken with or without food, either in the morning or evening. In this study dapagliflozin will be taken in the morning, after completion of certain required study procedures, shortly before breakfast defined as any time within 30 minutes before the ingestion of food.

3.2.3 Choice of outcome variables

HbA1c is the variable of choice for assessment of glycaemic control and was therefore chosen as one of the primary outcome variables. 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 such as insulin (Wilding et al 2009). Furthermore, because weight reduction and SBP lowering have been observed in other dapagliflozin studies (List et al 2009; Komoroski et al 2009a), these variables have been chosen as part of the primary 3-item endpoint of clinical benefit as well as key secondary objectives (see Table 4). The second primary endpoint is an approach to define clinical efficacy in a comprehensive manner. The motivation underlying the selected threshold values is detailed in Table 4.

Table 4 Efficacy variables with related objectives and rationale

Efficacy variable	Related objective	Rationale
HbA1c	Change in HbA1c compared to baseline at week 24. Change in HbA1c in patients with baseline HbA1c ≥8% and HbA1c ≥9% at week 24. Proportion of patients achieving a therapeutic glycaemic response defined as HbA1c <7.0% at week 24. Proportion of patients achieving a therapeutic response defined as a reduction in HbA1c of 0.5% or more at week 24.	HbA1c is the clinical and regulatory parameter used to estimate glycaemic efficacy in patients with type 2 diabetes. HbA1c targets for patients with type 2 diabetes range from <6.5% to <7.0% and ADA and EASD recently reached consensus on an HbA1c treatment target of 7.0% (Nathan et al 2009). 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.

Efficacy variable	Related objective	Rationale
3-item Clinical Benefit: HbA1c, Weight, and Blood Pressure Combined	Reduction in HbA1c from baseline by at least 0.5% or more and a reduction in relative body weight by 3% or more from baseline and a reduction in seated SBP by 3 mmHg or more from baseline.	Dapagliflozin is potentially efficacious in improving HbA1c, weight, and blood pressure combined. A reduction in HbA1c of 0.5% or more, the first endpoint of clinical benefit, is an accepted regulatory endpoint. A relative reduction in body weight of 3%, the second endpoint of clinical benefit, is similar to the weighted result of 22 long-term non-pharmacological weight loss interventions in T2DM (Norris et al 2005) and also similar to average long-term (52 weeks) results with pharmacotherapy in T2DM (Norris et al 2004). It is known that modest weight loss, such as 3% or 5%, has a long-term impact on glycaemic control. Furthermore, in a prospective analysis, intentional moderate (0.5% to 5%) weight loss in overweight T2DM patients was associated with a reduction in mortality (Williamson et al 2000). A 3% weight loss has recently been proposed as a regulatory threshold for weight maintenance (Hutchinson et al 2007; Stevens et al 2006). A reduction in SBP of 3 mmHg, the third item of clinical benefit, has been shown to be associated with a statistically significant reduction in CV events as well as stroke in a meta-analysis of 162341 patients with hypertension (BPLT 2003). The relevance of a 3 mmHg drop in SBP to prevent CVD in the population has been shown (Whelton et al 2002). The HOPE study with ramipril showed significant CV benefit in T2DM patients with 3 mm SBP reduction (HOPE 2000).

Efficacy variable	Related objective	Rationale
Weight	Change in per cent body weight from baseline after 24 weeks. Proportion of patients with a baseline BMI ≥27 kg/m^2 with a reduction in percent body weight of 5% or more after 24 weeks.	More than 85% of patients with type 2 diabetes are overweight (BMI ≥27 kg/m^2) or obese (BMI ≥30 kg/m^2). Increased weight is often observed with drug therapy for diabetes mellitus including metformin, sulfonylurea drugs and insulin. 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. Both 3% and 5% weight loss have been identified as relevant outcomes in patients with T2DM in terms of long-term impact on glycaemic control (Norris et al 2004; Norris et al 2005) and reduction of mortality (Williamson et al 2000).
Blood Pressure	Reduction in seated SBP from baseline to week 8 and week 24. Reduction in seated DBP at week 24. Proportion of patients with SBP <130 mmHg at week 24 in those with SBP≥130 mmHg at baseline. Proportion of patients rescued for failing to maintain blood pressure (SBP or DBP) below pre-specified rescue criteria at weeks 8, 16 and 24.	The American Diabetes Association and the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure guidelines recommend a blood pressure target of <130/80 in patients with diabetes (ADA 2009**;** JNC7 2004). Lowering blood pressure in patients with diabetes has been shown to reduce the risk of coronary heart disease events, stroke, retinopathy and nephropathy.
Fasting Plasma Glucose	Change in fasting plasma glucose (FPG) after one week and after 24 weeks. Proportion of patients rescued for failing to maintain FPG below pre-specified rescue criteria at weeks 4, 8, 16, and 24.	Fasting plasma glucose and postprandial glucose are well-established measures of glycaemic efficacy, and are considered by the CHMP to be acceptable secondary endpoints.

Efficacy variable	Related objective	Rationale
Fasting Lipids	Percent change in fasting lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, free fatty acids) at week 24.	Patients with type 2 diabetes have an increased prevalence of lipid abnormalities, which contributes to their high risk of cardiovascular disease (ADA 2009). For this reason, it is important to evaluate the lipid effects of anti-hyperglycaemic agents.

3.2.4 Choice of study population

Age

Different ages for men and women have been selected as inclusion criteria at enrolment to create similar 'high risk' of future cardiovascular events. Furthermore, two age strata will be studied: stratum 1 with patients <65 years and stratum 2 with patients of age 65 years and above. The reason is to ensure that a sufficient number of patients of age 65 years and greater will be studied. Age 65 years was chosen as it represents an accepted regulatory cut-off for elderly age groups in clinical studies. In line with the new FDA CV Guidance (FDA 2008), this study will include patients with a 'high risk' of subsequent cardiovascular events including those with age ≥65 years. In addition, it is of interest to evaluate efficacy and safety of dapagliflozin in relation to age, with the expectation that the elderly age group may exhibit a trends towards more renal impairment and higher prevalence of co-morbidities in relation to those with age <65 years.

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, 7.0%) reflects the most recent ADA and EASD treatment guidelines (ADA 2009; Nathan et al 2009). Although other guidelines recommend treatment to lower HbA1c targets, the results of recent studies suggest that these stricter targets may not be appropriate for all patients. The upper limit of this interval (ie, 10.0%) was chosen because insulin is generally the treatment of choice for patients with HbA1c values above this level. Higher HbA1c levels reflect hyperglycaemia which in the long run exposes patients with diabetes to a very high risk of developing micro- and macrovascular complications. The reduction in HbA1c is therefore chosen as a primary efficacy endpoint.

History of CV Events

Patients with diabetes and cardiovascular disease continue to have an unmet need for optimal glycaemic control (ADA 2009). This study will include such patients with a past history of CV events as defined in Section 4.1 because they are at a 'high risk' of subsequent cardiovascular events. Studying the efficacy and safety of dapagliflozin in such 'high risk' patients is in line with the new FDA CV Safety Guidance (FDA 2008). Furthermore, it is known that the time from diagnosis of a previous CV event is a factor that affects the risk of recurrent CV events (Alberts et al 2009; Donahoe et al 2007). In order to balance the risk of future cardiovascular events between treatment arms, patients will be stratified according to time from most recent qualifying CV event (1 year or less versus more than 1 year before enrolment) (see Section 3.1.1.4 and Section 4.1, item 6).

Insulin use

T2DM patients may be on existing insulin therapy. In the course of diabetes treatment, insulin can be added to OAD to improve glycaemic control (ADA 2009; Nathan et al 2006; Nathan et al 2009). In patients with T2DM, insulin therapy has been reported to improve glycaemic control, cause weight gain and risk of hypoglycaemia (Holman et al 2009). Insulin use may

also indicate advanced disease. Dapagliflozin has been used with insulin in patients with T2DM, both with a reduced insulin dose (Wilding et al 2009) and an unchanged insulin dose (one study in the Phase III programme).

Kidney Function

Several diabetes drugs, notably metformin and DPP-4 inhibitors, need to have their dose reduced in the presence of renal impairment, as measured indirectly from plasma creatinine levels. As detailed in Appendix K and Section 5.8, patients treated with metformin will need to discontinue metformin when creatinine clearance falls <60 ml/min or an increase in serum creatinine occurs ≥44 µmol/L (≥0.5 mg/dL) above baseline value (confirmed within one week). For patients not on metformin, discontinuation of study drug will occur:

- when creatinine clearance falls <60 ml/min, or
- when in subjects with baseline creatinine ≥123 µmol/L (≥1.4 mg/dL) an absolute increase in serum creatinine occurs ≥88 µmol/L (≥1.0 mg/dL), or
- when in subjects with baseline creatinine <123 µmol/L (<1.4 mg/dL) an absolute increase in serum creatinine occurs of ≥44 µmol/L (≥0.5 mg/dL).

Pregnancy or breast-feeding

Dapagliflozin has not been tested in pregnant women and the risks to embryo, foetus, and infant are unknown. For this reason, women who are pregnant or breastfeeding are excluded and women of childbearing age are instructed to take precautions to avoid becoming pregnant during the study.

Other

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

Inclusion criteria at enrolment (Visit 1) and start of placebo lead-in (Visits 2)

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

2. Prior diagnosis of type 2 diabetes

3. Age at enrolment visit

   - Men ≥45 years old
   - Women ≥50 years old

4. Anti-hyperglycaemic treatment should have been used uninterrupted on a daily basis for 8 weeks and stable for at least 4 weeks before enrolment and identical to one of the following:

   - Monotherapy or dual combination therapy with oral anti-diabetic drug(s) for example metformin, pioglitazone, sulfonylurea, acarbose, or a DPP-4 inhibitor (saxagliptin, sitagliptin, vildagliptin), except rosiglitazone which is not allowed for at least 8 weeks before enrolment (refer to Section 4.2, exclusion criteria 29), or
   - Insulin therapy in combination with oral anti-hyperglycaemic therapy, or
   - Insulin monotherapy

5. At enrolment: 7.2% ≤HbA1c ≤10.5% (value from blood sample obtained at screening)

6. Cardiovascular disease (Refer to Note 1), defined as:

   - Prior documented Coronary Heart Disease
     - History of myocardial infarction or
     - History of revascularization, or coronary artery stenosis >50%, confirmed with angiography or
     - Abnormal imaging at stress test, compatible with ischemia or prior myocardial infarction (Refer to Note 2), or
   - Prior documented Stroke or TIA, or
   - Prior documented Peripheral Artery Disease (PAD) treated with revascularization (amputation is not accepted)

Note 1: The time from the most recent diagnosis of above mentioned CV diseases is used to stratify patients at randomisation (see Section 3.1.1.4).

Note 2: A myocardial perfusion scan ('imaging') can be obtained following thallium, mIBI, or tetrofosmin administration during an exercise stress test or during the pharmacological equivalent of a stress test (using dipyridamole, adenosine, dobutamine or dopamine administration).

7. Hypertension, defined as follows:

   – Prior physician-made diagnosis of essential hypertension, ie, before screening, or

   – Treatment with two or more anti-hypertensive agents (diuretics, beta blockers, ace-inhibitors, angiotensin receptor blockers, or calcium channel antagonists), with one of the agents started for lowering blood pressure, or

   – Treatment with one anti-hypertensive agent and a past physician recording of a blood pressure exceeding 130/80 mmHg.

8. For patients on anti-hypertensive treatment, the anti-hypertensive treatment should have been used uninterrupted on a daily basis in the last 4 weeks before the enrolment.

9. 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 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) ; intrauterine device; levonorgestrel intra uterine system (eg, Mirina); Etonogestrel implants (eg, Implanon, Norplan); normal and low dose combined oral contraceptive pills; Norelgestromin/EE transdermal system; intravaginal device (eg, EE and etonogestrel); cerazette (desogestrel).

Inclusion criteria at randomisation (visit 4, laboratory values from visit 3):

Patients should fulfil inclusion criteria 1 to 9 (listed above) and the following criteria at randomisation:

10. HbA1c ≥7.0% and ≤10.0% at randomisation (value from blood sample obtained at Visit 3).

11. Uninterrupted monotherapy or dual combination therapy of oral diabetes drugs (with or without insulin) for at least 12 weeks before randomisation.

12. Insulin treatment for at least 12 weeks before randomisation, if administered.

13. The dose of anti-hyperglycaemic drugs and the insulin regimen should be stable for 8 weeks before randomisation.

14. For patients on current anti-hypertensive treatment the administration of anti-hypertensive drug(s) should be uninterrupted for 8 weeks before randomisation and dose should be stable for 4 weeks before randomisation.

15. Lipid lowering and/ or anti-platelet treatment should be uninterrupted for 4 weeks before randomisation, if administered.

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, and 4).

Endocrine and metabolic disorders

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

2. Use of 3 or more oral anti-hyperglycaemic drugs with or without insulin

3. History of diabetic ketoacidosis

4. 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

5. FPG >270 mg/dl (>15 mmol/L) at randomisation (sample will be taken at visit 3)

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 two months prior to enrolment
   - Less than two months post coronary artery revascularization

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 ≥165 mmHg and/or diastolic BP ≥100 mmHg

- At randomisation (Visit 4):
  Systolic BP ≥160 mmHg and/or diastolic BP ≥100 mmHg

Note: For assessment of this criterion, an average blood pressure should be used, calculated from 3 measurements. At Visit 4 measurements in each of the three positions: sitting, supine, and standing, should be assessed for eligibility (see Section 6.4.8.1).

Kidney disorders

12. Calculated creatinine clearance <60 mL/min

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

14. History of unstable or rapidly progressing renal disease

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

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

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

Infectious disease/immunologic disorders

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

Musculoskeletal disorders

26. Creatine Kinase (CK) >3X ULN

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

Reproductive status

28. Pregnant or breastfeeding patients

Prohibited medications

29. Rosiglitazone during 12 weeks prior to randomization

30. 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

31. Treatment with 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; topical or inhaled corticosteroids are allowed

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

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

Other standard criteria

34. Intolerance, contraindication or potential allergy or hypersensitivity to dapagliflozin, placebo, or formulation excipients

35. 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

36. Patients who, in the judgement of the investigator, may be at risk for dehydration

37. Acute or chronic metabolic acidosis

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

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

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

41. 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

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

43. Symptoms of any clinically relevant illness within 4 weeks prior to randomization including influenza-like illness that may be diagnosed as 'avian flu' or H1N1 influenza A.

44. Suspicion that the subject is infected according to World Health Organisation (WHO) risk categories 2 to 4 (See Appendix F)

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

45. Previous bone marrow transplant

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

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 products and all other medications including anti-hypertensive, lipid lowering and anti-platelet agents, oral anti-diabetic drugs and insulin may not be taken at home. Patients should bring all their medication including anti-hypertensive medication and study drug (if applicable) 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-diabetic drugs, insulin, lipid-lowering and anti-platelet agents within 30 minutes before breakfast.

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 286.5 mL of blood will be drawn from each patient during the entire duration of the clinical study (excluding optional genetic blood sample and extra blood samples taken at unscheduled visits), patients should be instructed to abstain from donating any blood during the clinical study and for 3 months following their last study visit.

Prohibited and restricted concomitant medications are listed in Sections 4.2 and 5.6

Fasting prior to laboratory assessments is described in Section 6.4.5.

5.2 Patient enrolment and randomisation, and initiation of investigational product

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 Visit 1, Visit 2 and Visit 4 determine patient eligibility. See Sections 4.1 and 4.2

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

Randomisation codes will be assigned at Visit 4 by way of a central randomisation using IWRS/IVRS, after all inclusion/exclusion criteria have been evaluated.

Re-screening is not allowed in the study.

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 investigational products (1:1) will be done via IWRS/IVRS at Visit 4 in balanced blocks in order to ensure approximate balance between the two treatment arms. Patients will be stratified at randomization into one of the 8 age-by-insulin use-by-time from

most recent qualifying CV event strata according to age group (<65 years versus ≥65 years at enrolment), use of insulin (No versus Yes at randomisation) and time from most recent qualifying CV event (more than 1 year versus 1 year or less (ie, within 12 months) before enrolment) (see Section 3.1.1.4). The trial expects to randomise equal numbers of patients to be enrolled within each age group. However, a moderate degree of imbalance between age strata is permitted (see Section 3.1.1.4). There is no restriction on the number of patients enrolled in each of the insulin use strata or time from most recent qualifying CV event strata.

The IWRS/IVRS will sequentially allocate the investigational products through the AstraZeneca prepared randomisation scheme and provide the randomisation number and the appropriate bottle numbers from Investigational Product Supply (IPS) available at the study centre. The Randomisation numbers will be prepared by the global randomization administrator at AstraZeneca and made available for IWRS/IVRS use.

The randomisation is carried out at the study level by way of a central randomisation within the 8 age-by-insulin use-by-time from most recent qualifying CV event strata and the assigned randomisation number and the associated bottle 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 at any time during the study conduct receives the incorrect randomised treatment, this must be corrected as soon as discovered. 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 or initiated on investigational product

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

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

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

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

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The study will be conducted in a double blind 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 delivery team at AstraZeneca or Bristol-Myers Squibb, at the investigational centres or any Contract Research Organization handling data will have access to the randomisation scheme, with the exception of the Investigational Product Supply 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. Only patients and investigators will remain blinded past the 24-week randomised treatment period. See Section 5.4.2 for further details.

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

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigator(s) and personnel who are independent to the study evaluation at the Patient Safety Department, AstraZeneca from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the 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 and Bristol-Myers Squibb retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until 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(s)

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

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

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

5.5.2 Doses and treatment regimens

Dapagliflozin 10 mg tablets, administered orally once daily for the 24-week double-blind treatment period and the 28-week and the 52-week site and patient blinded extension periods.

Matching placebo for dapagliflozin 10 mg administered orally once daily for the 4-week placebo lead-in period, the 24-week double-blind treatment period and the 28-week and the 52-week site- and patient-blinded extension periods.

The investigational product dapagliflozin and matching placebo will be taken orally, within 30 minutes before breakfast. The investigational product should be taken once daily and at approximately the same time of the day during the study period. Patients should be instructed to abstain from all food and beverages for 12 hours prior to each clinical visit; however, drinking water is allowed.. In this study dapagliflozin will be taken in the morning, after completion of certain required study procedures, shortly before breakfast defined as any time within 30 minutes before the ingestion of food.

At the randomization visit, study drug will be ingested as a witnessed dose after completing the BP measurements and all other visit procedures.

The appearance of the label on the bottle will be the same for all drug types including placebo lead-in.

Table 5 shows the drug dispensing scheme during the study.

Table 5 Drug Dispensing Scheme

Visit ID	No. of bottles to dispense of dapagliflozin 10 mg or matching placebo[a)]
Visit 1	N/A
Visit 2	1 bottle (Placebo Lead-In)[b)]
Visit 3	N/A
Visit 4	1 bottle
Visit 5	N/A

Visit ID	No. of bottles to dispense of dapagliflozin 10 mg or matching placebo[a)]
Visit 6	1 bottle
Visit 7	2 bottles
Visit 8	2 bottles
Visit 9	2 bottles
Visit 10	2 bottles
Visit 11	2 bottles
Visit 12	2 bottles
Visit 13	3 bottles
Visit 14	3 bottles
Visit 15	3 bottles
Visit 16	3 bottles
Visit 17	N/A
Visit 18	N/A

a) Each bottle contains 35 tablets.
b) The appearance of the label on the bottle will be the same for all drug types including placebo lead-in

5.5.3 Labelling

Labelling of the investigational product will be carried out by AstraZeneca or Contract Research Organisation (CRO) in accordance with current Good Manufacturing Practice (GMP)

Single panel labels or booklet labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

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, if applicable (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)
- Date dispensed (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"

5.5.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottles specifies the appropriate storage.

The dispensing and retention of reserve samples of investigational product will be performed with the FDA Code of Federal Regulations 21, Part 320 Bioavailability and Bioequivalence requirements.

5.6 Concomitant and post-study treatment(s)

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 will be reported:

- oral anti-diabetic drugs and/or insulin,
- anti-hypertensive drugs (including diuretics and some specified drugs that are known to have a blood pressure lowering effect, for example, medication used in treatment of congestive heart failure)

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.

5.6.1 Before randomisation

Patients should be on existing anti-hyperglycaemic therapy (OAD with or without insulin) for at least 8 weeks before enrolment. The anti-hyperglycaemic therapy should be stable for 8 weeks prior to randomisation and no changes including stopping or adding to OAD therapies are allowed in this period (see Section 4.1, inclusion criteria, and Table 2 in Section 3.1.1). Insulin should be administered uninterrupted for at least 8 weeks before enrolment and for 12 weeks prior to randomisation if the subject has been on insulin treatment before the study. Changes in insulin dose are allowed in the pre-randomisation period at screening(Visit S), Visit 1 (Enrolment) and Visit 2 and such change have been specified in Table 2 and Section 3.1.1).

Patients should have hypertension in the medical history as described in Inclusion criteria no. 7 in Section 4.1. Patients with or without current anti-hypertensive treatment are eligible for the study. Anti-hypertensive therapy should be uninterrupted for at least 4 weeks before enrolment and for 8 weeks before randomisation. It is recognized that investigators in different countries may have different guidelines for the management of patients with hypertension. Dose changes and withdrawal from or addition to anti-hypertensive drug therapies will be allowed at the screening and enrolment visits (see Table 2). Only dose changes will be allowed at Visit 2 (week –4). Investigators will follow country or regional guidelines for blood pressure treatment, for example guidelines from ADA 2009, JNC7 2004 or NICE 2009.

Existing lipid lowering or anti-platelet drug therapy may be changed at screening, enrolment, or at Visit 2, should be stable until randomisation, and shall be kept constant thereafter and during the double blind treatment period (see Table 2).

After enrolment, patients will enter the placebo lead-in phase to ensure that patients receive diet and lifestyle advise in addition to adequate background therapy for diabetes (concomitant medications), and that only patients with inadequate glycaemic control will be randomized and receive investigational product. Compliance to placebo will be recorded and discussed with the patients, if needed.

At Visit 4, the average daily insulin dose will be reduced by 25% beginning at breakfast or any first occurrence of insulin administration. See Section 3.1.1.4 and Table 1 for the procedures to be followed.

5.6.2 Randomised treatment period: Initiation of Rescue Therapy

5.6.2.1 Glycaemic rescue therapy during the randomised treatment period

The dose of anti-hyperglycaemic medications (oral anti-diabetic drugs and/or insulin) should not be increased or decreased between randomisation and week 104 (Visits 4 to 17) unless rescue criteria or a definition of hypoglycaemia (see Section 5.6.2.3) are met. The need for initiation of rescue therapy will be assessed based on FPG during the 24-week double blind treatment period, and based on HbA1c during the 28-week and 52-week site and patient

blinded extension periods. Numeric criteria are listed in Table 6. Glycaemic rescue is not a reason for discontinuation in this study.

Table 6 Glycaemic Rescue Criteria (24-week double blind treatment period)

Period	Central Laboratory FPG
From week 0 (Visit 4) to week 4 (Visit 6) including day of Visit 6	FPG >270 mg/dL (15.0 mmol/l)
From week 4 (Visit 6) to week 8 (Visit 7) including day of Visit 7	FPG >240 mg/dL (13.2 mmol/l)
From week 8 (Visit 7) to week 24 (Visit 9) including day of Visit 9	FPG >200 mg/dL (11.1 mmol/l)

If self-monitored FPG is above the upper limit defined for each period as described in Table 6, the patient should repeat the FPG on the same day. If the second result is also above the upper limit defined for each period as described in Table 6, the patient should contact the study centre and will be scheduled for a central laboratory FPG measurement within one week. If the FPG result of the central laboratory is above the upper limit of the treatment period as described in Table 6, the rescue criterion is met and a Rescue Visit will be scheduled within 5 working days to adjust the anti-hyperglycaemic therapy.

Table 7 Glycaemic Rescue Criterion (28-week site- and patient-blinded treatment period I and 52-week site- and patient-blinded extension period II)

Period	Central Laboratory HbA1c
From week 24 (Visit 9) to week 52 (Visit 13) including day of Visit 13.	Central Laboratory HbA1c >8.0% (repeated and confirmed)
From week 52 (Visit 13) to week 65 (Visit 14) including day of Visit 14.	Central Laboratory HbA1c >7.5% (repeated and confirmed)
From week 65 (Visit 14) to week 104 (Visit 17) excluding day of Visit 17	Central Laboratory HbA1c >7.0% (repeated and confirmed)

From week 24 (Visit 9) to week 104 (Visit 17), if self-monitored FPG is above 200 mg/dL, the patient should repeat the FPG on the same day. If the second result is also above 200 mg/dL, the patient should contact the study centre and will be scheduled for a central laboratory HbA1c measurement within one week.

Investigators are blinded to patients' HbA1c results throughout the study. However, after Visit 9 (week 24), during the 28-week and the 52-week site- and patient- blinded extension periods, a different glycaemic rescue criterion has been defined for the safety of the patients. From week 24 (Visit 9) to week 52 (Visit 13) patients with a central laboratory HbA1c value

greater than 8.0% confirmed by a repeated test within one week should be rescued. From week 52 (Visit 13) patients with a central laboratory HbA1c value greater than 7.5% and from week 65 (Visit 14) until the day before the day of week 104 (Visit 17) a central laboratory HbA1c value greater than 7.0%, respectively, confirmed by a repeated test within one week should be rescued. The central laboratory will notify the investigator to repeat HbA1c without providing an explanation, and if the repeated HbA1c value is at or above the defined level for the visit an instruction will be sent to the site by the Central Laboratory to start glycaemic rescue therapy in the patient.

Choice of rescue therapy for hyperglycaemia will be at the discretion of the investigator, who will follow country specific and/or regional guidelines, for example those published by ADA (ADA 2009), ADA and EASD combined (Nathan et al 2009) or (NICE 2009). These guidelines specify changes in OAD drug therapy. The use of rosiglitazone is not permitted. Those patients treated with insulin who meet the criteria for rescue should have their insulin dose increased by at least 10%, and all oral anti-diabetic medications, if any, should remain unchanged.

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

5.6.2.2 Insulin: Glycaemic Rescue Criteria for Patients on Insulin Therapy, or Dose Reduction

The dose of insulin should be kept constant as long as possible throughout the study. Patients who use insulin can qualify for rescue if criteria for glycaemic rescue are reached (see Section 5.6.2.1).

Rescue by changes in insulin dose is not a reason for discontinuation.

Under certain conditions patients may require changes in insulin dose that are not considered rescue therapy, as follows:

1. Any insulin dose change during hospitalisation is not considered an up-titration or a rescue as long as the insulin dose change is not for a period of more than 10 consecutive days and the primary reason for hospitalisation is not management of patient’s glycaemic control.

2. Similarly, if insulin requirement has increased temporarily, eg, due to an infection, it will not be considered an up-titration or rescue as long as such an increase is for a period of not more than 10 days and the insulin dose is expected to return to the baseline level once the precipitating condition has resolved.

3. If insulin requirement has increased temporarily if patients have to temporarily stop investigational product due to requirements of this clinical study protocol.

Dose Reduction

Dose reduction of daily insulin shall be ordered by the investigator under the following circumstances:

- Within the first 7 days of active randomised treatment, if the patient reports two or more readings of plasma glucose value ≤80 mg/dL (≤4.4 mmol/L).

- After the first 7 days of active randomised treatment, if the patient reports two or more readings of plasma glucose value ≤70 mg/dL (≤3.8 mmol/L). Patients should be encouraged to contact the investigator in such circumstances to allow the reduction of insulin dose.

Changes in concomitant insulin medication must be recorded in the appropriate sections of the eCRF.

5.6.2.3 Hypoglycaemia related medication changes

Hypoglycaemia is defined in Section 6.4.9.1. In case of any laboratory or clinically confirmed hypoglycaemia, the investigator will review the patient's circumstances for any likely cause of hypoglycaemia, for instance skipped meal(s), unexpected increase in exercise, alcohol or substance abuse, or concomitant medication including insulin and OAD. Patient related information such as the diary with glucose measurements will be reviewed. In case of any laboratory or clinically confirmed hypoglycaemia, the investigator has the discretion to make changes to the anti-hyperglycaemic medication but additional considerations are needed before the study drug (IP) can be discontinued. The consideration is that in this study, investigational product is added to existing OAD and, possibly, insulin. Patients should be kept on investigational product and adjustments should be made in the concomitant medications to prevent future occurrence of hypoglycaemia. Any changes in medication need to be recorded in the appropriate sections of the CRF. At the discretion of the investigator, for example, the daily dose of insulin can be reduced by an adequate amount (at least 10%), or adjustments can be made in OAD such as dose reduction or withdrawal of one or more OAD drugs. The changes made can be made permanent for the remainder of the treatment period and need to be recorded in the CRF.

5.6.2.4 Rescue Criteria for Hypertension

A. From the day of Visit 4 to the day of Visit 7. No changes in anti-hypertensive medications from week 0-8 are allowed except when the SBP exceeds 160 mmHg (repeated and confirmed after repeat diet and lifestyle advice), or DBP exceeds 100 mmHg (repeated and confirmed after repeat diet and lifestyle advice). Patients with a confirmed SBP ≥160 mmHg or DBP ≥100 mmHg should return for an Unscheduled Visit within 1 week. If the blood pressure still exceeds SBP ≥160 mm Hg or DBP ≥100 mm Hg, new anti-hypertensive medication should be added or dose changes in background anti-hypertensive medication should be made while continuing investigational product. In such case this visit will be considered a Rescue Visit. Changes in background medication will be recorded in the appropriate sections of the CRF. All patients will continue the scheduled visits and will be

followed for efficacy and safety endpoints. Rescue by adding anti-hypertensive drugs is not a reason to discontinue study treatment. In addition to these rescue criteria, investigators can alter anti-hypertensive medication if in the patient's best interest for example in case of angina (increase dose or change to beta blocker), or hypotension, or orthostatic hypotension.

B. From the day after Visit 7 to the day of Visit 9. No changes in anti-hypertensive medications from week 9 to 24 are allowed except when the SBP exceeds 140 mmHg (repeated and confirmed after repeat diet and lifestyle advice), or DBP exceeds 95 mmHg (repeated and confirmed after repeat diet and lifestyle advice). Patients with a confirmed SBP ≥140 mmHg or DBP ≥95 mmHg should return for an Unscheduled Visit within 1 week. If the blood pressure still exceeds SBP ≥140 mm Hg or DBP ≥95 mm Hg, new anti-hypertensive medication should be added or dose changes in background anti-hypertensive medication should be made while continuing investigational product. In such case this visit will be considered a Rescue Visit. Changes in background medication will be recorded in the appropriate sections of the CRF. All patients will continue the scheduled visits and will be followed for efficacy and safety endpoints. Rescue by adding anti-hypertensive drugs is not a reason to discontinue study treatment. In addition to these rescue criteria, investigators can alter anti-hypertensive medication if in the patient's best interest for example in case of angina (increase dose or change to beta blocker), or hypotension, or orthostatic hypotension.

C. From the day after Visit 9 to the day of Visit 17. The investigator will follow country-specific or regional guidelines for the treatment of arterial hypertension in patients with diabetes and cardiovascular disease. New anti-hypertensive medication can be added or doses of background anti-hypertensive medication can be changed. Changes in background medication will be recorded in the appropriate sections of the CRF. All patients will continue the scheduled visits and will be followed for efficacy and safety endpoints. Rescue by adding anti-hypertensive drugs is not a reason to discontinue study treatment. In addition to these rescue criteria, investigators can alter anti-hypertensive medication if in the patient's best interest for example in case of angina (increase dose or change to beta blocker), or hypotension, or orthostatic hypotension.

5.6.2.5 Anti-Hypertensive Drug Dose Reduction

During a study visit existing anti-hypertensive drug medication may be decreased if in the investigator's judgement the patient has symptomatic hypotension or has documented orthostatic hypotension (see Section 6.4.8.2). Such a dose reduction does not reflect rescue or a rescue visit. Investigators can alter anti-hypertensive medication if in the patient's best interest for example in case of renal impairment or angina.

Changes in anti-hypertensive drugs must be recorded in the appropriate section of the eCRF.

5.6.2.6 Adjustment of lipid lowering and anti-platelet therapy

Patients who need lipid lowering treatment are expected to have achieved stable lipid levels. Such patients shall be instructed to keep the lipid lowering medication constant throughout the study. In the event that changes in plasma lipid levels require an adjustment in lipid lowering

medication, country specific or regional guidelines need to be followed at the discretion of the investigator.

Patients who need anti-platelet therapy to prevent occlusive vascular events are expected to use low dose aspirin (approx. 80 mg daily) or, if clear aspirin intolerance exists, alternative drugs such as for instance clopidogrel. In the event that an adjustment in anti-platelet therapy is medically required, country specific or regional guidelines need to be followed at the discretion of the investigator.

Changes in lipid lowering drugs or anti-platelet drugs will not be considered a rescue and will be no reason to discontinue investigational product. If considered in the patient's best interest, new lipid lowering treatment or new anti-platelet treatment can be started during the study period. Changes in drugs or dose should be recorded in the appropriate modules of the eCRF.

5.6.3 Glycaemic, anti-hypertensive, lipid lowering and anti-platelet therapy after the randomised treatment

After completion of the blinded study treatment of dapagliflozin, or following discontinuation, patients need to receive anti-hyperglycaemic, anti-hypertensive, lipid lowering or anti-platelet drug therapy according to the investigator's judgement and according to local medical practice and country specific guidelines. Rosiglitazone will be allowed after discontinuation of study treatment.

5.6.4 Other concomitant medication

Other medication considered necessary for the patient's safety and well being may be given at the discretion of the investigator. (With the exception of medications listed in the Exclusion Criteria in Section 4.2). Changes in other concomitant medication must be recorded in the appropriate section of the eCRF.

5.6.5 Prohibited medications during study

1. Rosiglitazone during 12 weeks prior to randomization and during course of the study

2. 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 and during the course of the study.

3. Treatment with 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; topical or inhaled corticosteroids are allowed

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

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

5.7 Treatment compliance

The administration of all investigational products 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, excluding Visit 3 and Visit 5. The patient will be asked about compliance at each study visit; compliance will also be assessed based on returned tablet counts. Tablet counts will be recorded in the eCRF. Patients judged to be non-compliant (defined as taking less than 80% or more than 120% of the prescribed dose of investigational product) may continue in the study, but should be counselled on the importance of taking their study medication as prescribed.

5.7.1 Accountability

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

The study personnel will account for all study drugs dispensed to and returned from the patient.

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

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

- Deliveries of products from AstraZeneca or their designee are correctly received by the investigator or his or her designee;
- Such deliveries are recorded on an appropriate drug log.

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

The investigator is responsible for making sure

- That the investigational product are handled and stored safely and properly (see Section 5.5.4)

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

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

5.8 Discontinuation of investigational product

Patients may be discontinued from investigational product (IP) 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 Event, 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 study 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)

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

Development of any study specific criteria for discontinuation:

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

9. Major and/or frequent hypoglycaemic events, defined as ≥1 major event or recurring minor events (See 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

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

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

    – For all patients treated with metformin: calculated creatinine-clearance <60 mL/min or an increase in serum creatinine of ≥44 µmol/L (≥0.5 mg/dL) above the baseline value confirmed by a repeated measurement within one week.

    – For patients not treated with metformin: a) calculated creatinine clearance <60 ml/min or b) in subjects with baseline creatinine ≥123 µmol/L (≥1.4 mg/dL) an absolute increase in serum creatinine of ≥88 µmol/L (≥1.0 mg/dL), or c) in subjects with baseline creatinine <123 µmol/L (<1.4 mg/dL) an absolute increase in serum creatinine of ≥44 µmol/L (≥0.5 mg/dL).

12. CK >10x ULN confirmed at a repeated measurement preferably within 24 hours, but not exceeding 72 hours, see Section 5.8.1

13. Patients with a central laboratory ALT and/or AST >3x ULN will be scheduled for a follow-up visit within 3 days following the receipt of the result. See Appendix J for futher guidance. Patients should be discontinued from treatment if the initial **and** repeated laboratory tests meet any of the following criteria:

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

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

    ALT and/or AST are >8x ULN.

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

15. Increase of haematocrit level greater than an absolute value of 10% (or, >0.10) from baseline, or absolute haematocrit level of >55% (>0.55), confirmed with repeated laboratory test at unscheduled visit. This visit should be scheduled within 3 working days after receiving the first result, if possible. The patient will be asked about other conditions such as low fluid intake, smoking, urinary production, nycturia, other illnesses and changes in medication (use or increased use of diuretics), a brief physical examination will be done, and the haematology panel will be repeated (including haematocrit).

The following two criteria for temporary discontinuation apply to metformin-treated patients only:

- 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.

- 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 who decides to discontinue investigational product 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(s).

Patients who prematurely discontinue double blind study drug permanently should undergo Visit 17 (End of Treatment Visit) visit procedures (See Study Plan, Table 3 for assessments) These patient will have a Follow-up Visit (Visit 18) 3 weeks after treatment discontinuation.

Study drug should be returned by the patient.

If a patient is also withdrawn from study, refer to Section 5.9.

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

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 (13) will be scheduled for a follow-up visit within 3 calendar days following the receipt of the result. Patients should remain on study medication until the confirmatory results are obtained. See Appendix J for further guidance. If repeated liver function tests still are increased as outlined in Section 5.8 under listing (13), the patient should permanently discontinue all study medication and will be followed for safety (see Appendix J for further guidance).

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 study drug 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).

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.

Randomised patients

Randomised patients who have withdrawn their consent for study treatment before week 104 should return and complete Visit 17 (End of Treatment Visit) visit procedures (See Study Plan, Table 3 for assessments) as soon as possible. These patients should also be scheduled for a Follow-up Visit (Visit 18) three weeks after End of Treatment visit if they do not refuse to take part at this Follow-up Visit. 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.

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

Patients lost to follow-up are defined by the inability to reach the patient after 3 documented phone calls, faxes, or emails; inability to contact the patient through patient locator agencies (if allowed per national regulation); and lack of response by the patient to one letter by registered/certified mail. All attempts at contact should be documented in the patient's medical records. Patients lost to follow up will be withdrawn from 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 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 Web Based Data Capture (WBDC) system at the investigational centre within 72 hours after the scheduled visit (except for SAEs that should be entered within 1 calendar day). Trained study personnel will be responsible for entering data into the WBDC system according to the Instructions for the Investigator including the data entry instructions. Data includes observations, tests and assessments specified in the protocol.

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

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

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

The patients will be instructed to monitor their FPG at least every second day between Visits 2-9 and at least once a week between Visits 9-17. The FPG results, hypoglycaemic events and total daily dose of insulin will be recorded in the paper patient diary. Information will be entered by the trained study personnel into the eCRF.

Health-related quality of life (EQ-5D) questionnaire will be completed in paper. Data will be entered to the eCRF by trained study personnel.

6.2 Data collection and enrolment

Visit specific assessments and the order in which they should be performed are described in Table 3 and in Appendix E (Visit to Visit Guide).

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

In addition to what is specified in Table 3 for enrolment, the following demographic data will be collected and recorded in the appropriate sections of the eCRF:

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

6.2.1 Follow-up procedures

A Follow-up Visit (Visit 18) will be performed 18-24 days (3 weeks ±3 days) after the End of Treatment Visit (Visit 17), see Table 3 for further details.

Patients who prematurely discontinue double blind study drug treatment due to general or study specific discontinuation criteria will have a follow up visit 3 weeks after End of Treatment Visit (Visit 17).

6.3 Efficacy

6.3.1 Efficacy laboratory variables

Table 8 Efficacy laboratory variables

Visit	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17** EoT	**18**	**R**
Study Week	**-7**	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**65**	**78**	**91**	**104**	**107**	
HbA1c	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FPG[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Insulin, pro-insulin[a]					X					X				X		X		X		X
HOMA-2, HOMA-IR					X					X				X		X		X		X
Total cholesterol[a]		X			X					X				X		X		X		X
LDL-C[a]		X			X					X				X		X		X		X
HDL-C[a]		X			X					X				X		X		X		X
TG[a]		X			X					X				X		X		X		X
FFA[,a,,b]					X					X				X		X		X		X
hs-CRP[c]					X					X				X		X		X		X

[a] fasting
[b] free fatty acids;
[c] high sensitivity C-Reactive Protein.

The laboratory parameters that will be measured to assess efficacy are displayed in Table 8 by visit. The results from baseline and onwards will not be reported to the investigator, except for TC, HDL-C, LDL-C and TG which will be reported.

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. HbA1c will be blinded during the treatment period.

6.3.3 Body weight

The patient's weight will be recorded in kilogram (kg) to one decimal place, on a fasting stomach with light clothing and without shoes. All readings should be recorded as accurately as possible and the same scales should be used for all assessments for a given patient.

6.3.4 Blood pressure

Systolic and diastolic blood pressure are both an efficacy and safety variable in this study, measurement of BP is described in Section 6.4.8.

6.3.5 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.

6.4 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, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation

- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.
- Cancer
- Drug dependency/abuse

An overdose (defined as the accidental or intentional ingestion of any dose of the investigational product that is considered both excessive and medically important – see Section 13.2) 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

Adverse Events will be collected from the start of the lead-in period (Visit 2) throughout the treatment period and including the follow-up period (Visit 18).

SAEs will be recorded from the time of informed consent until the end of the study (Visit 18).

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)
- the date when the AE started and stopped
- maximum intensity

- whether the AE is serious or not
- investigator causality rating against the Investigational Product (yes or no)
- action taken with regard to investigational product
- outcome.

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

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

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

1. mild (awareness of sign or symptom, but easily tolerated)
2. moderate (discomfort sufficient to cause interference with normal activities)
3. severe (incapacitating, with inability to perform normal activities)
4. 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 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

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

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

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

Hypoglycaemic events

A separate section in the eCRF will be used to document all reported episodes of hypoglycaemia. 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. The Investigator is responsible for questioning the patient about all symptoms reported in the diary and for determining if they meet the clinical definition of hypoglycaemia. Only symptoms and/or blood glucose values deemed by the Investigator to meet the definition of hypoglycaemia should be reported on the hypoglycaemia eCRF pages (see Section 6.4.9.1).

Cardiovascular events

Cardiovascular (CV) events will be monitored in the study population and an independent CV adjudication committee will review events (See Section 6.4.10). CV events will be analyzed in conjunction with CV events observed in other Phase II and Phase III dapagliflozin studies and reported elsewhere.

6.4.4 Reporting of serious adverse events

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

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

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

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

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

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

6.4.5 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.

Due to the fasting laboratory assessments, 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 products and all other medications including anti-hypertensive, lipid lowering and anti-platelet agents, oral anti-diabetic drugs and insulin may not be taken at home. Patients should bring all their medication including anti-hypertensive medication and study drug, if applicable, 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-diabetic drugs, insulin, lipid-lowering and anti-platelet agents within 30 minutes before breakfast.

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.

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 complete list of safety laboratory variables is displayed in Table 9:

Table 9 Safety Laboratory Variables

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Resc[i)]
Study Week	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**65**	**78**	**91**	**104**	**107**	
Haematology																			
Haemoglobin	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Haematocrit	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Red blood cell count	X			X	X	X			X				X		X		X	X	X
White blood cell count and differential	X			X	X	X			X				X		X		X	X	X
Platelet count	X			X	X	X			X				X		X		X	X	X
Clinical chemistry (serum)																			
Aspartate Aminotransferase (AST, SGOT)	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Alanine Aminotransferase (ALT, SGPT)	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Alkaline Phosphatase (AP)	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lactate dehydrogenase	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Creatine Kinase (CK)	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Total Bilirubin (TB)[a]	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**Resc[i)]**
Study Week	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**65**	**78**	**91**	**104**	**107**	
Blood Urea Nitrogen (BUN)	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrolytes:	X			X	X	X	X	X	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	X	X
Albumin	X			X					X	X			X		X		X	X	X
Uric acid	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Creatine (SCr)	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Calculated creatinine clearance (Cockcroft-Gault formula)[b]	X			X		X	X	X	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	X	X	X	X	X
Serum Cystatin C				X					X	X			X		X		X	X	X

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Resc[i)]
Study Week	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**65**	**78**	**91**	**104**	**107**	
Serum Bone Metabolism Marker (Parathyroid Hormone (PTH), osteocalcin, 25 hydroxy-vitamin D, 1,25 dihydroxy-vitamin D)				X					X	X			X		X		X	X	X
FSH	X																		
TSH, Free T4[c)]	X			X															
Hepatitis Screen Panel[d)]	X																		
Central Laboratory Urinalysis																			
Glucose[e)]	X			X	X	X	X	X	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	X	X	X	X	X	X
pH	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Albumin	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Creatinine	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Calculated Urinary albumine:creatinine ratio (UACR)	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Resc[i)]
Study Week	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**65**	**78**	**91**	**104**	**107**	
Local Urinlysis																			
Pregnancy test[g)]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Culture at local laboratory at unscheduled visit[h)]																			

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. See Section 5.8. and Appendix K for details.
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 WOCBP (HCG minimum sensitivity of 25 IU/L) (dipstick analyzed at the study centre).
h) Refer to Section 6.4.9.2. (urinary and genital infections). In the event of patient reported signs and/or symptoms suggestive of an infection, a urine sample will be collected for culture at a subsequent unscheduled visit.
i) Rescue refers to Glycaemic Rescue Visit (Section 5.6.2.1). In case of a Rescue Visit due to Hypertension (Section 5.6.2.4), it will be at the discretion of the investigator to decide if any laboratory assessments are needed.

Efficacy laboratory samples are indicated in Table 8.

For blood volume see Section 7.1.

6.4.6 Physical examination

- A brief physical examination should include the cardiovascular system, lungs, abdomen, and extremities, and any organ system pertinent to the 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 1, and new findings discovered on subsequent physical examinations should be recorded as changes from baseline.

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, QRS durations, PR, QT and QTc intervals will be recorded from standard lead of the computerised ECG and will be entered in the eCRF. The ECG will be evaluated by the investigator and entered as 'Normal' or 'Abnormal' in the eCRF. If the ECG is evaluated as "Abnormal" the investigator should document the specific abnormality.

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 throughout the study. BP readings should be taken while the patient is in a comfortable seated position with the arm supported at the level of the heart. All readings should be recorded. Ideally, blood pressure should be measured with the same machine, at the same time of day, and by the same personnel at each visit. A standard mercury sphygmomanometer with a standardised cuff adapted to the size of the patient's arm is recommended. Oscillometric devices (such as 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.

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

At each visit, three blood pressure (BP) measurements separated by 2 minutes each will be done. All three BP readings should be recorded and entered in eCRF.

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.

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 three readings must be recorded.

If a new occurrence of previously absent orthostatic hypotension is demonstrated, it should be recorded in the appropriate section of the CRF. The investigator may consider to reduce concomitant anti-hypertensive medication to alleviate signs and symptoms of orthostatic hypotension, without discontinuation of investigational product. Refer to Section 5.6.2.5.

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 a glucometer 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 9 and at least once a week between visits 9 and 17. 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.

Glycaemic rescue criteria and relevant procedures are described in Section 5.6.2.

Hypoglycaemic events

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.

A hypoglycaemic event can be either:

- Symptoms of hypoglycaemia with a low blood glucose reading
- A low blood glucose reading
- Symptoms of hypoglycaemia without a blood glucose reading

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

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

- **Minor hypoglycaemic event**, defined as either a symptomatic event with a capillary or plasma glucose value <63 mg/dL (<3.5 mmol/L) but >54 mg/dL (3.0 mmol/L), and no need for external assistance, or an asymptomatic blood glucose measurement <63 mg/dL (<3.5 mmol/L).

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

If the patient experiences symptoms suggestive of hypoglycaemia and has an associated capillary or plasma glucose value ≥63 mg/dL (≥3.5 mmol/L), the event 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.

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 fingerstick value was obtained, and if so, the plasma glucose value
- Whether intervention was needed for recovery
- How the episode was treated
- Whether recovery was prompt after treatment
- Time of last anti-hyperglycaemic drug administration
- Time of last meal

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. For recording of hypoglycaemic events/symptoms suggestive of hypoglycaemic events as AEs, see Section 6.4.3.

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. It is not intended to supplant investigators' clinical judgement.

Urinary Tract Infections

Asymptomatic bacteriuria is defined as the presence of ≥105 colony forming units/mL of bacteria, in a properly collected voided urine specimen, without signs or symptoms typically attributed to urinary tract infection (UTI). Asymptomatic bacteriuria is prevalent among diabetic women, and is associated with pyuria in 70% of cases. Guidelines from the U.S. (Nicolle et al 2005) and Europe (European Association of Urology 2008) do not recommend screening for, or treatment of, asymptomatic bacteriuria in non-pregnant diabetic patients. In this study, the central laboratory will not routinely report the results of urinary dipstick tests for leukocyte esterase as a screening test for pyuria in surveillance urine examinations.

At every scheduled visit starting from the randomisation visit (ie, Visit 4), the investigator will question patients about symptoms of urinary tract infections, including but not limited to pain or burning or uncomfortable pressure in the lower abdomen/pelvic area while passing urine, blood in the urine, and symptoms of urinary urgency (a strong and uncontrolled urge to pass urine). If based on the response to these questions or other suggestive signs or symptoms (dysuria, urgency or frequency of urination, suprapubic or perineal discomfort, flank, back, or abdominal pain, costovertebral angle tenderness, nausea, vomiting, fever, chills, or sepsis) the investigator believes that a urinary tract infection may be present, urine cultures (in a local laboratory) should be obtained to confirm a presumptive diagnosis of cystitis, urinary tract infection, pyelonephritis, or prostatitis. Mid-stream clean catch urine collections are recommended. Clinical judgement and local standards of care should apply to decisions concerning therapy.

Investigational product should be 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 Tract Infections

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

Also, it is the investigator's responsibility to report, as applicable based on investigator's judgement and patient's medical history, related AEs as defined in Section 6.4.4. Additional information, including but not limited to completion of supplemental eCRFs may be requested for certain AEs and/or laboratory abnormalities which are reported/identified during the course of the study.

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

Between scheduled visits, patients may experience signs or symptoms that are potentially indicative of urinary or a genital tract infection. The patient should contact the investigator by telephone. In both instances, an unscheduled visit will be planned as soon as possible, preferably within 24 h. The investigator can obtain a midstream urine for culture to be performed at the local laboratory to demonstrate possible bacteriuria, or consider other possibilities including genital infections. The investigator will follow local guidelines to recommend treatment.

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 et al 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).

6.4.9.4 Congestive Heart Failure

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

6.4.9.5 Change in kidney function

Please see Appendix K for further guidance.

6.4.9.6 Hyponatraemia

Please see Appendix I for further guidance.

6.4.9.7 CK abnormalities

Please see Section 5.8.1, "Procedures for discontinuation of a patient from investigational product."

6.4.9.8 Liver function test abnormalities

Please see Section 5.8.1, "Procedures for discontinuation of a patient from investigational product " and Appendix J.

6.4.10 Independent Adjudication Committee

6.4.10.1 Cardiovascular Clinical Event Committee (CCEC)

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

Death including:

1. Cardiovascular Death
2. Non-cardiovascular Death

Myocardial Infarction (MI) including:

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

Fatal and Non-fatal Stroke including:

1. Ischaemic Stroke

2. Haemorrhagic Stroke

Serious Adverse Events of the following:

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

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

6.4.10.2 Hepatic Adjudication Committee

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

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

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

6.5 Patient reported outcomes (PRO)

The PRO questionnaire used in this study is the EuroQol (EQ-5D). The method for collecting the PRO data are presented below.

6.5.1 EuroQol (EQ-5D)

The EQ-5D is a generic, preference-based utility questionnaire and consists of two parts, the EQ VAS and the EQ-5D 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 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 into local languages have been performed according to a linguistic validation process.

6.5.2 PRO method

The EQ-5D will be self-administered using the paper version. The questions will be assessed at baseline (Visit 4), after 8 weeks (Visit 7), after 24 weeks (Visit 9) and after 52 weeks (Visit 13), after 78 weeks (Visit 15) and after 104 weeks (Visit 17). 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.

6.5.3 Administration of PRO questionnaire

It is important to administer the questionnaire according to recommendation for standardized administration. The patient should be informed about how important his/her participation is. The patients should complete the questionnaire before any other study related procedures take place and before any communication with the study personnel. The questionnaire 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, the study personnel will review the questionnaire for completeness only. The study personnel will enter the data in eCRF at the appropriate visit.

6.6 Pharmacokinetics (Not Applicable)

6.7 Pharmacodynamics (Not Applicable)

6.8 Pharmacogenetics

6.8.1 Collection of pharmacogenetic samples

The 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 9. 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.

For blood volume see Section 7.1.

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 286.5 mL, as follows:

Table 10 Volume of blood to be drawn from each patient

Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
Safety/Efficacy			
Haematology	2	16	32
Clinical chemistry [a)]	5	11	55
Clinical chemistry [b)]	10	2	20
Clinical chemistry [c)]	15	3	45
Clinical chemistry [e)]	8.5	3	25.5
Bicarbonate	3.5	10	35
HbA1c	2	19	38
FPG	2	18	36
Hepatitis screening panel [d)]	[d)]	1	[d)]
Total excluding pharmacogenetics			**286.5 mL**

a) Clinical chemistry and bicarbonate
b) Clinical chemistry and metabolic markers
c) Clinical chemistry, endocrine and metabolic markers
d) Included in clinical chemistry
e) Clinical chemistry, endocrine, metabolic markers and bicarbonate

7.2 Handling, storage and destruction of biological samples

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

Biological samples for future research be retained at Bristol-Myers Squibb Sample Bank and/or secure Central Laboratory owned by AstraZeneca for a maximum of 15 year following sample collection . The results from future analysis will not be reported in the Clinical Study Report.

7.2.1 Pharmacokinetic and/or pharmacodynamic samples NA

7.2.2 Pharmacogenetic 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 collection, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca and/or Bristol-Myers Squibb genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca and/or Bristol-Myers Squibb employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be double coded. The link between the patient enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Bristol-Myers Squibb Sample Bank. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analysed.

7.3 Labelling and shipment of biohazard samples

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

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the 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 or delegate at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

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

AstraZeneca and Bristol-Myers Squibb keep oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the Bristol-Myers Squibb Sample Bank 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 (pharmacogenetic sample), 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 the pharmacogenetic samples is not an integral part of the study, the patient 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/or Bristol-Myers Squibb
- 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.

All genetic samples stored at the central lab must be shipped to Bristol Myers-Squibb for registration in the Sample Bank system. AstraZeneca ensures the central laboratory(ies) and Bristol Myers-Squibb for registration in the Sample Bank holding the samples is/are informed about the withdrawn consent immediately. Bristol Myers-Squibb and/or Astrazeneca are responsible for destroying all genetic samples as required and document disposal. Bristol Myers-Squibb and AstraZeneca is responsible to inform the study site that samples destroyed as required with sending the proper documents to the investigator.

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. Pursuant to this wording, patients will authorise the collection, use and disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

The Master Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by AstraZeneca and Bristol-Myers Squibb will be identified by E-code and study code.

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

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

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

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

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

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

8.3 Ethics and regulatory review

An Ethics Committee 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 investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee 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 Events), where relevant.

Each Principal Investigator is responsible for providing the Ethics Committees/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

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

8.4 Informed consent

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 and where required in a new version of the study protocol (Revised Clinical Study Protocol).

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

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

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

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

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

8.6 Audits and inspections

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

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 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).

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.

9.3 Monitoring of the study

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

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that investigational product accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) 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 the Clinical Study Agreement for location of source data.

9.3.2 Direct access to source data in Japan (Not Applicable)

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 Q1 2010 and to end by Q1 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

Data management will be performed by Data Management Centre staff.

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

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

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

The study Data Management Plan will describe in greater detail the methods used to collect, check, and process clinical data. It will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process. Prior to breaking the treatment codes, all decisions on the evaluability of the data from each individual patient must have been made and documented. Following database lock, required amendments to the database due to critical errors will only be allowed with the appropriate supporting

documentation. Non-critical errors will not result in amendments to the database but will be captured via the appropriate documentation.

Management of external data

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

Dictionary coding

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

Management of genotype data

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

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

Data associated with biological samples

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

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

11.1 Calculation or derivation of efficacy variable(s)

Please see Section 6.3.1 for a description of specific efficacy variables derived from single laboratory measures.

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 day to first randomised dose, and the baseline value is the last assessment on or prior to the day of first randomised dose.

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 will be used for analysis.

11.1.3 3-item clinical benefit endpoint

As one of the two primary efficacy endpoints, it is defined as:

- an absolute drop of 0.5% or more from baseline HbA1c, and
- a relative drop of 3% or more from baseline for total body weight, and
- an absolute drop of 3 mmHg or more from baseline in seated systolic blood pressure.

The proportion of patients who meet this definition at week 24 will be analyzed. If no measurement for a patient is available at this time point for one or more of the 3 criteria, the LOCF rule will be applied to each missing value, followed by derivation of the 3-item endpoint. However, if a patient initiates rescue for glycaemic or blood pressure control prior to week 24, the patient will be classified as not meeting the definition of the 3-item clinical benefit endpoint regardless of the actual Week 24 or LOCF values obtained.

11.2 Calculation or derivation of safety variable(s)

11.2.1 Other significant adverse events (OAE)

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

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

11.2.2 Other safety variables

The safety evaluations will include analyses of AEs, laboratory parameters, ECG, vital signs (pulse and BP), orthostatic BP, hypoglycaemic events, calculated creatinine clearance, estimated GFR (eGFR) and physical examination. The analysis of safety will be based on the safety analysis set. Safety data gained during the 24-week double-blind treatment period, the

28-week and the 52-week extension periods and the 3-week safety follow-up period will be evaluated. Safety variables will be summarized descriptively. CV events will be analyzed in conjunction with CV events observed in other Phase II and Phase III dapagliflozin studies and the combined results will be reported elsewhere.

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

Males:

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

Females:

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

The MDRD equation will be used to calculate eGFR.

The mean of the 3 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).

Patients reporting at least one episode of hypoglycaemia between baseline and week 24 will be tabulated using counts and proportions.

11.3 Calculation or derivation of patient reported outcome variables

EuroQol (EQ-5D)

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 index includes five dimensions and each dimension has three levels: no problem, some problem and severe problem. Therefore, altogether there are 243 health states defined. A utility weight is assigned to each health state. Utility weights are elicited from general population surveys that used one of the available direct utility assessment methods.

The responses are straightforward to code and record. There is one response for each dimension, such that:

- level 1 (no problem) is coded as a '1'
- level 2 (some problem) is coded as a '2'
- level 3 (severe problem) is coded as a '3'

For comparative purposes, it is recommended that:

- missing response is coded as a '9'
- ambiguous response is coded as an '8'

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.

11.7 Calculation or derivation of health economic variables (Not applicable)

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

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

12.1 Description of analysis sets

The evaluation of efficacy will be performed for the full analysis set as outlined below. The primary efficacy variables and selected secondary variables will also be analyzed 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 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 a patient from an analysis set will be listed.

12.1.1 Efficacy analysis set

12.1.1.1 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.

12.1.1.2 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 endpoints 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.

12.1.2 Safety analysis set

The safety analysis set will include all patients who received at least one dose of randomised 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) 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 two primary objectives of this study are to show superiority of dapagliflozin versus placebo in terms of (1) change in HbA1c from baseline to week 24 and (2) likelihood of meeting all criteria of the 3-item clinical benefit composite at week 24. These objectives will

also be assessed in the overall study population and separately for each of two strata: patients less than 65 years of age and patients 65 years of age or older.

For the first primary efficacy variable, the following null hypothesis H01 related to each age stratum and the two strata combined will be tested against the alternative hypothesis HA1:

$$H01: \quad \mu T - \mu P \geq 0,$$

$$HA1: \quad \mu T - \mu P < 0,$$

where μT denotes the mean absolute change in HbA1c from baseline to week 24 in the group of patients treated with dapagliflozin (test medication, T) and μP the corresponding mean absolute change in the group of patients treated with placebo (placebo, P).

Similarly, for the second primary efficacy variable, the following null hypothesis H02 related to each age stratum and the two strata combined will be tested against the alternative hypothesis HA2:

$$H02: \quad \pi T - \pi P \leq 0,$$

$$HA2: \quad \pi T - \pi P > 0,$$

where πT denotes the probability of meeting all criteria of the 3-item clinical benefit endpoint at week 24 in the group of patients treated with dapagliflozin (test medication, T) and πP the corresponding probability in the group of patients treated with placebo (placebo, P). Four key secondary variables have been identified:

1. Absolute change in seated SBP from baseline to week 8

2. Relative change (%) in total body weight from baseline to week 24

3. Absolute change in seated SBP from baseline to week 24

4. Proportion of patients with a baseline BMI ≥ 27 kg/m^2 with a reduction of 5% or more in body weight from baseline to week 24.

A hierarchical testing procedure will be used to control the Type I error rate across the two primary and four key secondary endpoints, both in the overall population as well as within individual age strata. Initially, a Bonferroni multiplicity correction will be applied to the two tests associated with the primary efficacy variables in the overall study population so that each variable will be tested at $\alpha=0.025$ (2-sided). For a given primary efficacy variable, if the test for the overall population is statistically significant, an additional Bonferroni correction will be applied so that each test within age strata will be performed at $\alpha=0.0125$ (2-sided); however, no within-age strata tests will be performed if the test for the overall population is not statistically significant.

After performing all applicable tests for primary efficacy variables, testing of key secondary variables will be performed in a fixed order sequence (see above). The testing sequence will be applied separately for the overall population and also for each of the two age strata. The alpha level used for each of the three testing streams will depend on the results of tests for the primary variables in the corresponding population: α=0.05 (2-sided) if both primary variables are statistically significant; α=0.025 (2-sided) if only one of the primary variables is statistically significant; or no testing if the none of the primary variables are statistically significant. Thus, alpha levels may differ among the three populations for the key secondary variables. Within each population, inference for hypothesis testing will stop at the first occurrence of a failed test, regardless of how testing has progressed in the other two populations.

The primary and secondary efficacy analyses will be based on the full analysis set. The primary efficacy variables and selected secondary variables will also be analyzed 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. This LOCF approach will be used for all variables regardless of rescue medication. In addition, unless otherwise specified, if a patient initiates rescue medication (including an increase in dose of baseline medication), the last value taken on or before the first rescue dose will be used for analysis. This last rule will apply only to glycaemic and blood pressure variables (ie, rescue for glycaemic control applied only to analysis of HbA1c and FPG changes and responder derivations, whereas rescue for blood pressure control only applied to analysis of SBP and DBP changes and responder derivations).

The first primary efficacy variable, change in HbA1c from baseline to week 24, will be analyzed by an analysis of covariance (ANCOVA) model. When assessing the results overall, the model will include terms for treatment group, age-by-insulin use-by-time from most recent qualifying CV event group (8 levels), and baseline covariate. To help characterize the treatment effect, a secondary test for interaction between treatment group and age strata will be performed at the 0.10 level of significance; however, the results of this test will not alter the conclusion from the previously specified model since the effect of dapagliflozin versus placebo will be examined for each age stratum separately. When assessing the results within each age stratum, the ANCOVA model will include terms for treatment group, insulin use-by-time from most recent qualifying CV event group (4 levels), 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. For variables analyzed as percent change from baseline, the ANCOVA model will apply to logarithm-transformed data and resulting least-squares means and confidence intervals back-transformed to provide estimates in the original scale.

The second primary efficacy variable, proportion of patients at week 24 who meet all criteria of a 3-item clinical benefit composite, will be analyzed by the Cochran-Mantel-Haenszel (CMH) method. When assessing the results overall, the CMH model will include age-by insulin use-by-time from most recent qualifying CV event group as a strata variable. To help characterize the treatment effect, a secondary test for homogeneity of treatment effect between age strata will be performed at the 0.10 level of significance; however, the results of this test will not alter the conclusion of the previously specified model since the effect of dapagliflozin versus placebo will be examined in each age stratum separately. When assessing results within each age stratum, the CMH model will include insulin use-by-time from most recent qualifying CV event as a strata variable. The difference in response rates between dapagliflozin and placebo will be displayed along with a 95% confidence interval derived from asymptotic theory. P-values will be calculated from a chi-square test using the appropriate CMH model described above. If there are less than 5 responders on average by treatment group, an exact 95% confidence interval will instead be calculated along with the p-value from Fisher's exact test.

The proportion of patients achieving therapeutic glycaemic response, defined as HbA1c <7.0%, at week 24 will be analyzed using the methodology of Zhang et al 2008 and Tsiatis et al 2007 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 and age group. For each treatment group, the probability of response is first modelled using a logistic regression model with baseline HbA1c as the covariate. Treatment group estimates of response rate are then obtained by integrating each group's modelled probability of response over the observed distribution of baseline covariate (combined across groups). 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. Analyses will also be conducted separately within each age stratum. The same method will be applied for analyzing other proportions of patients achieving a pre-defined response derived from a single variable, including the key secondary variable proportion of patients with baseline BMI ≥27 kg/m^2 with a reduction of 5% or more in body weight from baseline to week 24.

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

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

the stratification factors of insulin use and time from qualifying CV event, will be defined in the SAP.

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 nevertheless in order to explore region effects. Region effects will be included in the statistical model in additional exploratory analyses if appropriate. Any pooling of countries with few patients in geographical clusters will be specified in the SAP before breaking the blind.

The mean change in EQ-5D and EQ VAS from baseline to each post-randomisation visit where evaluated will be summarized with descriptive statistics and point estimates with 95% confidence intervals. Full details of analysis methods for this instrument will be presented in the SAP.

12.2.2 Analysis after the 28-week double-blind extension period

All variables to be analyzed after the 24 weeks of double-blind treatment will be re-examined at the week 52 and the week 104 time points. 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 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 and the 52-week double-blind extension periods as well as during the 3-week safety follow-up period will be evaluated. Safety data will be presented by treatment group as well as by treatment group and age stratum. Safety variables will be summarized descriptively and missing data will be replaced using the LOCF approach where appropriate. A separate meta-analysis for adjudicated CV events from this study in conjuction with other dapagliflozin Phase II and Phase III studies is planed as requested by the new FDA CV guidance (FDA 2008). Results of analyses will be reported elsewhere.

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. The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2. A statistical analysis plan will be prepared where appropriate.

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 and 104 weeks of randomised treatment are considered to be supplemental.

12.3 Determination of sample size

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

The study has two primary endpoints for which the overall probability of a Type 1 error (Family-wise error rate) will be strictly controlled at no more than 0.05 by testing each primary endpoint at a significance level =0.025 in the overall population and 0.0125 within each age stratum. The sample size for this study is governed by the comparison with least power to achieve statistical significance; namely, for the within-age stratum comparison for the 3-item clinical benefit composite as explained below. Significance levels are expressed in terms of two-sided alternatives; however, all tests in practice will be performed against one-sided alternatives using one-half the significance levels reported here.

From post-hoc results of a Phase III dapagliflozin study, when patients meeting entry criteria like those in this current study were selected, the proportion who successfully attained the 3-item clinical benefit composite endpoint after 24 weeks of treatment and who did not meet the rescue criteria in the current study was estimated to be 18.0% for dapagliflozin 10 mg (0% for placebo). The present trial seeks to detect a treatment difference over placebo of 15 percentage points within either age stratum with high statistical power (90%). Given patients will be randomised with equal probability to dapagliflozin or placebo, it follows that 362 patients (181 per group) will provide 90% power to detect a difference in responder rates of 25% versus 10% (Δ=15%) within a given age stratum at a significance level =0.0125 using a chi-square test. If 3.7% of randomised patients fail to qualify for inclusion in the full analysis set due to missing baseline and/or all post-randomization values for this primary endpoint, then a total of 376 randomized patients at minimum are required for each age stratum. Since it is permitted to randomize as few as 40% of the total patient population in one of the age strata, it follows that in order to ensure at least 90% power for the treatment comparison in the smaller age stratum, the larger age stratum must randomize 564 patients (60% of total). Therefore, with respect to the 3-item clinical benefit composite endpoint, 940 randomized patients in total are needed for the study. This sample size provides >99% power to detect the same difference in the overall study population at a significance level =0.025.

With regard to the other primary efficacy variable, to detect a difference of 0.5% between dapagliflozin versus placebo for mean change in HbA1c from baseline to week 24, assuming a standard deviation (SD) =0.9%, 181 evaluable patients (full analysis set) for each treatment group within a given age stratum would provide >99% power for the analysis of each age stratum separately at a significance level =0.0125 using a two-sample t-test. The estimate of

the SD for this calculation is based on data from the same study used to estimate proportion of patients attaining the 3-item clinical benefit noted above.

12.4 Data monitoring committee

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

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

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

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

In the case of a medical emergency the investigator may contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician.

Name	Role in the study	Address & telephone number
	Study Delivery Team Leader responsible for the protocol	
	SDT Physician responsible for the protocol at central R&D 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 (see Section 6.4.3). 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.

13.3.1 Maternal exposure

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, 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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Clinical Study Protocol Appendix B	
Drug Substance	dapagliflozin
Study Code	D1690C00018
Edition Number	1
Date	

Appendix B
Additional Safety Information

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

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

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

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

Clinical Study Protocol Appendix C

Drug Substance	dapagliflozin
Study Code	D1690C00018
Edition Number	1
Date	

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	D1690C00018
Appendix Edition Number	2
Appendix Date	

Appendix D
Pharmacogenetics Research

GENETICS RESEARCH SYNOPSIS

A 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled phase III study with a 28-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with type 2 diabetes, cardiovascular disease and hypertension, who exhibit inadequate glycaemic control on usual care.

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

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

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

The study will be conducted in 940 randomised patients recruited from approximately 150 centres.

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

Objectives

To collect and store DNA for future exploratory research into genes that may influence response, eg, distribution, safety, tolerability and efficacy of dapagliflozin 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.

Study design

This is a 24-week, randomised, double-blind, age-stratified, placebo-controlled, 2-arm, parallel-group, multicentre global Phase III study with a 4-week placebo lead in period and a 28-week site-and patient-blinded extension period.

Optional blood sample for pharmacogenetics research (approximately 10 ml) can be collected at a single visit from Visit 4 (Randomisation Visit) to Visit 9.

Target patient population

Male and female patients with type 2 diabetes, cardiovascular disease (coronary heart disease, stroke or peripheral artery disease) and hypertension, who have inadequate glycaemic control (HbA1c ≥7.0% and ≤10.0%) on existing therapies.

Co-variables

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

Statistical methods

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

TABLE OF CONTENTS PAGE

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
eCRF	Electronic Case Report Form
DNA	Deoxyribonucleic acid
EDTA	Ethylenediamine tetra-acetic acid
ICH	International Conference on Harmonisation
mL	Millilitre

1. BACKGROUND AND RATIONALE

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

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

1.1 Rationale for genetic research

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

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

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

2. GENETIC RESEARCH OBJECTIVES

Genes that may be investigated include:

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

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

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Genetic research plan

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

The patient will be asked to participate in this genetic research at Visit 4. If the patient agrees to participate, a single blood sample will be taken for genetic research at Visit 4. If the sample isn't drawn at Visit 4, it may be drawn at any other scheduled visit after Visit 4 until Visit 9.

3.2 Selection of genetic research population

3.2.1 Study selection record

All patients will be asked to participate in this genetic research. Participation is voluntary and if a 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.

3.2.2 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.

3.2.3 Exclusion criteria

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

- Previous bone marrow transplant
- Whole blood transfusion in 120 days of genetic sample collection

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

3.2.4 Discontinuation of subjects from this genetic research

3.2.4.1 Criteria for discontinuation

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.

3.2.4.2 Procedures for discontinuation

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

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

- Withdraws consent for the sample to be kept for genetic research in the future and wishes the sample to be destroyed. Destruction of the sample (or the DNA extracted from the sample) will only be possible so long as the particular sample is traceable. In the event that genetic research has already been performed, AstraZeneca and Bristol-Myers Squibb will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

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

4. GENETIC MEASUREMENTS AND CO-VARIABLES

4.1 Summary of genetics objectives and analysis

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

The joint exploratory data analysis may be performed in the future by Statistical Genetics and Biomarkers in Exploratory Development, Global Biostatistics and Programming and the department of Pharmacogenomics in Clinical Discovery at Bristol-Myers Squibb and/or the AstraZeneca equivalent (including approved external service providers) to investigate if genetic variants (genotypes) are associated with clinical outcomes (phenotypes) such as, but not limited to, drug response, efficacy, safety, toxicity, and overall survival. The following potential analyses may be performed as appropriate:

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

4.2 Collection of samples for genetic research

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

A single venous blood sample (approximately 10 mL) will be collected into a vacutainer or similar blood collection tube containing ethylenediamine tetra-acetic acid (EDTA) and gently inverted a minimum of five times to mix thoroughly. Tubes will be labelled with the protocol study number, centre number, enrolment code and/or randomisation number and date of sample collection. No personal identifiers (patient name, initials, or date of birth) will be placed on the tube or accompanying documentation. A record of the date of the patient consent to the genetic research and the date of the blood sample collection will be recorded in the appropriate section of the electronic Case Report Form (eCRF).

Genotype is a stable parameter; therefore, if for any reason the blood sample is not drawn at Visit 4, it may be drawn at any other scheduled visit after Visit 4 until Visit 9. The genetic

blood sample should ideally be drawn through the same cannula used to draw blood samples required for the main study.

4.2.1 Sample processing and shipping

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

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

4.2.2 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.

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.

5. MANAGEMENT OF GENETIC RESEARCH DATA

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

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

5.1 Reporting of genotypic results

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

Individual patients will not be identified in any report or publication resulting from this work. The data and results of this study may be reviewed with collaborators and published, but neither the patient's name nor any other personal identifiers will appear in any publication or report.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

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

7. STUDY MANAGEMENT

7.1 Monitoring

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

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

7.2 Training of staff

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

7.3 Changes to the protocol

Any changes to the genetic research will comply with the principles described in Section 9.5 of the main body of the protocol.

7.4 Study agreements

The principal investigator at each centre must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol shall prevail. Specific reference to requirements relating to this genetic research will be included in the study agreement(s).

8. ETHICS

8.1 Ethics review

In addition to documenting Ethics Committee approval of the main study, approval must be obtained for this genetic research and the associated genetic informed consent from the relevant Ethics Committee. It must be clearly stated in the approval that this genetic research is approved. The investigator must submit written approval to AstraZeneca before any patients participates in this genetic research.

8.2 Ethical conduct of the study

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

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

8.3 Informed consent

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

8.4 Patient data protection

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

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

Due to the exploratory nature of this genetic research, there will be no routine communication of results to patients. Bristol-Myers Squibb or AstraZeneca will not provide individual genotype results to patient, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and to prevent genetic data from being linked to the identity of the patient. However, it must be recognised that there are exceptional circumstances where individuals may see both genetic data and a patients personal identifier,

for example in the case of a medical emergency, when AstraZeneca Physicians and investigators might know the patient's identity and might have access to the genetic data, or during regulatory audit where designated authorities must be permitted access to the relevant files.

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

9. LIST OF REFERENCES –NOT APPLICABLE

AstraZeneca

Clinical Study Protocol Appendix E	
Drug Substance	dapagliflozin
Study Code	D1690C00018
Edition Number	2
Date	

Appendix E
Visit to Visit Guide

TABLE OF CONTENTS PAGE

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 study drug 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. EQ-5D must be completed by patient at Visits 4, 7, 9, 13, 15 and 17 before any other procedures are done.

2. VISIT TO VISIT GUIDE

Table 1 Visit windows

Visit	Time	Time window (days)
Screening Visit	-7 weeks	≤14 days prior to Enrolment
Visit 1 (Enrolment)	-5 weeks	up to 14 days from Screening
Visit 2	-4 weeks	±3 days
Visit 3	-2 weeks	±3 days
Visit 4 (Randomisation)	0	±3 days
Visit 5	1 week	±3 days
Visit 6	4 weeks	±3 days
Visit 7	8 weeks	±3 days
Visit 8	16 weeks	±3 days
Visit 9	24 weeks	±7 days
Visit 10	28 weeks	±7 days
Visit 11	36 weeks	±7 days
Visit 12	44 weeks	±7 days
Visit 13	52 weeks	±7 days
Visit 14	65 weeks	±7 days
Visit 15	78 weeks	±7 days
Visit 16	91 weeks	±7 days

Table 1 Visit windows

Visit	Time	Time window (days)
Visit 17 (End of Treatment)	104 weeks	±3 days
Visit 18 (Follow-up)	107 weeks	±3 days

Visit 2, 3, 4 should be scheduled relative to Visit 1. 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 7.2% ≤HbA1c ≤10.5% will be scheduled for an enrolment visit within 14 days.

Patient should be fasting at the next visit.

2.2 Visit 1 – Enrolment (week –5)

The following procedures should be done in the order shown:

- Obtain written informed consent (ICF) before any other study associated procedures are done
- Inform the patient of the optional genetic section of the study
- Assess inclusion and exclusion criteria (see Section 4.1 and 4.2 in the Clinical Study Protocol (CSP))
- Allocate a unique Enrolment code (E-code) to the patient through IWRS/IVRS
- Do blood pressure and pulse examination (see Section 6.4.8.1 in the CSP)
- 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
- Do a urine pregnancy test (only applicable to women of childbearing potential)
- Measure patient's weight and height
- Obtain 12-lead Electrocardiogram (ECG) (see Section 6.4.7 in the CSP)
- Document patient demographics data (date of birth, gender, race and ethnic group)

- Document medical history
- Document concomitant medications; for anti-hyperglycaemic, anti-hypertensive, lipid lowering and anti-platelet medications daily dose should be recorded in eCRF
- SAEs are collected from the time point of signing the ICF
- 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)
- Give diet and lifestyle advice
- Ask the patient to be fasting for Visit 2 and explain the use of concomitant medications on the day of the visit
- 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 –4)

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:

- Assess inclusion and exclusion criteria
- Measure blood pressure and pulse
- Draw a blood sample and send to the central laboratory
- Do a urine pregnancy test (only applicable to women of childbearing potential)
- Measure patient's weight
- Document concomitant medications; for anti-hyperglycaemic, anti-hypertensive, lipid lowering and anti-platelet medications daily dose should be recorded in eCRF
- Collect and document AEs and 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 1 bottle 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; instruct patient how to record insulin dose, if applicable

- Give diet and lifestyle advice

- Schedule Visit 3 three weeks after Visit 1, 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.

2.4 Visit 3 (week –2)

Visit 3 will occur 3 weeks after Visit 1.

The following procedures should be done in the order shown:

- 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

- Do a urine pregnancy test (only applicable to women of childbearing potential)

- After blood pressure measurement, and blood and urine sampling, patient should take investigational product along with other medications. Patient should have a breakfast within 30 minutes after taking medications.

- Review patient's diary for glucometer values/hypoglycaemic events and insulin dose (if applicable) and dispense new diary

- Instruct patient that the insulin dose needs to be recorded daily and that the dose will be reduced by 25% at Visit 4

- Collect and document AEs and SAEs and fill in event forms when applicable

- Document concomitant medications; for anti-hyperglycaemic, anti-hypertensive, lipid lowering and anti-platelet medications daily dose should be recorded in eCRF
- Give diet and lifestyle advice
- Schedule Visit 4 five weeks after Visit 1, 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.

2.5 Visit 4 – Randomisation (week 0)

Randomisation Visit will be scheduled 5 weeks after Enrolment Visit. For patients treated with insulin, on the day of Randomisation the total daily insulin will be reduced by 25% (see CSP Section 3.1.1.4).

The following procedures should be done in the order shown:

- Ask patient to complete EQ-5D questionnaire
- 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
- Do a urine pregnancy test (only applicable to women of childbearing potential)
- Measure patient's weight
- Obtain 12-lead 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 9)
- Check returned study drug and complete drug accountability
- Review patient's diary for glucometer values/hypoglycaemic events and insulin dose (if applicable) and dispense new diary

- If applicable, calculate and record mean total daily insulin dose, and calculate the 25% reduced insulin dose, that will start on the day of randomisation (see Table 1 in the CSP)
- Instruct patient to use reduced insulin dose on the day of randomisation and during the study
- Perform a complete physical examination
- Randomise subject via IWRS/IVRS
- Verify Investigational Product kit via IWRS/IVRS and dispense IP (dapagliflozin/placebo)
- First dose of study drug should be witnessed. After blood pressure and weight measurements, and blood and urine sampling, patient should take investigational product along with other medications, including insulin, if applicable. 25% reduced insulin daily dose should be started on the day of randomisation. Patient should have a breakfast within 30 minutes after taking medications.
- Repeat discussion on new insulin dosing schedule with the patient.
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications; for anti-hyperglycaemic, anti-hypertensive, lipid lowering and anti-platelet medications daily dose should be recorded in eCRF
- Give diet and lifestyle advice
- Schedule Visit 5 one week 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.

2.6 Visit 5 (week 1)

Visit 5 will occur 1 week 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
- Do 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. Patient should have a breakfast within 30 minutes after taking medications.
- Review patient's diary for glucometer values/hypoglycaemic events and insulin dose (if applicable) and dispense new diary
- If applicable, calculate and record mean total daily insulin dose based on patient's diary
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications; for anti-hyperglycaemic, anti-hypertensive, lipid lowering and anti-platelet medications daily dose should be recorded in eCRF
- Perform brief physical examination (see details at Visit 2)
- Give diet and lifestyle advice
- Schedule Visit 6 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.

2.7 Visit 6 (week 4)

Visit 6 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
- Do 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. Patient should have a breakfast within 30 minutes after taking medications
- Review patient's diary for glucometer values/hypoglycaemic events and insulin dose (if applicable) and dispense new diary
- If applicable, calculate and record mean total daily insulin dose based on patient's diary
- Check drug accountability
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications; for anti-hyperglycaemic, anti-hypertensive, lipid lowering and anti-platelet medications daily dose should be recorded in eCRF
- Perform brief physical examination (see details at Visit 2)
- Do a re-supply of IP (Dapagliflozin/placebo) in IWRS/IVRS
- Do kit verification transaction in the IWRS/IVRS and dispense IP
- Give diet and lifestyle advice
- Schedule Visit 7 eight 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 8)

Visit 7 will occur 8 weeks after Visit 4.

The following procedures should be done in the order shown:

- Ask patient to complete EQ-5D questionnaire
- Do blood pressure and pulse examination
- Do orthostatic blood pressure and pulse examination
- Draw a blood sample and send to the central laboratory

- Take urine sample from the patient and send to central laboratory
- Do 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. Patient should have breakfast within 30 minutes from taking medications.
- Review patient's diary for glucometer values/hypoglycaemic events and insulin dose (if applicable) and dispense new diary
- If applicable, calculate and record mean total daily insulin dose based on patient's diary
- Check drug accountability
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications; for anti-hyperglycaemic, anti-hypertensive, lipid lowering and anti-platelet medications daily dose should be recorded in eCRF
- Perform brief physical examination (see details at Visit 2)
- Do a re-supply of IP (dapagliflozin/placebo) in IWRS/IVRS
- Do kit verification transaction in the IWRS/IVRS and dispense IP
- Give diet and lifestyle advice
- Schedule Visit 8 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.

2.9 Visit 8 (week 16)

Visit 8 will occur 16 weeks after Visit 4.

The following procedures should be done in the order shown:

- Do blood pressure and pulse examination
- Draw a blood sample and send to the central laboratory

- Take urine sample from the patient and send to central laboratory
- Do 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. Patient should have breakfast within 30 minutes from taking medications.
- Review patient's diary for glucometer values/hypoglycaemic events and insulin dose (if applicable) and dispense new diary
- If applicable, calculate and record mean total daily insulin dose based on patient's diary
- Check drug accountability
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications; for anti-hyperglycaemic, anti-hypertensive, lipid lowering and anti-platelet medications daily dose should be recorded in eCRF
- Perform brief physical examination (see details at Visit 2)
- Do a re-supply of IP (dapagliflozin/placebo) in IWRS/IVRS
- Do kit verification transaction in the IWRS/IVRS and dispense IP
- Give diet and lifestyle advice
- Schedule Visit 9 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.

2.10 Visit 9 (week 24)

Visit 9 will occur 24 weeks after Visit 4.

The following procedures should be done in the order shown:

- Ask patient to complete EQ-5D questionnaire
- Do blood pressure and pulse examination

- Do orthostatic blood pressure and pulse examination
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Do a urine pregnancy test (only applicable to women of childbearing potential)
- Measure patient's weight
- Do a 12-lead ECG
- After blood pressure and weight measurements, and blood and urine sampling, patient should take investigational product along with other medications. Patient should have breakfast within 30 minutes from taking medications.
- Review patient's diary for glucometer values/hypoglycaemic events and insulin dose (if applicable) and dispense new diary
- If applicable, calculate and record mean total daily insulin dose based on patient's diary
- Check drug accountability
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications; for anti-hyperglycaemic, anti-hypertensive, lipid lowering and anti-platelet medications daily dose should be recorded in eCRF
- Do a complete physical examination
- Do a re-supply of IP (dapagliflozin/placebo) in IWRS/IVRS
- Do kit verification transaction in the IWRS/IVRS and dispense IP
- Give diet and lifestyle advice
- Schedule Visit 10 twenty eight 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.

2.11 Visit 10 (week 28)

Visit 10 will occur 28 weeks after Visit 4.

The following procedures should be done in the order shown:

- Do blood pressure and pulse examination
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Do 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. Patient should have breakfast within 30 minutes from taking medications.
- Review patient's diary for glucometer values/hypoglycaemic events and insulin dose (if applicable) and dispense new diary
- If applicable, calculate and record mean total daily insulin dose based on patient's diary
- Check drug accountability
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications; for anti-hyperglycaemic, anti-hypertensive, lipid lowering and anti-platelet medications daily dose should be recorded in eCRF
- Perform brief physical examination (see details at Visit 2)
- Do a re-supply of IP (dapagliflozin/placebo) in IWRS/IVRS
- Do kit verification transaction in the IWRS/IVRS and dispense IP
- Give diet and lifestyle advice
- Schedule Visit 11 thirty six 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.

2.12 Visit 11 (week 36)

Visit 11 will occur 36 weeks after Visit 4.

The following procedures should be done in the order shown:

- Do blood pressure and pulse examination
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Do 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. Patient should have breakfast within 30 minutes from taking medications.
- Review patient's diary for glucometer values/hypoglycaemic events and insulin dose (if applicable) and dispense new diary
- If applicable, calculate and record mean total daily insulin dose based on patient's diary
- Check drug accountability
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications; for anti-hyperglycaemic, anti-hypertensive, lipid lowering and anti-platelet medications daily dose should be recorded in eCRF
- Perform brief physical examination (see details at Visit 2)
- Do a re-supply of IP (dapagliflozin/placebo) in IWRS/IVRS
- Do kit verification transaction in the IWRS/IVRS and dispense IP
- Give diet and lifestyle advice
- Schedule Visit 12 forty 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.

2.13 Visit 12 (week 44)

Visit 12 will occur 44 weeks after Visit 4.

The following procedures should be done in the order shown:

- Do blood pressure and pulse examination
- Do orthostatic blood pressure and pulse examination
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Do 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. Patient should have breakfast within 30 minutes from taking medications.
- Review patient's diary for glucometer values/hypoglycaemic events and insulin dose (if applicable) and dispense new diary
- If applicable, calculate and record mean total daily insulin dose based on patient's diary
- Check drug accountability
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications; for anti-hyperglycaemic, anti-hypertensive, lipid lowering and anti-platelet medications daily dose should be recorded in eCRF
- Perform brief physical examination
- Do a re-supply of IP (dapagliflozin/placebo) in IWRS/IVRS
- Do kit verification transaction in the IWRS/IVRS and dispense IP
- Give diet and lifestyle advice
- Schedule Visit 13 fifty two 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.

2.14 Visit 13

Visit 13 will occur 52 week after Visit 4.

The following procedures should be done in the order shown:

- Ask patient to complete EQ-5D questionnaire
- Do blood pressure and pulse examination
- Do orthostatic blood pressure and pulse examination
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Do a urine pregnancy test (only applicable to women of childbearing potential)
- Measure patient's weight
- Do a 12-lead ECG
- After blood pressure and weight measurements, and blood and urine sampling, patient should take investigational product along with other medications. Patient should have breakfast within 30 minutes from taking medications.
- Review patient's diary for glucometer values/hypoglycaemic events and insulin dose (if applicable)
- If applicable, calculate and record mean total daily insulin dose based on patient's diary
- Check drug accountability. Collect from patient all used and unused bottles with study drug.
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications; for anti-hyperglycaemic, anti-hypertensive, lipid lowering and anti-platelet medications daily dose should be recorded in eCRF
- Do a complete physical examination
- Do a re-supply of IP (dapagliflozin/placebo) in IWRS/IVRS
- Do kit verification transaction in the IWRS/IVRS and dispense IP
- Give diet and lifestyle advice

- Schedule Visit 14 sixty five 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

2.15 Visit 14

Visit 14 will occur 65 weeks after Visit 4.

The following procedures should be done in the order shown:

- Do blood pressure and pulse examination
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Do 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. Patient should have breakfast within 30 minutes from taking medications.
- Review patient's diary for glucometer values/hypoglycaemic events and insulin dose (if applicable) and dispense new diary
- If applicable, calculate and record mean total daily insulin dose based on patient's diary
- Check drug accountability
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications; for anti-hyperglycaemic, anti-hypertensive, lipid lowering and anti-platelet medications daily dose should be recorded in eCRF
- Perform brief physical examination (see details at Visit 2)
- Do a re-supply of IP (dapagliflozin/placebo) in IWRS/IVRS
- Do kit verification transaction in the IWRS/IVRS and dispense IP
- Give diet and lifestyle advice

- Schedule Visit 15 seventy eight 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.

2.16 Visit 15

Visit 15 will occur 78 week after Visit 4.

The following procedures should be done in the order shown:

- Ask patient to complete EQ-5D questionnaire
- Do blood pressure and pulse examination
- Do orthostatic blood pressure and pulse examination
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Do a urine pregnancy test (only applicable to women of childbearing potential)
- Measure patient's weight
- Do a 12-lead ECG
- After blood pressure and weight measurements, and blood and urine sampling, patient should take investigational product along with other medications. Patient should have breakfast within 30 minutes from taking medications.
- Review patient's diary for glucometer values/hypoglycaemic events and insulin dose (if applicable)
- If applicable, calculate and record mean total daily insulin dose based on patient's diary
- Check drug accountability. Collect from patient all used and unused bottles with study drug.
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications; for anti-hyperglycaemic, anti-hypertensive, lipid lowering and anti-platelet medications daily dose should be recorded in eCRF
- Do a complete physical examination

- Do a re-supply of IP (dapagliflozin/placebo) in IWRS/IVRS
- Do kit verification transaction in the IWRS/IVRS and dispense IP
- Give diet and lifestyle advice
- Schedule Visit 16 ninety one 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

2.17 Visit 16

Visit 16 will occur 91 weeks after Visit 4.

The following procedures should be done in the order shown:

- Do blood pressure and pulse examination
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Do 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. Patient should have breakfast within 30 minutes from taking medications.
- Review patient's diary for glucometer values/hypoglycaemic events and insulin dose (if applicable) and dispense new diary
- If applicable, calculate and record mean total daily insulin dose based on patient's diary
- Check drug accountability
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications; for anti-hyperglycaemic, anti-hypertensive, lipid lowering and anti-platelet medications daily dose should be recorded in eCRF
- Perform brief physical examination (see details at Visit 2)

- Do a re-supply of IP (dapagliflozin/placebo) in IWRS/IVRS
- Do kit verification transaction in the IWRS/IVRS and dispense IP
- Give diet and lifestyle advice
- Schedule Visit 17 one hundred and 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.

2.18 Visit 17 – End of Treatment Visit (week 104)

Visit 17 will occur 104 weeks 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 EQ-5D questionnaire
- Do blood pressure and pulse examination
- Do orthostatic blood pressure and pulse examination
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Do a urine pregnancy test (only applicable to women of childbearing potential)
- Measure patient's weight
- Do a 12-lead ECG
- After blood pressure and weight measurements, and blood and urine sampling, patient should take their medications. Patient should have breakfast within 30 minutes from taking medications.
- Review patient's diary for glucometer values/hypoglycaemic events and insulin dose (if applicable)
- If applicable, calculate and record mean total daily insulin dose based on patient's diary

- Check drug accountability. Collect from patient all used and unused bottles with study drug.
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications; for anti-hyperglycaemic, anti-hypertensive, lipid lowering and anti-platelet medications daily dose should be recorded in eCRF
- Do a complete physical examination
- Give diet and lifestyle advice
- Schedule Visit 18 three weeks after Visit 17
- Complete eCRF within 72 hours.

2.19 Visit 18 – Follow-up Visit (3 weeks after last intake of investigational product)

Visit 18 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:

- Do blood pressure and pulse examination
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Do 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 their medications. Patient should have breakfast within 30 minutes from taking medications.
- Collect and document AEs and SAEs and fill in event forms when applicable
- Perform brief physical examination (see details at Visit 2)
- Give diet and lifestyle advice
- Complete eCRF within 72 hours.

2.20 Rescue Visit

If the patient meets rescue criteria based on self-monitored glucose values between Visits 4 and 17, the patient should return to the study site within 1 week. Unscheduled visit will be performed to verify FPG value by the central laboratory. When a laboratory result indicates that a patient meets the rescue criteria, a Rescue Visit should be scheduled within 5 workdays. Glycaemic Rescue Criteria for initiation of rescue therapy are in Section 5.6.2 of the CSP.

The following procedures should be done in the order shown:

- Do blood pressure and pulse examination
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Do 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. Patient should have breakfast within 30 minutes from taking medications.
- Review patient's diary for glucometer values/hypoglycaemic events and insulin dose (if applicable)
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications; for anti-hyperglycaemic, anti-hypertensive, lipid lowering and anti-platelet medications daily dose should be recorded in eCRF
- Do a complete physical examination
- Give diet and lifestyle advice
- Complete eCRF within 72 hours.

Appendix F
WHO Risk Categories

WHO RISK CATEGORIES

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

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

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Clinical Study Protocol Appendix G

Drug Substance	dapagliflozin
Study Code	D1690C00018
Edition Number	1

Appendix G
New York Heart Association (NYHA) Classification

NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION

The NYHA classification will be based on the following definitions:

Class I No limitation:

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

Class II Slight limitation of physical activity:

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

Class III Marked limitation of physical activity:

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

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

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

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Clinical Study Protocol Appendix H

Drug Substance	dapagliflozin
Study Code	D1690C00018
Edition Number	1

Appendix H
EuroQol (EQ-5D)

EUROQOL (EQ-5D)

Health Questionnaire

English version for the UK

By placing a tick 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 ❑

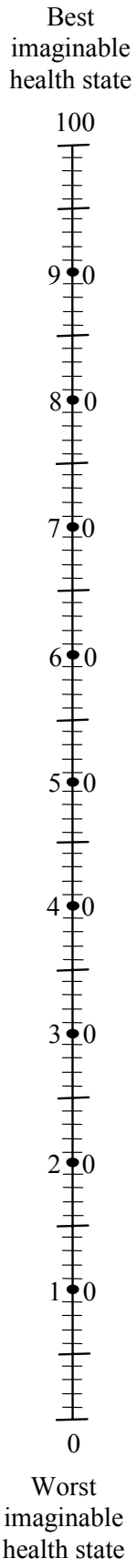
I am extremely anxious or depressed ❑

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.

Health Questionnaire

English version for the UK



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Clinical Study Protocol Appendix I

Drug Substance	dapagliflozin
Study Code	D1690C00018
Edition Number	1

Appendix I
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 126-129 mmol/L, the investigator's clinical judgment should apply concerning whether such patients should be entered into this algorithm.

Clinical Study Protocol Appendix J	
Drug Substance	dapagliflozin
Study Code	D1690C00018
Edition Number	2
Date	

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

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

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

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

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

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

- ALT and/or AST are >8 x ULN

In each of these situations, study medication will be discontinued, the Sponsor notified and the End of Treatment Visit performed within 3 days of the confirmed laboratory results (see Section 5.8.1). 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 18) 3 weeks

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

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

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

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

Guidance on Assessment of Hepatic Laboratory Abnormalities

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

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

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

Specialized Liver Panel

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

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

Liver Discontinuation Panel

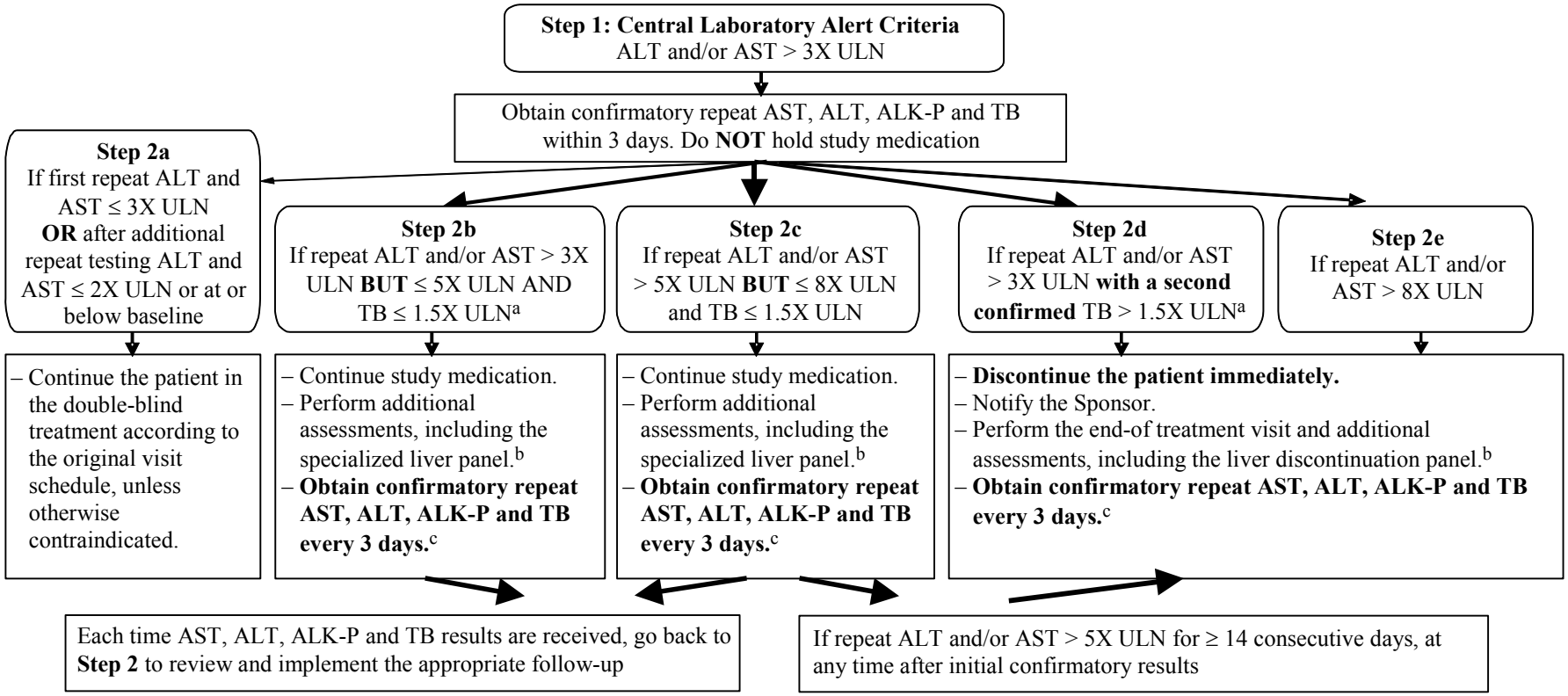
For patients who are discontinued from the study as a result of sustained elevated liver safety abnormalities, additional central laboratory tests will be performed at the time of End of Treatment Visit. Similar to the Specialized Liver Panel, these laboratory tests will study the possible causes of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

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

- Ceruloplasmin
- Toxoplasmosis
- Alpha-1 antitrypsin

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

Figure 1 Sustained elevated liver safety abnormalities flow chart



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

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

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

AstraZeneca

Clinical Study Protocol Appendix K

Drug Substance	dapagliflozin
Study Code	D1690C00018
Edition Number	2

Appendix K
Case Identification and Management of Decreased Renal Function

CASE IDENTIFICATION AND MANAGEMENT OF DECREASED RENAL FUNCTION

In order to standardise the definition and management of decreased renal function, the following guideline has been developed. Please note separate sections for patients who are treated with metformin and for those who are not treated with metformin (eg, Section 5.8 CSP).

FOR PATIENTS WHO ARE TREATED WITH METFORMIN:

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

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

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

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

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

FOR PATIENTS WHO ARE NOT TREATED WITH METFORMIN:

If a) calculated creatinine clearance is <60 ml/min or b) in subjects with baseline creatinine ≥123 µmol/L (≥1.4 mg/dL) an absolute increase occurs in serum creatinine of ≥88.4 µmol/L

(≥1.0 mg/dL) above the baseline value based on central laboratory results, or c) in subjects with baseline creatinine <123 µmol/L (<1.4 mg/dL) an absolute increase occurs in serum creatinine of ≥44.2 µmol/L (≥0.5 mg/dL) above the baseline value based on central laboratory results, this will be considered a case of "decreased renal function".

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

1. concurrent use of NSAIDS, antibiotics, or other medications known to affect measures of serum creatinine

2. volume depletion

3. urinary tract infection

4. obstructive uropathy.

Patients should return for repeat central laboratory testing as soon as possible, no later than 7 days after the abnormal result. Investigational drug should be interrupted pending the results of repeat testing. If after interruption creatinine-clearance is still <60 ml/min or if the serum creatinine value remains either ≥88.4 µmol/L (≥1.0 mg/dL) or ≥44.2 µmol/L (≥0.5 mg/dL) above the baseline value, respectively, the patient should permanently discontinue the study medication and be withdrawn from the study (in which case an Adverse Event must be reported).

If after interruption of investigational drug creatinine-clearance is ≥60 ml/min or if the serum creatinine value has decreased to <88.4 µmol/L (<1.0 mg/dL) or <44.2 µmol/L (<0.5 mg/dL) above baseline, respectively, investigational drug can be re-started if appropriate in the judgement of the investigator and following consultation with the study team physician. If the patient restarts investigational drug and creatinine-clearance is again <60 ml/min or the serum creatinine value increases again to ≥88.4 µmol/L (≥1.0 mg/dL) or ≥44.2 µmol/L (≥0.5 mg/dL) above baseline, respectively, the patient should permanently discontinue the study medication and be withdrawn from the study (in which case an Adverse Event must be reported).

Clinical Study Protocol Amendment

Amendment Number	1
Drug Substance	dapagliflozin
Study Code	D1690C00018
Protocol Dated	

A 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled phase III study with an 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with type 2 diabetes, cardiovascular disease and hypertension, who exhibit inadequate glycaemic control on usual care.

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

Centres affected by the Amendment:

This amendment affects all centres in the study.

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

Section of protocol affected:

Study title, Title page and Protocol synopsis, Page 2

Previous text:

A 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled phase III study with a 28-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with type 2 diabetes, cardiovascular disease and hypertension, who exhibit inadequate glycaemic control on usual care.

Revised text:

A 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled phase III study with a**n 80**-week extension period to evaluate the efficacy and safety of dapagliflozin 10

mg once daily in patients with type 2 diabetes, cardiovascular disease and hypertension, who exhibit inadequate glycaemic control on usual care.

Reason for Amendment:

To adjust the study title to put the study duration in line with the 52-week extension.

Section of protocol affected:

Protocol synopsis, Study centre(s) and number of patients planned, Page 2

Previous text:

…

Study period		Phase of development
Estimated date of first patient enrolled	Q1 2010	III
Estimated date of last patient completed	Q4 2011	

Revised text:

…

All ongoing patients who are still on study drug (approximately 600) will be offered to enter the 52-week site- and patient-blinded extension period II.

Study period		Phase of development
Estimated date of first patient enrolled	Q1 2010	III
Estimated date of last patient completed	Q4 201**2**	

Reason for Amendment:

To provide clarification on who can enter the new extension period. Adjusting the estimated date of last patient completed in line with the 52-week extension. The approximate number of patients to enter the extension period II was estimated according to the drop out rate in the study so far.

Section of protocol affected:

Protocol synopsis, Objectives of the 28-week extension period, Page 4

Previous text:

Objectives of the 28-week extension period:

- To assess the maintenance of efficacy of dapagliflozin 10 mg versus placebo over 52 weeks of treatment.
- To assess the safety and tolerability of dapagliflozin 10 mg over 52 weeks of treatment.

Revised text:

Objectives of the 28-week extension period I:

- To assess the maintenance of efficacy of dapagliflozin 10 mg versus placebo over 52 weeks of treatment.
- To assess the safety and tolerability of dapagliflozin 10 mg over 52 weeks of treatment.

Objectives of the 52-week extension period II:

- **To assess the maintenance of efficacy of dapagliflozin 10 mg versus placebo over 104 weeks of treatment.**
- **To assess the safety and tolerability of dapagliflozin 10 mg over 104 weeks of treatment.**

Reason for Amendment:

This study has been extended by 52 weeks to a total of an 80-week extension in order to obtain continued observations on long-term safety, tolerability and efficacy in the study population of high-risk patients.

The initial 28-week extension is now named ‘extension period I’ and the additional 52-week extension period II has been introduced.

Section of protocol affected:

Protocol synopsis, Study design, Page 4

Previous text:

This is a 24-week, randomised, double-blind, age-stratified, placebo-controlled, 2-arm, parallel-group, multicentre global Phase III study with a 4-week placebo lead in period and a 28-week site-and patient-blinded extension period. Patients will be stratified according to three factors: age at enrolment (<65 years vs. ≥65 years), insulin use at randomisation (No vs. Yes), and time from most recent qualifying cardiovascular (CV) event (>1 year versus ≤1 year).

Revised text:

This is a 24-week, randomised, double-blind, age-stratified, placebo-controlled, 2-arm, parallel-group, multicentre global Phase III study with a 4-week placebo lead in period and a 28-week **extension period I and a 52-week extension period II** site-and patient-blinded extension period**s**. Patients will be stratified according to three factors: age at enrolment (<65 years vs. ≥65 years), insulin use at randomisation (No vs. Yes), and time from most recent qualifying cardiovascular (CV) event (>1 year versus ≤1 year).

Reason for Amendment:

The initial 28-week extension is now named 'extension period I' and the additional 52-week extension period II has been introduced.

Section of protocol affected:

Protocol synopsis, Investigational product, dosage and mode of administration, Page 4

Previous text:

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

Revised text:

Dapagliflozin 10 mg tablets, administered orally once daily for the 24-week double-blind treatment period and the 28-week extension period **I and the 52-week extension period II**.

Reason for Amendment:

The initial 28-week extension is now named 'extension period I' and the additional 52-week extension period II has been introduced.

Section of protocol affected:

Protocol synopsis, Comparator, dosage and mode of administration, Page 4

Previous text:

Matching placebo for dapagliflozin 10 mg administered orally once daily for the 4-week placebo lead-in period, the 24-week double-blind treatment period and the 28-week extension period.

Revised text:

Matching placebo for dapagliflozin 10 mg administered orally once daily for the 4-week placebo lead-in period, the 24-week double-blind treatment period and the 28-week extension period **I and the 52-week extension period II.**

Reason for Amendment:

The initial 28-week extension is now named ‘extension period I’ and the additional 52-week extension period II has been introduced.

Section of protocol affected:

Protocol synopsis, Duration of treatment, Page 4

Previous text:

Within 14 days from initial screening patients will have an enrolment visit, then, after 7 days, patients will enter a 4-week placebo lead-in period (placebo will be given in a single-blind fashion, ie, blind to the patient only).Then they will be randomised to the 24-week double-blind treatment period followed by a 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 60 weeks.

Revised text:

Within 14 days from initial screening patients will have an enrolment visit, then, after 7 days, patients will enter a 4-week placebo lead-in period (placebo will be given in a single-blind fashion, ie, blind to the patient only). Then they will be randomised to the 24-week double-blind treatment period followed by a 28-week site- and patient-blinded extension period **I and a 52-week site- and patient-blinded extension period II.**. 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 **112** weeks.

Reason for Amendment:

The initial 28-week extension is now named ‘extension period I’ and the additional 52-week extension period II has been introduced. The total study duration was also adjusted.

Section of protocol affected:

1.3, Rationale for conducting this study, Page 18

Previous text:

…

An unmet medical need exists to improve the therapy of T2DM patients with such characteristics, who are considered to be at high risk of developing new complications of cardiovascular disease (Abbott et al 1998; Lehto et al 1997; Malmberg et al 2000; HOPE 2000). Dapagliflozin is a novel first-in-class drug that directly counters hyperglycaemia by inhibiting the extent of glucose reabsorption in the kidney proximal tubule with the result of

increased glucose urinary excretion (Komoroski et al 2009a; Komoroski et al 2009b). Dapagliflozin has been shown in other studies in the Phase III programme to improve glycaemic control as measured by a reduced HbA1c level (List et al 2009; Wilding et al 2009). Increased urinary volume has also been observed suggesting that dapagliflozin may act as a diuretic and may lower blood pressure (Komoroski et al 2009b). Dapagliflozin has also been associated with decrease in body weight in some patients (Wilding et al 2009). Therefore, dapagliflozin potentially provides clinically meaningful benefits to T2DM patients such as improved glycaemic control, reduction of blood pressure and body weight reduction. The efficacy of dapagliflozin on these items of clinical benefit will be tested in this study as well. Dapagliflozin's mechanism of action is insulin independent and this suggests that the drug can be efficacious in patients with or without insulin treatment. Based on observations in the Phase III development programme, dapagliflozin can be safely added to other oral anti-diabetes drugs, for example metformin and insulin.

Revised text:

…

An unmet medical need exists to improve the therapy of T2DM patients with such characteristics, who are considered to be at high risk of developing new complications of cardiovascular disease (Abbott et al 1998; Lehto et al 1997; Malmberg et al 2000; HOPE 2000). Dapagliflozin is a novel first-in-class drug that directly counters hyperglycaemia by inhibiting the extent of glucose reabsorption in the kidney proximal tubule with the result of increased glucose urinary excretion (Komoroski et al 2009a; Komoroski et al 2009b). Dapagliflozin has been shown in other studies in the Phase III programme to improve glycaemic control as measured by a reduced HbA1c level (List et al 2009; Wilding et al 2009). Increased urinary volume has also been observed suggesting that dapagliflozin may act as a diuretic and may lower blood pressure (Komoroski et al 2009b). Dapagliflozin has also been associated with decrease in body weight in some patients (Wilding et al 2009). Therefore, dapagliflozin potentially provides clinically meaningful benefits to T2DM patients such as improved glycaemic control, reduction of blood pressure and body weight reduction. The efficacy of dapagliflozin on these items of clinical benefit will be tested in this study as well. Dapagliflozin's mechanism of action is insulin independent and this suggests that the drug can be efficacious in patients with or without insulin treatment. Based on observations in the Phase III development programme, dapagliflozin can be safely added to other oral anti-diabetes drugs, for example metformin and insulin. **This study has been extended by 52 weeks to a total of 80 weeks in order to obtain continued observations on long-term safety, tolerability and efficacy in the study population of high-risk patients.**

Reason for Amendment:

An explanation for the need of the amendment was added.

Section of protocol affected:

1.4, Benefit/risk and ethical assessment, Potential risks, Page 18

Previous text:

…

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. In addition, 24-week data from a recent Phase III study with a number of 'high risk' patients with similar characteristics as defined for the present study did not reveal any new safety concerns. Data from this study are summarised in the Investigator Brochure.

None of the study procedures from the present study are likely to put patients at a risk beyond what is ordinarily encountered during the performance of routine medical examinations or 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 will conduct a real-time review of all safety information from all ongoing clinical dapagliflozin studies as they become available. Safety signal detection will include the integration of all available sources of safety information, including clinical study data, 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 programme 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 I), decreased renal function (Appendix K) and liver function abnormalities (Appendix J).

Revised text:

…

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. In addition, 24-week data from a recent Phase III study with a number of 'high risk' patients with similar characteristics as defined for the present

study did not reveal any new safety concerns. Data from this study are summarised in the Investigator Brochure. **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.**

None of the study procedures from the present study are likely to put patients at a risk beyond what is ordinarily encountered during the performance of routine medical examinations or 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 will conduct a real-time review of all safety information from all ongoing clinical dapagliflozin studies as they become available. Safety signal detection will include the integration of all available sources of safety information, including clinical study data, 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 programme 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), **microscopic hematuria (Section 6.4.9.3)**, hyponatraemia (Appendix I), decreased renal function (Appendix K) and liver function abnormalities (Appendix J).

Reason for Amendment:

To provide an update on the benefit/risk profile of dapagliflozin and also to introduce a new section on the follow-up of patients with microscopic hematuria.

Section of protocol affected:

1.4, Benefit/risk and ethical assessment, Potential benefits to patients, Page 19-20

Previous text:

All patients will continue to receive their existing background anti-hyperglycaemic therapy and the study protocol allows other existing therapies to be optimized before randomization to ensure that participants will receive optimal treatment according to country specific and/or regional guidelines. However, a direct benefit from randomised treatment cannot be assured as

one half of patients are expected to receive placebo. The expectation, based on previous Phase III studies, is that treatment with dapagliflozin is likely to improve glycaemic control (the extent however remains to be determined) because the effect does not seem to depend on age or CV risk factors as can be judged from previous data, and only moderate renal impairment is allowed. In this study, the dose of dapagliflozin (10 mg) has been chosen to provide efficacy in reducing hyperglycaemia while providing the best balance of benefit versus risk based on available information from previous studies. In addition, dapagliflozin is expected to decrease body weight (the extent of which needs to be determined) as well as lower blood pressure especially in patients with elevated baseline blood pressure. Furthermore, all patients including those who receive placebo treatment are expected to experience a benefit in the form of increased medical care/attention when participating in study procedures, which include at least 14 clinic visits with at least 13 physical examinations over the course of this 60-week study. Patients will also receive counselling for dietary and lifestyle 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 lifestyle counselling while they are participating in a clinical study. Rescue criteria for hyperglycaemia and hypertension have been defined according to guidelines in order to ensure adequate treatment for the participants.

Revised text:

All patients will continue to receive their existing background anti-hyperglycaemic therapy and the study protocol allows other existing therapies to be optimized before randomization to ensure that participants will receive optimal treatment according to country specific and/or regional guidelines. However, a direct benefit from randomised treatment cannot be assured as one half of patients are expected to receive placebo. The expectation, based on previous Phase III studies, is that treatment with dapagliflozin is likely to improve glycaemic control (the extent however remains to be determined) because the effect does not seem to depend on age or CV risk factors as can be judged from previous data, and only moderate renal impairment is allowed. In this study, the dose of dapagliflozin (10 mg) has been chosen to provide efficacy in reducing hyperglycaemia while providing the best balance of benefit versus risk based on available information from previous studies. In addition, dapagliflozin is expected to decrease body weight (the extent of which needs to be determined) as well as lower blood pressure especially in patients with elevated baseline blood pressure. Furthermore, all patients including those who receive placebo treatment are expected to experience a benefit in the form of increased medical care/attention when participating in study procedures, which include at least 1**8** clinic visits with at least 1**7** physical examinations over the course of this **112**-week study. Patients will also receive counselling for dietary and lifestyle 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 lifestyle counselling while they are participating in a clinical study. Rescue criteria for hyperglycaemia and hypertension have been defined according to guidelines in order to ensure adequate treatment for the participants.

Reason for Amendment:

To provide a schedule of the number of study visits and total duration in the new extension period.

Section of protocol affected:

2.5, Objectives for the 28-week extension period, Page 23

Previous text:

2.5 Objectives for the 28-week extension period

Revised text:

2.5 Objectives for the 28-week extension period **I**

Reason for Amendment:

The initial 28-week extension is now named 'extension period I'.

Section of protocol affected:

2.6

Previous text:

No previous text.

Revised text:

2.6 Objectives for the 52-week extension period II

- **To assess the maintenance of efficacy of dapagliflozin 10 mg versus placebo over 104 weeks of treatment.**
- **To assess the safety and tolerability of dapagliflozin 10 mg over 104 weeks of treatment.**

Reason for Amendment:

To define objectives for the 52-week extension period II.

Section of protocol affected:

3.1, Overall study design and flow chart, Page 23

Previous text:

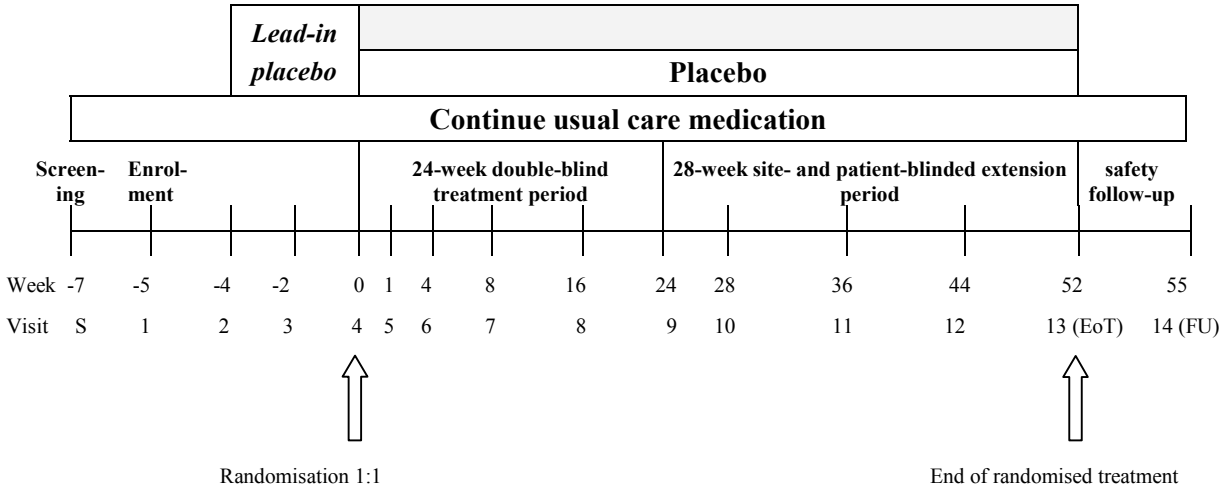
Study design

This is a 24-week randomized, double-blind, placebo-controlled, 2-arm, parallel-group, multicentre global Phase III study with a 4-week placebo lead in period and a 28-week site- and patient-blinded extension period in patients with type 2 diabetes with cardiovascular

disease and hypertension. Dapagliflozin 10 mg QD or matching placebo QD will be added to usual care of patients who have inadequate glycaemic control on their existing therapies.

…

Figure 1 Study flow chart



Before entry into the study, patients will be screened for an HbA1c level. Patients who meet the HbA1c inclusion criterion will be enrolled and examined for all inclusion and exclusion criteria. Patients will be re-examined for inclusion and exclusion criteria at Visit 2 (-4 weeks) and will enter a 4-week placebo lead-in period. During the lead-in period, laboratory test results will be obtained, patient compliance will be evaluated, and dosage of background therapy adjusted if needed (allowed changes are presented in Table 2). If applicable, at Visit 4 (Randomisation visit) the average daily insulin dose will be calculated, and on the same day the daily insulin dose will be reduced by 25%. (A recent publication (Wilding et al 2009) reports on the clinical experience in type 2 diabetes patients treated with placebo or dapagliflozin and a reduced insulin dose.) At Visit 4, patients who meet the inclusion and exclusion criteria, including HbA1c ≥7.0% and ≤10.0% (value from blood sample obtained at Visit 3) and a blood pressure less than 160/100 mmHg, will be randomised to the 24-week double-blind treatment period followed by a 28-week site-and patient-blinded extension period (see objectives of the extension period in Section 2.5). The 25%-reduced study dose of insulin and concomitant OADs, anti-hypertensive drugs, lipid lowering drugs and anti-platelet drugs should be kept constant throughout the entire 52-week treatment period. At randomisation, patients will be stratified according to age <65 years or ≥65 years, insulin use (No or Yes), and time from most recent qualifying CV event (more than 1 year versus 1 year or less (ie within 12 months) before enrolment) (see Section 4.1, Inclusion Criteria, item 6).

After either completion of the treatment periods or discontinuation from treatment, patients will enter a 3-week safety follow-up period without investigational product. The follow-up

visit (Visit 14 (FU)) 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 14) will be 60 weeks.

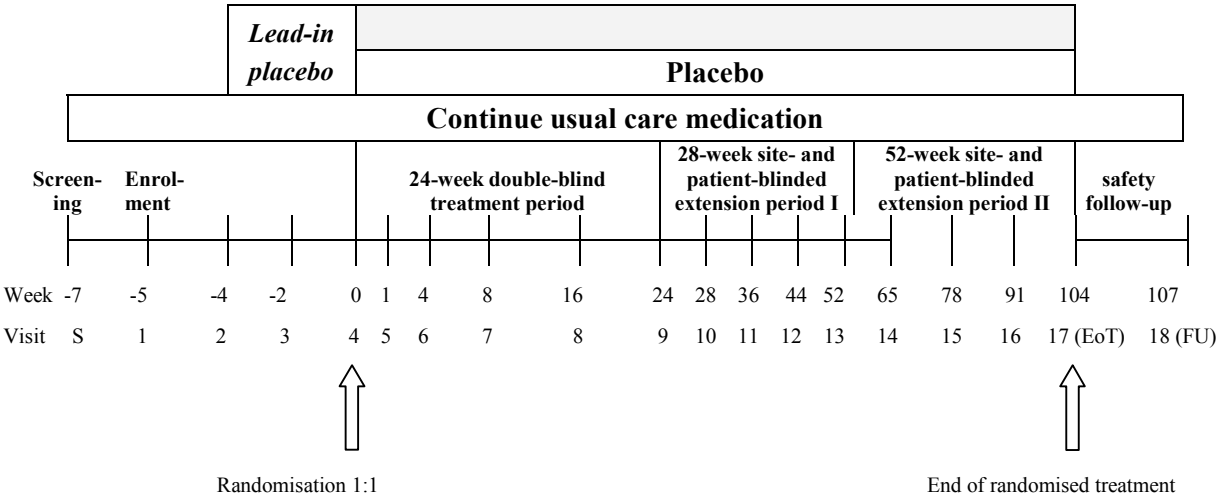
Revised text:

Study design

This is a 24-week randomized, double-blind, placebo-controlled, 2-arm, parallel-group, multicentre global Phase III study with a 4-week placebo lead in period and a 28-week site- and patient-blinded extension period **I and a 52-week site- and patient-blinded extension period II** in patients with type 2 diabetes with cardiovascular disease and hypertension. Dapagliflozin 10 mg QD or matching placebo QD will be added to usual care of patients who have inadequate glycaemic control on their existing therapies.

…

Figure 1 Study flow chart



Before entry into the study, patients will be screened for an HbA1c level. Patients who meet the HbA1c inclusion criterion will be enrolled and examined for all inclusion and exclusion criteria. Patients will be re-examined for inclusion and exclusion criteria at Visit 2 (-4 weeks) and will enter a 4-week placebo lead-in period. During the lead-in period, laboratory test results will be obtained, patient compliance will be evaluated, and dosage of background therapy adjusted if needed (allowed changes are presented in Table 2). If applicable, at Visit 4 (Randomisation visit) the average daily insulin dose will be calculated, and on the same day the daily insulin dose will be reduced by 25%. (A recent publication (Wilding et al 2009) reports on the clinical experience in type 2 diabetes patients treated with placebo or dapagliflozin and a reduced insulin dose.) At Visit 4, patients who meet the inclusion and exclusion criteria, including HbA1c ≥7.0% and ≤10.0% (value from blood sample obtained at

Visit 3) and a blood pressure less than 160/100 mmHg, will be randomised to the 24-week double-blind treatment period followed by a 28-week site-and patient-blinded extension period **I and a 52-week site- and patient-blinded extension period II** (see objectives of the extension period **I** in Section 2.5 **and of the extension period II in Section 2.6**). The 25%-reduced study dose of insulin and concomitant OADs, anti-hypertensive drugs, lipid lowering drugs and anti-platelet drugs should be kept constant throughout the entire **104**-week treatment period. At randomisation, patients will be stratified according to age <65 years or ≥65 years, insulin use (No or Yes), and time from most recent qualifying CV event (more than 1 year versus 1 year or less (ie, within 12 months) before enrolment) (see Section 4.1, Inclusion Criteria, item 6).

After either completion of the treatment periods or discontinuation from treatment, patients will enter a 3-week safety follow-up period without investigational product. The Follow-up Visit (Visit 1**8** (FU)) 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 1**8**) will be **112** weeks.

Reason for Amendment:

To adjust the text and study schedule in relation to the 52-week extension period II.

Section of protocol affected:

3.1.1.5, Extension period (Visits 9-13, week 24 to week 52)

Previous text:

Patients will return for follow-up visits at four- to eight-week intervals during the 28-week site-and patient-blinded extension 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. Glycaemic rescue criteria and relevant procedures are described in Section 5.6.2.

Diet and lifestyle modification will be reinforced at each visit during this period.

Patients will discontinue investigational product at the end of this treatment period (Visit 13, End of Treatment Visit).

Visit 13 (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 permanently should return and complete the procedures described for the End of Treatment Visit as soon as possible after the last intake of investigational product.

Patients who complete the scheduled study treatment and who prematurely discontinued study treatment permanently will have the Follow-up Visit (Visit 14) 3 weeks after the last intake of investigational product.

Revised text:

Extension period I (Visits 9-13, week 24 to week 52)

Patients will return for follow-up visits at four- to eight-week intervals during the 28-week site-and patient-blinded extension period **I**.

Extension period II (Visits 13-17, week 52 to week 104)

After the extension period I all ongoing patients on study drug will be asked to continue the study for another 52 weeks and will sign an informed consent form for extension period II.

After Visit 13 patients who consent will continue in the site- and patient-blinded extension period II with the same treatment given as at the end of the extension period I.

Patients will return for follow-up visits at thirteen-week intervals during the 52-week site- and patient-blinded extension period II.

During the two extension periods 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. Glycaemic rescue criteria and relevant procedures are described in Section 5.6.2.

Diet and lifestyle modification will be reinforced at each visit during th**es**e period**s**.

Patients will discontinue investigational product at the end of th**e** treatment period (Visit 1**7**, End of Treatment Visit).

Visit 17 (End of Treatment Visit, week 104)

At week **104** 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 permanently should return and complete the procedures described for the End of Treatment Visit as soon as possible after the last intake of investigational product.

Patients who complete the scheduled study treatment and who prematurely discontinued study treatment permanently will have the Follow-up Visit (Visit 1**8**) 3 weeks after the last intake of investigational product.

Reason for Amendment:

To clarify procedures and visits in the 52-week extension period II. Four more visits are planned and the 'End of Treatment' Visit is now Visit 17 (previously, Visit 13) and the 'follow-up' visit is now Visit 18 (previously, Visit 14). To clarify the need for re-consenting before the patients can enter the 52-week extension.

Section of protocol affected:

3.1.1.6, Follow-up period, title, Page 29

Previous text:

Follow-up period (Visit 14, week 55)

Revised text:

Follow-up period (Visit 1**8**, week **107**)

Reason for Amendment:

To update the text in relation to the 52-week extension period II.

Section of protocol affected:

3.1.2, Background therapy, paragraphs 2 and 3, Page 30

Previous text:

…

The dose of anti-hyperglycaemic medication(s) should not be increased or decreased between weeks 0-52 (Visits 4 and 13) unless rescue criteria (see Section 5.6.2) or a definition of hypoglycaemia (Section 5.6.2.3) are met. Patients who use insulin can qualify for rescue (ie, insulin uptitration; see Section 5.6.2.2) if criteria for glycaemic rescue are reached (see Section 5.6.2.1).

Anti-hypertensive medication(s) should not be changed between randomisation and week 52 (Visit 4 to 13) unless specific criteria are met. Rescue criteria have been defined (Section 5.6.2.4). Investigators can alter anti-hypertensive medication if in the patient's best interest such as in case of angina, or symptomatic hypotension, or orthostatic hypotension (see Section 5.6.2.5).

…

Revised text:

…

The dose of anti-hyperglycaemic medication(s) should not be increased or decreased between weeks 0-**104** (Visits 4 and 1**7**) unless rescue criteria (see Section 5.6.2) or a definition of

hypoglycaemia (Section 5.6.2.3) are met. Patients who use insulin can qualify for rescue (ie, insulin uptitration; see Section 5.6.2.2) if criteria for glycaemic rescue are reached (see Section 5.6.2.1).

Anti-hypertensive medication(s) should not be changed between randomisation and week **104** (Visit 4 to 1**7**) unless specific criteria are met. Rescue criteria have been defined (Section 5.6.2.4). Investigators can alter anti-hypertensive medication if in the patient's best interest such as in case of angina, or symptomatic hypotension, or orthostatic hypotension (see Section 5.6.2.5).

…

Reason for Amendment:

To update the text in relation to the 52-week extension period II.

Section of protocol affected:

Table 3, Study Plan, Page 31

Previous text:

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**	**12**	**13[c)]**	**14 FU**	**R[j)]**
Week	**-7**	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**55**	
Visit window (days) [a)]		(0)[b)]	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±3)	(±3)	
Screening informed consent and blood sample for HbA1c	X															
Informed consent		X														
Patient reported outcome (EQ-5D)					X			X		X				X		
Demography and medical history		X														
In-/Exclusion criteria		X	X		X											
Randomisation					X											
Brief physical examination			X			X	X	X	X		X	X	X		X	
Complete physical examination		X			X					X				X		X
Vital signs (BP, pulse)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Orthostatic BP					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**	**12**	**13**[c]	**14 FU**	**R**[j]
Week	**-7**	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**55**	
Visit window (days) [a]		(0)[b]	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±3)	(±3)	
Weight		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Height		X														
12-lead ECG		X			X					X				X		
Concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments [d]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test [e]		X	X	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	X	X
AEs			X	X	X	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	X			
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	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**	**12**	**13**[c)]	**14 FU**	**R**[j)]
Week	**-7**	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**55**	
Visit window (days) [a)]		(0)[b)]	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±3)	(±3)	
Dispense glucometer at V2; provide supplies, instructions			X	X	X	X	X	X	X	X	X	X	X			X
Dispense patient diary			X	X	X	X	X	X	X	X	X	X	X			X
Patient diary review for glucometer values/ hypoglycaemic events [f)]				X	X	X	X	X	X	X	X	X	X	X		X
Calculate average daily insulin dose					X [g)]	X [h)]	X [h)]	X [h)]	X [h)]	X [h)]	X [h)]	X [h)]	X [h)]	X [h)]		
Informed consent, blood sample for genetic research [i)]					(X)	(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) Specifications of laboratory parameters are shown in Table 8 and Table 9.
e) Pregnancy test will be done on all female patients who are not postmenopausal or hysterectomised.
f) Patients should be instructed to contact the investigator by phone if a hypoglycaemic event occurs, in cases specified in the patient diary.
g) On the day of Visit 4 (Randomisation Visit), daily insulin dose will be reduced by 25% from the average daily dose between visits 3 and 4.
h) The mean daily insulin dose will be calculated by the investigator. On visits 5-13 the calculated mean daily insulin dose is the average daily insulin use over the last 7 documented days before the actual visit.

i) Genetic informed consent must be obtained before genetic blood sample is taken. Blood sample donation is optional and can be done any time from Visit 4 (ie, randomisation) to Visit 9.
j) Rescue refers to a Glycaemic Rescue Visit (section 5.6.2.1). In case of a Rescue Visit due to hypertension (section 5.6.2.4), it will be at the discretion of the investigator to decide if any laboratory assessments are needed.

Revised text:

Table 3 Study Plan

	Screening	**Enrolment**	**Placebo lead-in**				**24-week double-blind treatment period**					**28-week site- and patient-blinded extension period I**				**52-week site- and patient-blinded extension period II**			**Follow-up**	**Rescue**
Visit	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**[c)]	**18 FU**	**R**[j)]
Week	**-7**	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**65**	**78**	**91**	**104**	**107**	
Visit window (days) a)		**(0)**[b)]	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±3)**	**(±3)**	
Screening informed consent and blood sample for HbA1c	**X**																			
Informed consent		X																		
Informed consent for the extension period II[k)]														**X**						

	Screening	Enrolment	Placebo lead-in				24-week double-blind treatment period					28-week site- and patient-blinded extension period I				52-week site- and patient-blinded extension period II			Follow-up	Rescue
Visit	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17[c)]**	**18 FU**	**R[j)]**
Week	**-7**	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**65**	**78**	**91**	**104**	**107**	
Visit window (days) a)		**(0)[b)]**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±3)**	**(±3)**	
Patient reported outcome (EQ-5D)					X			X		X				X		X		X		
Demography and medical history		X																		
In-/Exclusion criteria		X	X		X															
Randomisation					X															
Brief physical examination			X			X	X	X	X		X	X	X		X		X		X	
Complete physical examination		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 I				52-week site- and patient-blinded extension period II		Follow-up	Rescue
Visit	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17[c)]**	**18 FU**	**R[j)]**
Week	**-7**	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**65**	**78**	**91**	**104**	**107**	
Visit window (days) a)		**(0)[b)]**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±3)**	**(±3)**	
Vital signs (BP, pulse)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Orthostatic BP					X	X	X	X		X			X	X		X		X		
Weight		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height		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	X	X	X	X	X	X
Laboratory assessments d)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test e)		X	X	X	X	X	X	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	X	X	X	X	X	X
AEs			X	X	X	X	X	X	X	X	X	X	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 I				52-week site- and patient-blinded extension period II			Follow-up	Rescue
Visit	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17[c)]**	**18 FU**	**R[j)]**
Week	**-7**	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**65**	**78**	**91**	**104**	**107**	
Visit window (days) a)		**(0)[b)]**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±3)**	**(±3)**	
Dispense investigational product via IWRS/IVRS			X		X		X	X	X	X	X	X	X	X	X	X	X			
Drug accountability					X		X	X	X	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	X	X	X	X	X	X
Dispense glucometer at V2; provide supplies, instructions			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Dispense patient diary			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X

	Screening	Enrolment	Placebo lead-in				24-week double-blind treatment period				28-week site- and patient-blinded extension period I				52-week site- and patient-blinded extension period II		Follow-up	Rescue
Visit	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17[c)]**	**18 FU**	**R[j)]**
Week	**-7**	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**65**	**78**	**91**	**104**	**107**	
Visit window (days) a)		**(0)[b)]**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±3)**	**(±3)**	
Patient diary review for glucometer values/ hypoglycaemic events f)				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Calculate average daily insulin dose					Xg)	Xh)	Xh)	Xh)	Xh)	Xh)	Xh)	Xh)	Xh)	Xh)	Xh)	Xh)	Xh)	Xh)		
Informed consent, blood sample for genetic research i)					(X)	(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) Specifications of laboratory parameters are shown in Table 8 and Table 9.

e) Pregnancy test will be done on all female patients who are not postmenopausal or hysterectomised.
f) Patients should be instructed to contact the investigator by phone if a hypoglycaemic event occurs, in cases specified in the patient diary.
g) On the day of Visit 4 (Randomisation Visit), daily insulin dose will be reduced by 25% from the average daily dose between visits 3 and 4.
h) The mean daily insulin dose will be calculated by the investigator. On visits 5-17 the calculated mean daily insulin dose is the average daily insulin use over the last 7 documented days before the actual visit.
i) Genetic informed consent must be obtained before genetic blood sample is taken. Blood sample donation is optional and can be done any time from Visit 4 (ie, randomisation) to Visit 9.
j) Rescue refers to a Glycaemic Rescue Visit (section 5.6.2.1). In case of a Rescue Visit due to hypertension (section 5.6.2.4), it will be at the discretion of the investigator to decide if any laboratory assessments are needed.
k) Patients still on active study treatment who have not developed any reason for study discontinuation will be asked to continue the study for another 52 weeks.

Reason for Amendment:

To update Study Plan for the 52-week extension period II.

Section of protocol affected:

3.2.1, Study design and regulatory requirement, Page 34

Previous text:

This is a 24-week randomized, double-blind, age-stratified, placebo-controlled, 2-arm, parallel-group, multicentre global Phase III study with a 4-week placebo lead-in period and a 28-week site-and patient-blinded extension period. Dapagliflozin 10 mg once daily (QD) or matching placebo QD will be added to the therapies of patients with T2DM who have inadequate glycaemic control on their existing therapies consisting of stable doses of either monotherapy or dual combination therapy with metformin, pioglitazone, sulfonylurea, or a DPP-4 inhibitor (saxagliptin, sitagliptin, vildagliptin) for at least 12 weeks at randomisation, or insulin monotherapy, or insulin therapy in combination with oral anti-diabetic therapy. Studies with an active arm and placebo arm both added to usual care are specifically mentioned in the EMEA Guidance (CPMP/EWP/1080/00, 30 May 2002) and the FDA Guidance on Diabetes Mellitus (Feb 2008) as examples of designs to study long-term glycaemic efficacy. To emphasize the importance of obtaining more efficacy and safety data in elderly patients, age ≥65 years has been chosen as a factor for stratification. In order to balance the risk of future cardiovascular events between treatment arms, patients will be stratified according to time from most recent qualifying CV event (1 year or less versus more than 1 year before enrolment).

Revised text:

This is a 24-week randomized, double-blind, age-stratified, placebo-controlled, 2-arm, parallel-group, multicentre global Phase III study with a 4-week placebo lead-in period and a 28-week site-and patient-blinded extension period **I and a 52-week site- and patient-blinded extension period II**. Dapagliflozin 10 mg once daily (QD) or matching placebo QD will be added to the therapies of patients with T2DM who have inadequate glycaemic control on their existing therapies consisting of stable doses of either monotherapy or dual combination therapy with metformin, pioglitazone, sulfonylurea, or a DPP-4 inhibitor (saxagliptin, sitagliptin, vildagliptin) for at least 12 weeks at randomisation, or insulin monotherapy, or insulin therapy in combination with oral anti-diabetic therapy. Studies with an active arm and placebo arm both added to usual care are specifically mentioned in the EMEA Guidance (CPMP/EWP/1080/00, 30 May 2002) and the FDA Guidance on Diabetes Mellitus (Feb 2008) as examples of designs to study long-term glycaemic efficacy. To emphasize the importance of obtaining more efficacy and safety data in elderly patients, age ≥65 years has been chosen as a factor for stratification. In order to balance the risk of future cardiovascular events between treatment arms, patients will be stratified according to time from most recent qualifying CV event (1 year or less versus more than 1 year before enrolment).

Reason for Amendment:

To update the text in relation to the 52-week extension period II.

Section of protocol affected:

3.2.2, Study doses and control groups, Background therapy, paragraphs 1 and 4, Pages 34-35

Previous text:

Patients should have an HbA1c value of ≥7.2% and ≤10.5% at screening while on existing anti-diabetic therapy for at least 6 weeks and on stable therapy for at least 2 weeks at screening (to meet enrolment criteria, see Section 4.1), which indicates inadequate glycaemic control in spite of anti-hyperglycaemic therapy (Nathan et al 2009). Patients with a blood pressure higher than SBP ≥165 and DBP ≥100 mmHg at enrolment will not be enrolled in the study. Changes in anti-hyperglycaemic treatment will not be allowed at screening, at enrolment, placebo lead in period and during the entire 52 weeks treatment period. However, investigators will follow country or regional guidelines to optimize the treatment for blood pressure, plasma lipids and anti-platelet therapy according to the schedule in Table 2. Examples of guidelines are those published by the American Diabetes Association (ADA) (ADA 2009), National Institute for Health and Clinical Excellence (NICE) in the U.K. (NICE 2009), the Joint National Committee (JNC) (JNC7 2004) and European Society of Cardiology (ESC)(ESH/ESC 2007).

…

Investigators and patients should also keep constant the existing other therapies (anti-hypertensive drugs, lipid lowering drugs, anti-platelet drugs) while receiving investigational product during the entire 52-week study treatment period. (See Section 5.6).

Revised text:

Patients should have an HbA1c value of ≥7.2% and ≤10.5% at screening while on existing anti-diabetic therapy for at least 6 weeks and on stable therapy for at least 2 weeks at screening (to meet enrolment criteria, see Section 4.1), which indicates inadequate glycaemic control in spite of anti-hyperglycaemic therapy (Nathan et al 2009). Patients with a blood pressure higher than SBP ≥165 and DBP ≥100 mmHg at enrolment will not be enrolled in the study. Changes in anti-hyperglycaemic treatment will not be allowed at screening, at enrolment, placebo lead in period and during the entire **104** weeks treatment period. However, investigators will follow country or regional guidelines to optimize the treatment for blood pressure, plasma lipids and anti-platelet therapy according to the schedule in Table 2. Examples of guidelines are those published by the American Diabetes Association (ADA) (ADA 2009), National Institute for Health and Clinical Excellence (NICE) in the U.K. (NICE 2009), the Joint National Committee (JNC) (JNC7 2004) and European Society of Cardiology (ESC)(ESH/ESC 2007).

…

Investigators and patients should also keep constant the existing other therapies (anti-hypertensive drugs, lipid lowering drugs, anti-platelet drugs) while receiving investigational product during the entire **104**-week study treatment period. (See Section 5.6).

Reason for Amendment:

To update the duration of treatment with study drug in relation to the 52-week extension period II.

Section of protocol affected:

5.1, Restrictions during the study, Page 48

Previous text:

…

As up to approximately 245 mL of blood will be drawn from each patient during the entire duration of the clinical study (excluding optional genetic blood sample and extra blood samples taken at unscheduled visits), patients should be instructed to abstain from donating any blood during the clinical study and for 3 months following their last study visit.

…

Revised text:

…

As up to approximately **286.5** mL of blood will be drawn from each patient during the entire duration of the clinical study (excluding optional genetic blood sample and extra blood samples taken at unscheduled visits), patients should be instructed to abstain from donating any blood during the clinical study and for 3 months following their last study visit.

…

Reason for Amendment:

To provide an updated estimate of approximate volume of blood to be drawn from each patient after inclusion of 4 more visits with blood sampling.

Section of protocol affected:

5.5.2, Doses and treatment regimens, paragraphs 1 and 2, Pages 51-52

Previous text:

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 4-week placebo lead-in period, the 24-week double-blind treatment period and the 28-week site- and patient-blinded extension period.

…

Revised text:

Dapagliflozin 10 mg tablets, administered orally once daily for the 24-week double-blind treatment period and the 28-week **and the 52-week** site and patient blinded extension period**s**.

Matching placebo for dapagliflozin 10 mg administered orally once daily for the 4-week placebo lead-in period, the 24-week double-blind treatment period and the 28-week **and the 52-week** site- and patient-blinded extension period**s**.

…

Reason for Amendment:

To update the text in relation to the new extension period.

Section of protocol affected:

Table 5, Page 52

Previous text:

Table 5 Drug Dispensing Scheme

Visit ID	No. of bottles to dispense of dapagliflozin 10 mg or matching placebo[a)]
Visit 1	N/A
Visit 2	1 bottle (Placebo Lead-In)[b)]
Visit 3	N/A
Visit 4	1 bottle
Visit 5	N/A
Visit 6	1 bottle
Visit 7	2 bottles
Visit 8	2 bottles
Visit 9	2 bottles
Visit 10	2 bottles
Visit 11	2 bottles
Visit 12	2 bottles
Visit 13	N/A
Visit 14	N/A

a) Each bottle contains 35 tablets.
b) The appearance of the label on the bottle will be the same for all drug types including placebo lead-in

Revised text:

Table 5 Drug Dispensing Scheme

Visit ID	No. of bottles to dispense of dapagliflozin 10 mg or matching placebo[a)]
Visit 1	N/A
Visit 2	1 bottle (Placebo Lead-In)[b)]
Visit 3	N/A
Visit 4	1 bottle
Visit 5	N/A
Visit 6	1 bottle
Visit 7	2 bottles
Visit 8	2 bottles
Visit 9	2 bottles
Visit 10	2 bottles
Visit 11	2 bottles
Visit 12	2 bottles
Visit 13	**3 bottles**
Visit 14	**3 bottles**
Visit 15	**3 bottles**
Visit 16	**3 bottles**
Visit 17	N/A
Visit 18	N/A

a) Each bottle contains 35 tablets.
b) The appearance of the label on the bottle will be the same for all drug types including placebo lead-in

Reason for Amendment:

The table was updated including the four additional visits and the respective number of bottles to be dispensed at those visits.

Section of protocol affected:

5.6 Concomitant and post-study treatment(s), Page 54

Previous text:

…

Additionally, the total daily dose of the following medications will be reported:

- oral anti-diabetic drugs and/or insulin,
- anti-hypertensive drugs (including diuretics and drugs that are known to have a blood pressure lowering effect, for example, medication used in treatment of congestive heart failure),
- lipid lowering drugs and anti-platelet drugs.

…

Revised text:

…

Additionally, the total daily dose of the following medications will be reported:

- oral anti-diabetic drugs and/or insulin,
- anti-hypertensive drugs (including diuretics and **some specified** drugs that are known to have a blood pressure lowering effect, for example, medication used in treatment of congestive heart failure),

…

Reason for Amendment:

Clarification of intent to collect these medications in the eCRF.

Section of protocol affected:

5.6.2.1, Glycaemic rescue therapy during the randomised treatment period, Pages 55-56

Previous text:

The dose of anti-hyperglycaemic medications (oral anti-diabetic drugs and/or insulin) should not be increased or decreased between randomisation and week 52 (Visits 4 to 13) unless rescue criteria or a definition of hypoglycaemia (see Section 5.6.2.3) are met. The need for initiation of rescue therapy will be assessed based on FPG during the 24-week double blind treatment period, and based on HbA1c during the 28-week site and patient blinded extension period. Numeric criteria are listed in Table 6. Glycaemic rescue is not a reason for discontinuation in this study.

…

Table 7 **Glycaemic Rescue Criterion (28-week site- and patient-blinded treatment period)**

Period	Central Laboratory HbA1c
From week 24 (Visit 9) to week 52 (Visit 13).	Central Laboratory HbA1c >8.0% (repeated and confirmed)

Investigators are blinded to patients' HbA1c results throughout the study. However, after Visit 9 (week 24), during the 28-week site- and patient- blinded extension period, a different glycaemic rescue criterion has been defined for the safety of the patients,. Patients with a central laboratory HbA1c value greater than 8.0% confirmed by a repeated test within one week should be rescued. The central laboratory will notify the investigator to repeat HbA1c without providing an explanation, and if the repeated HbA1c value is at or above 8.0% an instruction will be sent to the site by the Central Laboratory to start glycaemic rescue therapy in the patient.

Choice of rescue therapy for hyperglycaemia will be at the discretion of the investigator, who will follow country specific and/or regional guidelines, for example those published by ADA (ADA 2009), ADA and EASD combined (Nathan et al 2009) or (NICE 2009). These guidelines specify changes in OAD drug therapy. The use of rosiglitazone is not permitted. Those patients treated with insulin who meet the criteria for rescue should have their insulin dose increased by at least 10%, and all oral anti-diabetic medications, if any, should remain unchanged.

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

Revised text:

The dose of anti-hyperglycaemic medications (oral anti-diabetic drugs and/or insulin) should not be increased or decreased between randomisation and week **104** (Visits 4 to 1**7**) unless rescue criteria or a definition of hypoglycaemia (see Section 5.6.2.3) are met. The need for initiation of rescue therapy will be assessed based on FPG during the 24-week double blind treatment period, and based on HbA1c during the 28-week **and 52-week** site and patient blinded extension period**s**. Numeric criteria are listed in Table 6. Glycaemic rescue is not a reason for discontinuation in this study.

…

Table 7 Glycaemic Rescue Criterion (28-week site- and patient-blinded treatment period **I and 52-week site- and patient-blinded extension period II**)

Period	Central Laboratory HbA1c
From week 24 (Visit 9) to week 52 (Visit 13) **including day of Visit 13**.	Central Laboratory HbA1c >8.0% (repeated and confirmed)

Period	Central Laboratory HbA1c
From week 52 (Visit 13) to week 65 (Visit 14) including day of Visit 14.	**Central Laboratory HbA1c >7.5% (repeated and confirmed)**
From week 65 (Visit 14) to week 104 (Visit 17) excluding day of Visit 17	**Central Laboratory HbA1c >7.0% (repeated and confirmed)**

From week 24 (Visit 9) to week 104 (Visit 17), if self-monitored FPG is above 200 mg/dL, the patient should repeat the FPG on the same day. If the second result is also above 200 mg/dL, the patient should contact the study centre and will be scheduled for a central laboratory HbA1c measurement within one week.

Investigators are blinded to patients' HbA1c results throughout the study. However, after Visit 9 (week 24), during the 28-week **and the 52-week** site- and patient- blinded extension period**s**, a different glycaemic rescue criterion has been defined for the safety of the patients. **From week 24 (Visit 9) to week 52 (Visit 13) p**atients with a central laboratory HbA1c value greater than 8.0% confirmed by a repeated test within one week should be rescued. **From week 52 (Visit 13) patients with a central laboratory HbA1c value greater than 7.5% and from week 65 (Visit 14) until the day before the day of week 104 (Visit 17) a central laboratory HbA1c value greater than 7.0%, respectively, confirmed by a repeated test within one week should be rescued.** The central laboratory will notify the investigator to repeat HbA1c without providing an explanation, and if the repeated HbA1c value is at or above **the defined level for the visit** an instruction will be sent to the site by the Central Laboratory to start glycaemic rescue therapy in the patient.

Choice of rescue therapy for hyperglycaemia will be at the discretion of the investigator, who will follow country specific and/or regional guidelines, for example those published by ADA (ADA 2009), ADA and EASD combined (Nathan et al 2009) or (NICE 2009). These guidelines specify changes in OAD drug therapy. The use of rosiglitazone is not permitted. Those patients treated with insulin who meet the criteria for rescue should have their insulin dose increased by at least 10%, and all oral anti-diabetic medications, if any, should remain unchanged.

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

Reason for Amendment:

To update the text in relation to the 52-week extension period II. To add a paragraph with an instruction for investigators in case of high FPG values that was not included in the original text by mistake. To apply rescue criteria for the 52-week extension in line with the guidelines.

Section of protocol affected:

5.6.2.4, Rescue Criteria for Hypertension, bullet C, page 58

Previous text:

C. From the day after Visit 9 to the day of Visit 13. […]

Revised text:

C. From the day after Visit 9 to the day of Visit 1**7.** […]

Reason for Amendment:

To update the text in relation to the 52-week extension period II.

Section of protocol affected:

5.8.1, Procedures for discontinuation of a patient from investigational product, paragraphs 2 and 7, Page 63

Previous text:

…

Patients who prematurely discontinue double blind study drug permanently should undergo Visit 13 (End of Treatment Visit) visit procedures (See Study Plan, Table 3 for assessments) These patient will have a Follow-up Visit (Visit 14) 3 weeks after treatment discontinuation.

…

Patients with increased liver function tests as defined in Section 5.8 under listing (11) will be scheduled for a follow-up visit within 3 calendar days following the receipt of the result. Patients should remain on study medication until the confirmatory results are obtained. See Appendix J for further guidance. If repeated liver function tests still are increased as outlined in Section 5.8 under listing (11), the patient should permanently discontinue all study medication and will be followed for safety (see Appendix J for further guidance).

Revised text:

…

Patients who prematurely discontinue double blind study drug permanently should undergo Visit 1**7** (End of Treatment Visit) visit procedures (See Study Plan, Table 3 for assessments) These patient will have a Follow-up Visit (Visit 1**8**) 3 weeks after treatment discontinuation.

…

Patients with increased liver function tests as defined in Section 5.8 under listing (1**3**) will be scheduled for a follow-up visit within 3 calendar days following the receipt of the result. Patients should remain on study medication until the confirmatory results are obtained. See Appendix J for further guidance. If repeated liver function tests still are increased as outlined in Section 5.8 under listing (1**3**), the patient should permanently discontinue all study medication and will be followed for safety (see Appendix J for further guidance).

Reason for Amendment:

To update the wording for the End of Treatment Visit and the Follow-up Visit and replacing Visit 13/14 with Visit 17/18 respectively. To correct a typo in the under listing number.

Section of protocol affected:

5.9, Withdrawal from study, Randomized patients, Page 64

Previous text:

…

Randomised patients

Randomised patients who have withdrawn their consent for study treatment before week 52 should return and complete Visit 13 (End of Treatment Visit) visit procedures (See Study Plan, Table 3 for assessments) as soon as possible. These patients should also be scheduled for a Follow-up Visit (Visit 14) three weeks after End of Treatment visit if they do not refuse to take part at this Follow-up Visit. 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.

…

Revised text:

…

Randomised patients

Randomised patients who have withdrawn their consent for study treatment before week **104** should return and complete Visit 1**7** (End of Treatment Visit) visit procedures (See Study Plan, Table 3 for assessments) as soon as possible. These patients should also be scheduled for a Follow-up Visit (Visit 1**8**) three weeks after End of Treatment Visit if they do not refuse to take part at this Follow-up Visit. 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.

…

Reason for Amendment:

To update the wording for the End of Treatment Visit and the Follow-up Visit and replacing Visit 13/14 with Visit 17/18 respectively.

Section of protocol affected:

6.1, Recording of data, paragraph 7, Page 65

Previous text:

…

The patients will be instructed to monitor their FPG at least every second day between Visits 2-9 and at least once a week between Visits 9-13. The FPG results, hypoglycaemic events and total daily dose of insulin will be recorded in the paper patient diary. Information will be entered by the trained study personnel into the eCRF.

…

Revised text:

…

The patients will be instructed to monitor their FPG at least every second day between Visits 2-9 and at least once a week between Visits 9-1**7**. The FPG results, hypoglycaemic events and total daily dose of insulin will be recorded in the paper patient diary. Information will be entered by the trained study personnel into the eCRF.

…

Reason for Amendment:

To replace Visit 13 with Visit 17 in the text.

Section of protocol affected:

6.2.1, Follow-up procedures, Page 66

Previous text:

A Follow-up Visit (Visit 14) will be performed 18-24 days (3 weeks ±3 days) after the End of Treatment Visit (Visit 13), see Table 3 for further details.

Patients who prematurely discontinue double blind study drug treatment due to general or study specific discontinuation criteria will have a follow up visit 3 weeks after End of Treatment Visit (Visit 13).

Revised text:

A Follow-up Visit (Visit 1**8**) will be performed 18-24 days (3 weeks ±3 days) after the End of Treatment Visit (Visit 1**7**), see Table 3 for further details.

Patients who prematurely discontinue double blind study drug treatment due to general or study specific discontinuation criteria will have a follow up visit 3 weeks after End of Treatment Visit (Visit 1**7**).

Reason for Amendment:

To update the wording for the End of Treatment Visit and the Follow-up Visit and replacing Visit 13/14 with Visit 17/18 respectively.

Section of protocol affected:

6.3.1, Table 8, Efficacy laboratory variables, Page 67

Previous text:

Table 8 Efficacy laboratory variables

Visit	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	13 EoT	**14**	**R**
Study Week	**-7**	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**55**	
HbA1c	X	X	X	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	X	X
Insulin, pro-insulin[a]					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
FFA[, a,,b]					X					X				X		X
hs-CRP[c]					X					X				X		X

[a] fasting
[b] free fatty acids;
[c] high sensitivity C-Reactive Protein.

Revised text:

Table 8 Efficacy laboratory variables

Visit	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17** EoT	**18**	**R**
Study Week	**-7**	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**65**	**78**	**91**	**104**	**107**	
HbA1c	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FPG[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Insulin, pro-insulin[a]					X					X				X		X		X		X
HOMA-2, HOMA-IR					X					X				X		X		X		X
Total cholesterol[a]		X			X					X				X		X		X		X
LDL-C[a]		X			X					X				X		X		X		X
HDL-C[a]		X			X					X				X		X		X		X
TG[a]		X			X					X				X		X		X		X
FFA[, a,,b]					X					X				X		X		X		X
hs-CRP[c]					X					X				X		X		X		X

[a] fasting
[b] free fatty acids;
[c] high sensitivity C-Reactive Protein.

Reason for Amendment:

To update the table to include the five additional visits with the respective efficacy variables.

Section of protocol affected:

6.4.3, Recording of adverse events, Page 69

Previous text:

Time period for collection of adverse events

Adverse Events will be collected from the start of the lead-in period (Visit 2) throughout the treatment period and including the follow-up period (Visit 14).

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

…

Revised text:

Time period for collection of adverse events

Adverse Events will be collected from the start of the lead-in period (Visit 2) throughout the treatment period and including the follow-up period (Visit 1**8**).

SAEs will be recorded from the time of informed consent until the end of the study (Visit 1**8**).

…

Reason for Amendment:

To update the numbering of the Follow-up Visit in line with the 52-week extension.

Section of protocol affected:

Table 9, Safety laboratory variables, Page 74

Previous text:

Table 9 Safety Laboratory Variables

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Resc[i)]
Study Week	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**55**	
Haematology															
Haemoglobin	X			X	X	X	X	X	X	X	X	X	X	X	X
Haematocrit	X			X	X	X	X	X	X	X	X	X	X	X	X
Red blood cell count	X			X	X	X			X				X	X	X
White blood cell count and differential	X			X	X	X			X				X	X	X
Platelet count	X			X	X	X			X				X	X	X
Clinical chemistry (serum)															
Aspartate Aminotransferase (AST, SGOT)	X			X	X	X	X	X	X	X	X	X	X	X	X
Alanine Aminotransferase (ALT, SGPT)	X			X	X	X	X	X	X	X	X	X	X	X	X
Alkaline Phosphatase (AP)	X			X	X	X	X	X	X	X	X	X	X	X	X
Lactate dehydrogenase	X			X	X	X	X	X	X	X	X	X	X	X	X
Creatine Kinase (CK)	X			X	X	X	X	X	X	X	X	X	X	X	X
Total Bilirubin (TB)[a]	X			X	X	X	X	X	X	X	X	X	X	X	X
Blood Urea Nitrogen (BUN)	X			X	X	X	X	X	X	X	X	X	X	X	X

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Resc[i)]
Study Week	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**55**	
Electrolytes: (- Sodium - Bicarbonate - Potassium - Chloride - Calcium - Magnesium - Phosphorus)	X			X	X	X	X	X	X	X	X	X	X	X	X
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	X
Serum Creatine (SCr)	X			X		X	X	X	X	X	X	X	X	X	X
Calculated creatinine clearance (Cockcroft-Gault formula)[b]	X			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	X
Serum Cystatin C				X					X	X			X	X	X
Serum Bone Metabolism Marker (Parathyroid Hormone (PTH), osteocalcin, 25 hydroxy-vitamin D, 1,25 dihydroxy-vitamin D)				X					X	X			X	X	X
FSH	X														

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Resc[i)]
Study Week	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**55**	
TSH, Free T4[c)]	X			X											
Hepatitis Screen Panel[d)]	X														
Central Laboratory Urinalysis															
Glucose[e)]	X			X	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	X	X
pH	X			X	X	X	X	X	X	X	X	X	X	X	X
Albumin	X			X	X	X	X	X	X	X	X	X	X	X	X
Creatinine	X			X	X	X	X	X	X	X	X	X	X	X	X
Calculated Urinary albumine:creatinine ratio (UACR)	X			X	X	X	X	X	X	X	X	X	X	X	X
Local Urinlysis															
Pregnancy test[g)]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Culture at local laboratory at unscheduled visit[h)]															

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. See Section 5.8. and Appendix K for details.
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 WOCBP (HCG minimum sensitivity of 25 IU/L) (dipstick analyzed at the study centre).
h) Refer to Section 6.4.9.2. (urinary and genital infections). In the event of patient reported signs and/or symptoms suggestive of an infection, a urine sample will be collected for culture at a subsequent unscheduled visit.

i) Rescue refers to Glycaemic Rescue Visit (section 5.6.2.1). In case of a Rescue Visit due to Hypertension (section 5.6.2.4), it will be at the discretion of the investigator to decide if any laboratory assessments are needed.

Revised text:

Table 9 Safety Laboratory Variables

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Resc[i)]
Study Week	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**65**	**78**	**91**	**104**	**107**	
Haematology																			
Haemoglobin	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Haematocrit	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Red blood cell count	X			X	X	X			X				X		X		X	X	X
White blood cell count and differential	X			X	X	X			X				X		X		X	X	X
Platelet count	X			X	X	X			X				X		X		X	X	X
Clinical chemistry (serum)																			
Aspartate Aminotransferase (AST, SGOT)	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Alanine Aminotransferase (ALT, SGPT)	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Alkaline Phosphatase (AP)	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Resc[i)]
Study Week	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**65**	**78**	**91**	**104**	**107**	
Lactate dehydrogenase	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Creatine Kinase (CK)	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Total Bilirubin (TB)[a]	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Urea Nitrogen (BUN)	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrolytes: (- Sodium - Bicarbonate - Potassium - Chloride - Calcium - Magnesium - Phosphorus)	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Total protein	X			X					X	X			X		X		X	X	X
Albumin	X			X					X	X			X		X		X	X	X
Uric acid	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Creatine (SCr)	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Calculated creatinine clearance (Cockcroft-Gault formula)[b]	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Resc[i)]
Study Week	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**65**	**78**	**91**	**104**	**107**	
Estimated Glomerular Filtration Rate (MDRD formula)	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Cystatin C				X					X	X			X		X		X	X	X
Serum Bone Metabolism Marker (Parathyroid Hormone (PTH), osteocalcin, 25 hydroxy-vitamin D, 1,25 dihydroxy-vitamin D)				X					X	X			X		X		X	X	X
FSH	X																		
TSH, Free T4[c)]	X			X															
Hepatitis Screen Panel[d)]	X																		
Central Laboratory Urinalysis																			
Glucose[e)]	X			X	X	X	X	X	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	X	X	X	X	X	X
pH	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Resc[i)]
Study Week	**-5**	**-4**	**-2**	**0**	**1**	**4**	**8**	**16**	**24**	**28**	**36**	**44**	**52**	**65**	**78**	**91**	**104**	**107**	
Albumin	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Creatinine	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Calculated Urinary albumine:creatinine ratio (UACR)	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local Urinlysis																			
Pregnancy test[g)]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Culture at local laboratory at unscheduled visit[h)]																			

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. See Section 5.8. and Appendix K for details.
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 WOCBP (HCG minimum sensitivity of 25 IU/L) (dipstick analyzed at the study centre).
h) Refer to Section 6.4.9.2. (urinary and genital infections). In the event of patient reported signs and/or symptoms suggestive of an infection, a urine sample will be collected for culture at a subsequent unscheduled visit.
i) Rescue refers to Glycaemic Rescue Visit (section 5.6.2.1). In case of a Rescue Visit due to Hypertension (section 5.6.2.4), it will be at the discretion of the investigator to decide if any laboratory assessments are needed.

Reason for Amendment:

To update the table to include the five additional visits with the respective safety laboratory variables.

Section of protocol affected:

6.4.9.1, Fasting plasma glucose concentrations and hypoglycaemic events, paragraph 2, Page 79

Previous text:

FPG should be self-monitored at least every second day between visits 2 and 9 and at least once a week between visits 9 and 13. 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.

Revised text:

FPG should be self-monitored at least every second day between visits 2 and 9 and at least once a week between visits 9 and 1**7**. 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.

Reason for Amendment:

To update the wording for Visit 18 in line with the 52-week extension.

Section of protocol affected:

6.4.9.3, **Microscopic Hematuria**

Previous text:

No previous text (new section was added replacing the previous Section 6.4.9.3)

Revised text:

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 website, 2011; Grossfeld et al, 2001). These Best Practice guidelines have been evaluated by Jung et al (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 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 website, 2011; Grossfeld et al, 2001).

Reason for Amendment:

To ensure that standard of care is followed in the workup of microscopic hematuria. This helps to address the observed lack of following standard of care practices in the workup of patients with microscopic hematuria.

Section of protocol affected:

6.4.9.3 to 6.4.9.7, Page 82

Previous text:

6.4.9.3, 6.4.9.4, 6.4.9.5, 6.4.9.6, 6.4.9.7

Revised text:

6.4.9.4, 6.4.9.5, 6.4.9.6, 6.4.9.7, 6.4.9.8

Reason for Amendment:

To renumber these sections after inclusion of the new section 6.4.9.3 Microscopic Hematuria.

Section of protocol affected:

6.5.2, PRO method, Page 84

Previous text:

The EQ-5D will be self-administered using the paper version. The questions will be assessed at baseline (Visit 4), after 8 weeks (Visit 7), after 24 weeks (Visit 9) and after 52 weeks (Visit 13). 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.

Revised text:

The EQ-5D will be self-administered using the paper version. The questions will be assessed at baseline (Visit 4), after 8 weeks (Visit 7), after 24 weeks (Visit 9), after 52 weeks (Visit 13), **after 78 weeks (Visit 15) and after 104 weeks (Visit 17)**. 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.

Reason for Amendment:

To update the text to include the additional visits where EQ-5D will be administered.

Section of protocol affected:

7.1, Volume of blood, Page 85

Previous text:

The total volume of blood that will be drawn from each patient in this study is 245 mL, as follows:

Table 10 Volume of blood to be drawn from each patient

Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
Safety/Efficacy			
Haematology	2	12	24
Clinical chemistry [a)]	5	6	30
Clinical chemistry [b)]	10	3	30
Clinical chemistry [c)]	17	3	51
Bicarbonate	3.5	12	42
HbA1c	2	15	30
FPG	2	14	28
Hepatitis screening panel [d)]	[d)]	1	[d)]
Pharmacogenetics	10	1	10
Total including pharmacogenetics			**245 mL**

a) Clinical chemistry
b) Clinical chemistry and metabolic markers
c) Clinical chemistry, endocrine and metabolic markers
d) Included in clinical chemistry

Revised text:

The total volume of blood that will be drawn from each patient in this study is **286.5** mL, as follows:

Table 10 Volume of blood to be drawn from each patient

Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
Safety/Efficacy			
Haematology	2	**16**	**32**
Clinical chemistry [a)]	5	**11**	**55**
Clinical chemistry [b)]	10	**2**	**20**
Clinical chemistry [c)]	1**5**	**3**	**45**
Clinical chemistry [e)]	**8.5**	**3**	**25.5**
Bicarbonate	3.5	1**0**	**35**
HbA1c	2	**19**	**38**
FPG	2	1**8**	**36**
Hepatitis screening panel [d)]	[d)]	1	[d)]
Total excluding pharmacogenetics			**286.5 mL**

a) Clinical chemistry **and bicarbonate**
b) Clinical chemistry and metabolic markers
c) Clinical chemistry, endocrine and metabolic markers
d) Included in clinical chemistry
e) Clinical chemistry, endocrine, metabolic markers and bicarbonate

Reason for Amendment:

To update the table with the new estimate of the blood volumes. To exclude the pharmacogenetics sample as it is optional.

Section of protocol affected:

9.5, Study timetable and end of study, Page 93

Previous text:

…

The study is expected to start in Q1 2010 and to end by Q1 2012.

…

Revised text:

…

The study is expected to start in Q1 2010 and to end by Q1 201**3**.

…

Reason for Amendment:

To update the text in line with the 52-week extension.

Section of protocol affected:

11.2.2, Other safety variables, Page 95

Previous text:

The safety evaluations will include analyses of AEs, laboratory parameters, ECG, vital signs (pulse and BP), orthostatic BP, hypoglycaemic events, calculated creatinine clearance, estimated GFR (eGFR) and physical examination. The analysis of safety will be based on the safety analysis set. Safety data gained during the 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. CV events will be analyzed in conjuction with CV events observed in other Phase II and Phase III dapagliflozin studies and the combined results will be reported elsewhere.

…

Revised text:

The safety evaluations will include analyses of AEs, laboratory parameters, ECG, vital signs (pulse and BP), orthostatic BP, hypoglycaemic events, calculated creatinine clearance, estimated GFR (eGFR) and physical examination. The analysis of safety will be based on the safety analysis set. Safety data gained during the 24-week double-blind treatment period, the 28-week **and the 52-week** extension period**s** and the 3-week safety follow-up period will be evaluated. Safety variables will be summarized descriptively. CV events will be analyzed in conjunction with CV events observed in other Phase II and Phase III dapagliflozin studies and the combined results will be reported elsewhere.

…

Reason for Amendment:

To update the text in line with the 52-week extension.

Section of protocol affected:

12.2.2, Analysis after the 28-week double-blind extension period, Page 102

Previous text:

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 SAP specific to this period. The results from the extension period will be reported separately.

Revised text:

All variables to be analyzed after the 24 weeks of double-blind treatment will be re-examined at the week 52 **and the week 104** time point**s**. 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 SAP specific to this period. The results from the extension period will be reported separately.

Reason for Amendment:

The variables for the objectives to be analyzed after 52 week extension period II were added.

Section of protocol affected:

12.2.3, Analysis of safety, Page 102

Previous text:

…

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 double-blind extension period as well as during the 3-week safety follow-up period will be evaluated. Safety data will be presented by treatment group as well as by treatment group and age stratum. Safety variables will be summarized descriptively and missing data will be replaced using the LOCF approach where appropriate. A separate meta-analysis for adjudicated CV events from this study in conjunction with other dapagliflozin Phase II and Phase III studies is planed as requested by the new FDA CV guidance (FDA 2008). Results of analyses will be reported elsewhere.

Revised text:

…

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 **and the 52-week** double-blind extension period**s** as well as during the 3-week safety follow-up period will be evaluated. Safety data will be presented by treatment group as well as by treatment group and age stratum. Safety variables will be summarized descriptively and missing data will be replaced using the LOCF approach where appropriate. A separate meta-analysis for adjudicated CV events from this study in conjunction with other dapagliflozin Phase II and Phase III studies is planned as requested by the new FDA CV guidance (FDA 2008). Results of analyses will be reported elsewhere.

Reason for Amendment:

To update the text with the 52-week extension.

Section of protocol affected:

12.2.5, Interim analyses, Page 102

Previous text:

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.

Revised text:

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 **and 104** weeks of randomised treatment are considered to be supplemental.

Reason for Amendment:

The 104-week time point was added.

Section of protocol affected:

14. List of references, Page 107

Previous text:

…

FDA 2008
U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CEDR). Guidance for Industry: Diabetes Mellitus – Evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Food and Drug Administration, Silver Spring, Maryland. 2008. Available at http://www.fda.gov/cder/guidance/index.htm

Holman et al 2009
Holman RR, Farmer AJ, Davies MJ, Levy JC, Darbyshire JL, Keenan JF et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. New Engl J Med 2009;361:1736-47.

…

JNC7 2004
The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High blood pressure. U.S. Department of Health and Human Services. National Institutes of Health, National Heart, Lung and Blood Institute. NIH Publication No. 04-5230. August 2004.

Kind 1996
Kind, P. The EuroQol instrument: an index of health-related quality of life. In: Spilker B, ed. Quality of Life and Pharmacoeconomics in Clinical trials. Second ed. Philadelphia, Lippincott-Raven Publishers, 1996:191-201.

…

Revised text:

American Urological Association (AUA) website, 2011
Hematuria Best Practice Statement: Asymptomatic Microscopic Hematuria in Adults: Summary of the AUA Best Practice Policy Recommendations. (2001). Electronic publication: http://www.auanet.org/content/homepage/homepage.cfm (Accessed May 2011).

…

FDA 2008
U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CEDR). Guidance for Industry: Diabetes Mellitus – Evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Food and Drug Administration, Silver Spring, Maryland. 2008. Available at http://www.fda.gov/cder/guidance/index.htm

Grossfeld et al, 2001
Grossfeld GD, Wolf JS Jr, Litwin MS, Hricak H, Shuler C, Agerter DC, Carrol PC. Asymptomatic Microscopic Hematuria in Adults: Summary of the AUA Best Practice Policy Recommendations. Am Fam Physician. 2001;63(6):1145-1155.

Electronic publication: http://www.aafp.org/afp/2001/0315/p1145.html (Accessed May 2011).

Holman et al 2009
Holman RR, Farmer AJ, Davies MJ, Levy JC, Darbyshire JL, Keenan JF et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. New Engl J Med 2009;361:1736-47.

…

JNC7 2004
The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High blood pressure. U.S. Department of Health and Human Services. National Institutes of Health, National Heart, Lung and Blood Institute. NIH Publication No. 04-5230. August 2004.

Jung 2011
Jung H, Gleason JM, Loo RK, Patel HS, Slezak JM, Jacobsen SJ. Association of hematuria on microscopic urinalysis and risk or urinary tract cancer. The Journal of Urology 2011; 185:1698-1703.

Kind 1996
Kind, P. The EuroQol instrument: an index of health-related quality of life. In: Spilker B, ed. Quality of Life and Pharmacoeconomics in Clinical trials. Second ed. Philadelphia, Lippincott-Raven Publishers, 1996:191-201.

…

Reason for Amendment:

Three references were added.

Section of protocol affected:

Clinical Study Protocol Appendix E, Section 1, Background, Page 3

Previous text:

…

4. EQ-5D must be completed by patient at Visits 4, 7, 9 and 13 before any other procedures are done.

Revised text:

…

4. EQ-5D must be completed by patient at Visits 4, 7, 9, 13**, 15 and 17** before any other procedures are done.

Reason for Amendment:

To update the text with the new visits where the questionnaire will be administered.

Section of protocol affected:

Clinical Study Protocol Appendix E, Section 2, Visit to Visit guide, Table 1, Page 3

Previous text:

Table 1 Visit windows

Visit	Time	Time window (days)
Screening Visit	-7 weeks	≤14 days prior to Enrolment
Visit 1 (Enrolment)	-5 weeks	up to 14 days from Screening
Visit 2	-4 weeks	±3 days
Visit 3	-2 weeks	±3 days
Visit 4 (Randomisation)	0	±3 days
Visit 5	1 week	±3 days

Table 1 Visit windows

Visit	Time	Time window (days)
Visit 6	4 weeks	±3 days
Visit 7	8 weeks	±3 days
Visit 8	16 weeks	±3 days
Visit 9	24 weeks	±7 days
Visit 10	28 weeks	±7 days
Visit 11	36 weeks	±7 days
Visit 12	44 weeks	±7 days
Visit 13 (End of Treatment)	52 weeks	±3 days
Visit 14 (Follow-up)	55 weeks	±3 days

Visit 2, 3, 4 should be scheduled relative to Visit 1. 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.

Revised text:

Table 1 Visit windows

Visit	Time	Time window (days)
Screening Visit	-7 weeks	≤14 days prior to Enrolment
Visit 1 (Enrolment)	-5 weeks	up to 14 days from Screening
Visit 2	-4 weeks	±3 days
Visit 3	-2 weeks	±3 days
Visit 4 (Randomisation)	0	±3 days
Visit 5	1 week	±3 days
Visit 6	4 weeks	±3 days
Visit 7	8 weeks	±3 days
Visit 8	16 weeks	±3 days
Visit 9	24 weeks	±7 days
Visit 10	28 weeks	±7 days
Visit 11	36 weeks	±7 days
Visit 12	44 weeks	±7 days
Visit 13	52 weeks	±7 days
Visit 14	**65 weeks**	**±7 days**
Visit 15	**78 weeks**	**±7 days**
Visit 16	**91 weeks**	**±7 days**
Visit 17 (End of Treatment)	**104 weeks**	**±3 days**

Table 1 Visit windows

Visit	Time	Time window (days)
Visit 18 (Follow-up)	**107 weeks**	**±3 days**

Visit 2, 3, 4 should be scheduled relative to Visit 1. 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.

Reason for Amendment:

Additional visits were included and the End of Treatment/Follow-up Visits were renamed to Visit17/Visit 18, respectively.

Section of protocol affected:

Clinical Study Protocol Appendix E, Section 2.14

Previous text:

None (new section was added replacing the previous Section 2.14)

Revised text:

2.14 Visit 13

Visit 13 will occur 52 week after Visit 4.

The following procedures should be done in the order shown:

- Ask patient to complete EQ-5D questionnaire
- Do blood pressure and pulse examination
- Do orthostatic blood pressure and pulse examination
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Do a urine pregnancy test (only applicable to women of childbearing potential)
- Measure patient’s weight
- Do a 12-lead ECG
- After blood pressure and weight measurements, and blood and urine sampling, patient should take investigational product along with other medications. Patient should have breakfast within 30 minutes from taking medications.
- Review patient’s diary for glucometer values/hypoglycaemic events and insulin dose (if applicable)

- If applicable, calculate and record mean total daily insulin dose based on patient's diary
- Check drug accountability. Collect from patient all used and unused bottles with study drug.
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications; for anti-hyperglycaemic, anti-hypertensive, lipid lowering and anti-platelet medications daily dose should be recorded in eCRF
- Do a complete physical examination
- **Do a re-supply of IP (dapagliflozin/placebo) in IWRS/IVRS**
- **Do kit verification transaction in the IWRS/IVRS and dispense IP**
- Give diet and lifestyle advice
- Schedule Visit 14 **sixty five 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

2.15 Visit 14

Visit 14 will occur 65 weeks after Visit 4.

The following procedures should be done in the order shown:

- Do blood pressure and pulse examination
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Do 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. Patient should have breakfast within 30 minutes from taking medications.
- Review patient's diary for glucometer values/hypoglycaemic events and insulin dose (if applicable) and dispense new diary

- If applicable, calculate and record mean total daily insulin dose based on patient's diary
- Check drug accountability
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications; for anti-hyperglycaemic, anti-hypertensive, lipid lowering and anti-platelet medications daily dose should be recorded in eCRF
- Perform brief physical examination (see details at Visit 2)
- Do a re-supply of IP (dapagliflozin/placebo) in IWRS/IVRS
- Do kit verification transaction in the IWRS/IVRS and dispense IP
- Give diet and lifestyle advice
- Schedule Visit 15 seventy eight 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.

2.16 Visit 15

Visit 15 will occur 78 week after Visit 4.

The following procedures should be done in the order shown:

- Ask patient to complete EQ-5D questionnaire
- Do blood pressure and pulse examination
- Do orthostatic blood pressure and pulse examination
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Do a urine pregnancy test (only applicable to women of childbearing potential)
- Measure patient's weight
- Do a 12-lead ECG

- After blood pressure and weight measurements, and blood and urine sampling, patient should take investigational product along with other medications. Patient should have breakfast within 30 minutes from taking medications.
- Review patient's diary for glucometer values/hypoglycaemic events and insulin dose (if applicable)
- If applicable, calculate and record mean total daily insulin dose based on patient's diary
- Check drug accountability. Collect from patient all used and unused bottles with study drug.
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications; for anti-hyperglycaemic, anti-hypertensive, lipid lowering and anti-platelet medications daily dose should be recorded in eCRF
- Do a complete physical examination
- Do a re-supply of IP (dapagliflozin/placebo) in IWRS/IVRS
- Do kit verification transaction in the IWRS/IVRS and dispense IP
- Give diet and lifestyle advice
- Schedule Visit 16 ninety one 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

2.17 Visit 16

Visit 16 will occur 91 weeks after Visit 4.

The following procedures should be done in the order shown:

- Do blood pressure and pulse examination
- Draw a blood sample and send to the central laboratory
- Take urine sample from the patient and send to central laboratory
- Do 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. Patient should have breakfast within 30 minutes from taking medications.
- Review patient's diary for glucometer values/hypoglycaemic events and insulin dose (if applicable) and dispense new diary
- If applicable, calculate and record mean total daily insulin dose based on patient's diary
- Check drug accountability
- Collect and document AEs and SAEs and fill in event forms when applicable
- Document concomitant medications; for anti-hyperglycaemic, anti-hypertensive, lipid lowering and anti-platelet medications daily dose should be recorded in eCRF
- Perform brief physical examination (see details at Visit 2)
- Do a re-supply of IP (dapagliflozin/placebo) in IWRS/IVRS
- Do kit verification transaction in the IWRS/IVRS and dispense IP
- Give diet and lifestyle advice
- Schedule Visit 17 one hundred and 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.

Reason for Amendment:

To update the Visit-to-Visit guide with the procedures to be completed during the additional visits scheduled in the 52-week extension. To replace the previous Section 2.14 with an updated Section 2.14 and add Sections 2.15 to 2.17 describing the change in Visit 13 to a regular visit and including additional visits 14-16.

Section of protocol affected:

Clinical Study Protocol Appendix E, Section 2.14, End of treatment Visit, Page 16

Previous text:

2.14 Visit 13 – End of Treatment Visit (week 52)

Visit 13 will occur 52 week after Visit 4.

…

Revised text:

2.18 Visit 1**7** – End of Treatment Visit (week **104**)

Visit 1**7** will occur **104** week**s** after Visit 4.

…

Reason for Amendment:

To renumber the section and updating the visit number and study duration.

Section of protocol affected:

Clinical Study Protocol Appendix E, Section 2.15, Follow-up visit, Page 17

Previous text:

2.15 Visit 14 – Follow-up Visit (3 weeks after last intake of investigational product)

Visit 14 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.

…

Revised text:

2.19 Visit 1**8** – Follow-up Visit (3 weeks after last intake of investigational product)

Visit 1**8** 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.

…

Reason for Amendment:

To renumber the section and update the study visit number.

Section of protocol affected:

Clinical Study Protocol Appendix E, Section 2.16, Rescue visit, Page 18

Previous text:

2.16 Rescue Visit

If the patient meets rescue criteria based on self-monitored glucose values between Visits 4 and 13, the patient should return to the study site within 1 week.

…

Revised text:

2.20 Rescue Visit

If the patient meets rescue criteria based on self-monitored glucose values between Visits 4 and 1**7**, the patient should return to the study site within 1 week.

…

Reason for Amendment:

To renumber the section and provide clarity on the rescue criteria during the 52-week extension.

Section of protocol affected:

Clinical Study Protocol Appendix J, Page 3

Previous text:

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.

…

Revised text:

Patient should also be scheduled for a Follow-up Visit (ie, procedures of Visit 1**8**) 3 weeks after discontinuation of investigational product. A referral consultation to a hepatologist or gastroenterologist (specializing in liver abnormalities) should be obtained.

…

Reason for Amendment:

To replace Visit 14 with Visit 18, as Visit 18 is now the Follow-up Visit.

Persons who initiated the Amendment:

Urszula Zurek

Clinical Study Protocol Amendment No 1
Appendix A

Drug Substance	dapagliflozin
Study Code	D1690C00018
Edition Number	1
Protocol Dated	

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled phase III study with an 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with type 2 diabetes, cardiovascular disease and hypertension, who exhibit inadequate glycaemic control on usual care.

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

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

AstraZeneca Research and Development
site representative

ASTRAZENECA SIGNATURE(S)

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AstraZeneca Research and Development site representative

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled phase III study with an 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with type 2 diabetes, cardiovascular disease and hypertension, who exhibit inadequate glycaemic control on usual care.

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

I agree to the terms of this amendment.

Centre No.:

Signature: