AstraZeneca

Revised Clinical Study Protocol	
Drug Substance	dapagliflozin
Study Code	D1690C00010
Edition Number	1
Date	

A 24-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, International Phase III Study with a 24-week Extension Period to Evaluate the Safety and Efficacy of Dapagliflozin 10 mg Daily in Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on a DPP-4 inhibitor (Sitagliptin) Alone or in Combination with Metformin

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, Placebo-Controlled, Parallel-Group, International Phase III Study with a 24-week Extension Period to Evaluate the Safety and Efficacy of Dapagliflozin 10 mg Daily in Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on a DPP-4 inhibitor (Sitagliptin) Alone or in Combination with Metformin

International Co-ordinating Investigator

Study centre(s) and number of patients planned

This international study will be conducted at approximately 85 study centres. It is estimated that 1080 patients will be screened to reach the target of 432 randomised patients during an enrolment period of approximately 9 months. It is expected that 5 to 6 patients will be randomised per centre.

Study period		**Phase of development**
Estimated date of first patient enrolled	QIV/2009	IIIb
Estimated date of last patient completed	QIV/2011	

Objectives

Primary Objective

The primary objective of this study is to compare the change from baseline in haemoglobin A1c (HbA1c) at 24 weeks between dapagliflozin and placebo in patients with type 2 diabetes who are inadequately controlled on sitagliptin alone or on sitagliptin plus metformin.

Key Secondary Objectives

- To compare the change in total body weight achieved with dapagliflozin versus placebo from baseline to week 24
- To compare the change in HbA1c in patients with baseline A1c ≥8% achieved with dapagliflozin versus placebo from baseline to week 24
- To compare the change in FPG achieved with dapagliflozin versus placebo from baseline to week 24
- To compare the change in seated systolic blood pressure (SBP) in patients with baseline seated SBP ≥130 achieved with dapagliflozin versus placebo from baseline to week 8
- To compare the change in 2-hour post liquid meal glucose achieved with dapagliflozin versus placebo from baseline to week 24
- To compare the proportion of patients achieving a therapeutic glycaemic response, defined as a reduction in HbA1c of ≥0.7% compared to baseline, with dapagliflozin versus placebo at week 24

Other Secondary Objectives

Efficacy

- To compare the effects of dapagliflozin versus placebo on the following additional variables: glycaemic control, blood pressure, weight and lipid metabolism over 24 weeks of treatment

Safety

- To evaluate the safety and tolerability of dapagliflozin by assessment of adverse events, laboratory values, electrocardiogram, pulse, blood pressure, hypoglycaemic events, calculated creatinine clearance, estimated glomerular filtration rate and physical examination findings over 24 weeks of treatment

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 24-week extension period

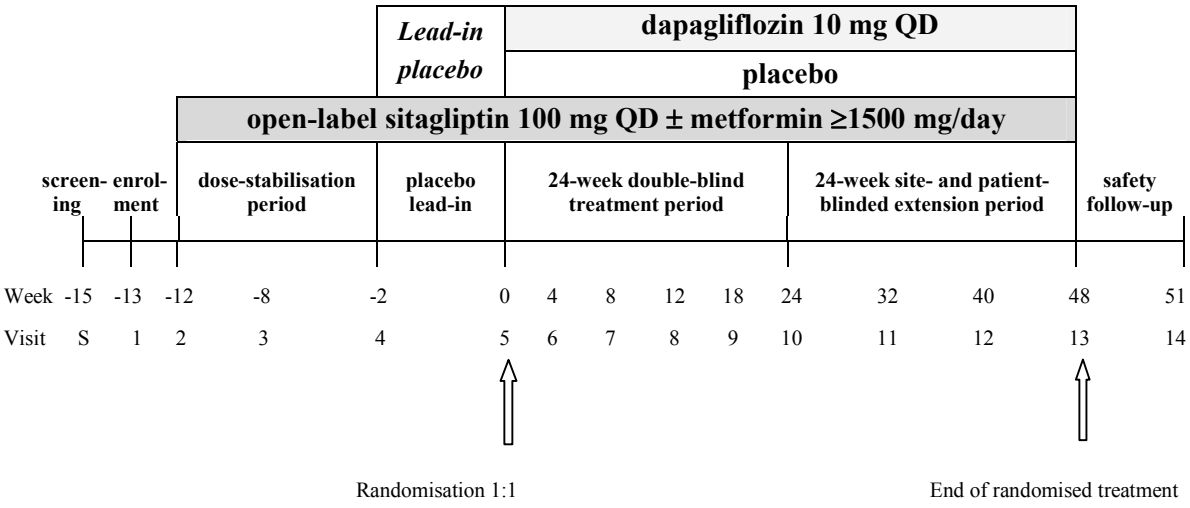
- To assess the maintenance of efficacy of dapagliflozin versus placebo over 48 weeks of treatment

– To assess the safety and tolerability of dapagliflozin over 48 weeks of treatment

Study design

This is a 24-week randomised, double-blind, placebo-controlled, 2-arm, parallel-group, multicentre study with a 10-week dose stabilisation period and a 24-week site- and patient-blinded extension period.

Figure 1 Study flow chart

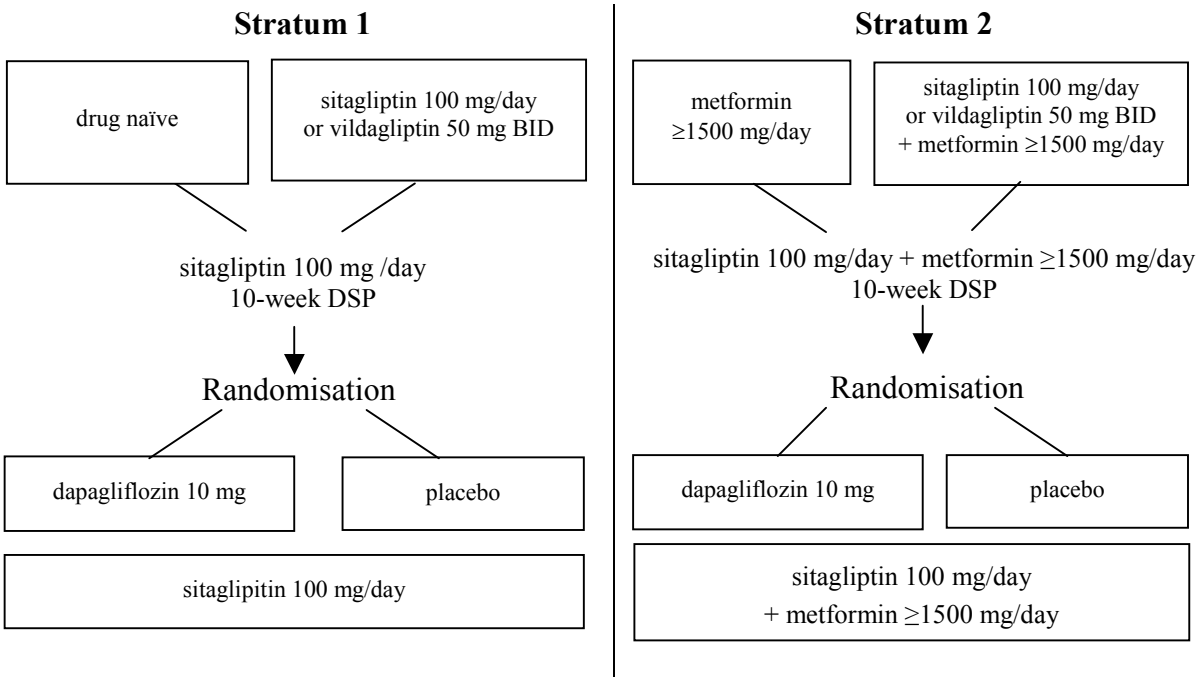


The study will consist of two strata (50:50) with randomisation within each stratum for each of the two treatment arms.

– *Stratum 1* (sitagliptin monotherapy group) will include all eligible patients who are drug-naïve or on a DPP-4 inhibitor at enrolment. Patients who are on vildagliptin will be switched to sitagliptin at the start of the dose-stabilisation period. (See Figure 2)

– *Stratum 2* (sitagliptin plus metformin group) will include all eligible patients who are on metformin ≥1500 mg/day monotherapy or on metformin ≥1500 mg/day + a DPP-4 inhibitor at enrolment. Patients who are on vildagliptin will be switched to sitagliptin at the start of the dose-stabilisation period. (See Figure 2)

Figure 2 Background Treatment Strata



Target patient population

Men and women with type 2 diabetes who:

- are ≥18 years old (for metformin-treated patients, the upper age limit will be determined by local prescribing guidelines)
- have inadequate glycaemic control, defined as:
  - HbA1c of ≥7.2 to ≤10% at enrolment for patients who are taking a DPP-4 inhibitor at study entry
  - HbA1c of ≥7.7 to ≤10.5% at enrolment for patients who are not taking a DPP-4 inhibitor at study entry
  - HbA1c of ≥7 to ≤10% at the start of the lead-in period for all patients
- are drug naïve (defined as no antihyperglycaemic therapy for at least 10 weeks prior to enrolment) or have been receiving one of the following antidiabetic treatments for at least 10 weeks prior to enrolment:
  - sitagliptin 100 mg alone
  - vildagliptin 50 mg BID alone

  - metformin IR or XR ≥1500 mg/day alone
  - sitagliptin 100 mg plus metformin ≥1500 mg/day
  - vildagliptin 50 mg BID plus metformin ≥1500 mg/day

- have not taken other OADs (Oral Antidiabetic Medication) in the 10 weeks prior to enrolment

Investigational product, dosage, mode of administration and duration of treatment

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

Comparator, dosage and mode of administration

- Matching placebo for dapagliflozin 10 mg administered orally once daily for the 2-week placebo lead-in period, the 24-week double-blind treatment period and the 24-week extension period.

Additional drug, dosage and mode of administration

- Open-label sitagliptin 100 mg tablets administered orally once daily for the 10-week dose-stabilisation period, the 2-week placebo lead-in period, the 24-week double-blind treatment period and the 24-week extension period.

- Open-label metformin IR 500 mg tablets administered orally twice daily with food at doses ≥1500 mg/day for the 10-week dose-stabilisation period, the 2-week placebo lead-in period, the 24-week double-blind treatment period and the 24-week extension period.

- Open label glimepiride 2 mg tablets administered orally at a dose of up to 6 mg/day to patients who require rescue therapy.

Duration of treatment

Following initial screening and a 1-week enrolment period, patients will enter a 10-week dose-stabilisation period followed by a 2-week placebo lead-in period. They will then be randomised to the 24-week double-blind treatment period followed by a 24-week site- and patient-blinded extension period. After either completion of the randomised treatment periods or discontinuation from treatment, patients will enter a 3-week follow-up period.

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

Outcome variables

Efficacy

Primary outcome variable:

- Change in HbA1c from baseline to week 24

Key secondary outcome variables:

- Change in total body weight from baseline to week 24
- Change in HbA1c in patients with baseline HbA1c ≥8% from baseline to week 24
- Change in FPG from baseline to week 24
- Change in seated SBP in patients with baseline seated SBP ≥130 mmHg from baseline to week 8
- Change in 2-hour post liquid meal glucose achieved with dapagliflozin versus placebo from baseline to week 24
- Proportion of patients achieving a therapeutic glycaemic response, defined as a reduction in HbA1c ≥0.7% compared to baseline, at 24 weeks

Other secondary outcome variables:

- Change in HbA1c in patients with baseline HbA1c >7.0% and <8.0%, ≥8.0% and <9.0%, and ≥9.0% from baseline to week 24
- Proportion of patients achieving a therapeutic glycaemic response, defined as HbA1c <7.0%
- Change in seated SBP from baseline to week 24
- Proportion of patients with baseline elevated blood pressure (BP) (baseline SBP ≥130 mmHg and/or baseline diastolic blood pressure (DBP) ≥80 mmHg) who achieve a seated BP of <130/80 mmHg at week 24
- Change in waist circumference from baseline to week 24
- Change in waist/hip ratio from baseline to week 24
- Proportion of patients discontinued for lack of efficacy or rescued for failing to maintain FPG below pre-specified rescue criteria at weeks 4, 8, 12, 18, and 24
- Change in body weight in patients with baseline HbA1c ≥9% from baseline to week 24

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

- Change in the following parameters from baseline to week 24:

- β-cell function (as measured by Homeostasis Model Assessment 2 [HOMA-2])

- Insulin resistance (as measured by HOMA-IR)

Safety

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

Statistical methods

The primary objective of this study is to assess the efficacy of dapagliflozin versus placebo overall in terms of the primary efficacy variable change in HbA1c from baseline to week 24. This objective will also be assessed separately for each of the two strata. The primary efficacy variable, change in HbA1c from baseline to week 24 , will be analysed by an analysis of covariance (ANCOVA) model. When assessing the results overall, the model will include terms for treatment group, strata, and baseline covariate. No formal test for interaction between treatment group and strata will be performed as the effects of the two dapagliflozin treatment groups will be examined for each stratum separately. When assessing the results within each stratum, the ANCOVA model will include terms for treatment group and baseline covariate. The ANCOVA model will be used to derive a least squares estimate of the treatment difference with 95% confidence interval and corresponding two-sided p-value. Further, two-sided 95% confidence intervals for the mean change within each treatment group as well as treatment group and stratum will be calculated.

A hierarchical closed testing procedure will be used to control the Type I error rate across the primary and key secondary objectives, based on results from the two strata combined. Analyses will also be conducted within each stratum to separately evaluate the effect in the two background treatment regimens. For variables found to be significant with the combined strata analysis, corresponding within-stratum treatment comparisons will be individually tested at a two-sided significance level of 0.050. For all other variables, nominal p-values will be reported for both overall and within-strata comparisons without significance testing.

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

To detect a difference of 0.5% between dapagliflozin versus placebo for change in HbA1c from baseline to week 24, assuming a standard deviation =1.1%, 103 evaluable patients (full analysis set) for each treatment group within each stratum would provide >99% power for the analysis of the two strata combined at a significance level =0.050 or 90% power for the

analysis of each stratum separately at a significance level =0.050. Assuming that 5% of the patients will not be evaluable in the full analysis set, 108 patients per treatment group within each stratum (432 patients total) are planned for randomisation.

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Appendix G Case Identification and Management of Decreased Renal Function

Appendix H Dapagliflozin Overall Benefits and Risks Assessment

Appendix I Algorithm on Management of Sustained Elevated Liver Safety Abnormalities

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.3.1)
ANCOVA	Analysis of covariance model
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC	Area under curve
BID	Twice daily
BMI	Body Mass Index
BP	Blood pressure
BUN	Blood urea nitrogen
CEC	Clinical Event Committee
CK	Creatinine kinase
Cm	Centimetre
CPMP	Committee for Proprietary Medicinal Products
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation due to Adverse Event
DNA	Deoxyribonucleic acid
DPP-4	Dipeptidyl-peptidase-4
DSP	Dose-stabilisation period
ECG	Electrocardiogram
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EMEA	European Medicines Agency
FDA	Food and Drug Administration

Abbreviation or special term	Explanation
FPG	Fasting plasma glucose
FSH	Follicle simulating hormone
GCP	Good Clinical Practice
HbA1c	Glycosylated Haemoglobin A1c
ICH	International Conference on Harmonisation
HDL-C	High density lipoprotein-cholesterol
HOMA	Homeostasis model assessment
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IWRS	Interactive Web Response System
Kg	Kilogram
LDL-C	Low density lipoprotein-cholesterol
LLOQ	Lower Limit of Quantification
MI	Myocardial infarction
MODY	Maturity-onset diabetes of the young
MTT	Liquid meal tolerance test
OAD	Oral antidiabetic medication
OAE	Other Significant Adverse Event (ie, adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment); see definition in Section 11.2
PPG	Postprandial glucose
PRO	Patient reported outcomes
PTH	Parathyroid hormone
PGx	Pharmacogenetics
QD	Daily
SAE	Serious adverse event (see definition in Section 6.3.2).
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SGLT	Sodium-Glucose Transporter
SmPC	Summary of Product Characteristics
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin

Abbreviation or special term	Explanation
TC	Total cholesterol
UACR	Urine albumin:creatinine ratio
ULN	Upper limit of normal
USPI	United States Package Insert
UTI	Urinary Tract Infection
WBDC	Web Based Data Capture
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background

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

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

Human SGLT2 mutations are associated with a condition known as familial renal glucosuria. These individuals have varying degrees of glucosuria; those who have loss of function in both alleles can excrete 100 g of glucose or greater per day. The majority of patients are asymptomatic, and their condition is diagnosed incidentally. Typically they do not have

hypoglycaemic episodes, electrolyte imbalance or increased risk of urinary tract infections (Santer et al 2003). Even the most severe form of the condition appears to be associated with a favourable prognosis (Scholl-Burgi et al 2004), although very few patients have been described in the literature. This human model of SGLT2 inhibition supports the potential safety of this mechanism as a treatment approach for type 2 diabetes by demonstrating that mild to moderate glucosuria in itself is not associated with significant adverse health consequences.

Dapagliflozin has been designed as a potent and selective inhibitor of SGLT2. This compound is being developed as an oral agent for the treatment of type 2 diabetes, and represents a novel therapeutic approach for the treatment of this disorder. Proof of concept for dapagliflozin in patients with type 2 diabetes has been established in a Phase IIb study over a dose range from 2.5 to 50 mg over 12 weeks, administered orally once daily. In this study, dapagliflozin treatment led to significant and clinically relevant reductions in FPG, postprandial glucose, and HbA1c levels throughout the entire dose range, and was associated with weight loss. Overall, adverse events and serious adverse events were balanced between the dapagliflozin and placebo groups. There was an increased incidence of dizziness (5% for dapagliflozin vs. 1.9% for placebo) and vulvovaginal infections (1.8% for dapagliflozin vs. 0% for placebo) in the dapagliflozin-treated patients. Overall, these findings support the further development of dapagliflozin and the implementation of pivotal studies of sufficient duration to more fully characterize the safety and efficacy of the 2.5, 5, and 10 mg doses.

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

1.2 Research hypothesis

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

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 program for dapagliflozin for the treatment of type 2 diabetes. This study intends to compare dapagliflozin with placebo in patients with type 2 diabetes who are inadequately controlled on sitagliptin monotherapy or on sitagliptin plus metformin therapy.

Sitagliptin is the first approved dipeptidyl peptidase 4 (DPP-4) inhibitor for the treatment of patients with type 2 diabetes. DPP-4 inhibitors are a relatively new class of oral antihyperglycaemic drugs that enhance glucose-mediated insulin secretion and suppress glucagon by reducing the clearance of glucagon-like peptide 1 (GLP-1). Sitagliptin is approved in the US as monotherapy and in both the EU and the US as add-on therapy to metformin.

Metformin is a biguanide; its major effect is to decrease hepatic glucose output and lower fasting glucose. It is recommended as the initial pharmacological therapy in both the US and

the EU because of its glycaemic efficacy, weight neutrality, low risk of hypoglycemia, good tolerability and relatively low cost (Nathan et al 2008).

Since many patients with type 2 diabetes do not reach glycaemic goals with metformin monotherapy or even with dual agent therapy, many will require an additional agent with an alternate mechanism of action. The combination of an agent that enhances glucose-mediated insulin secretion (sitagliptin) with an agent that inhibits renal glucose reabsorption (dapagliflozin) with or without an agent that decreases hepatic glucose output (metformin) may have additive glucose-lowering effects.

1.4 Benefit/risk and ethical assessment

Risk category

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

Potential risks

The potential risks associated with dapagliflozin that have been identified based upon the mechanism of action, the preclinical results, and the clinical experience to date, as well as precautions included in the Phase III programme to monitor and/or minimise these risks, are presented in dapagliflozin's Overall Benefits and Risks Assessment that is included in Appendix H.

In addition, all patients in this study will receive sitagliptin or sitagliptin plus metformin as background medication. Both of these medications are widely used anti-diabetic treatments that will be prescribed according to their approved labels. Thus, the benefits and risks associated with the background medication and comparator treatment are well established and presented in their respective approved prescribing information. No study procedure will put patients at a risk beyond those ordinarily encountered during the performance of routine medical examinations or 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 program as needed. Thus real-time, active safety surveillance will be conducted during the entire duration of this study. In addition, all dapagliflozin studies are subject to a carefully designed patient risk management plan that includes the temporary and if necessary permanent discontinuation of investigational product in individual patients in whom a potential health risk or a laboratory abnormality of clinical concern has been identified. Investigators are also provided guidance on appropriate management of potential risks such as hypoglycaemia (Section 6.3.9.1) urinary tract and genital infections (Section 6.3.9.2) hyponatraemia (Appendix F), and decreased renal function (Appendix G) and liver function abnormalities (Appendix I).

Potential benefits to patients

All patients will receive active background antihyperglycaemic therapy; however, a direct benefit from randomised treatment cannot be assured as one half of patients will receive placebo, and the efficacy of dapagliflozin in this clinical setting has yet to be established. In this study, the dose of dapagliflozin (10 mg) has been chosen to provide efficacy in reducing hyperglycaemia while mitigating the potential for AEs, based on previous clinical experience. In addition, dapagliflozin is expected to help decrease body weight (or prevent weight gain) as well as help lower blood pressure especially in patients with elevated baseline blood pressure. Patients are also expected to receive some benefit in the form of increased medical care/attention when participating in study procedures, which includes at least 14 clinic visits with at least 13 physical examinations over the 64-week study. Patients will also receive counseling on dietary and life-style modifications. It is commonly observed that even patients receiving placebo in diabetes studies show some improvement in glycaemic control, likely due to their increased compliance to dietary and life-style counseling while they are participating in a clinical study.

Informed consent and alternatives to participation

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

Conclusion

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

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to compare the change from baseline in haemoglobin A1c (HbA1c) at 24 weeks between dapagliflozin and placebo in patients with type 2 diabetes who are inadequately controlled on sitagliptin alone or on sitagliptin plus metformin.

2.2 Secondary objectives

2.2.1 Key Secondary Objectives

Six key secondary objectives are identified a priori for special consideration in this study, in addition to the primary objective. A hierarchical closed testing procedure will be applied in order to control the type I error rate to support secondary superiority claims of dapagliflozin compared to placebo for the following key secondary objectives. The flow of testing from one objective to the next will depend upon the overall results. Results within each stratum will also be examined.

- To compare the change in total body weight achieved with dapagliflozin versus placebo from baseline to week 24
- To compare the change in HbA1c in patients with baseline HbA1c ≥8% achieved with dapagliflozin versus placebo from baseline to week 24
- To compare the change in FPG achieved with dapagliflozin versus placebo from baseline to week 24
- To compare the change in seated systolic blood pressure (SBP) in patients with baseline seated SBP ≥130 achieved with dapagliflozin versus placebo from baseline to week 8
- To compare the change in 2-hour post liquid meal glucose achieved with dapagliflozin versus placebo from baseline to week 24
- To compare the proportion of patients achieving a therapeutic glycaemic response, defined as a reduction in HbA1c of ≥0.7% compared to baseline, with dapagliflozin versus placebo at week 24

2.2.2 Other Secondary Objectives

- To compare the change in HbA1c achieved with dapagliflozin versus placebo in patients with baseline HbA1c >7.0% and <8.0%, ≥8.0% and <9.0%, and ≥9.0% from baseline to week 24
- To compare the proportion of patients achieving a therapeutic glycaemic response, defined as a HbA1c <7.0% with dapagliflozin versus placebo at week 24

- To compare the change in seated SBP observed with dapagliflozin versus placebo from baseline to week 24
- To compare the proportion of patients with baseline elevated blood pressure (BP) (baseline SBP ≥130 mmHg and/or baseline diastolic blood pressure (DBP) ≥80 mmHg) who achieve a seated BP of <130/80 mmHg at week 24
- To compare the change in waist circumference observed with dapagliflozin versus placebo from baseline to week 24
- To compare the change in waist/hip ratio observed with dapagliflozin versus placebo from baseline to week 24
- To compare the proportion of patients discontinued for lack of efficacy or rescued for failing to maintain FPG below pre-specified rescue criteria with dapagliflozin versus placebo at weeks 4, 8, 12, 18, and 24
- To compare the change in body weight observed in patients with baseline HbA1c ≥9% with dapagliflozin versus placebo from baseline to week 24
- To compare the percent change in fasting lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides) observed with dapagliflozin versus placebo from baseline to week 24
- To compare the change in the following parameters observed with dapagliflozin versus placebo from baseline to week 24:
  - β-cell function (as measured by Homeostasis Model Assessment 2 [HOMA-2])
  - Insulin resistance (as measured by HOMA-IR)

2.3 Safety Objective

To evaluate the safety and tolerability of dapagliflozin by assessment of AEs, laboratory values, electrocardiogram, pulse, blood pressure, hypoglycaemic events, calculated creatinine clearance, estimated glomerular filtration rate and physical examination findings.

2.4 Pharmacogenetic Objective

To collect and store DNA for future exploratory research into genes that may influence response, eg, 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 24-week extension period

- To assess the safety and tolerability of dapagliflozin over 48 weeks of treatment.
- To assess the maintenance of efficacy of dapagliflozin versus placebo over 48 weeks of treatment.

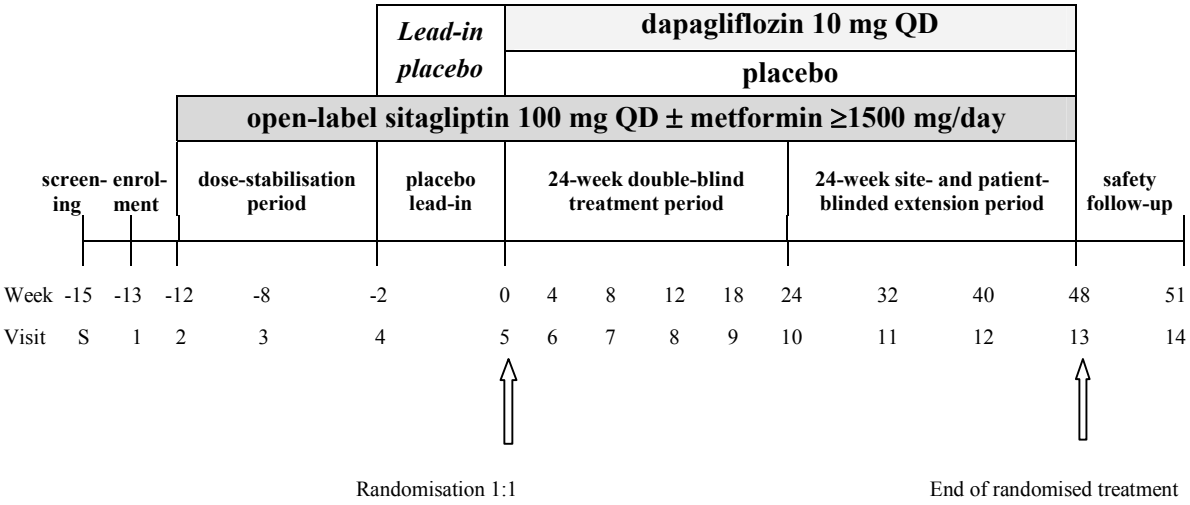
3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This is a 24-week, international, multicentre, randomised, double-blind, parallel-group, placebo-controlled, Phase III study with a 24-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg daily in patients with type 2 diabetes. Dapagliflozin or placebo will be added to the therapy of patients who have inadequate glycaemic control on sitagliptin (a DPP-4 inhibitor) alone or on sitagliptin in combination with metformin.
For the definition of inadequate glycaemic control see Section 4.1, Inclusion Criterion 5.

Figure 3 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. Pre-study antihyperglycaemic medication will be discontinued at start of the 10-week dose-stabilisation period (DSP). Open-label treatment with sitagliptin alone or in combination with metformin will be started for all patients, including those who were drug naïve at enrolment (for definition of "drug naïve" see Section 4.1, Inclusion Criterion 4). The objective of the DSP is to ensure that patients receive an adequate trial of background therapy, and that only patients with inadequate glycaemic control are randomised and receive investigational product. Patients will be re-examined for inclusion and exclusion criteria at the end of the DSP and will enter a 2-week placebo lead-in period. During the lead-in period, laboratory test results will be obtained, patient compliance will be evaluated, and background antihypertensive medication adjusted if needed. Patients will then be randomised to the 24-week double-blind treatment period followed by a 24-week site-and patient-blinded extension period (see objectives of the extension period in Section 2.5). After either completion of the treatment periods or discontinuation from treatment, patients will enter a 3-week follow-up period. The follow-up visit provides the opportunity to further evaluate changes in physical signs, symptoms or laboratory parameters that may be related to dapagliflozin. The total planned study duration from Visit 1 to the safety follow-up (Visit 14) will be 64 weeks.

This international study will be conducted at approximately 85 study centres. It is estimated that 1080 patients will be screened to reach the target of 432 randomised patients during an enrolment period of approximately 9 months. It is expected that 5 to 6 patients will be randomised per centre. Globally patients will be recruited to ensure a 50:50 ratio of patients in the 2 strata. Countries in North and South America will randomise approximately 30% of Stratum 2 patients and 80 – 100% of Stratum 1 patients. Countries in the European Union will

randomise approximately 70% of the Stratum 2 patients and 0 – 20% of Stratum 1 patients. Target numbers of patients to be randomised in total and per strata will be agreed with individual countries before the start of the study. Recruitment will be competitive between sites within the countries. Enrolment into the 2 strata will be stopped on country level once enough patients are screened to provide the globally projected number of randomised patients. Centres may be discontinued from the study if recruitment rates are poor and new centres may be added if necessary to achieve recruitment goals.

Study Periods

3.1.1 Screening Visit

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

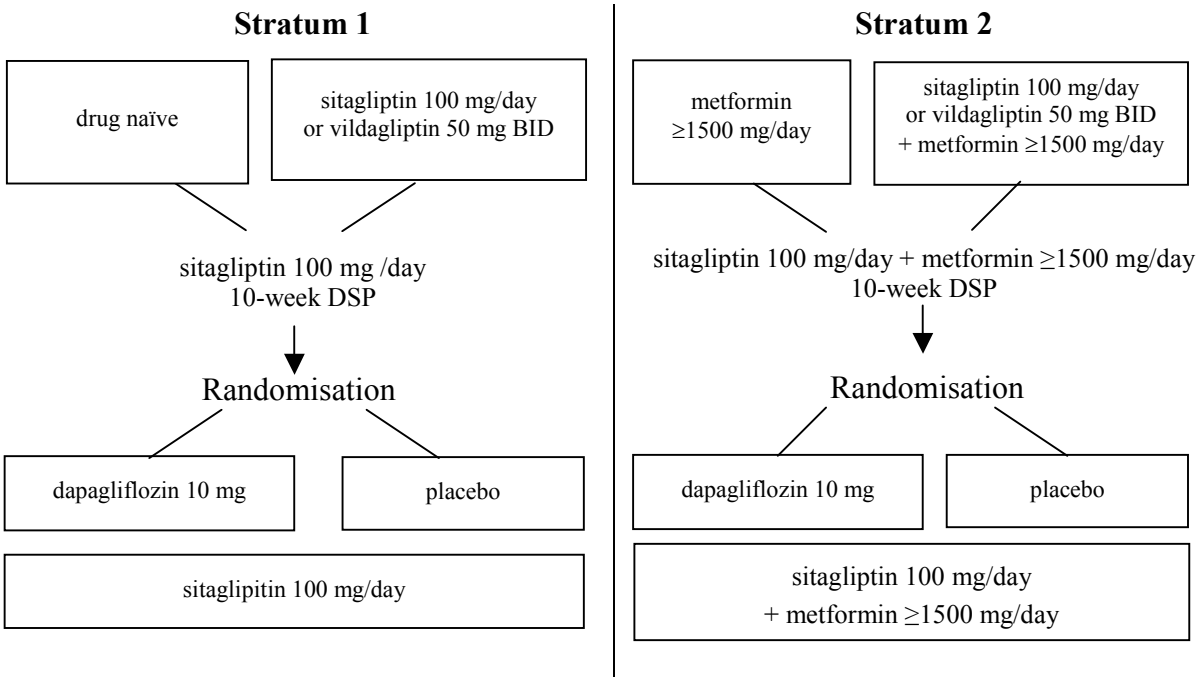
Patients will be allowed to proceed to Visit 1 only if they meet HbA1c inclusion criteria (Inclusion criterion 5, Section 4.1). Patients are not allowed to be re-screened. All patients who are screened should be listed on a patient screening log. See also Section 6.2.

3.1.2 Enrolment Visit (Visit 1, week –13)

Eligible patients will provide informed consent, undergo screening for all applicable inclusion and exclusion criteria, and submit laboratory samples. Patients will continue their current OAD therapy during this time. Diet and lifestyle advice will be given.

The study will consist of two strata (50:50) with randomisation within each stratum for each of the two treatment arms (see Figure 4).

Figure 4 Background Treatment Strata



The two strata are described below:

Stratum 1 (sitagliptin monotherpy group):

1. Patients entering the study on a stable dose of sitagliptin monotherapy 100 mg QD (daily) or vildagliptin monotherapy 50 mg BID (twice a day) for at least 10 weeks, with no other OAD therapy in the 10 weeks prior to enrolment

2. Patients who are drug naïve, defined as no OAD use for the 10 weeks prior to enrolment

Stratum 2 (sitagliptin plus metformin group):

1. Patients entering the study on dual therapy with metformin ≥1500 mg/day plus sitaglipin 100 mg QD or vildagliptin 50 mg BID for at least 10 weeks, with no other OAD therapy in the 10 weeks prior to enrolment

2. Patients entering the study on metformin monotherapy ≥1500 mg/day for at least 10 weeks, with no other OAD therapy in the 10 weeks prior to enrolment

3.1.3 Dose-stabilisation period (Visits 2 to 4, week –12 to week –2)

Visit 2

Visit 2 can be performed as a telephone visit if it is clear before the scheduled visit that a patient is not eligible based on the laboratory results from Visit 1 (see criteria in Section 4.1). The patient can be informed via telephone that he or she is not eligible for the study and that his or her participation in the study is terminated.

At Visit 2, all eligible patients will be given open-label sitagliptin 100 mg/day, and 50% of patients will be given open label metformin.

Detailed instructions for each stratum are described below:

Stratum 1

Stratum 1 will include all eligible patients who are not on metformin at study entry.

1. Patients entering the study on a stable dose of sitagliptin monotherapy 100 mg/day will be given open-label sitagliptin 100 mg/day and enter the DSP (Visit 2). Patients entering the study on a stable dose of vildagliptin 50 mg BID monotherapy will discontinue vildagliptin, start open-label sitagliptin 100 mg/day and enter the 10-week DSP.

2. Patients who have not received OADs for at least 10 weeks will be started on open-label sitagliptin 100 mg/day and enter the 10-week DSP (Visit 2).

Stratum 2

Stratum 2 will include all eligible patients who enter the study on metformin ≥1500 mg/day.

1. Patients entering the study on metformin ≥1500 mg/day plus sitaglipin 100 mg QD will be given open-label metformin (1500, 2000, or 2500 mg/day as outlined in Table 1) and sitagliptin 100 mg QD and enter the DSP (Visit 2). Patients taking metformin ≥1500 mg/day plus vildagliptin 50 mg BID at baseline will be given open-label metformin (as outlined in Table 1), discontinue vildagliptin, start open-label sitagliptin 100 mg/day and enter the DSP.

2. Patients entering the study on metformin monotherapy ≥1500 mg/day will be given open-label metformin (as outlined in Table 1) and open-label sitagliptin 100 mg/day, and enter the 10-week DSP (Visit 2).

The open-label metformin dose will remain stable throughout the study.

Table 1 Adjustment of metformin dose

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

A glucometer and a patient diary will also be provided to patients and they will be instructed to monitor their fasting plasma glucose (FPG) at least every second day and to enter the results into the patient diary. Investigators may instruct patients to monitor their FPG more often, according to their local treatment guidelines or clinical judgement. For FPG monitoring procedures and assessment of hypoglycaemic events please refer to Section 6.3.9.1.

Diet and lifestyle modification will be reinforced at each visit.

Adjustment of antihypertensive medication
There is no restriction on adjustment of antihypertensive medication within the guidelines of the approved antihypertensive labels and as clinically indicated during the DSP.

Visit 3

The safety and tolerability of sitagliptin will be assessed at Visit 3 (week –8). Patients who have an FPG >270 mg/dL (15 mmol/L) between week –8 and week 0 (visits 3 to 5) will be discontinued from the study and referred for additional antihyperglycaemic therapy.

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

At the beginning of the placebo lead-in period (Visit 4, week –2) patients will undergo repeat screening for all inclusion/exclusion criteria. Appropriate diet and exercise counselling will be provided to all patients at this visit. At Visit 4, eligible patients will be given placebo in a single-blind fashion (blind to the patient only) and will continue open-label sitagliptin 100 mg/day and, if applicable, open-label metformin.

Patients will be instructed to monitor their FPG at least every second day and to enter the results into the patient diary. Investigators may instruct patients to monitor their FPG more often, according to their local treatment guidelines or clinical judgement. Diet and lifestyle modification will be reinforced.

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

3.1.5 Randomisation and Double-blind Treatment Period (Visits 5-10, week 0 to week 24)

Randomisation visit (Visit 5)

Eligible patients will be randomised at Visit 5 (week 0, baseline) in a 1:1 ratio to receive either dapagliflozin 10 mg or placebo. There will be a planned 50:50 recruitment between strata. Randomisation will be performed within each stratum between each of the two treatment arms so that each of the treatment arms has approximately equal numbers of patients from Stratum 1 and Stratum 2.

Stratum 1

Patients will be randomised at Visit 5 (week 0, baseline) in a 1:1 ratio to receive either dapagliflozin10 mg QD plus open-label sitagliptin or placebo plus open-label sitagliptin.

Stratum 2

Patients will be randomised at Visit 5 (week 0) in a 1:1 ratio to receive either dapagliflozin 10 mg QD plus open-label sitagliptin and open-label metformin or placebo plus open-label sitagliptin and open-label metformin.

Double-blind Treatment Period (Visits 6-10)

After the randomisation visit, patients in both strata will have follow-up visits at four- to six-week intervals until the end of the randomised treatment period (Visit 10, 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 6.3.9.1.

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

The need for initiation of rescue therapy will be assessed based on criteria in Table 2. Procedures for rescue are described in Section 3.1.8.

Table 2 Criteria for initiation of rescue therapy during the randomised treatment period

Period	Central Laboratory FPG
From week 0 (Visit 5) to week 4 (Visit 6)	FPG >270 mg/dL (15 mmol/l)
From week 4 (Visit 6) to week 12 (Visit 8)	FPG >240 mg/dL (13.2 mmol/l)
From week 12 (Visit 8) to week 24 (Visit 10)	FPG >200 mg/dL (11.1 mmol/l) or HbA1c >8.0%

Adjustment of antihypertensive medication
Background antihypertensive medications should not be increased or decreased between weeks 0-8 (Visits 5 and 7). Exceptions to this rule are:

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

After week 8, changes in antihypertensive medication may be made as needed for appropriate blood pressure management. All medication changes, including dose modifications and the last blood pressure value measured before a medication change should be recorded in the eCRF.

3.1.6 Extension period (Visits 10-13, week 24 to week 48)

Patients will return for follow-up visits every 8 weeks during the long-term 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 6.3.9.1. Diet and lifestyle modification will be reinforced at each visit during this period.

The need for initiation of rescue therapy will be assessed based on criteria in Table 3. Procedures for rescue are described in Section 3.1.7.

Table 3 Criteria for initiation of rescue therapy during the extension period

Period	Central Laboratory HbA1c
From week 24 (Visit 10) to week 48 (Visit 13)	HbA1c >8.0%

Patients will discontinue investigational product at the end of this treatment period (Visit 13, week 48).

3.1.7 Follow-up period (Visit 14, week 51)

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.

3.1.8 Rescue therapy

To determine if rescue therapy is required, glycaemic parameters drawn at the central laboratory will be assessed at each visit from Visit 6 to Visit 12. If the patient meets rescue criteria based on self-monitored glucose values between visits 5 and 13, the patient should return to the study site within 1 week to have the FPG value verified by the central laboratory. Criteria for initiation of rescue therapy are specified in Table 2 for the period between visits 5 to 10 and in Table 3 for the period between visits 10 to 13.

When a laboratory result indicates that a patient meets the rescue criteria, a Rescue Visit should be scheduled within 5 workdays. Tests and examinations to be performed at a Rescue Visit are shown in Table 4. Patients will continue their study medication as before and will receive open-label rescue therapy with glimepiride. Administration and titration of glimepiride is described in Section 5.4.3.

The central laboratory FPG and HbA1c values measured after the initiation of the rescue medication will be reported to the investigator to ensure proper follow-up of the rescued patient.

Rescued patients with central laboratory HbA1c values greater than 8.0% despite a maximum tolerated dose of glimepiride for 12 weeks will be discontinued from the study and referred for additional antihyperglycaemic therapy. The procedures for discontinuation described in section 4.4.2 will apply.

Table 4 Study Plan

	Screening	**Enrolment**	**Dose-stabilisation period**		**Placebo lead-in**	**24-week double-blind treatment period**						**24-week site- and patient-blinded extension period**			**Follow-up visit**	**Rescue visit**
Visit	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**R**
Week	**-15**	**-13**	**-12**	**-8**	**-2**	**0**	**4**	**8**	**12**	**18**	**24**	**32**	**40**	**48**	**51**	
Visit window (days) [e]	(+7)	(0)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±3)	
Screening informed consent and blood sample for determination of HbA1c	X															
Informed consent		X														
Demography and medical history		X														
Inclusion/Exclusion criteria		X	X		X	X										
Randomisation						X										
Brief physical examination			X		X		X	X	X	X		X	X			
Complete physical examination		X				X					X			X	X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Orthostatic blood pressure						X	X	X	X		X			X	X	
Weight		X	X		X	X	X	X	X	X	X	X	X	X	X	X

	Screening	**Enrolment**	**Dose-stabilisation period**		**Placebo lead-in**	**24-week double-blind treatment period**						**24-week site- and patient-blinded extension period**			**Follow-up visit**	**Rescue visit**
Visit	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**R**
Week	**-15**	**-13**	**-12**	**-8**	**-2**	**0**	**4**	**8**	**12**	**18**	**24**	**32**	**40**	**48**	**51**	
Visit window (days) [e]	(+7)	(0)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±3)	
Height		X														
Waist and hip circumference						X					X			X		
Waist/hip ratio						X					X			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 [a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liquid meal tolerance test						X					X			X		X
Pregnancy test [b]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs, SAEs			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense open-label sitagliptin and/or metformin			X		X			X		X			X			
Dispense investigational product/placebo					X	X	X	X	X	X	X	X	X			
Drug accountability				X	X	X	X	X	X	X	X	X	X	X		

	Screening	Enrolment	Dose-stabilisation period		Placebo lead-in	24-week double-blind treatment period						24-week site- and patient-blinded extension period			Follow-up visit	Rescue visit
Visit	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**R**
Week	**-15**	**-13**	**-12**	**-8**	**-2**	**0**	**4**	**8**	**12**	**18**	**24**	**32**	**40**	**48**	**51**	
Visit window (days) [e]	(+7)	(0)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±3)	
Diet and life-style advice		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
Dispense patient diary			X	X	X	X	X	X	X	X	X	X	X			X
Patient diary review for /glucometer values/ hypoglycaemic events [c]				X	X	X	X	X	X	X	X	X	X	X		X
Informed consent, blood sample for genetic research [d]						(X)										

a) Specifications of laboratory parameters are shown in Table 8 and Table 9.
b) Pregnancy test will be done on all female patients who are not postmenopausal or hysterectomised.
c) Patients should be instructed to contact investigator by phone if a hypoglycaemic event occurs, in cases specified in the patient diary.
d) Genetic informed consent must be obtained before genetic blood sample is taken. Blood sample donation is optional and can be done any time from Visit 5 (ie, randomisation) to Visit 9.
e) Once a patient is randomised, all visits should be scheduled relative to Visit 5. Any slippage in time from one visit must not accumulate to affect other visits.

3.2 Rationale for study design, doses and control groups

3.2.1 Study design and regulatory requirement

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

3.2.2 Study doses and control groups

Control group

This is a placebo-controlled study.

Background therapy

Sitagliptin100 mg once daily is the dose approved by the FDA and the EMEA in patients who have a creatinine clearance greater than 50 mL/min (sitagliptin USPI, sitagliptin SmPC). Metformin is approved for use at doses up to 2550 mg in the US (metformin USPI) and up to 3000 mg in the EU.

Dapagliflozin

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

3.2.3 Choice of outcome variables

HbA1c is the variable of choice for assessment of glycaemic control and was therefore chosen as the primary outcome variable (FDA, EMEA). Because of its novel, complementary mechanism of action, dapagliflozin may have additive or synergistic HbA1c-lowering effects when given in combination with other antihyperglycaemic agents. Additionally, as beneficial effects on weight, SBP and FPG have been observed in other dapagliflozin studies, these variables have been chosen as key secondary objectives (see Table 5).

Table 5 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% from baseline to week 24. Proportion of patients achieving a therapeutic glycaemic response, defined as a reduction in HbA1c of ≥0.7%, from baseline to week 24. Change in HbA1c in patients with baseline HbA1c >7.0% and <8.0%, ≥8.0% and <9.0%, and ≥9.0% from baseline to week 24 Proportion of patients achieving a therapeutic glycaemic response, defined as HbA1c <7.0%	HbA1c is the clinical and regulatory parameter used to estimate glycaemic efficacy in patients with type 2 diabetes (CPMP 2002). HbA1c targets for patients with type 2 diabetes range from <6.5% (IDF 2005, AACE 2007) to <7% (ADA 2008). The degree of change in HbA1c in patients with type 2 diabetes is related to the baseline HbA1c level; patients with higher HbA1c at baseline tend to have greater reductions in HbA1c when treated with any antihyperglycaemic agent (Bloomgarden 2006).
Weight	Change in body weight from baseline to week 24. Change in body weight in patients with baseline HbA1c ≥9%	More than 85% of patients with type 2 diabetes are overweight (BMI ≥27 kg/m2) or obese (BMI ≥30 kg/m2) (CDC 2004). Weight loss is a fundamental goal for the majority of patients with type 2 diabetes since it has been shown to improve comorbid conditions such as hypertension, dyslipidemia, heart disease, osteoarthritis, and sleep apnea (NHLBI 1998).

Efficacy variable	Related objective	Rationale
Blood pressure	Change in SBP from baseline to week 8 in patients with baseline SBP ≥130 mmHg Change in seated SBP from baseline to week 24. Proportion of patients with baseline elevated blood pressure (baseline SBP ≥130 mmHg and/or baseline diastolic blood pressure (DBP) ≥80 mmHg) who achieve a seated blood pressure of <130/80 mmHg at week 24.	The American Diabetes Association and the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 2004) guidelines recommend a blood pressure target of <130/80 in patients with diabetes (ADA 2008, JNC 2004). Lowering blood pressure in patients with diabetes has been shown to reduce the risk of coronary heart disease events, stroke, retinopathy and nephropathy (JNC 2004).
Fasting Plasma Glucose and 2-hour post liquid meal glucose	Change in FPG from baseline to week 24. Change in 2-hour post liquid meal glucose from baseline to week 24 Proportion of patients discontinued for lack of efficacy or rescued for failing to maintain FPG on pre-specified rescue criteria at weeks 4, 8, 12, 18 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 (CPMP 2002).
Waist circumference, waist/hip ratio	Change in waist circumference from baseline to week 24. Change in waist/hip ratio from baseline to week 24.	The presence of excess fat in the abdomen out of proportion to total body fat is an independent predictor of risk factors and morbidity. Waist circumference is positively correlated with abdominal fat content (NHLBI 1998). In addition, waist-to-hip ratio has been significantly associated with myocardial infarction in all ethnic groups (Yusuf 2005).

Efficacy variable	Related objective	Rationale
Fasting lipids	Percent change in fasting lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides) from baseline to week 24.	Patients with type 2 diabetes have an increased prevalence of lipid abnormalities, which contributes to their high risk of cardiovascular disease (ADA 2008). For this reason, it is important to evaluate the lipid effects of antihyperglycaemic agents.
HOMA-2, HOMA-IR	Change in the following parameters from baseline to week 24: - β-cell function (as measured by Homeostasis Model Assessment 2 [HOMA-2]) - Insulin resistance (as measured by HOMA-IR)	β-cell dysfunction and insulin resistance contribute to the pathogenesis of type 2 diabetes; improvements in these parameters may be observed with improved glycaemic control (Poitout et al 2008).

3.2.4 Choice of study population

Age

The prevalence of type 2 diabetes increases with age; it is therefore important to assess the safety of antihyperglycaemic agents in elderly patients. In this study there is no upper age limit for patients who will receive sitagliptin alone as background therapy. In those patients who will receive metformin, the upper age limit will be based on local metformin prescribing guidelines.

HbA1c

The HbA1c inclusion criterion at randomisation was selected to include patients with a wide range of glycaemic control. The lower bound of this interval (ie, 7%) reflects the most recent American Diabetes Association treatment guidelines (ADA 2009). Although other guidelines recommend treatment to lower HbA1c targets, the results of a recent study suggest that these stricter targets may not be appropriate for all patients (ACCORD 2008, ADA 2009). 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 (ADA 2009).

Kidney Function

The exclusion criteria that relate to creatinine clearance are consistent with prescribing guidelines for metformin and sitagliptin 100 mg.

Pregnancy or breastfeeding

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

Other

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

Patient population should be selected without bias.

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

The following criteria apply to the enrolment (Visit 1). Exceptions are noted below.

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

2. Diagnosis of type 2 diabetes

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

4. Current antihyperglycaemic treatment:

(a) Drug naïve (defined as no antihyperglycaemic therapy for at least 10 weeks prior to enrolment), or

(b) Ongoing treatment with sitagliptin monotherapy 100 mg QD for at least 10 weeks prior to enrolment, or

(c) Ongoing treatment with vildagliptin monotherapy 50 mg BID for at least 10 weeks prior to enrolment, or

(d) Ongoing treatment with metformin IR or XR monotherapy ≥1500 mg/day at a stable dose for at least 10 weeks prior to enrolment, or

(e) Ongoing treatment with metformin IR or XR ≥1500 mg/day at a stable dose plus sitagliptin 100 mg/day for at least 10 weeks prior to enrolment, or

(f) Ongoing treatment with metformin IR or XR ≥1500 mg/day at a stable dose plus vildagliptin 50 mg BID for at least 10 weeks prior to enrolment.

Treatment with OADs other than those listed above within the 10 weeks prior to enrolment is not permitted.

Criteria a), b) and c) are not applicable in countries where DPP-IV inhibitors are not approved as monotherapy. Criteria a) and c) are not applicable in countries where sitagliptin monotherapy is approved for patients who are not eligible for metformin due to contraindications or intolerance.

Investigators must confirm that patients who are receiving sitagliptin monotherapy at enrolment qualify for sitagliptin monotherapy according to local labeling guidelines.

5. HbA1c:

At enrolment (Visit 1) and at the start of the dose-stabilisation period (Visit 2) - laboratory values from Screening Visit and Visit 1.

- ≥7.2% and ≤10.0% for patients entering the study on sitagliptin100 mg QD or vildagliptin 50 mg BID monotherapy, sitagliptin 100 mg QD plus metformin ≥1500 mg/day or vildagliptin 50 mg BID plus metformin ≥1500 mg/day

- ≥7.7% and ≤10.5% for patients who are drug naïve or who are treated with metformin ≥1500 mg/day monotherapy

At randomisation visit (Visit 5) – laboratory value from Visit 4:
- ≥7.0% and ≤10.0% for all patients

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

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

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

Definitions:

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

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

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

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

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

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

4.2 Exclusion criteria

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

The following criteria apply to enrolment (Visit 1) and randomisation visit (Visit 5). Laboratory value criteria apply at the start of dose-stabilisation period (Visit 2 – using laboratory values from Visit 1). Exceptions are noted below.

Endocrine and metabolic disorders

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

2. History of diabetic ketoacidosis

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

4. FPG >270 mg/dL (>15 mmol/L)

5. 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.

6. Diabetes insipidus

7. Thyroid-stimulating hormone (TSH) values outside normal range

Kidney disorders

8. Creatinine Clearance:

For patients treated with metformin:

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

For patients not treated with metformin:

- Calculated Creatinine Clearance <50 mL/min (calculated by Cockroft-Gault formula)

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

10. History of unstable or rapidly progressing kidney disease

11. Known condition of familial renal glucosuria

Hepatic disorders

12. 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

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

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

15. History of drug-induced liver enzyme elevations

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

Cardiovascular disorders

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

18. Significant cardiovascular history within the past 3 months prior to the screening visit, defined as: myocardial infarction, unstable angina pectoris, transient ischemic attack, unstable or previously undiagnosed arrhythmia, cardiac surgery or revascularization (coronary angioplasty or bypass grafts), or cerebrovascular accident. In addition, patients who have unstable cardiovascular disease at enrolment in the judgment of the investigator are excluded from the study.

19. Blood pressure:

At enrolment (Visit 1):

- Systolic BP ≥170 mmHg and/or diastolic BP ≥110 mmHg

At randomisation (Visit 5):

- Systolic BP ≥160 mmHg and/or diastolic BP ≥100 mmHg

Hematologic/oncologic disorders/conditions

20. Haemoglobin ≤10 g/dL (≤100 g/L) for men; haemoglobin ≤9.0 g/dL (≤90 g/L) for women

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

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

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

Infectious disease/immunologic disorders

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

Musculoskeletal disorders

25. Creatine Kinase (CK) >3X ULN

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

Reproductive status

27. Pregnant or breastfeeding patients

Prohibited medications

28. Use of antihyperglycaemic medications other than DPP-4 inhibitors or metformin during the 10 weeks prior to enrolment

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

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 (betametasone ≥1.2 mg, dexamethasone ≥1.5 mg, hydrocortisone ≥40 mg) per day within 30 days prior to enrolment; topical or inhaled corticosteroids are allowed

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

34. Intolerance, contraindication or potential allergy or hypersensitivity to dapagliflozin, metformin, sitagliptin, glimepiride, other sulfonylurea, sulphonamides, 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

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

43. Previous bone marrow transplant

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

4.3 Procedures for handling incorrectly included patients

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.

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

4.4 Withdrawal of patients

4.4.1 Criteria for discontinuation from the study

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

General discontinuation criteria:

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

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

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

4. Incorrectly enrolled patients (see section 4.3)

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

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

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

Study-specific discontinuation criteria:

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

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

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

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

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

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

10. Major and/or frequent hypoglycaemic events, defined as ≥1 major event or recurring minor events (see Section 6.3.9.1 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

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

12. Patients who have an FPG >270 mg/dL (15 mmol/L) between week –8 and week 0 (visits 3 to 5) during the dose-stabilisation period

13. Rescued patients with central laboratory HbA1C values greater than 8.0% despite a maximum tolerated dose of rescue therapy for 12 weeks

14. Change in kidney function (Please see Appendix G for further guidance):

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

- For patients not treated with metformin: calculated creatinine-clearance <50 mL/min or an increase in serum creatinine of ≥0.5 mg/dL above the baseline value confirmed by a repeated measurement within one week.

15. CK >10x ULN confirmed at a repeated measurement preferably within 24 hours, but not exceeding 72 hours, see Section 4.4.2

16. 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 I for futher guidance. Patients should be discontinued from study if the initial and repeat laboratory tests meet any of the following criteria:

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

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

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

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

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

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

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

4.4.2 Procedures for discontinuation of a patient from the study

Pre-randomisation

A patient that discontinues will always be asked about the reason(s) for discontinuation and the presence of any AEs. If possible, they will be seen and assessed by an investigator(s). AEs will be followed up (See Sections 6.3.3 and 6.3.4); patient diaries and study drug should be returned by the patient.

Randomised patients

Randomised patients who discontinue the study before week 48 should return and complete the procedures described for Visit 13 as soon as possible but at the latest 7 days after discontinuation. These patients should also be scheduled for a follow-up visit (ie, procedures of Visit 14) three weeks after discontinuation of investigational product. 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 and open-label metformin and sitagliptin, alternative antihyperglycaemic treatment will be initiated according to the investigator's judgement and according to local medical practice.

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

Patients with increased liver function tests as defined in Section 4.4.1 under listing (16) 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 I for further guidance. If repeat liver function tests still are increased as outlined in Section 4.4.1 under listing (16), the patient should permanently discontinue all study medication and be withdrawn from the study (see Appendix I for further guidance).

4.4.2.1 Procedures for discontinuation from genetic aspects of the study

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

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

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

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

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

5. STUDY CONDUCT

5.1 Restrictions during the study

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

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

Patients should not take investigational products or open-label sitagliptin or metformin on the morning of the clinic 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 206 mL of blood will be drawn from each patient during the entire duration of the clinical study (excluding optional genetic blood sample and extra blood samples taken at unscheduled visits), patients should be instructed to abstain from donating any blood during the clinical study and for 3 months following their last study visit.

Prohibited and restricted concomitant medications are listed in Sections 4.2 and 4.4.1. Fasting prior to laboratory assessments is described in Section 6.3.5.

5.2 Patient enrolment and randomisation

The principal investigator 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#”.

3. From Visit 1 to Visit 5 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 strictly sequentially within strata as patients are eligible for randomisation.

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

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

5.2.1 Procedures for randomisation

Randomisation to study treatment with stratification will be done via an Interactive Web Response System (IWRS) on Visit 5 in balanced blocks in order to ensure approximate balance among treatment arms and strata. The IWRS will allocate a randomisation code according to a randomisation scheme prepared by AstraZeneca.

The number and size of tablets will be identical for the investigational products for the 2 treatment arms. Clinical supplies will be identified by random kit numbers, where each kit number is specific to a treatment arm. For randomised patients, the IWRS will provide an appropriate kit number to match the assigned randomised treatment from those kits available at the centre.

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

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

5.3 Blinding and procedures for unblinding the study

5.3.1 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. Sitagliptin and metformin will be open-label.

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 Products department at AstraZeneca or their designee, where the information is needed to package study medication, and the drug safety departments at Bristol-Myers Squibb and AstraZeneca. Only patients and investigators will remain blinded past the 24-week randomised treatment period. See Section 5.3.2 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.

5.3.2 Methods for unblinding the study

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

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

Bristol-Myers Squibb retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient during the 24-week randomised treatment period have been made and documented.

5.4 Treatments

5.4.1 Identity of investigational products and additional drugs

Table 6 Identity of investigational products and additional drugs

Investigational product/ Study Drug / Rescue Medication	Dosage form and strength	Manufacturer
Dapagliflozin 10 mg	Biconvex, diamond shape, green tablet 10 mg (Size: 11 mm)	Bristol-Myers Squibb or designee

Investigational product/ Study Drug / Rescue Medication	Dosage form and strength	Manufacturer
Matching placebo for dapagliflozin 10 mg	Biconvex, diamond shape, green tablet (Size: 11 mm)	Bristol-Myers Squibb or designee
Sitagliptin 100 mg	Light beige, round shaped tablet with "112" on one side and plain on the other side, 100 mg	Merck or designee
Glucophage® (metformin hydrochloride, immediate release) 500 mg	Film coated, white to off-white round tablet, 500 mg	Merck or designee
Glimepiride 2 mg	2 mg tablet	Determined by which brand is registered and available locally on the market

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).

Commercial packs of sitagliptin will be supplied by AstraZeneca or their designee. The sitagliptin packs will contain 98 tablets in Europe and Latin America and 100 tablets in the USA. The packs will be labelled with labels or booklets, depending on availability. The labels will fulfil GMP Annex 13 requirements and local regulatory guidelines.

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

Commercial packs of glimepiride will be sourced by AstraZeneca or their designee or prescribed by local investigator. The packs will be labelled with labels or booklets, depending on availability. The labels will fulfil GMP Annex 13 requirements and local regulatory guidelines. If the commercial packs are prescribed, local labelling and country specific requirements will be applied.

5.4.2 Doses and treatment regimens

The investigational product dapagliflozin and matching placebo will be taken orally, with or without food. The investigational product should be taken once daily and at approximately the

same time of the day during the study period. Sitagliptin should be taken once daily and may be taken with or without food; metformin should be taken twice daily with or after a meal. Patients should be instructed to abstain from all food and beverages for 12 hours prior to each clinical visit; however, drinking water is allowed. In the morning prior to each visit, acceptable concomitant medications can be taken with water only.

- Dapagliflozin 10 mg tablets, administered orally for the 24-week double-blind treatment period and the 24-week extension period
- Matching placebo for dapagliflozin 10 mg administered orally for the 2-week placebo lead-in period, the 24-week double-blind treatment period and the 24-week extension period
- Open-label sitagliptin 100 mg tablets administered orally for the 10-week DSP, the 2-week placebo lead-in period, the 24-week double-blind treatment period and the 24-week extension period
- Open-label metformin IR 500 mg tablets administered orally at doses ≥1500 mg/day for the 10-week DSP, the 2-week placebo lead-in period, the 24-week double-blind treatment period and the 24-week extension period.

Table 7 Drug dispensing scheme:

Visit ID	No. of bottles to dispense of dapagliflozin 10 mg or matching placebo[a]	No. of commercial packs to be dispensed of sitagliptin 100 mg, open label[b]	No. of commercial packs to be dispensed of metformin 500 mg, open label[c] (Stratum 2 only)
Visit 1	N/A	N/A	N/A
Visit 2	N/A	1 commercial pack	3-4 commercial packs
Visit 3	N/A	N/A	N/A
Visit 4	1 bottle (Lead-In)	1 commercial pack	3-4 commercial packs
Visit 5	1 bottle	N/A	N/A
Visit 6	1 bottle	N/A	N/A
Visit 7	1 bottle	1 commercial pack	3-4 commercial packs
Visit 8	2 bottles	N/A	N/A
Visit 9	2 bottles	2 commercial packs	5-9 commercial packs
Visit 10	2 bottles	N/A	N/A
Visit 11	2 bottles	N/A	N/A
Visit 12	2 bottles	1 commercial pack	3-4 commercial packs
Visit 13	N/A	N/A	N/A
Visit 14	N/A	N/A	N/A

[a] Each bottle contains 35 tablets.
[b] Each commercial pack contains 98 or 100 tablets.
[c] Each commercial pack contains 100 tablets.

5.4.3 Additional study drug

Open-label glimepiride 2 mg, at a dose of up to 6mg/day, will be administered to patients who require rescue therapy. The glimepiride dose can be titrated up in 2 mg increments if FPG continues to be above the thresholds outlined in Table 2 and Table 3 until the maximum dose of 6 mg/day is reached. Dosage increases should be made in increments of no more than 2 mg at 1-2 week intervals. All rescue decisions will be based on the central laboratory FPG values. Glimepiride should be taken once daily with a glass of water and taken shortly before or during a substantial breakfast or shortly before or during the first main meal, as instructed in the label.

5.4.4 Labelling

Labelling of the investigational product and additional drugs will be carried out by AstraZeneca or a Contract Research Organization (CRO) in accordance with current Good Manufacturing Practice (GMP). The labels will be translated into local languages and in

accordance with local regulations for each participating country. The labels will fulfil GMP Annex 13 requirements and/or local regulatory. All investigational products will be labelled.

The labels will include at least the following information:

- Name of sponsor (AstraZeneca)
- Study drug(s) dosage form, route of administration, and quantity of dosage units
- Study code
- Order number (to identify the contents and packaging operation)
- Enrolment code (will be added by the investigator when product is dispensed)
- Kit ID (if applicable)
- Visit number, if applicable (will be added by the investigator when product is dispensed)
- Directions for use. (For oral use.)
- The name of the principal investigator, if applicable (will be added by the investigator when product is dispensed)
- Date dispensed (will be added by the investigator when product is dispensed)
- The period of use, eg, expiry date
- Storage conditions, if applicable
- The following standard statements
  - "for clinical trial use only"
  - "keep out of reach of children".

5.4.5 Storage

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

5.5 Concomitant and post-study treatment(s)

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

appropriate sections of the eCRF. Background antihypertensive medications should not be increased between weeks 0-8 unless the patient has a confirmed SBP ≥160 mmHg or DBP ≥100 mmHg on or after week 4. Background antihypertensive medications should not be decreased between weeks 0-8 unless in the investigator's judgement the patient has symptomatic hypotension or has documented orthostatic hypotension during a study visit. The investigator should inform the study physician of any changes in anti-hypertensive medications during the first 8 weeks. After week 8, changes in antihypertensive medication may be made as needed for appropriate blood pressure management.

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

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

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

For prohibited and restricted medication, see Exclusion Criteria (Section 4.2) and Discontinuation Criteria (Section 4.4.1).

5.6 Treatment compliance

The administration of all medication (including investigational product) must be recorded in the appropriate sections of the Case Report Forms.

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

5.6.1 Accountability

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

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

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

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

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

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

The investigator is responsible for making sure

- That the investigational product and additional study drugs are handled and stored safely and properly (see Section 5.4.5)
- That the investigational product and additional study drugs are only dispensed to study patients in accordance with this protocol.

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

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

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The investigator will ensure that all data collected in the study are provided to AstraZeneca. He/she ensures the accuracy, completeness, legibility and timeliness of the data recorded in the appropriate sections of the eCRF and according to any instructions provided.

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

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

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

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

The patients will be instructed to monitor their FPG at least every second day between Visits 2-10 and at least once a week between visits 10-13. The results and information about hypoglycaemic events should be entered by the patient into a paper diary.

6.2 Screening and demography procedures

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

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

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

6.2.1 Follow-up procedures

A follow-up (Visit 14) will be performed 18-24 days (3 weeks ±3 days) after the end of the double-blind treatment period, see Table 4 for further details.

6.3 Safety

It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The principal investigator is responsible for ensuring this.

6.3.1 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.

6.3.2 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) should be reported as an SAE using the most relevant SAE criteria, as judged by the Investigator.

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

6.3.3 Recording of adverse events

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

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

Variables

The following variables will be recorded in the eCRF for each AE; description of the AE, the date when the AE started and stopped, maximum intensity, whether the AE is serious or not, causality rating (yes or no), action taken with regard to investigational product and outcome.

Maximum intensity will be graded according to the following definitions:

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

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 6.3.2. 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 an 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 an SAE.

The Investigator will assess causal relationship between Investigational Product and AEs, 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?”

Causal relationship in cases where the disease under study has deteriorated due to lack of effect will be classified as no reasonable possibility.

For SAEs causal relationship will also be assessed for additional study drug and/or other medication. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as “yes”.

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

Adverse Events based on signs and symptoms

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

Adverse Events based on examinations and tests

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and other safety variables will only be reported as AEs if they are clinically significant, fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product, or require the patient to receive specific corrective therapy. If a deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Clinically relevant deterioration in non-protocol-mandated measurements will be reported as AE(s).

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

Hypoglycaemic events

A separate section in the eCRF will be used to document all reported episodes of hypoglycaemia. 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 6.3.2). 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 6.3.9.1).

Follow-up of unresolved adverse events

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

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

AE dictionary

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

6.3.4 Reporting of serious adverse events

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

The AstraZeneca representative will work with the Investigator to compile all the necessary information and ensure that Bristol-Myers Squibb receives a report by day 1 (ie, immediately but no later than the end of the next business day) for **all** SAEs.

All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s). SAEs will be recorded from the time of informed consent. SAE information will be entered and submitted into the WBDC system on the relevant eCRF modules. If the system is unavailable, the Investigator should fax a paper back-up SAE report to the AstraZeneca representative immediately, recognising that the same reporting time frames still apply. The Investigator is responsible for completing the eCRF as soon as the system becomes available again. The AstraZeneca representative will forward all information relevant to the SAE to Bristol-Myers Squibb Pharmacovigilance via fax or email.

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

6.3.5 Laboratory safety assessment

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

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

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

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

For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.3.

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

Table 8 Safety laboratory variables

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	R
Study Week	**-13**	**-12**	**-8**	**-2**	**0**	**4**	**8**	**12**	**18**	**24**	**32**	**40**	**48**	**51**	
Haematology															
Haemoglobin	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
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
Alanine Aminotransferase (ALT, SGPT)	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
Creatine Kinase (CK)	X				X	X	X	X	X	X	X	X	X	X	X
Total Bilirubin (TB)	X				X	X	X	X	X	X	X	X	X	X	X
Blood Urea Nitrogen (BUN)	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	R
Study Week	**-13**	**-12**	**-8**	**-2**	**0**	**4**	**8**	**12**	**18**	**24**	**32**	**40**	**48**	**51**	
Electrolytes:	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
Albumin	X				X			X		X			X	X	X
Uric acid	X				X	X	X	X	X	X	X	X	X	X	X
Serum Creatinine (SCr)	X				X	X	X	X	X	X	X	X	X	X	X
Calculated creatinine clearance (Cockroft-Gault formula)[a]	X				X	X	X	X	X	X	X	X	X	X	X
Estimated Glomerular Filtration Rate (MDRD formula)[b]	X				X			X		X			X	X	X
Serum Cystatin C					X					X			X	X	X
Serum Bone Metabolism Marker (Parathyroid Hormone (PTH) and 25 hydroxy-vitamin D)					X					X			X	X	X
FSH[f]	X														
TSH	X														

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	R
Study Week	**-13**	**-12**	**-8**	**-2**	**0**	**4**	**8**	**12**	**18**	**24**	**32**	**40**	**48**	**51**	
Hepatitis Screen Panel[e]	X														
Urinalysis															
Glucose[b]	X				X	X	X	X	X	X	X	X	X	X	X
Blood by dipstick[c]	X				X	X	X	X	X	X	X	X	X	X	X
Albumin	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
Calculated Urinary albumine:creatinine ratio (UACR)	X				X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a) Creatinine clearance will be calculated by the method of Cockcroft and Gault. Patients with a calculated creatinine-clearance <60 ml/min or an increase in serum creatinine of ≥0.5 mg/dL (≥44.2 µmol/L) above the baseline value, will have their metformin held and a repeated serum creatinine test within one week. For details, see Section 4.4.2. The eGFR will be estimated by the abbreviated Modification of Diet in Renal Disease (MDRD) formula (Levey et al 1999) and reported by central laboratory.

b) Results will be blinded.

c) Microscopy if dipstick positive for blood.

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

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

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

For blood volume see Section 7.1

6.3.6 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 5, and new findings discovered on subsequent physical examinations should be recorded as changes from baseline.

6.3.7 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.

6.3.8 Vital signs

6.3.8.1 Pulse and blood pressure

Pulse and blood pressure measurements will be performed before blood samples are taken. One pulse measurement will be taken after the patient has been sitting and resting for at least 5 minutes The pulse measurement will be followed by three blood pressure (BP) measurements separated by 2 minutes each. All three BP readings should be recorded. At Visit 1, before entry into the dose-stabilisation or placebo lead-in periods, the seated BP will be recorded three times in both the left and the right arms. All three measurements should be made in one arm before transferring the cuff to the other arm. The arm with the highest mean seated BP readings will be the one used for all subsequent readings. The average of the three BP readings will be used for study analyses. BP readings should be taken while the patient is in a comfortable seated position with the arm supported at the level of the heart. All readings should be recorded. Ideally, blood pressure should be measured with the same machine, at the same time of day, and by the same personnel at each visit.

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

- a mercury sphygmomanometer is not available, or

- a mercury sphygmomanometer is available, but site staff is not practiced in its use

- use of mercury devices is restricted by local law.

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

6.3.8.2 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 2 minutes apart. All three readings must be recorded. For study analyses, the average of the three BP and pulse readings will be used.

Standing BP and pulse

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

6.3.9 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 5.

6.3.9.1 Fasting plasma glucose concentrations and hypoglycaemic events

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

FPG should be self-monitored at least every second day between visits 2 and 10 and at least once a week between visits 10 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.

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

If self-monitored FPG is above 270 mg/dL (15 mmol/L) from week -8 (Visit 3) to week 4 (Visit 6), above 240 mg/dL (13.2 mmol/L) from week 4 (Visit 6) to week 12 (Visit 8), or above 200 mg/dL (11.1 mmol/L) from week 12 (Visit 8) to week 24 (Visit 10), the patient should repeat the FPG on the same day. If the second FPG value is above 270 mg/dL (15 mmol/L), 240 mg/dL (13.2 mmol/L) or 200 mg/dL (11.1 mmol/L), respectively, the patient should contact the study centre and be scheduled for a central laboratory FPG measurement within one week. 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 antihyperglycaemic 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 6.3.3.

6.3.9.2 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:

Asymptomatic bacteriuria is defined as the presence of $\geq 10^5$ colony forming units/mL of bacteria, in a properly collected voided urine specimen, without signs or symptoms typically attributed to urinary tract infection. Asymptomatic bacteriuria is prevalent among diabetic women, and is associated with pyuria in 70% of cases. Neither guidelines from the US (Nicolle et al 2005, USPST 2004) nor Europe (European Association of Urology 2008) recommend screening for, or treatment of, asymptomatic bacteriuria in non-pregnant diabetic patients. In this study, the central laboratory will 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 5), 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 held in patients with clinical evidence of upper tract UTI (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 urinary tract infection. Whether additional therapy is prescribed because of culture results should be determined by Investigator judgement, after consultation with the Study Team Physician.

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 6.3. 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.

6.3.10 Congestive Heart Failure

The risk of electrolyte abnormalities, volume depletion, and impaired renal function is enhanced when two diuretics are used in combination. For this reason, caution should be exercised when administering dapagliflozin, which has a modest diuretic effect, to 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.

6.3.11 Change in kidney function

Please see Appendix G for further guidance.

6.3.12 Hyponatremia

Please see Appendix F for further guidance.

6.3.13 CK abnormalities

Please see section 4.4.2, "Procedures for discontinuation of a patient from the study."

6.3.14 Liver function test abnormalities

Please see Appendix I for further guidance.

6.3.15 Independent Adjudication Committee

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

1. Death including:
2. Cardiovascular Death
3. 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 Efficacy

6.4.1 Efficacy laboratory variables

Table 9 Efficacy laboratory variables

Visit	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	R
Study Week	**-15**	**-13**	**-12**	**-8**	**-2**	**0**	**4**	**8**	**12**	**18**	**24**	**32**	**40**	**48**	**51**	
HbA1c	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
Glucose, Insulin, C-peptide during MTT						X					X			X		X
HOMA-2, HOMA-IR						X					X			X		X
Total cholesterol[a]		X				X					X			X		X
LDL-C[a]		X				X					X			X		X
HDL-C[a]		X				X					X			X		X
TG[a]		X				X					X			X		X

[a] fasting

The laboratory parameters that will be measured to assess efficacy are displayed in Table 9 by visit. The results from baseline and onwards will not be reported to the investigator unless the values meet the defined discontinuation criteria in Section 4.4.1, except for TC, HDL-C, LDL-C and TG which will be reported. In addition, if rescue medication is initiated, the central laboratory FPG and HbA1c values will be reported to the investigator to ensure proper follow-up of the rescued patient.

6.4.2 HbA1c

HbA1c is the primary assessment for the determination of glycaemic efficacy accepted by the FDA and the EMEA. The primary outcome variable for this study is the change in HbA1c from baseline to the end of the 24-week randomised treatment period. HbA1c will be analysed by a central laboratory according to the procedures described in the Laboratory Manual which will be distributed to each study site during site initiation.

6.4.3 Blood pressure

As BP is both an efficacy and safety variable in this study, measurement of BP is described in Sections 6.3.8.1 and 6.3.8.2.

6.4.4 Weight and height

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

6.4.5 Body Mass Index (BMI)

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

6.4.6 Waist and hip circumference

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

The hip circumference is measured in the standing position at the maximal circumference over the buttocks with a centrally-supplied measuring tape.

6.4.7 Waist-hip ratio (WHR)

WHR is a calculated ratio between waist circumference and hip circumference (waist circumference / hip circumference, measured in centimetres) and will be computed by AstraZeneca.

6.4.8 Liquid Meal Tolerance Test (MTT)

MTTs are scheduled to occur at Week 0 (Visit 5), Week 24 (Visit 10), and Week 48 (Visit 13), (or Rescue visit, or Visit due to discontinuation). The MTT visit should be rescheduled within 3 days if the patient did not comply with all of the following:

- Patient fasted for at least 12 hours prior to the visit
- Patient abstained from tobacco, alcohol, and caffeine for 24 hours prior to the MTT.

One bottle (237 mL) of Nestle Boost™ Plus Drink will be used as liquid meal supplement.

At Week 0 (Visit 5, randomization), study medication is given within 2 hours AFTER MTT is complete.

- Draw the blood sample for Time 0 glucose, insulin, C-peptide and other laboratory tests due at the visit
- Administer the liquid meal supplement over 10 minutes, starting immediately after Time 0 blood sample is drawn
- Draw specimens for post-liquid meal glucose, C-peptide and insulin at 120 minutes
- Give study medication within 2 hours **AFTER** MTT is complete.

At Week 24 (Visit 10) and Week 48 (Visit 13) (or at Rescue Visit, or at Visit due to discontinuation), the study medication is given 1 hour BEFORE administration of the liquid meal supplement.

- Give study medication 1 hour **BEFORE** administration of the liquid meal supplement
- Draw the blood sample for Time 0 glucose, insulin, C-peptide and other laboratory tests due at the visit
- Administer the liquid meal supplement over 10 minutes, starting immediately after Time 0 blood sample is drawn
- Draw specimens for post-liquid meal glucose, C-peptide and insulin at 120 minutes.

6.4.9 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.

6.4.10 Patient reported outcomes (PRO) (not applicable)

6.5 Pharmacokinetics (Not applicable)

6.6 Pharmacodynamics (Not applicable)

6.7 Pharmacogenetics

AstraZeneca and Bristol-Myers Squibb intend to perform genetic research in the dapagliflozin clinical development programme to explore how genetic variations may affect the clinical parameters associated with dapagliflozin response. Collection of DNA samples from populations with well described clinical characteristics may aid in the identification of future drug targets and projects to validate identified targets. Future research may suggest other genes or gene categories as candidates for influencing not only response to dapagliflozin but

also susceptibility to type 2 diabetes and other metabolic disease for which dapagliflozin may be evaluated. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to disease susceptibility and drug action.

6.7.1 Collection of samples

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

For blood volume see Section 7.1.

6.8 Health economics (Not applicable)

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

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

Table 10 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety/Efficacy	Clinical chemistry	8.5	11	93.5
	Haematology	4.0	14	56.0
FPG		4.0	14	56.0
MTT (glucose, insulin, C-peptide)		6.2	3	18.6
Genotyping [a]		10.0	1	10.0
Total				224.1 (234.1)[b]

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

7.2 Handling, storage and destruction of biological samples

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

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

For information on genetic samples, see **Appendix E**.

7.2.1 Pharmacogenetic samples

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

7.3 Labelling and shipment of biohazard samples

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

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

7.4 Chain of custody of biological samples

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

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

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

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

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

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

7.5 Withdrawal of informed consent for donated biological samples

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

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

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

The principal investigator:

- Ensures patients withdrawal of informed consent is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed/destroyed and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destructed and the action documented returned to the study site.

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

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

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with 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 E.

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

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

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

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

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

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

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

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

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

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

8.4 Informed consent

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

The principal investigator(s) at each centre will:

- Ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure that the patients are notified that they are free to discontinue from the study at any time
- Ensure that the patient are given the opportunity to ask questions and allowed time to consider the information provided
- Ensure that the patient’s signed and dated informed consent is obtained before conducting any procedure specifically for the study, including the following:
  - Withholding or discontinuation of treatment
  - Collection of blood and urine samples

  - Physical examination including ECG

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

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

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

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

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

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

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

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

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

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

8.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, 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
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator.
- Discuss the specific requirements of the genetic research with the investigator(s) (and other personnel involved with the study).

9.2 Training of study site personnel

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

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

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

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

9.3 Monitoring of the study

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

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, and that investigational product accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) incl. verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Perform source verification of the genetic consent of participating patients and ensure that the investigational team is adhering to the specific requirements of this genetic research
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed/destructed accordingly, and the action is documented, and reported to the patient

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

9.3.1 Source data

Refer to Clinical Study Agreement for location of source data.

9.4 Study agreements

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

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

9.5 Study timetable and end of study

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

The study is expected to start in QIV 2009 and to be completed by QIV 2011.

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

10. DATA MANAGEMENT BY ASTRAZENECA

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. Site personnel will enter the data in the eCRFs. 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. Clean file occurs when all data have been declared clean and signed by the investigator. The data will be frozen and then locked to prevent further editing. A 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.

Concomitant medications will be coded using the Bristol-Myers Squibb Drug Dictionary. AEs and medical history will be coded using MedDRA.

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.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

11.1 Calculation or derivation of safety variable(s)

11.1.1 Other significant adverse events (OAE)

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

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

11.1.2 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 24-week extension period and the 3-week safety follow-up period will be evaluated. Safety variables will be summarized descriptively.

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

Males:

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

Females:

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

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. Comparisons between the treatment groups will be analyzed using two-sided Fisher's exact tests.

All other safety variables will be summarized descriptively.

11.2 Calculation or derivation of efficacy variables

Please see section 6.4 for a description of specific efficacy variables.

11.2.1 Change and percent change from baseline

Change from baseline will be calculated as absolute difference between the value measured at or derived for a specific time point after baseline minus baseline value. Baseline is defined as the last value collected on/or prior to Visit 5 (randomisation).

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

11.2.2 Last observation carried forward (LOCF)

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

11.3 Calculation or derivation of pharmacokinetic variables (Not applicable)

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

11.5 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.

11.6 Calculation or derivation of health economics variables (Not applicable)

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA OR DELEGATE

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 variable and selected secondary variables may be reanalyzed using the per-protocol analysis set if more than 10% of the patients in any treatment group by stratum 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 Safety analysis set

The safety analysis set will include all randomised patients who received at least one dose of study medication and who provide any safety records. Patients who were dispensed the wrong randomised treatment (ie those randomised to dapagliflozin 10 mg but actually given placebo, or vice versa) 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.

12.1.2 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.

12.1.3 Per-protocol analysis set

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

12.2 Methods of statistical analyses

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

The primary objective of this study is to show superiority of dapagliflozin versus placebo overall in terms of the primary efficacy variable change in HbA1c from baseline to week 24. This objective will also be assessed separately for each of two strata: patients on background therapy of sitagliptin monotherapy and patients on background therapy of sitagliptin plus metformin.

The following null hypothesis H_0 related to the two strata combined will be tested against the alternative hypothesis H_A ($\alpha = 0.050$, two-sided):

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

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

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

Six key secondary variables have been identified:

- Change in total body weight from baseline to week 24
- Change in HbA1c in patients with baseline HbA1c ≥8.0% from baseline to week 24
- Change in FPG from baseline to week 24
- Change in SBP in patients with baseline seated SBP ≥130 from baseline to week 8
- Change in 2-hour post meal liquid glucose from baseline to week 24
- Proportion of patients achieving a therapeutic glycaemic response, defined as a reduction in HbA1c ≥0.7% compared to baseline, at week 24

A hierarchical closed testing procedure will be used to control the Type I error rate across the primary and key secondary objectives, based on data from the two strata combined. Analyses will also be conducted within each stratum to separately evaluate the effect in the two background treatment regimens. For variables found to be significant with the combined strata analysis, corresponding within-stratum treatment comparisons will be individually tested at a two-sided significance level of 0.050. For all other variables, nominal p-values will be reported for both overall and within-strata comparisons without significance testing.

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

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

The LOCF approach means that for all changes (or percent changes) from baseline to a specific time point post-baseline, analyses will be based on measurements available at that time point or the last post-baseline measurement prior to the time point, if no measurement is available at that time point. Unless otherwise specified, if a patient initiates rescue medication, the last value taken on or before the first rescue dose will be used for analysis.

The primary efficacy variable, change in HbA1c from baseline to week 24, will be analyzed by an analysis of covariance (ANCOVA) model. When assessing the results overall, the model will include terms for treatment group, strata, and baseline covariate. No formal test for interaction between treatment group and strata will be performed as the effects of the two dapagliflozin treatment groups will be examined for each stratum separately. When assessing the results within each stratum, the ANCOVA model will include terms for treatment group and baseline covariate. The ANCOVA model will be used to derive a least squares estimate of the treatment difference with 95% confidence interval and corresponding two-sided p-value. Further, two-sided 95% confidence intervals for the mean change within each treatment group as well as treatment group and stratum will be calculated. The same method will be applied for analyzing other continuous efficacy variables.

The proportion of patients achieving therapeutic glycaemic response, defined as a reduction in HbA1c $\geq$0.7% at week 24, will be analyzed using the methodology of Zhang, Tsiatis and Davidian and Tsiatis, Davidian, Zhang and Lu when there are at least 5 responders on average by treatment group. For proportion of responders, estimates, confidence intervals, and tests will be obtained using this methodology with adjustment for baseline HbA1c and strata. For each treatment group, the probability of response is first modeled using a logistic regression model with baseline HbA1c and strata as terms. Treatment group estimates of response rate are then obtained by integrating each group's modeled probability of response over the observed distribution of baseline covariate and strata (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 stratum. The same method will be applied for analyzing other proportions of patients achieving a pre-defined response.

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

The time course of continuous variables will be presented using standard descriptive summary statistics calculated at each scheduled measuring time point and the last individual measuring time point. Moreover, standard descriptive summary statistics will be calculated for the change (absolute or percent) from baseline to each scheduled measuring time point after baseline and the last individual measuring time point. Additional analyses by stratum will be included where appropriate.

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

12.2.2 Analysis after the 24-week site- and patient-blinded extension period

All variables to be analyzed after the 24 weeks of double-blind treatment will be re-examined at the week 48 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.

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 24-week site- and patient-blinded extension period as well as during the 3-week safety follow-up period will be evaluated. Safety data will be presented by treatment group as well as by treatment group and stratum. Safety variables will be summarized descriptively and missing data will be replaced using the LOCF approach where appropriate.

12.2.4 Analysis of pharmacogenetic variables

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

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

12.3 Determination of sample size

The sample size for this study was selected to demonstrate a difference in the mean change in HbA1c from baseline to week 24 between dapagliflozin and placebo within each of the two strata: patients on background therapy of sitagliptin monotherapy and patients on background therapy of sitagliptin plus metformin.

To detect a difference of 0.5% between dapagliflozin versus placebo for change in HbA1c from baseline to week 24, assuming a standard deviation (SD) =1.1%, 103 evaluable patients (full analysis set) for each treatment group within each stratum would provide >99% power for the analysis of the two strata combined at a significance level =0.050 or 90% power for the analysis of each stratum separately at a significance level =0.050. Assuming that 5% of the patients will not be evaluable in the full analysis set, 108 patients per treatment group within each stratum (432 patients total) are planned for randomisation.

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

12.4 Interim analyses

No interim analyses are planned. 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 48 weeks of randomised treatment are considered to be supplemental.

12.5 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 neither required nor appropriate for this study.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.3.4.**

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 at the AstraZeneca Research and Development site shown below.

Name	**Role in the study**	**Address & telephone number**
	Study Delivery Team Leader responsible for the protocol	
	Study Delivery Team Physician responsible for the protocol at central R&D site	
State local contact persons below		
Local contact persons can be added in wet-ink. <<If applicable for the study: The address, telephone and fax number to other parties involved in the study eg, CRO, Central Laboratory>>		

13.2 Overdose

An 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 an SAE (see Section 6.3.4). If an overdose is suspected, monitoring of vital functions as well as treatment as appropriate should be performed.

13.3 Pregnancy

All outcomes of pregnancy must be reported to AstraZeneca.

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 and/or metformin and/or sitagliptin 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	D1690C00010
Appendix Edition Number	1.0
Appendix Date	

Appendix B
Additional Safety Information

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

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

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

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

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Clinical Study Protocol: Appendix C

Drug Substance	Dapagliflozin
Study Code	D1690C00010
Edition Number	1.0
Date	

Appendix C
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. Cat 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. Cat 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 Cat 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.

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Clinical Study Protocol: **Appendix D**	
Drug Substance	Dapagliflozin
Study Code	D1690C00010
Appendix Edition Number	1.0

Appendix D
New York Heart Association (NYHA) Classification

NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION

The NYHA classification will be based on the following definitions:

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

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

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

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

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***Clinical Study Protocol*: Appendix E**	
Drug Substance	Dapagliflozin
Study Code	D1690C00010
Appendix Edition Number	1.0

Appendix E
Optional Genetic Research

GENETICS RESEARCH SYNOPSIS

A 24-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, International Phase III Study with a 24-week Extension Period to Evaluate the Safety and Efficacy of Dapagliflozin 10mg Daily in Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on a DPP-4 inhibitor (Sitagliptin) Alone or in Combination with Metformin

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 432 randomised patients recruited from approximately 85 centres.

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

Objectives

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

Study design

The study is a 24-week, multicentre, randomised, double-blind, placebo-controlled, parallel-group, international Phase 3 study with a 24-week extension period to evaluate the safety and efficacy of dapagliflozin 10 mg daily in patients with type 2 diabetes who have inadequate glycaemic control on a DPP-4 inhibitor (sitagliptin) alone or in combination with metformin. A 10 ml (approximately) optional blood sample for genetic research can be collected at a single visit from Visit 5 (randomization visit) to Visit 9.

Target patient population

Men or women who are ≥18 years old (and ≤79 for metformin-treated patients) at the enrolment visit (Visit 1) diagnosed with type 2 diabetes, who fulfil the inclusion criteria for the study, and who give informed consent for this genetic research.

Co-variables

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

Statistical methods

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

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

1. BACKGROUND

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

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

1.1 Rationale for genetic research

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

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

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

2. GENETIC RESEARCH OBJECTIVES

Genes that may be investigated include:

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

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

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Genetic research plan

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

The patient will be asked to participate in this genetic research at Visit 5. If the patient agrees to participate, a single blood sample will be taken for genetic research at Visit 5. If the sample isn't drawn at Visit 5, it may be drawn at any other scheduled visit after Visit 5 until Visit 9.

3.2 Selection of genetic research population

3.2.1 Study selection record

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

3.2.2 Inclusion criteria

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

- Provide informed consent for the genetic sampling and analyses.

3.2.3 Exclusion criteria

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

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

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

3.2.4 Discontinuation of patients from this genetic research

3.2.4.1 Criteria for discontinuation

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

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

3.2.4.2 Procedures for discontinuation

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

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

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

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

4. GENETIC MEASUREMENTS AND CO-VARIABLES

4.1 Summary of genetics objectives and analysis

The purpose of this genetic research is to generate a resource for future exploratory pharmacogenetic research studies. DNA obtained from the blood sample and health information collected from the main clinical study 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 5, it may be drawn at any other scheduled visit after Visit 5 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 Storage and coding of DNA samples

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

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

AstraZeneca

Clinical Study Protocol:	**Appendix F**
Drug Substance	Dapagliflozin
Study Code	D1690C00010
Appendix Edition Number	1.0

Appendix F
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 5.4.2 in the CSP.
    - If the repeat sodium concentration within 7 days of restarting the investigational product is ≥130 mmol/L, further management should be based on composite of sodium concentration, clinical assessment of the patient and an evaluation of underlying cause of hyponatraemia.
- If the repeat sodium concentration within 3 days is <130 mmol/L
  - If there is **no** suspected new, temporary, and reversible cause of hyponatraemia based on clinical assessment (other than investigational product), investigational product will be discontinued. Patients will have an end of treatment visit and a follow-up visit three weeks after discontinuation of investigational product as specified in section 5.4.2 in the CSP.
  - If there is **a** suspected new, temporary, and reversible cause of hyponatraemia based on clinical assessment (other than investigational product), investigational product will continue to be interrupted. The suspected cause of hyponatraemia should be identified and corrected. The serum sodium will be rechecked in another 7 days.
    - If the repeat sodium concentration within 7 days is <130 mmol/L, investigational product will be discontinued. Patients will have an end of treatment visit and a follow-up visit three weeks after discontinuation of investigational product as specified in section 5.4.2 in the CSP.

- If the repeat sodium level concentration within 7 days is ≥130 mmol/L investigational product may be restarted unless otherwise contraindicated. Serum sodium will be rechecked in 7 days after restarting the investigational product, and further management should be based on composite of sodium concentration, clinical assessment of the patient and an evaluation of underlying cause of hyponatraemia.

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

Clinical Study Protocol: Appendix G

Drug Substance	Dapagliflozin
Study Code	D1690C00010
Appendix Edition Number	1.0

Appendix G
Case Identification and Management of Decreased Renal Function

CASE IDENTIFICATION AND MANAGEMENT OF DECREASED RENAL FUNCTION

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

FOR PATIENTS WHO ARE TREATED WITH METFORMIN:

If calculated 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 calculated creatinine-clearance is <50 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:

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

6. volume depletion

7. urinary tract infection

8. 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 <50 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 ≥50 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 <50 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).

AstraZeneca

Clinical Study Protocol: Appendix H

Drug Substance	Dapagliflozin
Study Code	D1690C00010
Edition Number	1.0
Date	

Appendix H
Dapagliflozin Overall Benefit and Risk Assessment

Overall Benefits and Risks Assessment

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1. SUMMARY OF RISKS

Six clinical pharmacology studies have been completed in the dapagliflozin program. In these studies, 116 healthy subjects and 38 subjects with type 2 diabetes mellitus (T2DM) have received at least 1 single oral dose (2.5 – 500 mg and 5 – 100 mg, respectively) of dapagliflozin. Forty subjects (24 healthy volunteers [range of mean duration of exposure: 1-14 days] and 16 subjects with T2DM [mean duration of exposure: 13 days]) have received doses ≥ 100 mg of dapagliflozin. Multiple daily doses of dapagliflozin were given to 30 healthy subjects (2.5 – 100 mg) and 39 subjects with T2DM (5 – 100 mg) for up to 14 days. In a Phase 2b clinical study 279 subjects received 1 of 5 doses of dapagliflozin (2.5 mg, 5 mg, 10 mg, 20 mg or 50 mg) for 12 weeks. A second Phase 2b study is ongoing. Data from approximately 514 subjects who have been exposed to dapagliflozin indicate that it is generally safe and well tolerated at doses up to 50 mg for 12 weeks or in single doses up to 500mg.

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

1.1 Identified Risk

1.1.1 Vaginal/Vulvovaginal Infections

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

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

1.2 Potential Risks

1.2.1 Urinary Tract Infections

Dapagliflozin increases the urinary excretion of glucose, a potential substrate for urinary

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

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

1.2.2 Hypoglycemia

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

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

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

1.2.3 Dehydration/Hypovolemia/Hypotension

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

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

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

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

1.2.4 Serum electrolyte abnormalities

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

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

1.2.5 Renal impairment

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

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

1.2.6 Bone Fracture

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

In the Phase 3 program we plan to implement a bone safety monitoring plan through a combination of close monitoring of electrolytes and hormones involved in bone metabolism in all studies and the monitoring of serum biomarkers of bone metabolism in selected studies. Also, in a Phase III study of 24-month duration, dual-energy x-ray absorptiometry (DEXA) scan will be obtained periodically to evaluate bone density.

1.2.7 Increased hematocrit

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

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

1.2.8 Increased creatine phosphokinase

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

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

1.2.9 Non clinical Toxicology findings

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

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

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

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

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

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

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

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

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

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

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

2. SUMMARY OF BENEFITS

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

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

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

3. OVERALL BENEFITS AND RISKS ASSESSMENT

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

4. RECENTLY COMPLETED STUDIES

An additional phase 2b study (MB102009) has been completed and two Phase 3 studies (MB 102013 and MB 102 014) short-term treatment periods have been concluded but not yet reported. Thus, the results from these studies are preliminary.

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

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

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

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

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

AstraZeneca

Clinical Study Protocol Appendix I	
Drug Substance	dapagliflozin
Study Code	D1690C00010
Edition Number	1
Date	

Appendix I
Algorithm on Management of Sustained Elevated Liver Safety Abnormalities

ALGORITHM ON MANAGEMENT OF SUSTAINED ELEVATED LIVER SAFETY ABNORMALITIES

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

Patients with a central laboratory ALT and/or AST > 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 can not 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 etiologies. In addition, specialized blood sampling will be performed to evaluate liver function as well as identify potential causes of laboratory elevation(s). The Investigator should continue to monitor the 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 > 3xULN and TB > 1.5xULN

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

- ALT and/or AST are > 8xULN

In each of these situations, study medication will be discontinued, the Sponsor notified and the Early Termination (End-of-Treatment) visit performed within 3 days of the confirmed laboratory results (see Section 4.4.2). At the Early Termination (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 (i.e. procedures of Visit 14) 3 weeks after discontinuation of investigational product. A referral consultation to a hepatologist or gastroenterologist (specializing in liver abnormalities) should be obtained.

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

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

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

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 > 3X ULN confirmed with a repeated test will have the following performed within 3 days of the confirmed laboratory results:

- AE assessment
- Physical Examination for jaundice and other signs of liver diseases
- Review of relevant risk factors and current history focusing on possible causes of the increased ALT and/or AST and/or TB, including:
  - Use of suspect concomitant medication [including over-the-counter (i.e., acetaminophen/paracetamol), herbal and vitamin preparations]
  - Recent alcohol consumption or recreational drug/narcotic use
  - Recent unaccustomed physical exertion

  - Occupational or environmental exposure to hepatotoxins
  - Other conditions which may cause liver diseases or which may cause abnormal test results

- Specialized Liver 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

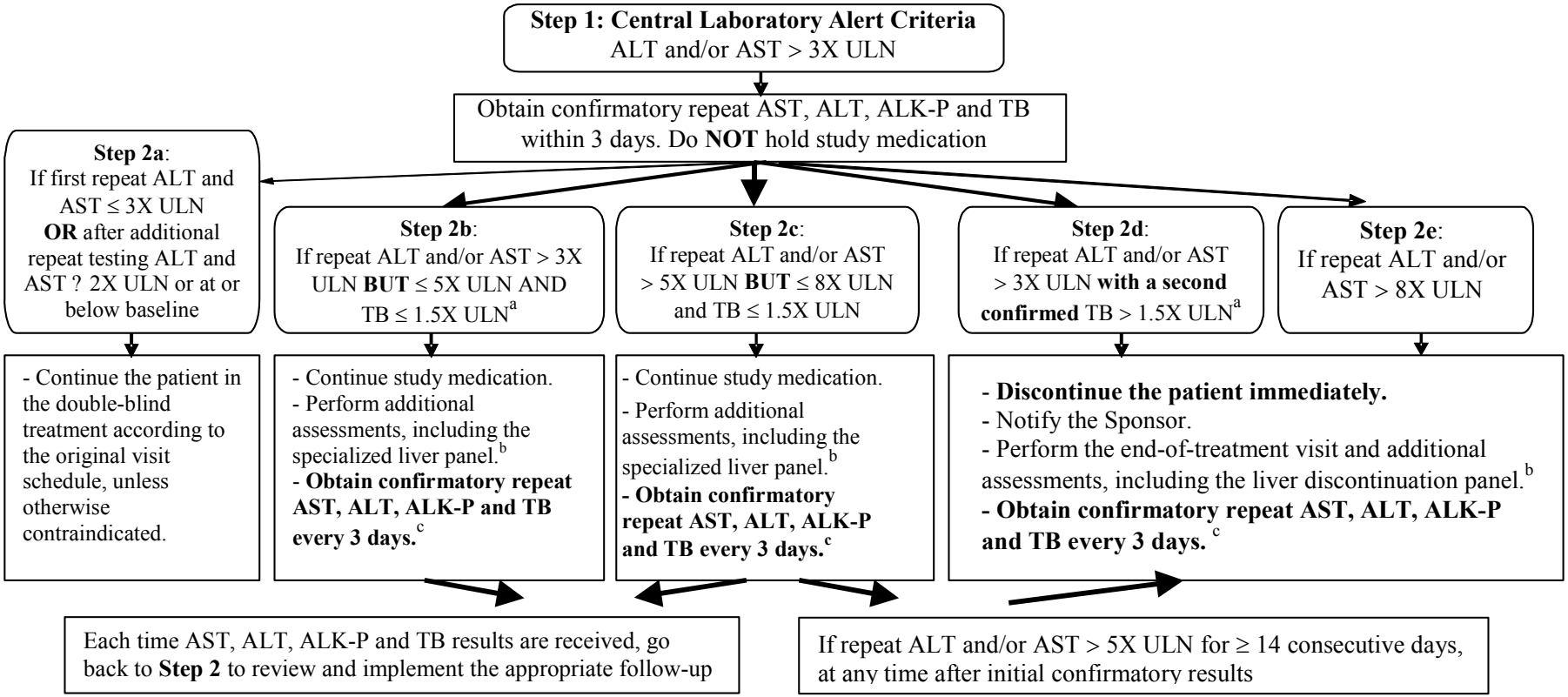
Liver Discontinuation Panel

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 Early Termination (End-of-Treatment) visit. Similar to the Specialized Liver Panel, these laboratory tests will study the possible causes of the increased ALT and/or AST and/or TB, and may include, but are not limited to, the following tests:

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

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

Figure 1 Sustained elevated liver safety abnormalities flow chart



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

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

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

Clinical Study Protocol Amendment	
Amendment Number	1
Drug Substance	dapagliflozin
Study Code	D1690C00010
Date	
Protocol Dated	

A 24-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, International Phase III Study with a 24-week Extension Period to Evaluate the Safety and Efficacy of Dapagliflozin 10 mg Daily in Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on a DPP-4 inhibitor (Sitagliptin) Alone or in Combination with Metformin

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden.

Centres affected by the Amendment:

This amendment will affect all centres in the study.

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

1. Section of protocol affected:

1.4 Benefit/risk and ethical assessment

Previous text:

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 program as needed. Thus real-time, active safety surveillance will be conducted during the entire duration of this study. In addition, all dapagliflozin studies are subject to a carefully designed patient risk management plan that includes the temporary and if necessary permanent discontinuation of investigational product in individual patients in whom a potential health risk or a laboratory abnormality of clinical concern has been identified. Investigators are also provided guidance on appropriate management of potential risks such as hypoglycaemia (Section 6.3.9.1) urinary tract and genital infections (Section 6.3.9.2) hyponatraemia (Appendix F), and decreased renal function (Appendix G).

Revised text:

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 program as needed. Thus real-time, active safety surveillance will be conducted during the entire duration of this study. In addition, all dapagliflozin studies are subject to a carefully designed patient risk management plan that includes the temporary and if necessary permanent discontinuation of investigational product in individual patients in whom a potential health risk or a laboratory abnormality of clinical concern has been identified. Investigators are also provided guidance on appropriate management of potential risks such as hypoglycaemia (Section 6.3.9.1) urinary tract and genital infections (Section 6.3.9.2) hyponatraemia (Appendix F), decreased renal function (Appendix G) **and liver function abnormalities (Appendix I)**.

Reason for Amendment:

The purpose of this amendment is to expand existing procedures for the ongoing review of hepatic laboratory tests and hepatic events. A recent observation of the dapagliflozin program safety database revealed a slightly higher incidence of aminotransaminase elevations in dapagliflozin-treated subjects compared with placebo. An internal expert panel was convened which recommended implementation of additional hepatic laboratory monitoring across the program. Using the US Food and Drug Administration (FDA) Guidance for Industry, Drug-

Induced Liver Injury: Premarketing Clinical Evaluation (July 2009) as a reference, this amendment describes the changes being implemented in addition to the routine safety surveillance procedures already in place.

2. Section of protocol affected:

3.1 Overall study design and flow chart

Previous text:

This international study will be conducted at approximately 85 study centres. It is estimated that 1080 patients will be screened to reach the target of 432 randomised patients during an enrolment period of approximately 9 months. It is expected that 5 to 6 patients will be randomised per centre. Globally patients will be recruited to ensure a 50:50 ratio of patients in the 2 strata. Countries that have sitagliptin monotherapy approved will randomise 100% of Stratum 1 patients and approximately 30% of Stratum 2 patients. Countries that do not have sitagliptin monotherapy approved will randomise approximately 70% of the Stratum 2 patients. Target numbers of patients to be randomised in total and per strata will be agreed with individual countries before the start of the study. Recruitment will be competitive between sites within the countries. Enrolment into the 2 strata will be stopped on country level once enough patients are screened to provide the globally projected number of randomised patients. Centres may be discontinued from the study if recruitment rates are poor and new centres may be added if necessary to achieve recruitment goals.

Revised text:

This international study will be conducted at approximately 85 study centres. It is estimated that 1080 patients will be screened to reach the target of 432 randomised patients during an enrolment period of approximately 9 months. It is expected that 5 to 6 patients will be randomised per centre. Globally patients will be recruited to ensure a 50:50 ratio of patients in the 2 strata. **Countries in North and South America will randomise approximately 30% of Stratum 2 patients and 80 – 100% of Stratum 1 patients. Countries in the European Union will randomise approximately 70% of the Stratum 2 patients and 0 – 20% of Stratum 1 patients.** Target numbers of patients to be randomised in total and per strata will be agreed with individual countries before the start of the study. Recruitment will be competitive between sites within the countries. Enrolment into the 2 strata will be stopped on country level once enough patients are screened to provide the globally projected number of randomised patients. Centres may be discontinued from the study if recruitment rates are poor and new centres may be added if necessary to achieve recruitment goals.

Reason for Amendment:

Labelling and therapeutic use of DPP-IV inhibitors is different by regions. Conditions are updated to follow the change of approved indications of sitagliptin in the European Union. Formerly approved for combination therapy only, sitagliptin was approved in September 2009 by the European Commission for use as monotherapy when metformin is inappropriate due to contraindications or intolerance.

3. Section of protocol affected:

3.1.5 Randomisation and Double-blind Treatment Period

Previous text:

The investigator should inform the study physician of any changes in antihypertensive medication during the first 8 weeks.

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

Revised text:

After week 8, changes in antihypertensive medication may be made as needed for appropriate blood pressure management. All medication changes, including dose modifications, **and the last blood pressure value measured before a medication change** should be recorded in the eCRF.

Reason for Amendment:

The sentence about informing the study physician is deleted to avoid misunderstanding. There is no need to contact the Study Physician directly. Information about medication changes is to be recorded in the eCRF where it is available for review by the Study Physician.

Wording is added to ensure that the last blood pressure value measured before the change of medication is recorded in the eCRF.

4. Section of protocol affected:

Table 4 Study Plan

Previous text:

	Screening	**Enrolment**	**Dose-stabilisation period**		**Placebo lead-in**	**24-week double-blind treatment period**						**24-week site- and patient-blinded extension period**			**Follow-up visit**	**Rescue visit**
Visit	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**R**
Week	**-15**	**-13**	**-12**	**-8**	**-2**	**0**	**4**	**8**	**12**	**18**	**24**	**32**	**40**	**48**	**51**	
Visit window (days) [e]	(+7)	(0)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±3)	
Dispense open-label sitagliptin and/or metformin			X	**X**	X	**X**	**X**	X	**X**	X	**X**	**X**	X			

Revised text:

	Screening	**Enrolment**	**Dose-stabilisation period**		**Placebo lead-in**	**24-week double-blind treatment period**						**24-week site- and patient-blinded extension period**			**Follow-up visit**	**Rescue visit**
Visit	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**R**
Week	**-15**	**-13**	**-12**	**-8**	**-2**	**0**	**4**	**8**	**12**	**18**	**24**	**32**	**40**	**48**	**51**	
Visit window (days) [e]	(+7)	(0)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±3)	
Dispense open-label sitagliptin and/or metformin			X		X			X		X			X			

Reason for Amendment:

Dispensing of open-label medication is not required at Visits 3, 5, 6, 8, 10 and 11 as it has been adjusted to pack sizes.

5. Section of protocol affected:

4.1 Inclusion criteria

Previous text:

4. Current antihyperglycaemic treatment:

- Drug naïve (defined as no antihyperglycaemic therapy at.for at least 10 weeks prior to enrolment), or
- Ongoing treatment with sitagliptin monotherapy 100 mg QD for at least 10 weeks prior to enrolment, or
- Ongoing treatment with vildagliptin monotherapy 50 mg BID for at least 10 weeks prior to enrolment, or
- Ongoing treatment with metformin IR or XR monotherapy ≥1500 mg/day for at least 10 weeks prior to enrolment, or
- Ongoing treatment with metformin IR or XR ≥1500 mg/day plus sitagliptin 100 mg/day for at least 10 weeks prior to enrolment, or
- Ongoing treatment with metformin IR or XR ≥1500 mg/day plus vildagliptin 50 mg BID for at least 10 weeks prior to enrolment.
- Treatment with OADs other than those listed above within the 10 weeks prior to enrolment is not permitted.

Revised text:

4. Current antihyperglycaemic treatment:

a) Drug naïve (defined as no antihyperglycaemic therapy for at least 10 weeks prior to enrolment), or

b) Ongoing treatment with sitagliptin monotherapy 100 mg QD for at least 10 weeks prior to enrolment, or

c) Ongoing treatment with vildagliptin monotherapy 50 mg BID for at least 10 weeks prior to enrolment, or

d) Ongoing treatment with metformin IR or XR monotherapy ≥1500 mg/day **at a stable dose** for at least 10 weeks prior to enrolment, or

e) Ongoing treatment with metformin IR or XR ≥1500 mg/day **at a stable dose** plus sitagliptin 100 mg/day for at least 10 weeks prior to enrolment, or

f) Ongoing treatment with metformin IR or XR ≥1500 mg/day **at a stable dose** plus vildagliptin 50 mg BID for at least 10 weeks prior to enrolment.

Treatment with OADs other than those listed above within the 10 weeks prior to enrolment is not permitted.

Criteria a), b) and c) are not applicable in countries where DPP-IV inhibitors are not approved as monotherapy . Criteria a) and c) are not applicable in countries where sitagliptin monotherapy is approved in patients who are not eligible for metformin due to contraindications or intolerance.

Investigators must confirm that patients who are receiving sitagliptin monotherapy at enrolment qualify for sitagliptin monotherapy according to local labeling guidelines.

Reason for Amendment:

To emphasize that doses of metformin must be stable during the 10 weeks before enrolment.

To allow treatment with sitagliptin monotherapy in the study according to locally approved indications only.

6. Section of protocol affected:

4.1 Inclusion criteria

Previous text:

5. HbA1c:
At enrolment (Visit 1) and at the start of the dose-stabilisation period (Visit 2):

- ≥7.2% and ≤10.0% for patients entering the study on sitagliptin100 mg QD or vildagliptin 50 mg BID monotherapy, sitagliptin 100 mg QD plus metformin ≥1500 mg/day or vildagliptin 50 mg BID plus metformin ≥1500 mg/day

- ≥7.7% and ≤10.5% for patients who are drug naïve or who are treated with metformin ≥1500 mg/day monotherapy

At the start of the placebo lead-in period (Visit 4) and at the randomisation visit (Visit 5):

- − ≥7.0% and ≤10.0% for all patients

Revised text:

5. HbA1c:
At enrolment (Visit 1) and at the start of the dose-stabilisation period (Visit 2) - ***laboratory values from Screening Visit and Visit 1****:*

- ≥7.2% and ≤10.0% for patients entering the study on sitagliptin100 mg QD or vildagliptin 50 mg BID monotherapy, sitagliptin 100 mg QD plus metformin ≥1500 mg/day or vildagliptin 50 mg BID plus metformin ≥1500 mg/day

- ≥7.7% and ≤10.5% for patients who are drug naïve or who are treated with metformin ≥1500 mg/day monotherapy

At randomisation (Visit 5) ***– laboratory value from Visit 4****:*

- – ≥7.0% and ≤10.0% for all patients

Reason for Amendment:

To clarify which laboratory values apply at visits where inclusion criteria will be assessed.

7. Section of protocol affected:

4.1 Inclusion criteria

Previous text:

The following criteria apply to the enrolment, dose-stabilisation period, placebo lead-in and randomisation visits (Visits 1, 2, 4, and 5). Exceptions are noted below.

Revised text:

The following criteria apply to the enrolment (Visit 1). Exceptions are noted below.

Reason for Amendment:

To clarify at which visits the criteria apply.

8. Section of protocol affected:

4.1 Inclusion criteria

Previous text:

6. Women of childbearing potential who comply with the following:

- Use an adequate method of contraception to avoid pregnancy throughout the study and for up to 4 weeks after the study in such manner that the risk of pregnancy is minimized. Adequate methods of contraception are: oral contraceptives; Norplant

implants; Depo-Provera injections; intrauterine devices; barrier methods (diaphragm, cervical cap or condom) when used in combination with a spermicide

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

Women of childbearing potential are defined as:

- Any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥12 consecutive months or serum follicle stimulating hormone level >40 mIU/mL)

- Women who are using oral, implanted or injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (eg, vasectomy), should be considered to be of child-bearing potential.

Revised text:

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

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

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

Definitions:

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

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

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

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

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

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

Reason for Amendment:

The word "serum" is deleted to clarify that only urine pregnancy testing is performed for the study.

Recently, an AstraZeneca guidance document was published that provides definitions for women of childbearing potential, women not of childbearing potential, and postmenopausal women. The protocol is updated with the definitions contained in the new guidance.

9. Section of protocol affected:

4.2 Exclusion criteria

Previous text:

The following criteria apply to the enrolment, dose-stabilisation period, placebo lead-in and randomisation visits (Visits 1, 2, 4, and 5). Exceptions are noted below.

Revised text:

The following criteria apply to the enrolment (Visit 1) and randomisation visits (Visit 5). Laboratory value criteria apply at the start of dose-stabilisation period (Visit 2, using laboratory values from Visit 1) Exceptions are noted below.

Reason for Amendment:

To clarify at which visits the criteria apply.

10. Section of protocol affected:

4.2. Exclusion criteria

Previous text:

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

Revised text:

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

Reason for Amendment:

To allow patients with successfully treated in situ cervix carcinoma to enter the study.

11. Section of protocol affected:

4.2. Exclusion criteria

Previous text:

25. Creatinine Kinase (CK) >3X ULN

Revised text:

25. Creatine Kinase (CK) >3X ULN

Reason for Amendment:

To correct typographical error.

12. Section of protocol affected:

4.4.1. Criteria for discontinuation from the study

Study-specific discontinuation criteria

Previous text

16. Increase of ALT and/or AST >3x ULN **and** increase of TB>1.5x ULN confirmed at a repeated measurement within one week, see Section 4.4.2.

17. Increase of ALT or AST >5x ULN confirmed at a repeated measurement within one week, see Section 4.4.2.

Revised text

16. 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 I for further guidance**. Patients should be discontinued from study if the initial **and** repeat laboratory tests meet any of the following criteria:

A) ALT and/or AST are >3x ULN **and** TB>1.5x ULN
B) ALT and/or AST are >5x ULN for ≥ 14 consecutive days, at any time after initial confirmatory results
C) ALT and/or AST are >8x ULN.

Reason for Amendment:

The purpose of this amendment is to expand existing procedures for the ongoing review of hepatic laboratory tests and hepatic events. A recent observation of the dapagliflozin program safety database revealed a slightly higher incidence of aminotransaminase elevations in dapagliflozin-treated subjects compared with placebo. An internal expert panel was convened which recommended implementation of additional hepatic laboratory monitoring across the program. Using the US Food and Drug Administration (FDA) Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009) as a reference, this amendment describes the changes being implemented in addition to the routine safety surveillance procedures already in place.

13. Section of protocol affected:

4.4.2 Procedures for discontinuation of a patient from the study

Previous text:

Patients with increased liver function tests as defined in Section 4.4.1 under listings (16) and (17) will have their investigational product and open-label metformin held and have repeat liver function tests within one week. If repeat liver function tests still are increased as outlined in Section 4.4.1 under listings (16) and (17), the patient should permanently discontinue all study medication and be withdrawn from the study (in which case an Adverse Event must be reported). Otherwise investigational product and open-label metformin may be resumed unless otherwise contraindicated.

Revised text:

Patients with increased liver function tests as defined in Section 4.4.1 under listing (16) 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 I for further guidance. If repeat liver function tests still are increased as outlined in Section 4.4.1 under listing (16), the patient should permanently discontinue all study medication and be withdrawn from the study (see Appendix I for further guidance).

Reason for Amendment:

The purpose of this amendment is to expand existing procedures for the ongoing review of hepatic laboratory tests and hepatic events. A recent observation of the dapagliflozin program safety database revealed a slightly higher incidence of aminotransaminase elevations in dapagliflozin-treated subjects compared with placebo. An internal expert panel was convened which recommended implementation of additional hepatic laboratory monitoring across the program. Using the US Food and Drug Administration (FDA) Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009) as a reference, this amendment describes the changes being implemented in addition to the routine safety surveillance procedures already in place.

14. Section of protocol affected:

5.4.1. Identity of investigational products and additional drugs

Previous text:

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
Sitagliptin 100 mg	Light beige, round shaped tablet with "112" on one side and plain on the other side, 100 mg	Merck or designee
Glucophage® (metformin hydrochloride, immediate release) 500 mg	Film coated, white to off-white round tablet, 500 mg	Merck or designee
Glimepiride 2 mg	Green, oblong shaped tablet with a break line on both sides, 2 mg. (Size approx. 11 x 5.5 mm)	Actavis or designee or prescribed by investigator if feasible

Revised text:

Investigational Product / Study Drug / Rescue Medication	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
Sitagliptin 100 mg	Light beige, round shaped tablet with "112" on one side and plain on the other side, 100 mg	Merck or designee
Glucophage® (metformin hydrochloride, immediate release) 500 mg	Film coated, white to off-white round tablet, 500 mg	Merck or designee
Glimepiride 2 mg	**2 mg tablet**	**Determined by which brand is registered and available locally on the market**

Reason for Amendment:

To correct wording: sitagliptin and metformin are not Investigational Products but Study Drugs; glimepiride is Rescue Medication.

To allow use of any brand of glimepiride 2 mg tablets registered in the participating countries.

15. Section of protocol affected:

5.4.2 Doses and treatment regimens

Previous text:

None.

Revised text:

Drug dispensing scheme:

Visit ID	No. of bottles to dispense of dapagliflozin 10 mg or matching placebo[a]	No. of commercial packs to be dispensed of sitagliptin 100 mg, open label[b]	No. of commercial packs to be dispensed of metformin 500 mg, open label[c] (Stratum 2 only)
Visit 1	N/A	N/A	N/A
Visit 2	N/A	1 commercial pack	3-4 commercial packs
Visit 3	N/A	N/A	N/A
Visit 4	1 bottle (Lead-In)	1 commercial pack	3-4 commercial packs
Visit 5	1 bottle	N/A	N/A
Visit 6	1 bottle	N/A	N/A
Visit 7	1 bottle	1 commercial pack	3-4 commercial packs
Visit 8	2 bottles	N/A	N/A
Visit 9	2 bottles	2 commercial packs	5-9 commercial packs
Visit 10	2 bottles	N/A	N/A
Visit 11	2 bottles	N/A	N/A
Visit 12	2 bottles	1 commercial pack	3-4 commercial packs
Visit 13	N/A	N/A	N/A
Visit 14	N/A	N/A	N/A

[a] Each bottle contains 35 tablets.
[b] Each commercial pack contains 98 or 100 tablets.
[c] Each commercial pack contains 100 tablets.

Reason for Amendment:

Drug Dispensing Scheme is added to aid correct dispensing.

16. Section of protocol affected:

5.5 Concomitant and post-study treatment(s)

Previous text:

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

Revised text:

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

Reason for Amendment:

The total daily dose of insulin will also be required to be recorded in the eCRF.

17. Section of protocol affected:

5.6 Treatment compliance

Previous text:

The administration of all medication (including investigational products) must be recorded in the appropriate sections of the Case Report Forms.

Revised text:

The administration of all medication (including investigational **product**) must be recorded in the appropriate sections of the Case Report Forms.

Reason for Amendment:

To correct typographical error.

18. Section of protocol affected

6.3.5 Laboratory safety assessment

Previous text:

None.

Revised text:

Table 7 Safety laboratory variables, footnote "f)" to FSH:

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

Reason for Amendment:

A footnote is added to specify which patients will require an FSH level.

19. Section of protocol affected

6.3.8.1 Pulse and blood pressure

Previous text:

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. A standard mercury sphygmomanometer with a standardized cuff adapted to the size of the patient's arm should be used (oscillometric devices such as Dinemap may be used, but must be calibrated every 6 months with a mercury sphygmomanometer. Aneroid devices should not be used). All three BP readings should be recorded. At Visit 1, before entry into the dose-stabilisation or placebo lead-in periods, the seated BP will be recorded three times in both the left and the right arms. All three measurements should be made in one arm before transferring the cuff to the other arm. The arm with the highest mean seated BP readings will be the one used for all subsequent readings. The average of the three BP readings will be used for study analyses. BP readings should be taken while the patient is in a comfortable seated position with the arm supported at the level of the heart. All readings should be recorded. Ideally, blood pressure should be measured with the same machine, at the same time of day, and by the same personnel at each visit.

Revised text:

Pulse and blood pressure measurements will be performed before blood samples are taken. One pulse measurement will be taken after the patient has been sitting and resting for at least 5 minutes. The pulse measurement will be followed by three blood pressure (BP) measurements separated by 2 minutes each. All three BP readings should be recorded. At Visit 1, before entry into the dose-stabilisation or placebo lead-in periods, the seated BP will be recorded three times in both the left and the right arms. All three measurements should be made in one arm before transferring the cuff to the other arm. The arm with the highest mean seated BP readings will be the one used for all subsequent readings. The average of the three BP readings will be used for study analyses. BP readings should be taken while the patient is in a comfortable seated position with the arm supported at the level of the heart. All readings should be recorded. Ideally, blood pressure should be measured with the same machine, at the same time of day, and by the same personnel at each visit.

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

- a mercury sphygmomanometer is not available, or

- a mercury sphygmomanometer is available, but site staff is not practiced in its use

- use of mercury devices is restricted by local law.

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

Reason for Amendment:

To ensure that pulse and blood pressure measurements are performed before blood samples are taken.

Sale of all mercury containing measuring devices has been restricted under Directive 2007/51/EC of the European Parliament and of the Council with effect from 3 April 2009. Investigational site qualifications revealed that mercury sphygmomanometers are not in use in many centres. The text has been amended to adjust requirements to local practices and at the same time ensure accuracy of measurements by requiring appropriate calibration of oscillometric devices.

20. Section of protocol affected:

6.3.8.2 Orthostatic blood pressure

Previous text:

Supine BP and pulse

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

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

Revised text:

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 **2 minutes apart**. All three readings must be recorded. For study analyses, the average of the three BP and pulse readings will be used.

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

Reason for Amendment:

To eliminate inconsistency in time between repeat measurements.

21. Section of protocol affected:

6.3.14 Liver function test abnormalities

Previous text:

Please see section 4.4.2, "Procedures for discontinuation of a patient from the study."

Revised text:

Please see Appendix I for further guidance.

Reason for Amendment:

The purpose of this amendment is to expand existing procedures for the ongoing review of hepatic laboratory tests and hepatic events. A recent observation of the dapagliflozin program safety database revealed a slightly higher incidence of aminotransaminase elevations in dapagliflozin-treated subjects compared with placebo. An internal expert panel was convened which recommended implementation of additional hepatic laboratory monitoring across the program. Using the US Food and Drug Administration (FDA) Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009) as a reference, this amendment describes the changes being implemented in addition to the routine safety surveillance procedures already in place.

22. Section of protocol affected:

6.4.8 Liquid Meal Tolerance Test (MTT)

Previous text:

- Subject fasted for at least 10 hours prior to the visit

Revised text:

- Patient fasted for at least **12 hours** prior to the visit

Reason for Amendment:

To resolve a discrepancy in fasting time required: patients are required to be fasting for 12 hours before safety and efficacy blood sampling, which will occur at the same time as Time 0 of the MTT.

23. Section of protocol affected:

8.3. Ethics and Regulatory review

Previous text:

An Ethics Committee must approve the final study protocol, including the final version of the Informed Consent Form and any other written information to be provided to the patients **eCRF**.

Revised text:

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

Reason for Amendment:

Word "eCRF" is deleted to correct typographical error.

24. Section of protocol affected:

13.2 Overdose

Previous text

An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important.

Revised text:

An overdose is defined as the accidental or intentional ingestion of any dose of **investigational** product that is considered both excessive and medically important.

Reason for Amendment:

To correct typographical error.

25. Section of protocol affected:

Clinical Study Protocol Appendix H – Dapagliflozin Overall Benefit and Risk Assessment

Previous text

Dapagliflozin Overall Benefit and Risk Assessment, dated 23 February 2009.

Revised text:

Dapagliflozin Overall Benefit and Risk Assessment, **dated**

Reason for Amendment:

The overall risk benefit assessment has been updated taking into account new information given in Investigators Brochure General Addendum 02 dated 17 July 2009. This included safety data from recently completed studies and two not yet reported studies. Detailed information are available in the updated Clinical Study Protocol Appendix H – Dapagliflozin Overall Benefit and Risk Assessment.

26. Section of protocol affected:

Clinical Study Protocol Appendix I - Algorithm on Management of Sustained Elevated Liver Safety Abnormalities

Previous text:

None.

Revised text:

See attached pages for Clinical Study Protocol Appendix I.

Reason for Amendment:

The purpose of this amendment is to expand existing procedures for the ongoing review of hepatic laboratory tests and hepatic events. A recent observation of the dapagliflozin program safety database revealed a slightly higher incidence of aminotransaminase elevations in dapagliflozin-treated subjects compared with placebo. An internal expert panel was convened which recommended implementation of additional hepatic laboratory monitoring across the program. Using the US Food and Drug Administration (FDA) Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009) as a reference, this amendment describes the changes being implemented in addition to the routine safety surveillance procedures already in place.

Clinical Study Protocol Amendment No 1
Appendix A

Drug Substance	dapagliflozin
Study Code	D1690C00010
Edition Number	1
Date	
Protocol Dated	

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A 24-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, International Phase III Study with a 24-week Extension Period to Evaluate the Safety and Efficacy of Dapagliflozin 10 mg Daily in Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on a DPP-4 inhibitor (Sitagliptin) Alone or in Combination with Metformin

This Clinical Study Protocol Amendment 1 has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this amendment.

AstraZeneca Research and Development
site representative

ASTRAZENECA SIGNATURE(S)

A 24-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, International Phase III Study with a 24-week Extension Period to Evaluate the Safety and Efficacy of Dapagliflozin 10 mg Daily in Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on a DPP-4 inhibitor (Sitagliptin) Alone or in Combination with Metformin

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I agree to the terms of this amendment.

AstraZeneca Research and Development site representative

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A 24-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, International Phase III Study with a 24-week Extension Period to Evaluate the Safety and Efficacy of Dapagliflozin 10 mg Daily in Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on a DPP-4 inhibitor (Sitagliptin) Alone or in Combination with Metformin

This Clinical Study Protocol Amendment 1 has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this amendment.

AstraZeneca Research and Development site representative

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A 24-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, International Phase III Study with a 24-week Extension Period to Evaluate the Safety and Efficacy of Dapagliflozin 10 mg Daily in Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on a DPP-4 inhibitor (Sitagliptin) Alone or in Combination with Metformin

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This Clinical Study Protocol Amendment 1 has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this amendment.

Centre No.:

Signature:

AstraZeneca

Clinical Study Protocol: Appendix H

Drug Substance	Dapagliflozin
Study Code	D1690C00010
Edition Number	1.0
Date	

Appendix H
Dapagliflozin Overall Benefit and Risk Assessment

Overall Benefits and Risks Assessment

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1. SUMMARY OF RISKS

Six clinical pharmacology studies have been completed in the dapagliflozin program. In these studies, 116 healthy subjects and 38 subjects with type 2 diabetes mellitus (T2DM) have received at least 1 single oral dose (2.5 – 500 mg and 5 – 100 mg, respectively) of dapagliflozin. Forty subjects (24 healthy volunteers [range of mean duration of exposure: 1-14 days] and 16 subjects with T2DM [mean duration of exposure: 13 days]) have received doses ≥ 100 mg of dapagliflozin. Multiple daily doses of dapagliflozin were given to 30 healthy subjects (2.5 – 100 mg) and 39 subjects with T2DM (5 – 100 mg) for up to 14 days. In a Phase 2b clinical study 279 subjects received 1 of 5 doses of dapagliflozin (2.5 mg, 5 mg, 10 mg, 20 mg or 50 mg) for 12 weeks. A second Phase 2b study is ongoing. Data from approximately 514 subjects who have been exposed to dapagliflozin indicate that it is generally safe and well tolerated at doses up to 50 mg for 12 weeks or in single doses up to 500mg.

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

1.1 Identified Risk

1.1.1 Vaginal/Vulvovaginal Infections

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

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

1.2 Potential Risks

1.2.1 Urinary Tract Infections

Dapagliflozin increases the urinary excretion of glucose, a potential substrate for urinary

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

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

1.2.2 Hypoglycemia

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

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

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

1.2.3 Dehydration/Hypovolemia/Hypotension

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

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

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

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

1.2.4 Serum electrolyte abnormalities

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

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

1.2.5 Renal impairment

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

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

1.2.6 Bone Fracture

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

In the Phase 3 program we plan to implement a bone safety monitoring plan through a combination of close monitoring of electrolytes and hormones involved in bone metabolism in all studies and the monitoring of serum biomarkers of bone metabolism in selected studies. Also, in a Phase III study of 24-month duration, dual-energy x-ray absorptiometry (DEXA) scan will be obtained periodically to evaluate bone density.

1.2.7 Increased hematocrit

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

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

1.2.8 Increased creatine phosphokinase

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

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

1.2.9 Non clinical Toxicology findings

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

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

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

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

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

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

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

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

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

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

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

2. SUMMARY OF BENEFITS

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

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

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

3. OVERALL BENEFITS AND RISKS ASSESSMENT

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

4. RECENTLY COMPLETED STUDIES

An additional phase 2b study (MB102009) has been completed and two Phase 3 studies (MB 102013 and MB 102 014) short-term treatment periods have been concluded but not yet reported. Thus, the results from these studies are preliminary.

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

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

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

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

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

AstraZeneca

Clinical Study Protocol Appendix I	
Drug Substance	dapagliflozin
Study Code	D1690C00010
Edition Number	1
Date	

Appendix I
Algorithm on Management of Sustained Elevated Liver Safety Abnormalities

ALGORITHM ON MANAGEMENT OF SUSTAINED ELEVATED LIVER SAFETY ABNORMALITIES

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

Patients with a central laboratory ALT and/or AST > 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 can not 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 etiologies. In addition, specialized blood sampling will be performed to evaluate liver function as well as identify potential causes of laboratory elevation(s). The Investigator should continue to monitor the 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 > 3xULN and TB > 1.5xULN

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

- ALT and/or AST are > 8xULN

In each of these situations, study medication will be discontinued, the Sponsor notified and the Early Termination (End-of-Treatment) visit performed within 3 days of the confirmed laboratory results (see Section 4.4.2). At the Early Termination (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 (i.e. procedures of Visit 14) 3 weeks after discontinuation of investigational product. A referral consultation to a hepatologist or gastroenterologist (specializing in liver abnormalities) should be obtained.

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

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

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

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 > 3X ULN confirmed with a repeated test will have the following performed within 3 days of the confirmed laboratory results:

- AE assessment
- Physical Examination for jaundice and other signs of liver diseases
- Review of relevant risk factors and current history focusing on possible causes of the increased ALT and/or AST and/or TB, including:
  - Use of suspect concomitant medication [including over-the-counter (i.e., acetaminophen/paracetamol), herbal and vitamin preparations]
  - Recent alcohol consumption or recreational drug/narcotic use
  - Recent unaccustomed physical exertion

  - Occupational or environmental exposure to hepatotoxins
  - Other conditions which may cause liver diseases or which may cause abnormal test results

- Specialized Liver 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

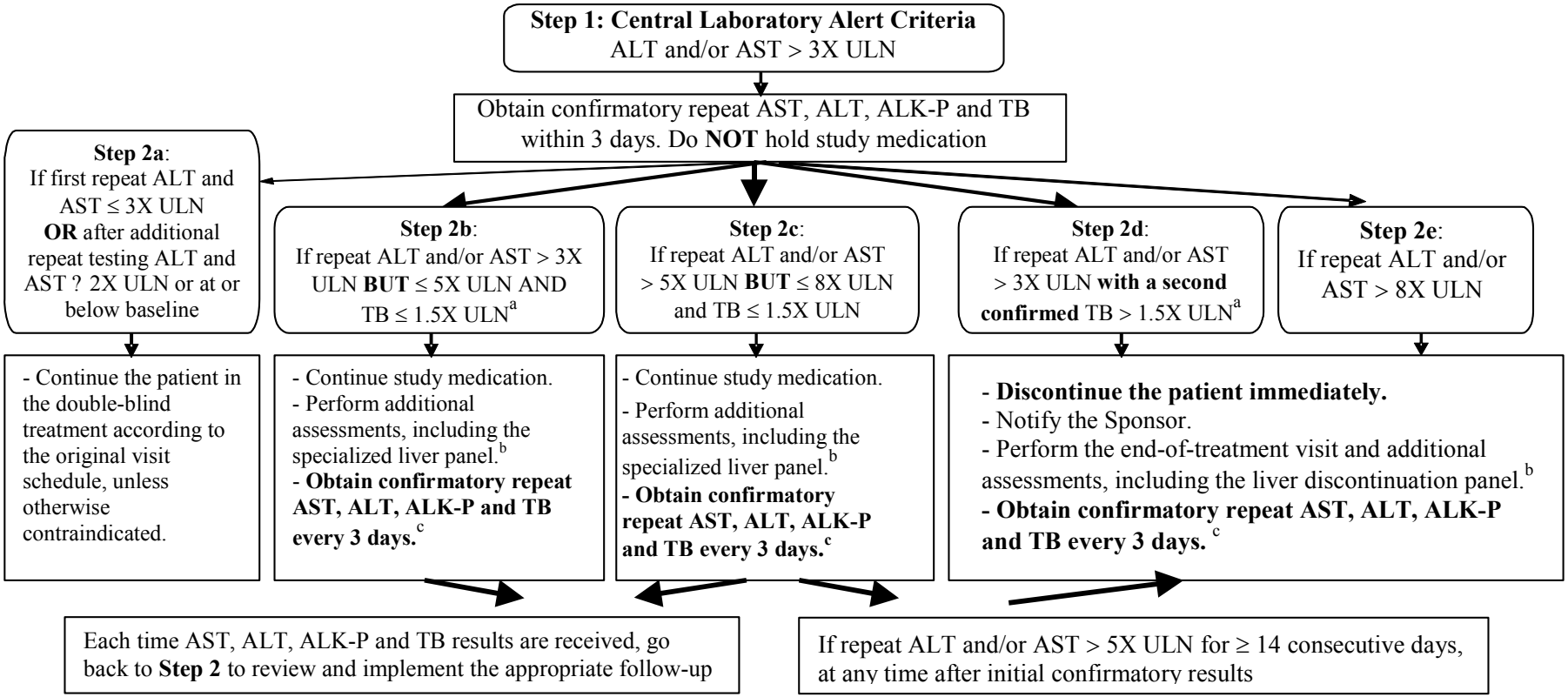
Liver Discontinuation Panel

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 Early Termination (End-of-Treatment) visit. Similar to the Specialized Liver Panel, these laboratory tests will study the possible causes of the increased ALT and/or AST and/or TB, and may include, but are not limited to, the following tests:

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

For specific details regarding the Specialized Liver Panel 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.