AstraZeneca

Revised Clinical Study Protocol

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DECLARE

Dapagliflozin Effect on CardiovascuLAR Events

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients with Type 2 Diabetes

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

AstraZeneca Research and Developmen site representative

[redacted]

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
1.0	05 Apr 2013		
2.0	19 Dec 2013		
3.0	28 Apr 2014		
4.0	Version never used		
5.0	25 Sep 2016		

PROTOCOL SYNOPSIS

DECLARE

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A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients with Type 2 Diabetes

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

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Study center(s) and number of patients planned

This international study will be conducted at approximately 1200 centers. It is estimated that approximately 27000 patients will be enrolled to reach the target of approximately 17150 randomized patients during a recruitment period of approximately 3 years.

Study period		**Phase of development**
Estimated date of first patient enrolled	Q2 2013	3b
Estimated date of last patient completed	Q2 2019	

Objectives

Primary objective

The primary objective is to determine the effect of dapagliflozin relative to placebo on cardiovascular outcomes when added to current background therapy in patients with type 2

diabetes mellitus (T2DM) with either established cardiovascular disease or at least two cardiovascular risk factors.

This objective will be evaluated in two steps. The first step will determine if dapagliflozin is non-inferior to placebo for the incidence of the composite endpoint of cardiovascular death, myocardial infarction (MI), or ischemic stroke assessed with a non-inferiority margin of 1.3.

If this is met the second step will determine if dapagliflozin reduces the incidence of the co-primary endpoints: the composite of cardiovascular death, myocardial infarction (MI), or ischemic stroke and the composite of hospitalization for heart failure or CV death compared to placebo

Secondary objective

The secondary objective is to determine whether treatment with dapagliflozin compared with placebo when added to current background therapy in patients with T2DM with either established cardiovascular disease or at least two cardiovascular risk factors in addition to T2DM will result in a reduction of:

- Renal composite endpoint: Confirmed sustained ≥40% decrease in eGFR to eGFR <60 ml/min/1.73m^2 and/or ESRD (dialysis ≥90 days or kidney transplantation, confirmed sustained eGFR <15ml/min/1.73m^2) and/or renal or CV death

- All-cause mortality

Safety objectives

Safety and tolerability will be assessed from overall adverse events, serious adverse events, adverse events of special interest, and laboratory test results. The assessment will include an evaluation of the incidence of adjudicated bladder cancer and liver injury.

Exploratory objectives

Other efficacy objectives are to determine whether treatment with dapagliflozin compared with placebo when added to current background therapy in patients with T2DM and either established cardiovascular disease or at least two cardiovascular risk factors in addition to T2DM will result in a reduction of:

- The individual components of the co-primary efficacy endpoints (cardiovascular death, MI, ischemic stroke or hospitalization for heart failure)

- The composite endpoint of cardiovascular death, MI, ischemic stroke, hospitalization for heart failure, hospitalization for unstable angina pectoris, or hospitalization for coronary or non-coronary revascularization and the additional individual components of hospitalization for unstable angina pectoris and hospitalization for coronary or non-coronary revascularization

- Glycosylated hemoglobin A1c (HbA1c)
- Initiation of insulin therapy in patients not receiving insulin therapy at baseline
- Need for any of the following: An increase in dose for an oral anti-diabetes medication, a ≥ 25% increase in insulin dose or the addition of new anti-diabetes medication for ≥ 3 months
- Major hypoglycemia and/or hospitalization for hypoglycaemia
- Development of Albuminuria
- Development of albuminuria
- Albuminuria
- Decrease in eGFR
- Albumin to Creatinine ratio
- Body weight
- Retinal laser and/or intraocular treatment due to development of and/or deterioration in diabetic retinopathy
- Blood pressure
- Peripheral revascularization/limb ischemic event
- Surgical amputation and related events
- Any stroke (ischemic, hemorrhagic, or undetermined)

[redacted]

Study design

This is a multicenter, randomized, double blind, placebo-controlled Phase 3b study to evaluate whether treatment with dapagliflozin reduces major adverse cardiovascular events in patients with T2DM and with either known cardiovascular disease or at least two risk factors for cardiovascular disease in addition to T2DM. In addition, this study will seek to definitively exclude unacceptable cardiovascular risk in these patients from dapagliflozin. All patients should

receive standard of care therapy for T2DM as well as for co-morbidities and cardiovascular risk factors (e.g., dyslipidemia, hypertension) based on accepted guidelines and local best practices.

Target patient population

Approximately 17150 patients (see Section 12.3 Determination of sample size) with documented history of established cardiovascular disease (secondary prevention) or two or more risk factors for cardiovascular disease in addition to T2DM (e.g., age, hyperlipidemia, hypertension, recent smoking history-primary prevention) will be randomized from sites throughout the world. For example, recruitment will be monitored to randomize approximately 30% of patients each from North America and Europe. The proportions of primary and secondary prevention patient populations overall and by region will be monitored to ensure a minimum of approximately 33 % of randomized patients from the secondary prevention patient population overall and to avoid large differences between regions.

Patients who are treated with any oral and/or parenteral glucose-lowering medications (with the exception of rosiglitazone, pioglitazone, and other sodium glucose cotransporter 2 [SGLT2] inhibitors) at the time of enrollment, as well as treatment naïve or non-medically treated (e.g., diet) patients will be enrolled and will receive either dapagliflozin 10 mg qd or matching placebo in addition to standard of care treatment for T2DM and co-morbidities.

Investigational product, dosage and mode of administration

Dapagliflozin 10 mg tablets administered orally once daily for a predicted median of 4.5 years and an anticipated total duration of a 6-year double-blind treatment period.

Comparator, dosage and mode of administration

Matching placebo for dapagliflozin 10 mg administered orally once daily for the 4-8 week placebo run-in period and for a predicted median of 4.5 years and an anticipated total duration of a 6-year double-blind treatment period.

Duration of treatment

The study is cardiovascular event–driven with a predicted median of 4.5 years and an anticipated total duration of 6 years.

Outcome variable(s):

Primary variables:

The co-primary outcome variables of the study are the composite endpoint of cardiovascular death, myocardial infarction, or ischemic stroke (time to first event) and the composite endpoint of hospitalization for heart failure or CV death (time to first event). All components of these composites will be adjudicated.

Secondary variables:

- Renal composite endpoint: Confirmed sustained ≥40% decrease in eGFR to eGFR <60 ml/min/1.73m^2 (using CKD-EPI equation) and/or ESRD (dialysis ≥90 days or kidney transplantation, confirmed sustained eGFR <15ml/min/1.73m^2) and/or renal or CV death (time to first event)

- All-cause mortality (time to event)

Exploratory variables:

- The individual components of the co-primary endpoints (cardiovascular death, MI, ischemic stroke, and hospitalization for heart failure) (time to first event)

- The composite endpoint of cardiovascular death, MI, ischemic stroke, hospitalization for heart failure, hospitalization for unstable angina pectoris, or hospitalization for coronary or non-coronary revascularization and the additional individual components of hospitalization for unstable angina pectoris and hospitalization for coronary or non-coronary revascularization (time to first event)

- HbA1c

- Initiation of insulin therapy in patients not receiving insulin therapy at baseline

- Need for an increase in dose for oral anti-diabetes medication or ≥25% increase in insulin dose for ≥3 months or addition of new anti-diabetes medication

- Major hypoglycemia and/or hospitalization for hypoglycaemia

- Development of confirmed sustained macroalbuminuria (UACR ≥300 mg/g) in subjects without macroalbuminuria at baseline (time to first event)

- Development of confirmed sustained albuminuria in patients without albuminuria at baseline (UACR ≥30 mg/g; time to first event)

- Regression in sustained confirmed albuminuria (defined in three ways: 1. Baseline microalbuminuria to normoalbuminuria, 2. Baseline macroalbuminuria to microalbuminuria, 3. The previous two combined) (proportions)

- eGFR (sustained confirmed decrease ≥30% to sustained confirmed eGFR <60 ml/min/1.73m^2 using CKD-EPI equation; time to first event)

- eGFR (sustained confirmed decrease ≥40% to sustained confirmed eGFR <60 ml/min/1.73m^2 using CKD-EPI equation; time to first event)

- Albumin to Creatinine Ratio (adjusted mean percent change after 2 and at 3 years)

- Change in body weight at 2 years and at 3 years

- Proportion of patients with 5% body weight loss and 10 % body weight loss after 2 years and after 3 years
- Retinal laser and/or intraocular treatment due to development of and/or deterioration in diabetic retinopathy
- Blood pressure change from baseline
- Peripheral revascularization/limb ischemic event
- Surgical amputation and related events
- Any stroke (ischemic, hemorrhagic, or undetermined)

Primary safety variable:

The primary safety variable is the composite endpoint of cardiovascular death, MI or ischemic stroke (time to first event).

Other safety variables

Safety and tolerability will be assessed from overall adverse events, serious adverse events, adverse events of special interest and laboratory test results. The assessment will include an evaluation of the incidence of bladder cancer and liver injury. All possible malignancies (excluding non-melanoma skin cancer) and liver injury will be independently adjudicated.

Statistical methods

1390 MACE events will be required to have 85% power to demonstrate superiority of dapagliflozin to placebo if the true HR is 0.85, i.e., a 15% relative risk reduction, with a one-sided alpha of 2.31%. To achieve this number of MACE events, we have designed the study with the following condition. 17150 randomized patients will be required for the study if both patients from a primary prevention population and from a secondary prevention population will be included, with an assumed annual event rate of 2.1% on placebo, and an annual withdrawal rate of 1.0% over a 3-year accrual period and 3-year minimum follow-up.

The co-primary variables are the time to first event included in the composite endpoint of cardiovascular death, MI, or ischemic stroke and the composite for hospitalization for heart failure or cardiovascular death. The primary analyses will be based on the Full Analysis Set (FAS), using events adjudicated and confirmed to meet endpoint definitions by the Clinical Event adjudication Committee (CEC). The analysis will be performed using the Cox proportional hazards model with a factor for treatment group stratified by cardiovascular risk category (established cardiovascular disease, or multiple risk factors without established cardiovascular disease), and baseline hematuria.

A closed test procedure will control for overall Type I error rate across the analyses of the primary and secondary objectives.

A Data Monitoring Committee (DMC) will be appointed jointly by the Sponsors and the academic leadership of the study. The DMC will be responsible for safeguarding the interests of the patients in the outcome study by assessing the safety of the intervention during the trial, and for reviewing the overall conduct of the trial. They will review overall safety in the trial and specifically the incidence of bladder cancers and potential drug induced liver injury (DILI) cases. In addition, the DMC will have the responsibility to assess the data at the 2 interim analyses occurring when 1/3 and 2/3 of the MACE events have accumulated, and make recommendations based upon stopping guidelines.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ACS	Acute coronary syndrome
AE	Adverse event (see definition in Section 6.4.2)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ANCOVA	Analysis of Covariance
AZ	AstraZeneca
BMI	Body Mass Index
BMS	Bristol-Myers Squibb
CBC	Complete blood count
CEC	Clinical Event Adjudication Committee
CI	Confidence Interval
CrCl	Creatinine Clearance
CRF	Case Report Form (electronic/paper)
CRO	Contract Research Organization
CSA	Clinical Study Agreement
CT	Computed Tomography
CV	Cardiovascular
DAE	Discontinuation of Investigational Product due to Adverse Event
DBP	Diastolic blood pressure
DES	Data Entry Site
DILI	Drug induced liver injury
DMC	Data Monitoring Committee
DMG	Data Monitoring Group (Cognizant)
DNA	Deoxyribonucleic acid
DXA	Dual energy x-ray absorptiometry

Abbreviation or special term	Explanation
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
Ecode	Enrollment Code
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EoT	End of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GPV&E	Global Pharmacovigilance and Epidemiology (BMS)
GRAND	Global Randomization system
HbA1c	Glycosylated hemoglobin A1c
HR	Hazard Ratio
HsCRP	High sensitivity C-reactive protein
ICH	International Conference on Harmonization
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational Product
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LIMS	Laboratory Information Management System
MACE	Major adverse cardiac event
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MODY	Maturity-onset diabetes of the young
NMP-22	Nuclear Matrix Protein-22
OAD	Oral anti-diabetes medication

Abbreviation or special term	Explanation
OAE	Other Significant Adverse Event (see definition in Section 11.2.1)
PAI-1	Plasminogen activator inhibitor
[redacted]	[redacted]
POP	Project Operational Procedures
PI	Principal Investigator
SAE	Serious adverse event (see definition in Section 6.4.3).
SAP	Statistical Analysis Plan
SCSM	Supply Chain Study Management
SBP	Systolic blood pressure
SEER	Surveillance, Epidemiology and End Results
SGLT2	Sodium glucose cotransporter 2
SUSARs	Suspected Unexpected Serious Adverse Reactions
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
TIA	Transient ischemic attack
TIMI	Thrombolysis in Myocardial Infarction
USA	United States of America
UTI	Urinary tract infection
WBDC	Web Based Data Capture
WOCBP	Women of child bearing potential

1. INTRODUCTION

1.1 Background

Dapagliflozin is the first in a new class of compounds referred to as sodium glucose cotransporter 2 (SGLT2) inhibitors. SGLT2 is localized to the renal proximal tubule where it reabsorbs most of the ~180 g of glucose normally filtered through the glomeruli each day. SGLT2 inhibition therefore leads to pharmacologically controlled glucosuria. Dapagliflozin is a highly selective and reversible inhibitor of SGLT2. A pharmacokinetic half-life of 12.5 hours, due to the C-aryl glucoside-derived chemical structure, allows for the oral administration of dapagliflozin once daily. Inhibition of glucose reabsorption leads to subsequent glycemic effects, including fasting plasma glucose (FPG) lowering and ultimately, effects on hemoglobin A1c (HbA1c). The glycemic-lowering effect induced by SGLT2 inhibition is independent of the presence of insulin. Because of this insulin-independent mechanism of action, dapagliflozin is expected to have consistent effects on glycemic control in a wide spectrum of patients with T2DM, whether used as monotherapy at an early stage of disease or in combination with other oral anti-diabetes drugs (OADs) and/or insulin at a later stage, and may also be more likely to maintain its efficacy over time.

More than 85% of patients with T2DM are overweight or obese, which also perpetuates the disease (Campbell 2009). Additional weight gain further augments insulin resistance and negatively impacts cardiovascular risk factors such as hypertension and dyslipidemia. Efforts by patients to lose weight as part of a therapeutic lifestyle program can be undermined by therapies that lead to weight gain, such as thiazolidinediones (TZDs), sulfonylureas (SUs), or insulin. Hypoglycemia is also a clinically important barrier to optimizing treatment with insulin and SUs, both of which are second-line options in current treatment algorithms. Hypertension (JNC-7 2004) and dyslipidemia (Gastaldelli A et al 2007) commonly coexist with T2DM and are risk factors for both micro and macrovascular complications. The UKPDS (UKPDS 1998) and HOT (Hanson L 1999) trials demonstrated reductions in cardiovascular events among patients with T2DM when treated to blood pressures of approximately 140/80 to 85 mmHg, and substantial benefits have been seen when multiple risk factors in combination are addressed. Despite these data, more than 50% of patients fail to achieve target values for blood pressure, and only ~12% meet combined target values for blood pressure, low-density lipoprotein cholesterol, and glucose. Efforts to identify new treatment paradigms that are independent of insulin and have a potentially positive impact on weight and blood pressure and little or no negative effect on lipids have led to the development of dapagliflozin.

1.1.1 Cardiovascular data on dapagliflozin

Anti-diabetes medications have been proven to reduce microvascular complications, but the reduction of macrovascular complications (myocardial infarction and stroke) remains elusive. A meta-analysis of 145 adjudicated cardiovascular (CV) events from the comprehensive Phase 2b and 3 dapagliflozin clinical program (Cardiovascular events meta-analysis report: Dapagliflozin) resulted in an estimate for the hazard ratio for dapagliflozin versus comparator for the primary composite endpoint(adjudicated CV death, myocardial infarction, stroke or hospitalization for

unstable angina) of 0.819 (95% Confidence Interval (CI): 0.583, 1.152). The estimated incidence rate ratio versus comparator was 0.820, 0.527 and 0.757 for 2.5, 5 and 10 mg dapagliflozin, respectively. The results of the secondary composite endpoint and other sensitivity analyses (including the major adverse cardiovascular events [MACE] of CV death, MI and stroke only) were consistent with the primary result**.** These hypothesis-generating data, along with an overall positive benefit-risk profile for dapagliflozin and positive effects on CV risk factors as described below in Section 1.1.2 "Effect of dapagliflozin on CV risk factors", indicate that dapagliflozin treatment may lower CV risk in patients with T2DM.

1.1.2 Effect of dapagliflozin on cardiovascular risk factors

1.1.2.1 Effect on blood pressure

Blood pressure reductions were expected in the dapagliflozin Phase 3 program due to the mode of action of SGLT2 inhibition, which is associated with an osmotic diuretic and natriuretic effect. Because the studies were primarily designed to evaluate glycemic and body weight endpoints, and were not designed to rigorously evaluate blood pressure efficacy, background antihypertensive medications were not controlled. Change in systolic blood pressure (SBP) and diastolic blood pressure (DBP) in overall study populations was primarily analyzed as a safety endpoint due to the potential risks of hypotension and hypovolemia, and as an exploratory efficacy variable in select studies. Exploratory efficacy analyses for SBP were pre-specified in 4 of the 11 Phase 3 studies and analyzed post hoc for the remainder of the studies to evaluate consistency of effect across the program.

Change in SBP and DBP in patients with baseline SBP >140 mmHg was a pre-specified exploratory efficacy endpoint in the majority of the Phase 3 dapagliflozin studies. Patients in this subgroup meet JNC-7 criteria for stage 1 hypertension and are expected to gain the greatest benefit from reductions in blood pressure. Although there were few patients in this subgroup (n=32 to 123 per treatment group), modest SBP reductions were observed. In the three add-on combination therapy studies in the Phase 3 dapagliflozin program, SBP decreases versus placebo ranged from -2.8 mmHg to -4.9 mmHg in the 10 mg groups.

In all of the Phase 3 monotherapy and placebo-controlled add-on combination therapy studies, numerical reductions versus placebo in SBP were observed in the dapagliflozin treatment groups. Placebo-corrected changes in SBP ranged from -1.3 mmHg to -5.3 mmHg for patients treated with dapagliflozin 10 mg. Similar reductions in SBP were observed in the active comparator and initial combination therapy studies. In both subgroups (SBP >140 mmHg and SBP ≤ 140 mmHg), dapagliflozin 2.5, 5, and 10 mg resulted in placebo-corrected SBP and DBP reductions; reductions in both SBP and DBP appeared to be greater in the hypertensive subgroup.

1.1.2.2 Effect on body weight and composition

Dapagliflozin, with its unique mechanism of action leading to persistent loss of calories in the urine and subsequent negative energy balance, causes a body weight loss with reduction in total body fat. In the 6 placebo controlled studies in the dapagliflozin Phase 3 program, the placebo-corrected mean weight reductions over 24 weeks ranged from -0.46 to -2.16 kg and were statistically significant for the 5 and 10 mg doses of dapagliflozin in all but one study. In patients

receiving stable doses of metformin and SU, dapagliflozin 5 and 10 mg induced a statistically significant reduction in weight compared to placebo over 24 weeks. Dapagliflozin added to insulin also resulted in significant weight loss compared to placebo-treated patients. Patients treated with pioglitazone and placebo gained 1.64 kg during the 24 weeks of the study period, while the weight of patients treated with pioglitazone and dapagliflozin remained close to baseline. When directly compared to SU, treatment with dapagliflozin resulted in weight loss of -3.22 kg versus weight gain of 1.44 kg with glipizide on metformin background. A significantly greater proportion of patients in the dapagliflozin group (33.3%), compared to glipizide (2.5%), experienced body weight loss by at least 5% from baseline to Week 52. Treatment with dapagliflozin 5 or 10 mg in combination with metformin also resulted in greater mean reductions in total body weight at 24 weeks compared to treatment with metformin alone. The type of weight loss achieved is of clinical importance as total body fat correlates positively with key CV risk factors, most strongly with insulin resistance (Vega GL 2006). Study D1690C00012 was designed to address this question, with reduction in total body weight as the primary endpoint. Treatment with dapagliflozin 10 mg as add-on to metformin in patients with treatment failure on metformin resulted in a statistically significant mean weight reduction of -2.08 kg ($p<0.0001$) compared to placebo plus metformin. The majority of weight loss was attributable to a reduction in total body fat mass, as measured by dual energy X-ray absorptiometry (DXA). A statistically significant mean placebo-corrected reduction of 1.5 cm in waist circumference was observed in the dapagliflozin group, consistent with the reduction in body weight and loss of body fat mass. The proportion of patients attaining a weight loss of 5% or more was also statistically significantly greater in the dapagliflozin group (30.5%) compared to the placebo group (4.3%).

Exploratory analyses in Study D1690C00012 also showed favorable effects on the distribution of body mass. Due to the relatively greater amount of fat loss in patients treated with dapagliflozin versus placebo, there was an increase in the percentage of lean tissue mass relative to total body weight in the dapagliflozin treated patients (difference between treatment groups of 0.9% as measured by DXA). An exploratory analysis in a subset of patients utilizing magnetic resonance imaging suggested that the decrease in body fat mass was partly attributable to a decrease in visceral adipose tissue, which is associated with abnormalities in glucose and lipid metabolism (Gastaldelli A et al 2007); an approximately 10% reduction in visceral adipose tissue volume was observed in the dapagliflozin group compared to a <1.5% change in the placebo group.

1.1.2.3 Effect on lipids

Fasting lipids were an exploratory efficacy variable in all of the Phase 3 studies with the exception of D1690C00012. No consistent treatment effect was observed for changes in total cholesterol or free fatty acids; small numerical increases in high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), and decreases in triglycerides (TG) were observed across the studies. Placebo-corrected adjusted mean percent changes for dapagliflozin 10 mg ranged across short-term studies as follows: 2.0 to 6.5 for HDL-C, -0.9 to 10.6 for LDL-C, and -10.8 to 1.4 for TG.

1.1.2.4 Effect on uric acid and inflammatory markers

Uric acid has been implicated as a cardiovascular risk marker (Heinig M et al 2006). Uric acid concentrations decreased in all dapagliflozin groups; placebo-corrected mean reductions ranged from -0.45 to -0.8 mg/dL (-26.77 to -47.58 µmol/L) and in the initial combination therapy studies, mean reductions were -0.75 and -0.72 mg/dL (-44.61 to -42.83 µmol/L). Mean baseline uric acid concentrations in all groups were approximately 5 mg/dL.

No consistent pattern was seen for other inflammatory biomarkers including high sensitivity C-reactive protein (hsCRP), plasminogen activator inhibitor-1 (PAI-1), and fibrinogen.

1.2 Research hypothesis

The goal of this study is to determine the effect of dapagliflozin on CV outcomes relative to placebo. As discussed in Section 3.2, hypothesis-generating data derived from a meta-analysis of the Ph2b and 3 adjudicated MACE and hospitalization for heart failure suggests a possible favorable effect of dapagliflozin on CV risk.

1.3 Rationale for conducting this study

CV disease is the major cause of mortality and an important cause of morbidity in patients with T2DM. While epidemiological data suggest that poor glycemic control is linked to an increased CV risk, so far, clinical trials have failed to definitively demonstrate that glucose lowering reduces this risk. Data from several large outcome studies demonstrated no significant reduction in CV risk with intensive glycemic control (Duckworth et al 2009, Skyler et al 2009, ACCORD Study Group 2008). Furthermore, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study showed increased mortality in patients receiving intensive glycemic control with a target HbA1c of <6% (Skyler et al 2009, ACCORD Study Group 2008). Thus, an anti-diabetes therapy that provides reduced CV risk in addition to glucose lowering properties may be of great importance to clinical care of patients with T2DM. Preliminary, hypothesis-generating data from the Phase 2b and 3 program as well as the beneficial effects of dapagliflozin on CV risk factors (i.e., body weight, visceral adiposity, blood pressure) as described above in Section 1.1.2 suggest that dapagliflozin may have a CV protective effect. The purpose of this Phase 3b clinical study is to determine the effect that dapagliflozin has on the incidence of the composite endpoints MACE (CV death, MI, and ischemic stroke) and the composite of CV death or hospitalization for heart failure in patients with T2DM compared to placebo.

1.4 Benefit/risk and ethical assessment

For an overall risk/benefit assessment of dapagliflozin, see the Investigator's Brochure/package leaflet.

The results from the completed and ongoing studies in the dapagliflozin Phase 2b/3 program in over 6,000 patients combined with the results from clinical pharmacology studies support the oral dose of dapagliflozin 10 mg once daily in a wide range of patients with T2DM, as either monotherapy, or add-on combination therapy with metformin, a sulphonylurea, Dipeptidyl peptidase-4 (DPP4) inhibitor or insulin.

At the time of writing this clinical study protocol no available anti-diabetes agents are indicated for CV risk reduction in patients with T2DM. The Phase 2b/3 program has not only established the efficacy and safety of dapagliflozin in lowering glucose concentrations (as assessed by HbA1c) but also provided hypothesis-generating data suggesting lower incidence of MACE with dapagliflozin treatment. This clinical study will test this hypothesis in a rigorous fashion. The potential results of such a study may offer substantial benefit to patients with T2DM.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective is to determine the effect of dapagliflozin relative to placebo on cardiovascular outcomes when added to current background therapy in patients with type 2 diabetes mellitus (T2DM) with either established cardiovascular disease or at least two cardiovascular risk factors.

This objective will be evaluated in two steps. The first step will determine if dapagliflozin is non-inferior to placebo for the incidence of the composite endpoint of cardiovascular death, myocardial infarction (MI), or ischemic stroke assessed with a non-inferiority margin of 1.3. If this is met the second step will determine if dapagliflozin reduces the incidence of the co-primary endpoints: the composite of cardiovascular death, myocardial infarction (MI), or ischemic stroke and the composite of hospitalization for heart failure or CV death compared to placebo.

2.2 Secondary objectives

The secondary objective is to determine whether treatment with dapagliflozin compared with placebo when added to current background therapy in patients with T2DM with either established cardiovascular disease or at least two cardiovascular risk factors in addition to T2DM will result in a reduction of:

- Renal composite endpoint: Confirmed sustained ≥40% decrease in eGFR to eGFR <60 ml/min/1.73m^2 and/or ESRD (dialysis ≥90 days or kidney transplantation, confirmed sustained eGFR <15ml/min/1.73m^2) and/or renal or CV death
- All-cause mortality

2.3 Safety objectives

Safety and tolerability will be assessed from overall adverse events, serious adverse events, adverse events of special interest and laboratory test results. The assessment will include an evaluation of the incidence of adjudicated bladder cancer and liver injury.

2.4 Exploratory objectives

Other efficacy objectives are to determine whether treatment with dapagliflozin compared with placebo when added to current background therapy in patients with T2DM and either established cardiovascular disease or at least two cardiovascular risk factors in addition to T2DM will result in a reduction of:

- The individual components of the co-primary efficacy endpoints (cardiovascular death, MI, ischemic stroke or hospitalization for heart failure)
- The composite endpoint of cardiovascular death, MI, ischemic stroke, hospitalization for heart failure, hospitalization for unstable angina pectoris, or hospitalization for coronary or non-coronary revascularization and the additional individual components of hospitalization for unstable angina pectoris and hospitalization for coronary or non-coronary revascularization
- HbA1c
- Initiation of insulin therapy in patients not receiving insulin therapy at baseline
- Need for any of the following: An increase in dose for an oral anti-diabetes medication, a $\geq$ 25% increase in insulin dose, or the addition of new anti-diabetes medication for $\geq$ 3 months
- Major hypoglycemia and/or hospitalization for hypoglycaemia
- Development of macrolbuminuria
- Development of albuminuria
- Albuminuria
- Decrease in eGFR
- Albumin to Creatinine ratio
- Body weight
- Retinal laser and/or intraocular treatment due to development of and/or deterioration in diabetic retinopathy
- Blood pressure
- Peripheral revascularization/limb ischemic event
- Surgical amputation and related events

- Any stroke (ischemic, hemorrhagic, or undetermined)

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3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca (AZ) and Bristol-Myers Squibb (BMS) standard procedures.

3.1 Overall study design and flow chart

This is a multicenter, randomized, double-blind, placebo-controlled Phase 3b study to determine the effect of dapagliflozin relative to placebo on MACE and the composite of CV death or hospitalization for heart failure in patients with T2DM and with either known cardiovascular disease or at least two risk factors for cardiovascular disease in addition to T2DM. It is estimated that approximately 27000 patients will be enrolled to reach the target of 17150 randomized patients. The anticipated duration of the study is approximately 6 years, including an anticipated enrollment period of 3 years and a median follow-up period of 4.5 years. Closeout of the trial will commence when a predetermined number of adjudicated CV events required to test the study hypothesis is reached.

All patients should be treated according to regional standards of care for diabetes (HbA1c goals) and other cardiovascular risk factors (e.g., hypertension, hyperlipidemia).

The study will recruit T2DM patients at increased risk for CV events according to the two categories below:

- Patients with established CV disease (secondary prevention)
- Patients with at least 2 CV risk factors, but without established CV disease (primary prevention)

Approximately 17150 patients meeting all eligibility criteria at approximately 1200 study sites will be randomized (1:1) to receive either dapagliflozin or placebo.

Enrollment of patients based on disease state, geographic region, and gender will be monitored and may be capped to ensure adequate representation.

All potentially eligible patients will undergo an enrollment visit. Each patient will sign an Informed Consent Form (ICF) prior to having any enrollment evaluations performed. Patients who fulfill all eligibility requirements will enter into a 4 to 8 week placebo run-in period during

which they will be given placebo in a single-blind fashion (blind to patient only) and assessed for compliance (80 to 120%, unless a reason for non-compliance is judged acceptable by the Investigator).

Approximately 4 to 8 weeks after entering the run-in period, based upon Investigator discretion, patients will be expected to undergo a randomization visit. Patients may withdraw prior to the randomization visit, or be withdrawn by study staff for any reason. At this visit patients will be re-evaluated by study staff to determine if after testing performed at enrollment, after assessment of compliance, and any clinical changes that may have occurred during the run-in period, the patient remains eligible and committed to participation in the study. If for any reason, prior to or during the randomization visit the patient is no longer eligible or interested in participating in the trial, he or she will be considered a run-in failure, will not be randomized and will not have additional follow up.

If a patient is committed to participation, completes placebo run-in period and continues to meet criteria at the randomization visit, he or she will be randomized and will receive either dapagliflozin 10 mg daily or matching placebo in a double-blind fashion.

During the randomized treatment period, diet and life-style modification will continue to be reinforced.

An independent Data Monitoring Committee (DMC), a blinded independent Clinical Event adjudication Committee (CEC) (see Section 12.4) and Executive and Steering Committees (see Section 12.5) will be selected by the Sponsors and the academic leadership.

The study plan, including enrollment, randomization and follow-up visits, is outlined in Table 1. If the study would need to be prolonged to accrue the predetermined number of the primary endpoint events (1390), visits and assessments will be added according to the same schedule as described in the study plan (Table 1).

Patients will return every 6 months for assessment of events related to the objectives of the study, tolerability and safety. Assessment of treatment compliance and provision of IP will be done at these 6-month visits. In addition, phone contacts will be performed at a 3-month interval in between regular visits. Patients have the option to visit the center at these 3-month time points if desired; however, this is not required. If a patient prematurely discontinues IP, an End of Treatment (EoT) visit will be completed, with the patient continuing in the study for follow-up. Following the decision of the Executive Committee to close the trial, all Investigators will receive communication to complete a Closing Visit for both patients still being treated with investigational product (IP) and patients who have prematurely discontinued IP. The latter patients should have completed the EoT visit in connection with the discontinuation of IP and subsequently attended the scheduled visits to capture any adverse events (AEs), suspected CV events, body weight and anti-diabetes medication. Refer to Section 5.8 for details on procedures for discontinuing patients from IP.

The Investigator/qualified designee will arrange for the Closing Visit as soon as possible after the date estimated by the Executive Committee as the end-of-study date. Patients who have a regularly scheduled visit (according to Table 1) within approximately 8 weeks after the end of study date can use the scheduled visit as the closing visit.

All randomized patients, whether taking randomized IP or not, should be followed up to the end of the study for vital status, CV events and occurrence of malignancies. Vital status based on publicly available sources and local data privacy laws/practices in cases where patients have withdrawn consent will also be investigated at the study end. It is recommended that anyone being followed by regular telephone contacts or a contact at study closure attend the final visit in person. The approach taken should be registered in the eCRF, and medical records.

Visit 1 Enrollment (within 4 to 8 weeks prior to randomization)

Potentially eligible patients will undergo an enrollment visit (which should occur 4 to 8 weeks prior to the anticipated date of randomization) and following their signed informed consent, inclusion/exclusion criteria will be reviewed. Demography (date of birth, gender, race and ethnic group), prior and concomitant medication and relevant medical history will be recorded. Patients will have their vital signs (pulse and BP), height and body weight recorded along with a blood sample for laboratory assessments of HbA1c, serum creatinine, TB, ALT, and AST . [redacted] Women of childbearing potential (WOCBP) will be tested for pregnancy.

Patients will be tested for hematuria at the enrollment visit using a dipstick at the site and an urinalysis using microscopy at the central laboratory. Patients with hematuria (confirmed by microscopy) in whom no immediate or benign cause for hematuria is identified as judged by the Investigator (e.g., menstruation, kidney stone, urinary tract infection [UTI] where hematuria is subsequently resolved after successful treatment), should be referred by the Investigator to their primary care physician to consider conducting an evaluation of the hematuria for the potential existence of bladder cancer as a reason for the hematuria. The evaluation should be performed as per local standard of care and/or professional society guidance (see Appendix G for AUA guidelines). Patients who are diagnosed with bladder cancer and patients with hematuria in whom an evaluation (as judged by the Investigator) did not exclude bladder cancer are not allowed to be randomized.

Placebo run-in period (within 4 to 8 weeks prior to randomization)

Patients determined to be eligible for the study will be entered into a run-in period and will be given placebo to assess compliance. Patients also must adhere to reasonable placebo compliance in the run-in period in order to be randomized (80 – 120%, unless a reason for non-compliance is judged acceptable by the Investigator).

Diet and life-style advice will be reinforced.

If at any time during the run-in period, patients are determined to be non-compliant, develop a condition that would not meet entry criteria, laboratory assessment reveals exclusions, or the

patient chooses not to participate, the patient will be considered a run-in failure. If for any reason during the run-in period, the Investigator feels the patient is not likely to be compliant with study therapy and procedures the patient should be considered a run-in failure and not randomized. The Investigator should document the reason for run-in failure.

Visit 2 Randomization

Patients who meet all inclusion criteria and none of the exclusion criteria (described in Section 4.1) and are not run-in failures for reasons listed above will be randomized into the study at Visit 2. This visit should occur 4-8 weeks after the enrollment visit.

Patients will have the following evaluations performed: concomitant medication and additional medical history will be recorded and patients will be asked about any AEs that may have occurred since the previous visit. Patients will be asked whether they have undergone any urinary tract investigations since last visit. If a urinary tract investigation has been performed it should be recorded in the eCRF (for instructions on recording of AE's see section 6.4.4.) A physical exam will be performed. Vital signs (pulse and BP), body weight and waist and hip circumference will be recorded. WOCBP will be tested for pregnancy. Diet and life-style advice will be reinforced.

Run in medication will be returned and compliance assessed. Blood sample for laboratory measurements of CBC, serum creatinine, TB, ALT, AST, ALP, fasting serum glucose and lipids (LDL-Cholesterol, HDL Cholesterol, Triglyceride, Total Cholesterol), uric acid and electrolytes (sodium, potassium, chloride, bicarbonate, calcium, phosphorus and magnesium) will be obtained and sent to the central laboratory. A Urine sample for urinalysis including microscopy and urine albumin to creatinine ratio will be obtained and sent to the central laboratory. Biomarker [redacted] samples will be obtained where applicable.

Patients will be tested for hematuria using urine dipstick at the site. Patients who meet all criteria, but have a urine dipstick result indicative (positive or trace) of hematuria at randomization may be randomized into the study. If hematuria is confirmed by microscopy at the central laboratory, and if no immediate or benign cause is identified as judged by the Investigator (e.g., menstruation, kidney stone, urinary tract infection [UTI] where hematuria is subsequently resolved after successful treatment), patients should undergo evaluation by the investigator or another qualified professional. The evaluation may include but is not limited to tests such as urine cytology, NMP-22 or abdominal CT scans. The choice of tests should be per local standard of care and/or professional society guidance (see Appendix G for AUA guidelines).

Patients meeting all inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio to receive either 10 mg per day dapagliflozin or matching placebo Randomization will be stratified by CV risk category (established CV disease; multiple risk factors without established CV disease) and baseline hematuria status. Refer to section 5.2.1.

Telephone contacts/visits 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25 (months 3, 9, 15, 21, 27, 33, 39, 45, 51, 57, 63 and 69)

The patients will be contacted every 3 months between regular site visits by the Investigator/study site personnel to record any AEs, suspected CV events, IP status and use of concomitant medication. Patients will be asked whether they have undergone any urinary tract investigations since the last visit. If a urinary tract investigation has been performed it should be recorded in the eCRF. Patients have the option to visit the center at these time points if desired; however, this is not required. An unscheduled visit may be conducted as a result of the phone contact (e.g., to follow-up on suspected CV events).

Visits 4, 8, 12, 16, 20 and 24 (months 6, 18, 30, 42, 54 and 66)

Suspected CV events and AEs will be recorded and reported in accordance with the Event Reporting Manual. Patients will be asked whether they have undergone any urinary tract investigations since the last visit. If a urinary tract investigation has been performed it should be recorded in the eCRF. WOCBP will be tested for pregnancy. Vital signs (pulse and BP) and body weight will be taken. An optional physical examination may be performed to evaluate an AE or as judged by the Investigator. IP will be returned and compliance assessed and new bottles of IP will be dispensed via the Interactive voice response system/Interactive web response system (IVRS/IWRS). Concomitant medication will be recorded and diet and life-style advice will be reinforced.

At Visit 4 only, a blood sample for laboratory measurements HbA1c, serum creatinine, TB, ALT, AST, fasting serum glucose and lipids (LDL-Cholesterol, HDL-Cholesterol, Triglyceride, Total Cholesterol) will be obtained and sent to the central laboratory. Biomarker sampling will be obtained at Visit 4 where applicable. Urinalysis including microscopy and urine albumin to creatinine ratio will be obtained and sent to the central laboratory.

Visits 6, 10, 14, 18 and 22 (months 12, 24, 36, 48 and 60)

Suspected CV events and AEs will be recorded and reported in accordance with the Event Reporting Manual. Patients will be asked whether they have undergone any urinary tract investigations since the last visit. If a urinary tract investigation has been performed it should be recorded in the eCRF. An optional physical examination may be performed to evaluate an AE or as judged by the Investigator. Vital signs (pulse and BP), body weight, as well as blood sampling for laboratory assessments of HbA1c, CBC, fasting serum glucose and lipids (LDL-Cholesterol, HDL Cholesterol, Triglyceride, Total Cholesterol), serum creatinine, TB, ALT, AST, uric acid and ALP will be done. WOCBP will be tested for pregnancy. IP will be returned and compliance assessed and new bottles of IP via the IVRS/IWRS will be dispensed. Concomitant medication will be recorded. Urinalysis including microscopy and urine albumin to creatinine ratio will be completed. Diet and life-style advice will be reinforced.

End of Treatment Visit (completed for patients who prematurely discontinue IP)

Patients who prematurely discontinue IP will have a full assessment completed at time of discontinuation. Suspected CV events and AEs will be recorded and reported in accordance with the Event Reporting Manual. Patients will be asked whether they have undergone any urinary tract investigations since the last visit. If a urinary tract investigation has been performed it should be recorded in the eCRF. A physical examination will be performed. Vital signs (pulse and BP), body weight measurement, as well as blood sampling for laboratory assessments of HbA1c, CBC, fasting serum glucose and lipids (LDL-Cholesterol, HDL Cholesterol, Triglyceride, Total Cholesterol), serum creatinine, TB, ALT, AST, ALP, uric acid and electrolytes (sodium, potassium, chloride, bicarbonate, calcium, phosphorus and magnesium) will be done. For patients who are discontinued before Visit 4, a sample for biomarker analysis should be obtained.

WOCBP will be tested for pregnancy. IP will be returned and compliance assessed. Concomitant medication will be recorded. Urinalysis including microscopy and urine albumin to creatinine ratio will be completed. Diet and life-style advice will be reinforced.

End of treatment is not indicative of end of follow up and is not the same as withdrawn consent. Following the End of Treatment visit, patients who prematurely discontinued IP are expected to continue the regularly scheduled study visits as planned. All efforts must be made to maintain follow up according to the original visit schedule, ideally with in-person visits. If that is not possible, regular telephone follow-up should be performed according to the original visit schedule. AEs, suspected CV events, body weight and anti-diabetes medications will be recorded at these visits. AEs will be followed up (see Section 6.4.4). Lab assessment could be performed at all onsite visits also after End of Treatment as described for the scheduled study visits based on investigator judgment. All patients that discontinued IP due to predefined liver or renal criteria need to be monitored until abnormalities stabilize and the patient is asymptomatic (see Appendix D).

All efforts should be made to obtain all relevant information, including information on malignancies. Where permissible by local law, the informed consent forms will include language to grant the option to employ outside companies to assist in ascertainment of the vital status of lost patients using publicly available source.

Closing Visit (completed for all patients at the end of the study)

The Closing Visit should occur within approximately 8 weeks following the closing date as declared by the Executive Committee.

1. **Patients still on randomized IP at the time of Closing Visit -** For patients currently on randomized IP, a full assessment should be completed at the Closing Visit as described in Table 1. They comprise the following: recording of suspected CV events and AEs will be recorded and reported in accordance with the Event Reporting Manual. Patients will be asked whether they have undergone any urinary tract investigations since the last visit. If a urinary tract investigation has been performed it should be recorded in the eCRF. A

physical examination, vital signs (pulse and BP), body weight measurement, as well as blood sampling for laboratory assessments of HbA1c, CBC, fasting serum glucose and lipids (LDL-Cholesterol, HDL Cholesterol, Triglyceride, Total Cholesterol), serum creatinine, TB, ALT, AST, ALP, uric acid and electrolytes (sodium, potassium, chloride, bicarbonate, calcium, phosphorus and magnesium) will be done. Urinalysis including microscopy and urine albumin to creatinine ratio, pregnancy testing of WOCBP, recording of concomitant medication, and return of IP, including compliance assessment, will be done.

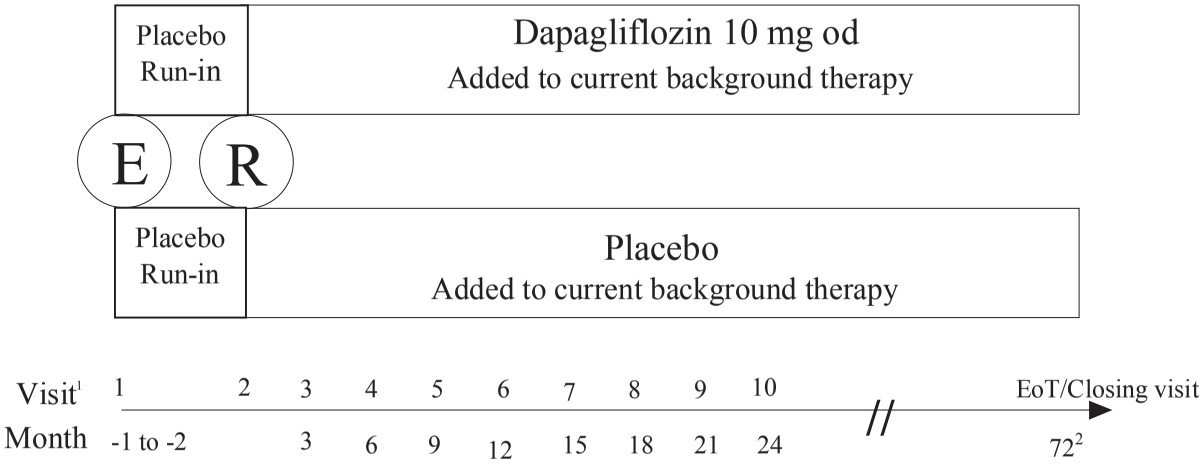
2. **Patients who prematurely discontinued from randomized IP (have already completed full assessment at EoT visit) –** For patients who prematurely discontinued randomized IP and completed the End of Treatment visit as described in Table 1, the modified Closing Visit will be completed and will comprise the following: recording of suspected CV events and AEs, body weight and anti-diabetes medications, ideally with an in-person visit. Patients will be asked whether they have undergone any urinary tract investigations since the last visit. If a urinary tract investigation has been performed it should be recorded in the eCRF. All efforts should be made to obtain all relevant information, including information on malignancies outcomes, taking into account locally applicable privacy laws. Where permissible by local law, the informed consent forms may include language to grant the option to employ outside companies to track down updated contact information or vital status of lost patients using publicly available source.

1. Suspected CV events include all fatal events and all events comprised by the primary objective and the secondary objective (see Sections 2.1 and 2.2).

Unscheduled visits

Unscheduled visits or phone contacts may be performed for safety laboratory follow-up (see Section 6.4.6), or event follow-up in case of early discontinuation of IP. Phone contacts or unscheduled visits can also be done any time during the study at the discretion of the Investigator.

Figure 1 Study flow chart



E = Enrollment, R = Randomization, EoT = End of Treatment

[1] Documented phone calls with each patient will be performed at a 3-month interval in between regular visits (i.e., 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25). This visit has an option to be a center visit if patient requests

[2] The study is CV-event driven with an anticipated total duration of 6 years, including an enrollment period of 3 years and follow-up period of 3 to 6 years. If study duration is reduced or extended, visits will be withdrawn or added as required every 3 months until the study is closed.

Table 1 Study Plan

Activity	**Enrollment**	**Randomization**	**Year 1**				**Year 2+[l]**				
Visit number[a,b,c,d]	**1**	**2**	**3 phone contact**	**4**	**5 phone contact**	**6**	**7 phone contact**	**8**	**9 phone contact**	**10**	**EoT/ Closing visit**
Study month	**Week –4 to –8**	**Day 1**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**72**
Informed consent	X										
Demography and relevant history (including smoking status)	X										
Additional medical history		X									
Inclusion/exclusion criteria	X	X									
Randomization		X									
Physical examination[e]		X									X
Vital signs (BP, pulse and body weight)[f]	X	X		X		X		X		X	X
Waist and Hip circumference		X									
Height	X										
Concomitant medication[g]	X	X	X	X	X	X	X	X	X	X	X
Pregnancy testing[h]	X	X		X		X		X		X	X

Activity	**Enrollment**	**Randomization**	**Year 1**				**Year 2+[l]**				
Visit number[a,b,c,d]	**1**	**2**	**3 phone contact**	**4**	**5 phone contact**	**6**	**7 phone contact**	**8**	**9 phone contact**	**10**	**EoT/ Closing visit**
Study month	**Week –4 to –8**	**Day 1**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**72**
Non fasting Laboratory assessments [i]	X										
Fasting Laboratory assessments[j]		X		X		X				X	X
Urine dipstick (for hematuria)	X	X									
Urinalysis with microscopy	X	X		X		X				X	X
[redacted]	[redacted]										
[redacted]		[redacted]									
Sample for biomarker research where applicable[k]		X		X							
Adverse events and CV events [m]	X	X	X	X	X	X	X	X	X	X	X
Recording of Urinary Tract Investigations		X	X	X	X	X	X	X	X	X	X

Activity	**Enrollment**	**Randomization**	**Year 1**				**Year 2+[l]**				
Visit number[a,b,c,d]	**1**	**2**	**3 phone contact**	**4**	**5 phone contact**	**6**	**7 phone contact**	**8**	**9 phone contact**	**10**	**EoT/ Closing visit**
Study month	**Week –4 to –8**	**Day 1**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**72**
Dispense pre-randomization placebo through IVRS/IWRS	X										
Dispense investigational product through IVRS/IWRS		X		X		X		X		X	
IP compliance		X	X	X	X	X	X	X	X	X	X
Diet and lifestyle advice	X	X		X		X		X		X	X

[a] Documented phone calls with each patient will be performed at a 3-month interval in between regular visits to follow up on events, concomitant medication and adherence to treatment. This visit has an option to be a center visit if patient requests.

[b] Unscheduled visits may be done for safety lab follow-up, event follow-up or in case of early discontinuation of IP.

[c] Visits will be repeated every 6 months and also phone calls every 3 months, according to the previous pattern until the Closing Visit as required. If the study needs to be prolonged to accrue the number of required primary endpoint events, visits would be added, i.e. assessments according to Year 2 may be repeated

[d] At the close of the study all patients will return for the Closing Visit. Patients who prematurely discontinued IP will come in for an EoT visit at the time of their discontinuation from IP. Subsequently, these patients need only be assessed for AEs, CV events, body weight and anti-diabetes medications at follow-up visits and a final closing visit at the close of the study.

[e] Physical exam according to Section 6.4.7 at randomization and EoT/Closing visit. An optional physical examination may be performed at any other in-office visit to evaluate an AE or as judged by the Investigator.

[f] For patients who prematurely discontinued from randomized IP and have already completed full assessment at EOT visit only Body weight needs to be performed at the closing visit

[g] Concomitant medications will be recorded according to Section 5.6

[h] Women of child bearing potential.

[i] [redacted]

[j] Laboratory assessments will be done at a central laboratory, details on each visit see 3.1. Electrolytes to be obtained at V2 and EoT/Closing visit

[k] ICF for biomarker sample is an addendum to the main ICF. For patient who is discontinued before Visit 4 , a biomarker sample should be drawn at the End of Treatment visit.

[l] Assessment and procedure schedule for Year 3 onwards will be the same as for Year 2 until the Closing visit

[m] To be recorded also for patients who prematurely discontinued IP, includes all AEs and all events comprised by the primary objective and the secondary objective. Please see section 6.4.4. Only events that fall into the following categories are collected in this study: serious AEs (as defined in 6.4.3), AEs leading to discontinuation of IP, suspected CV events and AEs of special interest. AEs of special interest in this study fall into the following categories: suspect neoplasm (benign, malignant or unspecified), hepatic events, hypoglycemic events that are major (as defined in 6.4.4.5), fractures, renal events, symptoms of volume depletion, hypersensitivity reactions (serious or lead to discontinuation of IP), urinary tract infections (serious or lead to discontinuation of IP) and genital infections (serious or lead to discontinuation of IP).

A description of the visit structure including the window for completion of the planned visits is depicted in Table 2.

Table 2 Visit design and visit windows

Visit ID	Visit description	Visit window
Visit 1	Enrollment/ Placebo Run-In Period	4 weeks minimum – 8 weeks (+ 14 days) maximum
Visit 2	Randomization	Day 1
Visit 3	Telephone contact	3 months (±14 days) after Visit 2
Visit 4	Treatment	6 months (±14 days) after Visit 2
Visit 5	Telephone contact	9 months (±14 days) after Visit 2
Visit 6	Treatment	12 months (±14 days) after Visit 2
Visit 7	Telephone contact	15 months (±14 days) after Visit 2
Visit 8	Treatment	18 months (±14 days) after Visit 2
Visit 9	Telephone contact	21 months (±14 days) after Visit 2
Visit 10	Treatment	24 months (±14 days) after Visit 2
Visit X[a]	Telephone contact	XX months (±14 days) after Visit 2
Visit X[a]	Treatment	XX months (±14 days) after Visit 2
	End of Treatment[b]	Once patient prematurely discontinues IP
	Closing Visit	Within approximately 8 weeks of the study closing date

[a] Visits will be repeated according to the previous pattern until the Closing visit as required.
[b] EoT assessments will be done at a planned or unscheduled visit when a patient is prematurely discontinuing randomized treatment.

3.2 Rationale for study design, doses and control groups

The aims of the study are to definitively exclude unacceptable CV risk with dapagliflozin treatment and to test the hypothesis that treatment with dapagliflozin reduces CV events in high-risk patients. As described above, a meta-analysis of 145 adjudicated CV events from the comprehensive Phase 2b and 3 clinical program resulted in an estimate for the hazard ratio for dapagliflozin versus comparator for the primary composite endpoint of adjudicated CV death, myocardial infarction, stroke or hospitalization for unstable angina of 0.819 (95% CI: 0.583, 1.152), and thus supports testing the hypothesis. Currently, there is no clearly established risk benchmark for approved anti-diabetes agents in terms of CV events, and, therefore, placebo is the appropriate comparator in this study. The patient population of T2DM at higher risk for CV events is appropriate as this population may benefit the most from a treatment that, in

addition to glucose lowering may also reduce CV risk. A composite assessment that includes CV death, MI or ischemic stroke, is the most rigorous way to assess CV effects of any given treatment. The study will be double-blind, single-dummy, to minimize the risk of bias.

4. PATIENT SELECTION CRITERIA

Investigator(s) should keep a record of patients who were considered for participation.

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

4.1 Inclusion criteria

Patients should meet all inclusion criteria at the time of randomization. If at the time of enrollment it is known that the patient will not meet criteria after a successful run-in period they should not be entered into run in.

For inclusion in the study patients should fulfill the following criteria:

1. Provision of informed consent prior to any study specific procedures (including run-in)

2. Female or male aged ≥ 40 years

3. Diagnosed with T2DM (See Appendix E for details)

4. High Risk for CV event defined as having either established CV disease and/or multiple risk factors:

   - Established CV Disease (See Appendix E for details)

   OR

   No known cardiovascular disease AND at least two cardiovascular risk factors in addition to T2DM, defined as:

   - Age ≥ 55 years in men and ≥ 60 in women

   AND presence of at least 1 of the following additional risk factors (see Appendix E for details)

   - Dyslipidemia
   - Hypertension
   - Current Tobacco use

5. WOCBP must take precautions to avoid pregnancy throughout the study and for 4 weeks after intake of the last dose.

   - WOCBP must have a negative urine pregnancy test. WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization

(hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal.

- WOCBP must be willing to use a medically accepted method of contraception that is considered reliable in the judgment of the Investigator.

[redacted]

4.2 Exclusion criteria

Patients should not meet any exclusion criteria at the time of randomization. If at the time of enrollment, it is known that the patient will not meet criteria after a successful run-in period he/she should not be entered into run in.

1. Use of the following excluded medications:
   - Current or recent (within 24 months) treatment with pioglitazone and/or use of pioglitazone for a total of 2 yearsor more during lifetime
   - Current or recent (within 12 months) treatment with rosiglitazone
   - Previous treatment with any SGLT2 inhibitor
   - Any patient currently receiving chronic (>30 consecutive days) treatment with an oral steroid at a dose equivalent to oral prednisolone ≥10 mg (e.g., betamethasone ≥1.2 mg, dexamethasone ≥1.5 mg, hydrocortisone ≥40 mg) per day
2. Acute cardiovascular event[e.g., acute coronary syndrome (ACS), transient ischemic attack (TIA), stroke, any revascularization, decompensated HF, sustained ventricular tachycardia <8 weeks prior to randomization. Patients with acute cardiovascular events can be enrolled in the run-in period as long as randomization does not occur within 8 weeks of the event.
3. Systolic BP >180 or diastolic BP >100 mmHg at randomization. Patient should be excluded if either the systolic BP is elevated (> 180 mmHg) or the diastolic BP is elevated (> 100 mmHg) on both measurements (see section 6.4.8.1)
4. Diagnosis of Type 1 diabetes mellitus, MODY, or secondary diabetes mellitus
5. History of bladder cancer or history of radiation therapy to the lower abdomen or pelvis at any time
6. History of any other malignancy within 5 years (with the exception of successfully treated non-melanoma skin cancers)
7. Chronic cystitis and/or recurrent urinary tract infections (3 or more in the last year)
8. Any conditions that, in the opinion of the Investigator, may render the patient unable to complete the study including but not limited to cardiovascular (NYHA class IV CHF, recurrent ventricular arrhythmias) or non-cardiovascular disease (e.g., active

malignancy with the exception of basal cell carcinoma, cirrhosis, chronic lung disease, severe autoimmune disease) and/or a likely fatal outcome within 5 years

9. Pregnant or breast-feeding patients

10. Involvement in the planning and/or conduct of the study or other dapagliflozin studies (applies to AZ, BMS, Hadassah and Thrombolysis in Myocardial Infarction [TIMI] or representative staff and/or staff at the study site)

11. Previous enrollment or randomization in the present study

12. Active participation in another clinical study with IP and/or investigational device

13. Individuals at risk for poor protocol or medication compliance during run-in period (reasonable compliance defined as 80 – 120%, unless a reason for non-compliance is judged acceptable by the Investigator). If for any reason, the Investigator believes that the patient will not tolerate or be compliant with IP or study procedures, the patient should not be randomized and considered a run-in failure.

Patients will be excluded during run-in and should not be randomized if the following are observed from laboratory or observation during enrollment and run-in assessments:

14. HbA1c ≥12% or HbA1c<6.5% from the central laboratory (nb, the proportion of subjects with an HbA1c between 6.5 % and < 7.0 % will be capped at approximately 5 % of the study)

15. AST or ALT >3x ULN or Total bilirubin >2.5 x ULN

16. CrCl < 60 ml/min (based on the Cockroft-Gault equation)

17. Hematuria (confirmed by microscopy at Visit 1) with no explanation as judged by the Investigator up to randomization. If bladder cancer is identified, patients are not eligible to participate.

18. Any reason the Investigator believes the patient is not likely to be compliant with the study medication and protocol.

[redacted]

Procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

There are no specific dietary or activity restrictions.

Restricted concomitant medications are listed in Section 5.6.1.

5.2 Patient enrollment and randomization and initiation of investigational product

The Principal Investigator or delegate will:

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

2. Determine patient eligibility. See Sections 4.1 and 4.2

3. Assign potential patient a unique enrollment number via an IVRS/IWRS, consisting of country, study center and a patient specific number, beginning with 'E' on Visit 1.

4. Dispense placebo run-in treatment at enrollment to confirm compliance. Placebo run-in period should be a minimum of 4 weeks before randomizing the patient.

5. Assign eligible patient unique randomization code (patient number) via an IVRS/IWRS on Visit 2.

Patients can only be randomized into the study once.

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

5.2.1 Procedures for randomization

To help identify non-adherent patients, the study includes a 4 to 8 week placebo run-in period (+ 14 days)starting at Visit 1. Randomization to IP will be done via an IVRS/IWRS at Visit 2 in balanced blocks in order to ensure approximate balance between the two treatment arms (1:1). Randomization will be stratified by CV risk category (established CV disease; multiple risk factors without established CV disease) and baseline hematuria status. Approximately 17150 patients will be randomized in this study. Enrollment of patients based on disease state, geographic region, and gender will be monitored and may be capped to ensure adequate representation. For example, recruitment will be monitored to randomize approximately 30% of patients each from North America and Europe.

The enrollment code (E-code) assigned at Visit 1 will be used to identify the patient throughout study participation.

The IVRS/IWRS will allocate the IP through the AZ prepared randomization scheme and provide the randomization number and the appropriate Kit IDs from IP available at the study center. Randomization numbers will be prepared by the global randomization administrator at AstraZeneca and made available for IVRS/IWRS use.

The randomization codes will be computer generated by AstraZeneca R&D or representative using AZ Global Randomization system (GRAND) using balanced blocks and allowing an approximately equal number of patients per treatment group within each country. The randomization codes will be loaded into the IVRS/IWRS database.

Detailed instruction on use of the IVRS/IWRS system will be provided to the Investigational sites.

5.3 Procedures for handling patients incorrectly enrolled or randomized or initiated on investigational product

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

The following steps should be taken in the event that a patient who does not meet Inclusion/Exclusion criteria is found to have been inadvertently randomized.

(a) The Investigator or monitor should inform the TIMI Hotline Physician immediately. Ensuring patient safety must always be the number one priority.

(b) If, after discussion between the TIMI Hotline Physician and the Investigator, it is judged that continued treatment would pose an undue safety risk to the patient, IP should be discontinued. The patient should remain in the study for follow-up in accordance with defined study procedures including follow-up of clinical outcomes.

(c) In those cases where continuation on IP is judged to not pose a concern related to safety and disease management, IP should be continued and the rationale for allowing the patient to remain on IP must be clearly documented.

If a patient receives the incorrect randomized treatment at any time during the study, this must be corrected as soon as discovered. An unscheduled visit should be completed as soon as possible. The treatment should be corrected at that visit but in any event no later than the next scheduled visit. Until the treatment is corrected, the patient should discontinue the IP.

The TIMI Hotline is to ensure all such decisions are appropriately documented.

All randomized patients are expected to continue in the study with regularly scheduled follow-up per Section 3.1, whether on or off IP.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The blinding is ensured by using double-blind, single-dummy technique. The active tablets and the respective placebo tablets will be identical in size, color, smell, and taste. The bottles with investigational products will be labeled with unique identification numbers allocated from the IVRS/IWRS.

No member of the study delivery team at AZ, BMS, Hadassah, TIMI, or personnel at study centers or any clinical research organization (CRO) handling data will have access to the randomization scheme during the conduct of the study, with the exception of the AZ personnel generating the randomization scheme as well as AZ Supply Chain Study Management (SCSM), AZ Patient Safety Department and the CRO companies providing the IVRS/IWRS and carrying out the packaging and labeling of investigational products. The DMC will be provided with fully or partially unblinded data at regular intervals to fulfill their review commitment as specified in the DMC charter.

5.4.2 Methods for unblinding patients treatment assignment

Unblinding can be carried out in emergencies by the Investigator(s) or pharmacists at the study center and the personnel who are independent of the study evaluation at AZ Patient Safety Department. The DMC will have access to the individual treatment codes and will be able to merge these with the collected study data while the study is ongoing (see Section 12.4.2).

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the Investigator(s) or pharmacists and to AZ Patient Safety Department from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each center.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment assignment. In such an emergency, the Investigator will, if time and circumstances permit, contact the TIMI Hotline prior to breaking the treatment code. The Investigator documents and reports the action to the TIMI Hotline without revealing the treatment given to subject to the TIMI Hotline-

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

5.5 Treatments

5.5.1 Identity of investigational product(s)

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

Each bottle for placebo run-in contains 35 tablets. Each bottle for treatment contains 210 tablets (6 months treatment).

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

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

5.5.2 Doses and treatment regimens

Duration of dosing:

- Dapagliflozin 10 mg tablets, administered orally once daily for a predicted median of 4.5 years and an anticipated total duration of a 6-year double-blind treatment period.

- Matching placebo for dapagliflozin 10 mg administered orally once daily for the 4-8 week placebo run-in period and for a predicted median of 4.5 years and an anticipated total duration of a 6-year double-blind treatment period.

The investigational product (IP) dapagliflozin or matching placebo will be taken orally. The IP should be taken once daily in the morning and at approximately the same time of the day during the study period.

At the randomization visit, IP should be ingested during the patient visit after completing the BP measurements and all other visit procedures.

5.5.3 Additional IP (Not applicable)

5.5.4 Labeling

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

5.5.5 Storage

All IPs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle and the Investigator Brochure specify the appropriate storage conditions.

5.6 Concomitant and post-study treatment(s)

Background medication and post-study treatment will not be provided by the Sponsor.

5.6.1 Prohibited medication

Treatment with pioglitazone, rosiglitazone, and any SGLT2 inhibitors other than IP is not permitted for the duration of the study.

5.6.2 Use with medications known to cause hypoglycemia

Insulin secretagogues, such as sulphonylureas, may cause hypoglycemia. Therefore, a lower dose of the insulin secretagogue or injectable insulin may be considered by the Investigator to reduce the risk of hypoglycemia when used in combination with study medication.

5.6.3 Anti-diabetes medication

Patients should be treated for diabetes with glycemic goals as recommended by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) in their 2012 joint Position Statement (Inzucchi et al 2012). In brief, the ADA/EASD recommends lowering HbA1c to < 7.0% in most patients. Less stringent HbA1c goals, e.g. 7.5 to 8% or even slightly higher may be appropriate for patients with a history of severe hypoglycemia, advance complications, extensive comorbid conditions and those in whom the target is difficult to attain despite intensive self-management education, repeated counseling, and effective doses of multiple glucose-lowering agents, including insulin. The proposed treatment algorithm recommends healthy eating, weight control, and increased physical activity; if drug therapy is required, metformin should be considered as initial therapy, and then additional drug classes may be added as outlined in Appendix F.

Patients are eligible for adjustments in their anti-diabetes treatment at the Investigator's discretion and based on local treatment guidelines and best practices. This may include discontinuing or changing the dose(s) of concomitant anti-diabetes medication(s) as well as adding other anti-diabetes treatments. Regardless of the need for a change in a concomitant medication, patients will remain on the randomized IP unless they meet specific criteria for discontinuation of IP.

Anti diabetic medication needs to be recorded in the appropriate sections of the eCRF. At visit 2 (randomization) all antidiabetic medications (including dose changes) should be documented even if with a duration of < 3 months.

5.6.4 Other medications

All patients should be treated according to regional standards of care for CV risk factors (e.g., blood pressure, lipids, antithrombotic treatment) and HbA1c.

Other medication(s), which are considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator.

Concomitant medications need to be recorded in the appropriate sections of the eCRF only if they are taken for a duration of > 3 months. At visit 2 (randomization) all antihypertensive medications should be documented even if with a duration of < 3 months..

In addition, all new or changed concomitant medications that the patient is treated with when an AE (as defined by the CSP section 6.4.4.) occur needs to be recorded on a specific eCRF page, regardless of the treatment duration. Note that this should also apply to concomitant medications which have been discontinued before the start of the AE, if judged as important by the investigator..

5.7 Treatment compliance

The administration of all medications (including IP) should be recorded in the appropriate sections of the eCRF, for all concomitant medication this is described in detail in section 5.6.3 and 5.6.4.

Patients will be asked to return all unused IP and empty bottles to the site at each scheduled visit. Tablet counts will be recorded in the eCRF. Compliance will be discussed at each study visit and assessed based on returned IP as follows: the Investigator will make a subjective judgment of the compliance based on 2 categories ("reasonable": ≤ 20% deviation from expected number of tablets; and "questionable": >20% deviation). If compliance is "questionable", the Investigator should counsel or instruct the patient on the importance of taking his/her IP as prescribed. Patients judged to have questionable compliance (defined as taking less than 80% or more than 120% of the prescribed dose of IP) will continue in the study, but should be counseled on the importance of taking their IP as prescribed.

5.7.1 Accountability

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

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

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

5.8 Discontinuation of investigational product

Patients may be discontinued from IP in the following situations:

- Patient decision. The patient is at any time free to discontinue IP, without prejudice to further treatment. Patients who choose to discontinue IP are expected to continue in the study until the closing of the study (see Section 5.8.1)
- Safety reasons as judged by the Investigator, or by AZ and/or a representative.

Study-specific discontinuation criteria are listed below:

- Liver criteria:
  - ALT and/or AST >3 times the upper limit of normal (ULN) **and** concomitant TB >2 times ULN confirmed at a repeated measurement at the central laboratory (which should be obtained within 3 days, whenever possible, following receipt of the initial laboratory results)
  - ALT and/or AST >8 times ULN confirmed at a repeated measurement at the central laboratory (which should be obtained within 3 days, whenever possible, following receipt of the initial laboratory results)
  - ALT and/or AST >5 times ULN confirmed at the central laboratory and sustained over a period of 14 days or more

  (See Appendix D for further details)

- Kidney criteria:

  If at any time the patient´s CrCl (based on Cockroft-Gault) falls below 30 ml/min calculated at the central laboratory and confirmed at a repeated central laboratory measurement (to be obtained within 4 days, whenever possible), the patient should be discontinued from IP.

  If at any time the patient´s CrCl (based on Cockroft-Gault) falls below 30 ml/min calculated at local laboratory, a central laboratory CrCl should be obtained promptly. If the CrCl is confirmed by the central laboratory and persists at a repeated central laboratory measurement (to be obtained within 4 days, whenever possible), the patient should be permanently discontinued from IP.

- Bladder cancer:
  - If at any time the patient is diagnosed with bladder cancer, the patient should be discontinued from IP.

- Pregnancy:
  - Pregnancy (discontinue IP and notify the TIMI Hotline), see Section 13.3.

Temporary discontinuations for any reason and for any duration are allowed; if the Investigator judges that the potential benefit outweighs the risk in any patient who discontinued IP, administration of IP may be re-started.

If during the placebo run-in period IP is discontinued, this would be considered a run-in failure and not study discontinuation. Such a patient would not be randomized into the study.

- Cases where patients are incorrectly randomized (i.e., the patient does not meet the required inclusion/exclusion criteria for the study) should be discussed with the TIMI Hotline prior to any actions being taken (see Section 5.3).

- *Discontinuation of IP does not mean discontinuation of follow-up*. Study assessments should be continued in all patients (see Section 5.8.1).

5.8.1 Procedures for discontinuation of a patient from investigational product

A patient who decides, and/or is recommended by treating physician or the Investigator to permanently discontinue IP, will always be asked about the reason(s) and the presence of any AEs. All efforts must be taken to ensure that the patient will be seen and assessed by an Investigator, and as scheduled for other patients, complete all assessments of the EoT Visit. Following the EoT, regularly scheduled study visits are expected to continue as planned. AEs, suspected CV events, body weight and anti-diabetes medications will be recorded at the follow up visits (see Section 6.2). At the end of the study, the Closing Visit should preferably be an in-person visit to the site and should include collection of AEs, suspected CV events, body weight and anti-diabetes medications.

Alternatively, if the patient does not agree to this option, a modified follow up through regular telephone contacts or a contact at study closure should be arranged.

Whether a patient attends a visit or is contacted by telephone, once a possible event that may require adjudication is noted, medical records must be obtained and submitted to the CEC for adjudication of the event.

Restart of IP

Whenever possible, restart of IP should be encouraged. Even if an EoT visit was completed due to the discontinuation of IP, this should not prevent complete study follow-up procedures including restart of randomized treatment. All efforts must be taken to assure that the patient will be seen and assessed by an Investigator, and as scheduled for other patients. Patients fulfilling a study specific discontinuation criterion should never be restarted on IP.

Patients suspected of pregnancy will discontinue IP immediately. If it is confirmed by pregnancy test that there is no pregnancy, the IP can be restarted. (See Section 13.3).

If a patient is withdrawn from the study, see Section 5.9.

5.9 Withdrawal from study

Patients are at any time free to completely withdraw from the study (which means permanent discontinuation of IP and all follow-up assessments) without prejudice to further treatment. Discontinuation of IP in itself is not considered withdrawal of consent.

Withdrawal of consent should only occur if the patient refuses any further assessments or contact whatsoever. Patients who do not want regular in-person follow up after cessation of IP should be offered alternative methods of follow up including periodic telephone follow up, contact at study closure, or assessment of health status via treating physicians or medical records. Such patients would then not be viewed as withdrawal of consent. The Investigator must explain to the patient all options for continued participation, and document which options were refused by the patient and the reason for refusal. Withdrawal of consent must be ascertained and documented in writing by the Investigator who must inform the TIMI Hotline and document the withdrawal of consent in the eCRF and medical records. Patients will be asked about the reason(s) for withdrawal. Adverse events will be accessed (See Sections 6.4.4 and 6.4.5) and IP returned. For patients who withdraw from the study, direct ascertainment of health status at the end of the study or vital status via public records will be performed in compliance with local privacy laws/practices.

Withdrawn patients will not be replaced.

5.10 Lost to follow up patients

To prevent patients being lost to follow-up, their contact details, including next of kin contacts should be collected initially and updated regularly by the site staff or representative. The Investigator should educate the patient on the importance of contact with the Investigator throughout the study. Repeated attempts will be made to locate and obtain pertinent medical information for patients who are initially lost to follow up. A patient will be classified as lost to follow up only if he/she has failed to return for the required study visits and his/her vital status remains unknown despite multiple attempts to contact him/her via telephone, fax, e-mail, certified letter or through patient locator agencies (if allowed by national regulation). Where permissible by local law, the informed consent forms will include language to grant the option to employ outside companies to assist in obtaining updated contact information or ascertainment of vital status of lost patients using publicly available source.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

A Web-Based Data Capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRF as specified in the study protocol and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The Investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site.

All suspected events included in the composite endpoint of CV death, MI, or ischemic stroke and secondary CV endpoints will be recorded in the respective appropriate modules of the eCRF. Investigators are also required to provide the CEC copies of source documents, e.g., medical records (discharge summary, death certificate, autopsy report, etc). Refer to the Event Reporting Manual for further details.

6.2 Data collection at enrollment, randomization and follow-up

6.2.1 Enrollment procedures

The following data will be collected at enrollment (V1) and recorded in the appropriate sections of the eCRF (see Table 1).

- Date of signed informed consent
- Inclusion and exclusion criteria
- Demography: Date of birth, gender, race, and ethnic group
- WOCBP must have a negative urine pregnancy test
- Blood sampling for laboratory assessments of HbA1c, serum creatinine (creatinine clearance will be based on the Cockroft-Gault equation), TB, ALT, AST,
- Urinalysis (including microscopy)
- Urine dipstick for assessment of hematuria
- Medical history information including presence of T2DM, history of CV disease, CV risk factors, smoking status
- Vital signs (pulse and BP), height, and body weight
- Prior and concomitant medication
- Dispensing of IP for run-in period via an IVRS/IWRS
- [redacted]

6.2.2 Randomization

The following data will be collected at randomization (V2) and recorded in the appropriate sections of the eCRF (see Table 1)

- Inclusion /exclusion criteria
- Additional medical history including history of malignancies
- Date of randomization
- WOCBP must have a negative urine pregnancy test
- Recording of AEs
- Recording of Urinary Tract Investigations
- Recording of concomitant medication
- vital signs (pulse and BP), body weight and waist and hip circumference
- Blood sampling for laboratory assessments of CBC, fasting serum glucose and lipids (LDL-Cholesterol, HDL-Cholesterol,Triglyceride, Total Cholesterol), serum creatinine (creatinine clearance will be based on the Cockroft-Gault equation), TB, ALT, AST, ALP, uric acid, electrolytes (sodium, potassium, chloride, bicarbonate, calcium, phosphorus and magnesium)
- Urinalysis (including microscopy and urine albumin to creatinine ratio)
- Urine dipstick for assessment of hematuria.
- Dispensing of IP via an IVRS/IWRS
- Blood sampling for biomarker [redacted], where applicable

6.2.3 Follow-up procedures

Patients on randomized treatment, also where IP was interrupted and restarted, should attend all remaining visits for assessments, procedures, and provision of IP (according to Table 1) until the end of the study.

Randomized patients who discontinue randomized IP prematurely should complete the procedures described for EoT Visit at the time of the discontinuation of IP. Following discontinuation of IP, these patients should attend the remaining study visits or will be contacted by phone to have AEs and suspected CV events recorded until the end of the study. The Closing Visit should preferably be a visit at the site.

[redacted]

The following assessments will be done at the follow-up visits:

- Telephone contact (or optional center visit) visits 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25 (months 3, 9, 15, 21, 27, 33, 39, 45, 51, 57, 63 and 69):
  - Recording of AEs
  - Recording of CV events
  - Recording of Urinary Tract Investigations
  - Recording of use of IP
  - Recording of concomitant medication
- Visits 4, 8, 12, 16, 20 and 24 (months 6, 18, 30, 42, 54 and 66):
  - Recording of AEs
  - Recording of CV events
  - Recording of Urinary Tract Investigations
  - Vital signs: body weight, pulse and BP
  - An optional physical examination may be performed to evaluate an AE or as judged by the Investigator.
  - Pregnancy test for WOCBP
  - Return of IP and assessment of compliance
  - Dispensing of new IP
  - Recording of concomitant medication
  - Visit 4 only:
    - Blood sample for laboratory measurements of, HbA1c, serum creatinine (creatinine clearance will be based on the Cockroft-Gault equation), TB, ALT, AST, fasting serum glucose and lipids (LDL-Cholesterol, HDL Cholesterol, Triglyceride, Total Cholesterol)
    - Sampling for biomarker research where applicable
    - Urinalysis including microscopy and urine albumin to creatinine ratio
- Visits 6, 10, 14, 18 and 22 (months 12, 24, 36, 48 and 60):
  - Recording of AEs
  - Recording of CV events
  - Recording of Urinary Tract Investigations

- Pregnancy test for WOCBP
- Return of IP and assessment of compliance
- Dispensing of new IP
- Recording of concomitant medication
- Blood sampling for assessments of HbA1c, CBC, fasting serum glucose and lipids (LDL-Cholesterol, HDL-Cholesterol,Triglyceride, Total Cholesterol), serum creatinine (creatinine clearance will be based on the Cockroft-Gault equation), TB, ALT, AST, ALP, uric acid
- Urinalysis including microscopy and urine albumin to creatinine ratio
- Vital signs: body weight, pulse and BP
- An optional physical examination may be performed to evaluate an AE or as judged by the Investigator.

- End of Treatment (for patients who prematurely discontinued from randomized IP):
  - Recording of AEs
  - Recording of CV events
  - Recording of Urinary Tract Investigations
  - Pregnancy test for WOCBP
  - Return of IP and assessment of compliance
  - Recording of concomitant medication
  - Blood sampling for laboratory assessments of HbA1c, CBC, fasting serum glucose and lipids (LDL-Cholesterol, HDL-Cholesterol,Triglyceride, Total Cholesterol) serum creatinine (creatinine clearance will be based on the Cockroft-Gault equation), TB, ALT, AST, ALP, uric acid, electrolytes (sodium, potassium, chloride, bicarbonate, calcium, phosphorous and magnesium), and urinalysis including microscopy and, urine albumin to creatinine ratio
  - For patient who is discontinued before Visit 4 a biomarker sample should be drawn.
  - Physical examination including vital signs: body weight, pulse and BP
- Closing Visit (completed for all patients at the end of the study, regardless of IP status)
  - **Patients still on randomized IP at the time of Closing Visit:**
    - Recording of AEs
    - Recording of CV events
    - Recording of Urinary Tract Investigations
    - Pregnancy test for WOCBP

- Return of IP and assessment of compliance
- Recording of concomitant medication
- Blood sampling for laboratory assessments of HbA1c, CBC, fasting glucose and lipids (LDL-Cholesterol, HDL-Cholesterol,Triglyceride, Total Cholesterol), serum creatinine (creatinine clearance will be based on the Cockroft-Gault equation), TB, ALT, AST, ALP, uric acid, electrolytes (sodium, potassium, chloride, bicarbonate, calcium, phosphorous and magnesium) and urinalysis including microscopy and urine albumin to creatinine ratio
- Physical examination including vital signs: body weight, pulse and BP

- **Patients who prematurely discontinued from IP (have already completed full assessment at EoT):**
  - Recording of AEs
  - Recording of CV events
  - Recording of Urinary Tract Investigations
  - Body weight
  - Recording of anti-diabetes medications

6.3 Efficacy

6.3.1 Primary variable

The primary outcome variables of the study are the composite endpoint of cardiovascular death, myocardial infarction, or ischemic stroke (time to first event) and the composite endpoint of hospitalization for heart failure or CV death (time to first event). All components of these composites will be adjudicated.

6.3.2 Secondary variables

- Renal composite endpoint: Confirmed sustained ≥40% decrease in eGFR to eGFR <60 ml/min/1.73m^2 (using CKD-EPI equation) and/or ESRD (dialysis ≥90 days or kidney transplantation, confirmed sustained eGFR <15ml/min/1.73m^2) and/or renal or CV death (time to first event)
- All-cause mortality (time to event)

6.3.3 Exploratory variables

- The individual components of the primary endpoint (cardiovascular death, MI, ischemic stroke and hospitalization for heart failure) (time to first event)
- The composite endpoint of cardiovascular death, MI, ischemic stroke, hospitalization for heart failure, hospitalization for unstable angina pectoris, or hospitalization for coronary or non-coronary revascularization and the additional

individual components of hospitalization for unstable angina pectoris and hospitalization for coronary or non-coronary revascularization (time to first event)

- HbA1c
- Initiation of insulin therapy in patients not receiving insulin therapy at baseline
- Need for any of the following: an increase in dose for an oral anti-diabetes medication, a ≥ 25% increase in insulin dose, or the addition of new anti-diabetes medication for ≥ 3 months
- Major hypoglycemia and/or hospitalization for hypoglycaemia
- Development of confirmed sustained macroalbuminuria (UACR ≥300 mg/g) in subjects without macroalbuminuria at baseline
- Development of confirmed sustained albuminuria in patients without albuminuria at baseline (UACR ≥30 mg/g; time to first event)
- Regression in sustained confirmed albuminuria (defined in three ways:
- 1. Baseline microalbuminuria to normoalbuminuria, 2. Baseline macroalbuminuria to microalbuminuria, 3. The previous two combined) (proportions)
- eGFR (sustained confirmed decrease ≥30% to sustained confirmed eGFR <60 ml/min/1.73m2 using CKD-EPI equation; time to first event)
- eGFR (sustained confirmed decrease ≥40% to sustained confirmed eGFR <60 ml/min/1.73m2 using CKD-EPI equation; time to first event)
- Albumin to Creatinine Ration (adjusted mean percent change after 2 and at 3 years)
- Change in body weight at 2 years and at 3 years
- Proportion of patients with 5% body weight loss and 10 % body weight loss after 2 years and after 3 years
- Retinal laser and/or intraocular treatment due to development of and/or deterioration in diabetic retinopathy
- Blood pressure change from baseline
- Peripheral revascularization/limb ischemic event
- Surgical amputation and related events
- Any stroke (ischemic, hemorrhagic, or undetermined)

6.4 Safety

6.4.1 Primary safety variable

The primary safety outcome variable of the study is the composite endpoint of cardiovascular death, MI, or ischemic stroke (time to first event). These events will be adjudicated.

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

6.4.2 Definition of adverse events

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

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

Refer to section 6.4.4 for definitions of AEs to be collected in this study.

6.4.3 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

Any event representing a known or possible malignancy or neoplasm not known to be benign (e.g. mass observed on imaging felt to be a possible malignancy), laboratory abnormalities fulfilling the Hy's law definition (ALT/AST>3xULN and total bilirubin >2xULN) or overdose (defined as the accidental or intentional ingestion of any dose of the investigational product that is considered both excessive and medically important, for further dosing

information please refer to the IB.) should be reported as an SAE using the most relevant SAE criteria, as judged by the Investigator.

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

6.4.4 Recording of adverse events

From signing of the informed consent and throughout the study until and including the last visit/contact (i.e., Closing Visit), patients should be asked whether they experienced any AEs.

Only events that fall into the following categories are collected in this study: serious AEs (as defined in 6.4.3), AEs leading to discontinuation of IP, suspected CV events, elective coronary and non-coronary revascularisations, heart failure, potential diabetic ketoacoidosis, amputation and related events and AEs of special interest. AEs of special interest in this study fall into the following categories: suspect neoplasm (benign, malignant or unspecified), hepatic events, hypoglycemic events that are major (as defined in 6.4.4.5), fractures, renal events, symptoms of volume depletion, hypersensitivity reactions (serious or lead to discontinuation of IP), urinary tract infections (serious or lead to discontinuation of IP) and genital infections (serious or lead to discontinuation of IP).

Prior to first intake of randomized IP, an event should be recorded on the AE and SAE pages only if it qualifies as an SAE.

Follow-up of unresolved adverse events

Any AEs that are recorded according to the CSP and are unresolved at the last visit/contact (i.e., Closing Visit) in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AZ retain the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary, except for patients who have withdrawn consent and explicitly did not allow any further contact from Study personnel.

Any follow-up of ongoing SAEs after database lock will be reported to the AZ representative, who will notify the Patient Safety data entry site.

Variables

The following variables will be collected for each recorded AE;

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not

- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- Whether this event is potentially a clinical endpoint /event of special interest
- Outcome.

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

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.3. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE. If the intensity of an AE changes, only the maximum intensity of the event will be recorded; however, the AE intensity should be recorded at the time of reporting.

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

- Mild (awareness of event but easily tolerated)
- Moderate (discomfort enough to cause some interference with usual activity)
- Severe (inability to carry out usual activity)

Causality collection

The Investigator will assess causal relationship between IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

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

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

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarized in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and other safety variables should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

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

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 if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

6.4.4.1 Hepatic disorders

All patients with a confirmed result of AST and/or ALT >3x ULN, will have additional central laboratory tests performed throughout the study. For patients who are discontinued from the IP as a result of sustained elevated liver safety abnormalities, additional central laboratory tests will be performed at the time of end of Treatment Visit, see CSP Appendix D Algorithm on Management of Sustained Elevated Liver Safety Abnormalities.

Pre-defined liver enzyme elevations will undergo adjudication. The definitions of events to be adjudicated are provided in the Event Reporting Manual. For all events identified for adjudication, the Investigator will complete the appropriate eCRF pages and provide source documentation as detailed in the Event Reporting Manual.

6.4.4.2 Hematuria

All events of hematuria (microscopic and/or macroscopic) during the study should be worked up for a possible cause. If no immediate or benign cause is identified as judged by the Investigator (e.g., menstruation, kidney stone, urinary tract infection [UTI] where hematuria is subsequently resolved after successful treatment), patients should undergo further evaluation by the investigator or another qualified professional. The evaluation may include but is not limited to tests such as urine cytology, NMP-22 or abdominal CT scans. The choice of tests should be per local standard of care/professional society guidance (see Appendix G for AUA guidelines). The patient should continue to receive IP treatment during these investigations (unless otherwise contraindicated). All confirmed events of bladder cancer should lead to the discontinuation of investigational product. (Refer to sections 5.8 and 5.8.1).

6.4.4.3 Possible malignancies

All possible malignancies (except for non-melanoma skin cancer) will be reported by the site into a malignancy specific form in the eCRF in addition to the SAE form. All possible malignancies will be identified from entries in the eCRF malignancy form.

The identified events will be independently adjudicated. For all events identified for adjudication, the Investigator will complete the appropriate eCRF pages and provide source documentation as detailed in the Event Reporting Manual. The Investigator should clearly describe the event as benign or malignant if known. All confirmed events of bladder cancer should lead to the discontinuation of investigational product. (Refer to sections 5.8 and 5.8.1).

6.4.4.4 Renal disorders

The efficacy and safety of dapagliflozin use in patients with type 2 diabetes has not been fully characterized for those who develop moderate renal impairment during ongoing treatment. Patients with a decrease in renal function defined as creatinine clearance (CrCl, based on Cockroft-Gault) <60 ml/min (but ≥ 30 ml/min) should continue on IP, but additional monitoring is required as specified below.

Patients with creatinine clearance (CrCl, based on Cockroft-Gault) < 60 ml/min:

At all scheduled and unscheduled visits patients should be asked for symptoms of volume depletion as well as other adverse events and vital signs should be assessed (including blood pressure measurement).

Renal function should be monitored by central lab at least every 6 months but frequency might be increased depending on clinical situation and judgement of the investigator.

Patients with creatinine clearance (CrCl, based on Cockroft-Gault) < 45 ml/min:

If the creatinine clearance (CrCl, based on Cockroft-Gault) falls below 45 ml/min the patient should be scheduled for a re-test within 4 days whenever possible.

If CrCl (based on Cockroft-Gault) is ≥45 ml/min the patient can resume normal visit schedule.

If CrCl is still <45 ml/min the Investigator should consider re-testing CrCl within one to two weeks whenever possible. In addition, the Investigator should consider evaluating the patient for potentially reversible causes of renal dysfunction including: concurrent use of NSAIDS, antibiotics, or other medications known to affect creatinine clearance; volume depletion; urinary tract infection and obstructive uropathy. Further re-testing and evaluation should be done every second week until stabilization. The Investigator should also repeat the CrCl test at the next scheduled 3-month visit.

Patients with creatinine clearance (CrCl, based on Cockroft-Gault) < 30 ml/min:

If at any time the patient´s CrCl (based on Cockroft-Gault) falls below 30 ml/min calculated at the central laboratory and confirmed at a repeated central laboratory measurement (to be obtained within 4 days, whenever possible), the patient should be discontinued from IP.

If at any time the patient´s CrCl (based on Cockroft-Gault) falls below 30 ml/min calculated at local laboratory, a central laboratory CrCl should be obtained promptly. If the CrCl is confirmed by the central laboratory and persists at a repeated central laboratory measurement (to be obtained within 4 days, whenever possible), the patient should be discontinued from IP.

Estimated GFR (eGFR) will also be calculated and used for analysis, however decisions on IP discontinuation will be based on CrCl (refer to Section 12.2).

Any patient that is discontinued from IP due to deterioration in renal functions should be monitored closely by the investigator until abnormalities stabilize and the patient is asymptomatic.

6.4.4.5 Hypoglycemic events

At each visit the Investigator will inquire about occurrence of major hypoglycemic events according to the below definition.

- **Major hypoglycemic event** defined as symptomatic events requiring external assistance due to severe impairment in consciousness or behavior, and prompt recovery after glucose or glucagon administration. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low blood glucose concentration.

Hypoglycemic episodes or symptoms of hypoglycemia should only be reported in the eCRF if the event fulfills the definition of a major hypoglycemic event, the protocol criteria for an SAE (see Section 6.4.3) or leads to discontinuation of IP. For major hypoglycemic episodes additional details (e.g., glucose measurements) will be recorded in the eCRF.

6.4.4.6 Volume depletion

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

6.4.4.7 UTI

If the Investigator believes that a UTI may be present, a properly collected set of urine cultures should be obtained and sent to a local laboratory prior to initiation of antibiotic therapy to confirm a presumptive diagnosis of cystitis, urinary tract infection, pyelonephritis. Clinical judgment and local standards of care should apply to decisions concerning therapy.

In patients with clinical evidence of upper UTI (e.g., pyelonephritis) or presumed urosepsis, the Investigator may consider temporarily stopping IP until the course of treatment of the infection has been completed and clinical recovery has occurred. It is recommended that a follow-up urine culture is obtained within 7 days of clinical recovery from a documented UTI.

UTIs that are serious or lead to discontinuation of IP should be reported in the eCRF.

6.4.4.8 Asymptomatic bacteriuria

During enrollment, randomized treatment and follow up of patients in this trial, the Investigator may discover a patient with asymptomatic bacteriuria. Asymptomatic bacteriuria is defined as the presence of $\geq 10^5$ colony forming units/mL of bacteria, in a properly collected voided urine specimen, without signs or symptoms typically attributed to urinary tract infection. Asymptomatic bacteriuria is prevalent among diabetic women, and is associated with pyuria in 70% of cases. Neither guideline from the US (Levey **et al 2009** Levey AS, Stevens LA, Schmid CH, Zhang Y(L), Castro AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T and Coresh J. A New Equation to Estimate Glomerular Filtration Rate. Ann Intern Med. 2009 May 5; 150(9): 604–612.

Nicolle et al 2005, USPST 2004) nor Europe (European Association of Urology 2008) recommend treatment of asymptomatic bacteriuria in non-pregnant diabetic patients.

6.4.4.9 Adjudication of suspected CV endpoints

Suspected CV outcome events in the study including the primary objective and secondary objective will be centrally adjudicated by an independent clinical events committee.

Suspected CV outcome events in the study will be identified either by the Investigator or by electronic review of reported AEs. For all events identified for adjudication the Investigator will complete the appropriate modules of the eCRF and provide source documentation. Guidance for “reporting potential clinical endpoints” is provided in the Event Reporting Manual. Definitions of CV events are detailed in the CEC Charter.

6.4.4.10 Fractures

Published data suggest the presence of diabetes is associated with an increased risk in bone fractures, and bone fracture has been included as a potential risk for dapagliflozin due to the possible effects of dapagliflozin on body weight, renal tubular handling of calcium and phosphorus, or metabolism of vitamin D. However, in the clinical development programme, treatment with dapagliflozin was not associated with any clinically relevant changes in markers of bone formation and resorption. Also there was no indication of an increased risk of fractures in patients with mild renal impairment or normal renal function. All fractures should be reported in the eCRF.

6.4.4.11 Genital infections

Increase in the urinary excretion of glucose may create a potential substrate for genital tract pathogens. The diagnosis of vaginitis, vulvovaginitis, vulvitis or balanitis can be made basedon physical examinations, culture of secretions or a therapeutic response to treatment of fungal or other vaginal pathogens. Clinical judgment and local standards of care should apply to decisions concerning therapy. Genital infections that are serious or lead to discontinuation of IP should be reported in the eCRF.

6.4.4.12 Hypersensitivity reactions

Hypersensitivity reactions (e.g., generalized urticaria), some serious, have been reported for other SGLT2-inhibitors. However, it is not known if it is a class effect or not. Hypersensitivity reactions that are serious or lead to discontinuation of IP should be reported in the eCRF.

6.4.4.13 Amputation and related events

Patients with diabetes have an increased risk for amputations. To ensure that data on amputation will be systematically collected, amputations and related events should be recorded. Events related to amputation should be reported as AE/SAE if relevant, and details regarding the amputation procedure will be captured in a specific eCRF.

6.4.5 Reporting of serious adverse events

Investigators and other study site personnel must inform appropriate AZ representatives and TIMI via the WBDC system of any SAE that occurs in the course of the study immediately or within 24 hours of when he or she becomes aware of it. Follow-up information on SAEs must also be reported by the Investigator with the same time frame.

The AZ representative or delegate will work with the Investigator to compile all the necessary information and ensure that all the necessary information is provided to the Patient Safety data entry site within one calendar day of initial receipt for fatal and life threatening events and within three calendar days of initial receipt for all other SAEs.

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

The Investigator and/or Sponsor are responsible for informing the Ethics Committee (EC) about the SAE as per local requirements.

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

6.4.5.1 Protocol-specific exceptions to SAE reporting by the sponsor

The sponsor will separate potential cardiovascular events included in the primary objectives as well as the secondary objective from other SAEs reported by the Investigator. Events confirmed to meet the defined criteria of the CV adjudication will not be reported to health authorities to avoid unnecessary unblinding of efficacy endpoints. Events failing to meet the criteria will be processed as normal following final adjudication. (See 6.4.4.9 for further information on the adjudication of CV events).

6.4.6 Laboratory safety assessment

The laboratory variables that will be measured to assess safety and the visits at which they will be measured are shown in the Study Plan (see Table 1 and section 3.1).

The date and time of sampling will be recorded on the laboratory requisition form. A central laboratory will process the samples and results will be reported back to the site.

Due to the fasting laboratory assessments at Visit 2, 4 6, 10, 14, 18, 22 end of treatment visit/closing Visit patients will be instructed to abstain from all food and beverages for 12 hours prior to the clinic visit (drinking water and taking prescribed medications are allowed). Patients should not drink alcohol within 24 hours of each visit.

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

Regarding procedures for blood collection, labeling and shipment, see section 7.3.

For blood volume see Section 7.1.

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

6.4.6.1 Unscheduled laboratory assessments

- Patients will be tested for hematuria at the enrollment and randomization visits as well as during randomized treatment. For further details see Table 1 and Section 6.4.4.2.

- If ALT and/or AST >3 times ULN **and** increase of TB >2 times ULN (based on either local or central laboratory results), the investigator should obtain a repeated measurement at the central laboratory (and at a local laboratory in addition to the central laboratory if deemed appropriate) within 3 days (see Appendix D). If the increase is confirmed or worsens, the patient should be discontinued from IP. Similarly, an increase of ALT or AST >8 times ULN – confirmed at a repeated measurement within up to 3 days, as well as ALT or AST > 5 time ULN confirmed over a period of 14 days or more, should lead to discontinuation of IP (see Section 5.8).

- If a doubling of serum creatinine (from baseline), a serum creatinine >6.0 mg/dL (530 umol/L), a decrease in eGFR of ≥30% from baseline to eGFR <60 ml/min/1.73m2 or an eGFR value of <15 ml/min is observed, based on either a central or a local laboratory result, a new central laboratory measurement of serum creatinine must be obtained at earliest possible time.

- In addition, if a doubling of serum creatinine (from baseline), a serum creatinine >6.0 mg/dL (530 umol/L), a decrease in eGFR of ≥30% to eGFR <60 ml/min/1.73m2 or an eGFR value of <15 ml/min based on a central laboratory result, a new central laboratory measurement of serum creatinine must be obtained after at least four weeks.

- If the creatinine clearance (CrCl, based on Cockroft-Gault) falls below 45 ml/min the patient should be scheduled for a re-test within 4 days whenever possible. A new central laboratory measurement of serum creatinine must be obtained, creatinine clearance will be calculated and provided by the central laboratory.

- If at any time the patient´s CrCl (based on Cockroft-Gault) falls below 30 ml/min calculated at the central laboratory and confirmed at a repeated central laboratory measurement (to be obtained within 4 days, whenever possible). A new central laboratory measurement of serum creatinine must be obtained, creatinine clearance will be calculated and provided by the central laboratory.

- For cases of suspected urinary tract infection, a properly collected set of urine cultures should be obtained and sent to a local laboratory prior to initiation of antibiotic therapy.

- For other safety laboratory follow-up at the discretion of the investigator, as available in the unscheduled laboratory kit.

6.4.7 Physical examination

A physical examination including cardiovascular system will be performed at Visit 2 and End of Treatment or Closing Visit.

An optional physical examination may be performed at any other in-office visit to evaluate an AE or as judged by the Investigator.

6.4.8 Vital signs

Vital signs will be assessed following the study plan (see Table 1). Body weight and height will be measured as part of vital signs.

6.4.8.1 Pulse and blood pressure

Pulse and BP will be measured twice (5 minutes apart) before any blood sampling is done using a standardized cuff adapted to the size of the patient's arm after the patient has been sitting and resting for least 5 minutes. For timings of assessments, see Table 1.

6.4.8.2 Body weight and height

The patient's body weight will be recorded in kilograms, to 1 decimal place, with light clothing and no shoes and recorded at Visits 1 and each subsequent study visit. The patient's height will be recorded at Visit 1 in centimeters, with no shoes.

6.4.8.3 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 expiration. The hip circumference is measured in the standing position at the maximal circumference over the buttocks with a measuring tape.

6.4.8.4 Waist-hip ratio (WHR)

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

6.5 Patient reported outcomes (PRO) (Not applicable)

6.6 Pharmacokinetics (Not applicable)

6.7 Pharmacodynamics (Not applicable)

[redacted]

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 3 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	5 (approx.)	9	45 (approx.)
	Hematology	2 (approx.)	7	14 (approx.)
HbA1c		2 (approx.)	8	16 (approx.)
Total				75-160[ab]

[a] Includes a margin for additional visits in case study lasts >72 months as well as for unscheduled sampling

[b] [redacted] biomarker samples (see Appendix I, where applicable) is an additional approximately 32 mL.

7.2 Handling, storage and destruction of biological samples

After the analyses are complete the samples will be either completely consumed during the analytical process, disposed of after analysis or retained for further use as described in section 7.2.1. A Laboratory Manual for Investigators giving detailed instructions will be provided to each study center prior to the start of the study. The Investigator should follow the procedures defined in the Laboratory Manual.

7.2.1 Handling, storage and destruction of biological samples for future research

Biological samples for future research can be retained at AstraZeneca, or a representative on behalf of AstraZeneca, for a maximum of 20 years following the finalization of the CSR. The results from future analysis will not be reported in the CSR but separately in a CSR Amendment/Errata/Scientific Report or Scientific Publication. [redacted] For further guidance regarding the optional biomarker samples refer to Appendix I.

7.3 Labeling and shipment of biohazard samples

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

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labeling, 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 center keeps full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

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

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

7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, AZ is not obligated to destroy the results of this research.

As collection of the biological samples is an optional part of the study, then the patient may continue in the study.

The Principal Investigator:

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

AZ ensure the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2 Patient data protection

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

AZ will not provide individual [redacted] 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 [redacted]c data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the [redacted] data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AZ Physician or representative or an Investigator might know a patient's identity and also have access to his or her [redacted] data. Also Regulatory authorities

may require access to the relevant files, though the patient's medical information and the [redacted] files would remain physically separate.

8.3 Ethics and regulatory review

An Ethics Committee (EC) or Institutional Review Board (IRB) should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the ECs/IRBs should be given in writing. The Investigator should submit the written approval to the AZ representative before enrollment of any patient into the study.

The ECs/IRBs should approve all advertising used to recruit patients for the study.

AZ or its delegate should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the ECs/IRBs annually.

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

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

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

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

8.4 Informed consent

The Principal Investigator(s) at each center will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time

- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an EC/IRB.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Study Chairman and AZ, TIMI and Hadassah.

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

The amendment is to be approved by the relevant ECs/IRBs and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AZ or its delegate will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to ECs/IRBs see Section 8.3.

If a protocol amendment requires a change to a center's ICF, AZ and the center's ECs/IRBs are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each ECs/IRBs.

8.6 Audits and inspections

Authorized representatives of AZ, a regulatory authority, or an EC/IRB may perform audits or inspections at the center on historical performance, including retention records and 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 Clinical Study Protocol, (GCP, ICH guidelines and any applicable regulatory requirements). The Investigator will contact AZ immediately if contacted by a regulatory agency about an inspection at the center.

9. STUDY MANAGEMENT BY ASTRAZENECA OR DELEGATE

9.1 Pre-study activities

Sites that the TIMI study organization, the Hadassah Medical Center, BMS and/or AZ have had previous experience with will participate in the study. A new determination of the suitability of the Investigator site will be based on a number of factors, including but not limited to historical performance including retention records and confirmatory telephone contact with site personnel. In cases where the site personnel are markedly changed or the site has not worked previously with the TIMI study organization, the Hadassah Medical Center, BMS and/or AZ, further examination may be needed. The information on the site suitability will be documented.

9.2 Training of study site personnel

Before the first patient is entered into the study, a representative of the TIMI study Group, of the Hadassah Medical Center or an AZ or other 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 the WBDC system(s) utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of the 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

Monitoring of the site, site documents and data will be performed based on the monitoring plan.

Site visits will occur on a regularly scheduled basis unless “for cause”.

The monitor will confirm the following:

- There is a complete patient file for each patient enrolled in the study
- There is an informed consent for the patient and this consent process has been administered correctly
- The monitor will review the patient file to ensure that all study endpoints (i.e., the composite endpoint of CV death, MI or ischemic stroke and other secondary endpoints) have been recorded onto the eCRF and that the adjudication packets are complete. Likewise, the monitor will review all AEs or SAEs that have been recorded on the eCRF. Also key is the need to ensure that all events and data are adequately captured according to the Event Reporting Manual.

At the time of the monitor visit, it is appropriate to discuss the study progress with site personnel to confirm all processes and procedures in the protocol are being adhered to correctly, data in the eCRFs are being recorded in a timely manner, [redacted] samples are being handled correctly, and IP accountability checks are being performed.

9.3.1 Source data

Refer to the Clinical Study Agreement (CSA) for location of source data.

9.4 Study agreements

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

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

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.5 Study timetable and end of study

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

The study is expected to start in Q2 2013 and to end by Q2 2019.

However, as the study is event driven, the accrual of the predetermined number of events included in the composite endpoint of CV death, MI or ischemic stroke will finally determine the duration of the study.

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

10. DATA MANAGEMENT BY COGNIZANT DMG

The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgery history will be classified according to the terminology of the latest version the MedDRA. Medications will be classified according to the AZDD (AstraZeneca Drug Dictionary).

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Management of external data

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

Serious Adverse Event (SAE) Reconciliation

SAE Reconciliation Reports are produced and reconciled with Patient Safety database and/or the Investigational Site.

Management of [redacted] data

[redacted] data generated in this study will be stored in the AZ 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 AZ, and/or TIMI Study Group secure databases to facilitate exploratory [redacted] analyses.

Any results from this [redacted] will be reported separately from the clinical study report for the main study.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of efficacy variable(s)

The co-primary efficacy endpoints are MACE (composite of CV death, MI or ischemic stroke) and the composite of CV death or heart failure. Each will be evaluated as the time to the first event included in the composite. The general intent is to analyze patients from the date of randomization up until the date of study closure visit. For the primary endpoint, the time of event will be determined by the adjudicated date of first primary event. Patients without an adjudicated primary event will be censored at the earliest date among the following: non-CV death, withdrawal of consent, and last documented contact (e.g. the study closure visit). The last documented contact may be by office visit or by telephone call directly with the patient or by contact with a caregiver where it is possible to gain knowledge of possible CV events or death. Other sources of contact may also include written response to a mailed inquiry or email, and review of medical records.

The rules for censoring for the secondary time to event endpoints are the same, with the two exceptions: 1) that CV death will be included as a censoring point for the endpoint of hospitalization for heart failure and 2) non-CV deaths are events for the endpoint of all-cause mortality (and not censoring points).

A patient may have 1 or more events. However, only a patient's first occurring event will contribute to the analysis of each specified endpoints.

Only events adjudicated and confirmed by the CEC will be included in the time-to-event endpoints.

11.2 Calculation or derivation of safety variable(s)

The baseline value of each safety laboratory test or physical exam endpoint is defined as the last assessment on or before the date of randomization. Change from baseline will be calculated.

11.2.1 Other significant adverse events (OAE)

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

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

11.3 Calculation of renal variables

The following formulas will be used to determine creatinine clearance and estimate glomerular filtration rate.

Estimated creatinine clearance using the method of Cockcroft and Gault:

$$CrCl = \frac{(140 - age) \times (weight\ in\ kg)}{serum\ creatinine\ (mg/dL) \times 72} \quad (\times 0.85\ for\ females)$$

Estimated GFR using MDRD equation:

$eGFR\ (mL/min/1.73m^2) = 175 \times (SCr)^{-1.154} \times (Age)^{-0.203} \times (0.742\ if\ female) \times (1.212\ if\ black)$

Estimated GFR using CKD-EPI equation (Levey et al 2009):

$eGFR\ (mL/min/1.73m^2) = 141 \times \min(SCr/k,1)^{a} \times \max(SCr/k,1)^{-1.209} \times 0.993^{Age} \times [1.018\ if\ female] \times [1.159\ if\ black]$

k is 0.7 for females and 0.9 for males, a is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/k or 1, and max indicates the maximum of SCr/k or 1.

11.4 Calculation or derivation of patient reported outcome variables (Not applicable)

11.5 Calculation or derivation of pharmacokinetic variables (Not applicable)

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

[redacted]

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 Full analysis set (FAS)

All patients who have been randomized to study will be included irrespective of their protocol adherence and continued participation in the study. Patients will be analyzed according to their randomized IP assignment (not to which treatment they actually received) irrespective of whether the event occurred before or following discontinuation of IP. Patients who withdraw consent to participate in the study (or are lost to follow-up) will be included up to the date of

their study termination except for vital status known through public records (for use in the analysis of all cause mortality). All primary and secondary variables will be analyzed using the FAS. The FAS will be considered the primary analysis set for the primary and secondary variables and for the exploratory efficacy variables.

12.1.2 Safety analysis set

All patients who received at least 1 dose of randomized dapagliflozin or placebo and who have data observed at any time after first randomized dose till the end of the study will be included in the safety population. Throughout the safety results sections, erroneously treated patients (patients randomized to one of the treatment groups but actually given the other treatment) will be accounted for in the actual treatment group. Patients with erroneous treatment would be analyzed according to that treatment only if they only received the erroneous treatment and none of the correct treatment. All safety variables, except for the non inferiority testing of the primary composite variable, will be analyzed using the safety analysis set. The Safety analysis set will be considered the primary analysis set for malignancies and fractures.

12.1.3 An on-treatment analysis set

An on-treatment analysis set will also be created. The on-treatment population is defined as all randomized patients who have received at least one dose of investigational product and who have data observed at any time after first randomized dose till the end of the study. However, only those observations collected during treatment with IP or within a certain number of days of the last dose of investigational product will be part of this analysis set, as noted below:

- Primary, secondary, and categorical exploratory variables: 30 days
- Continuous exploratory and safety variables (e.g. changes in lab values and vital signs): 7 days
- SAEs: 30 days

AEs of special interest, that are not serious: 7days

12.2 Methods of statistical analyses

12.2.1 Demographics and baseline characteristics

Demographic and baseline characteristics will be summarized, using frequency distributions and summary statistics based on the FAS data set, for each treatment group as well as for all patients combined.

Additional summaries of demographic and baseline characteristics may be performed for specific subgroups of interest.

12.2.2 Primary variables

The primary variables are the time to first event included in the composite endpoint of CV death, MI, or ischemic stroke and the time to first event included in the composite endpoint of

CV death or hospitalization for heart failure. The primary analysis will be based on the FAS population, using events adjudicated and confirmed by the CEC.

Hazard Ratios (HR) and Confidence Intervals (CIs) will be derived from a Cox proportional hazards model with a factor for treatment group stratified by CV risk category (established CV disease, or multiple risk factors without established CV disease) and baseline hematuria.

The assumption of proportional hazards for the factor for treatment groups will be assessed visually using log-cumulative hazard plots. The effect of any departures from proportional hazards will be discussed as part of the presentation of results of the analyses. Additionally a stratified log-rank test will be assessed to further investigate the assumption of proportional hazards. Additionally, the assumption of proportional hazards for the factor for treatment group will be evaluated with a model which assess the treatment effect in categorized time intervals (< 1 year and >= 1 year).

The primary analysis will use each patient's last contact as the censoring date for patients that complete the study without any primary events. To test the robustness of the primary endpoint results, censoring at the fixed calendar end-of-study date (the date that the executive committee instructs the sites to commence final visits) will be used in a sensitivity analysis.

The contribution of each component of each of the primary composite endpoints to the overall treatment effect will be examined. Methods similar to those described for the primary analysis will be used to separately analyze the time from randomization to the first occurrence of each component of the primary composite endpoints. This will be done for CV death all MI, all ischemic stroke and all hospitalizations for heart failure. Nominal p-values will be presented. Non-fatal MI and Non-fatal stroke will only be presented descriptively.

Subgroup analyses to evaluate variation in treatment effect will be performed on the basis of tests for interaction using the Cox model. Tests for the interaction with treatment for each of these subgroup variables will be performed. Additionally, Cox proportional hazards models will be performed to examine treatment effects within each subgroup separately. The p-values for the subgroup analyses will not be adjusted for multiple comparisons as the tests are exploratory and will be interpreted descriptively. HRs and 95% confidence intervals will be reported for each subgroup. Relevant subgroups will be detailed in the SAP.

A sensitivity analysis of the primary objectives will be performed using an on-treatment analysis set. Additionally, exploratory proportional hazards models will determine whether control for baseline CV risk category and baseline hematuria has any effect on the relative risk associated with randomized treatment.

HRs and CIs for overall analysis and subgroups will be presented with forest plots. Kaplan Meier estimates of the cumulative incidence to the first occurrence of any event in the primary endpoint will be calculated and plotted, for overall analysis and for the three individual components.

Kaplan-Meier plots by CV risk category will be presented, by treatment, for overall analysis and for the individual components.

Control of Type I error

The Type I error rate for the analysis of the primary endpoint will be adjusted for the interim analyses performed by the DMC.

For the primary endpoint the following hypothesis will be tested at the 2.31% 1-sided level:

H_{01}: HR [dapagliflozin:placebo] ≥1.30

vs

H_{11}: HR [dapagliflozin:placebo] <1.30.

If the null hypothesis is rejected, then an increased CV risk of 1.30 for dapagliflozin-treated patients is ruled out and superiority will then be tested in terms of:

H_{02}: HR [dapagliflozin:placebo] ≥1

vs

H_{12}: HR [dapagliflozin:placebo] <1

and

H_{03}: HR [dapagliflozin:placebo] ≥1

vs

H_{13}: HR [dapagliflozin:placebo] <1

in a closed test procedure. See Section 12.2.4 for a description of the full closed testing procedure including the secondary variables.

12.2.3 Secondary variables

Secondary efficacy time to event variables will be analyzed similar to the primary variable.

For time to decrease of ≥40% to eGFR <60 ml/min/1.73m^2 or an eGFR value of <15 ml/min/1.73m^2, confirmation is required, meaning that the observation should be present at two central laboratory measurements separated with at least 4 weeks. Time to onset would be

the first of the two subsequent laboratory assessments. If no confirmation can be obtained the observation will not be included in the main analyses, but a sensitivity analysis will be conducted including also all non confirmed observations. Initiation of renal replacement therapy is defined as dialysis for at least 90 days or kidney transplantation.

12.2.4 Summary of closed test procedure

Type I error will be controlled at a one-sided 0.025 level for multiplicity across primary and secondary objectives and in consideration of planned interim analyses. Table 4 provides a plan for how the procedure will function.

Table 4 Confirmatory Testing Procedures Using One-sided Alphas

H1: Non-inferiority for the primary composite endpoint (alpha = 0.0231)[a]	
Now the alpha will split into independent testing of the co-primary composites in parallel	
H02: Superiority for the primary composite endpoint (alpha = 50% of primary alpha)[c]	H03: Superiority for hospitalization for heart failure or CV death (alpha = 50% of primary alpha)[c]
• Renal composite endpoint: Confirmed sustained ≥40% decrease in eGFR to eGFR <60 ml/min/1.73m^2 and/or ESRD (initiation of renal replacement therapy or kidney transplantation, confirmed sustained eGFR <15ml/min/1.73m^2) and/or renal or CV death [b]	
• All-cause mortality[d]	

[a] The alpha of 0.0231 represents the final one-sided significance level to be used when the study has been completed in entirety. At an interim analysis, testing for superiority will occur, and the alpha for superiority will be replaced by 0.000095 at the first and 0.00614 at the second interims. Non-inferiority will be tested only at the completion of the study.

[b] With the exception of all-cause mortality, secondary endpoints will only be tested once, at the completion of the trial or if the decision is made to terminate the trial early. The alpha will be controlled for the overall Type I error across the primary and secondary endpoints and across the interims and final analysis.

[c] If this analysis occurs at completion of the trial, the alpha will be 0.01155 (50% of 0.0231) for superiority for MACE and 0.01155 (50% of 0.0231) for superiority for hospitalization for heart failure or CV death. Details of the closed testing procedure and control of multiplicity across the primary and secondary objectives are contained within the statistical analyses plan section 4.4.3.

[d] All-cause mortality is assessed at interim analyses as part of the stopping guidelines. At the interim analyses, it will be tested second following MACE. If the study terminates at an interim analysis, all-cause mortality will remain as the 2nd endpoint following the test for superiority of MACE. If the final analysis occurs at the completion of the trial, all-cause mortality will be tested as presented in this table.

12.2.5 Exploratory efficacy variables

Change from baseline to each visit measurement for HbA1c, BP variables, and other non-categorical variables will be analyzed by a repeated measures method. The model will include terms for treatment group, CV risk category, baseline hematuria, visit, visit*treatment group and baseline as a covariate. The model will be used to derive a least squares estimate of the treatment difference with 95% confidence interval and corresponding two-sided nominal p-

value. Further, two-sided 95% confidence intervals for the mean change within each treatment group will be calculated. Missing data will not be imputed. This model will be used to assess the timepoints at 2 and 3 years as specifically noted in the objectives although summaries at all visits will also be presented.

For time to albuminuria/macroalbuminuria, and for time to decrease in eGFR (using CKD-EPI equation), confirmation is required, meaning that the observation should be present at two central laboratory measurements separated with at least 4 weeks. Time to onset would be the first of the two subsequent laboratory assessments. If no confirmation can be obtained the observation will not be included in any analyses. Initiation of renal replacement therapy is defined as dialysis for at least 90 days or kidney transplantation.

Change from baseline to each visit measurement for body weight will be analyzed by a repeated measures method. All non missing visit data will be used. The model will include terms for treatment group, CV risk category, baseline hematuria, visit, visit*treatment group and baseline measurement as a covariate. The model will be used to derive a least squares estimate of the treatment difference with 95% confidence interval and corresponding two-sided p-value. Further, two-sided 95% confidence intervals for the mean change within each treatment group will be calculated. Missing data will not be imputed. This model will be used to assess the timepoint of 3 years corresponding to the objectives although summaries at all visits will also be presented.

Percent change from baseline to each visit measurement for Albumin to Creatinine ratio will be analyzed by a repeated measures method. All non missing visit data will be used. The model will include terms for treatment group, CV risk category, baseline hematuria, visit, visit*treatment group and baseline measurement as a covariate. The 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 percent change within each treatment group will be calculated. Missing data will not be imputed. This model will be used to assess the timepoint of 3 years corresponding to the objectives although summaries at all visits will also be presented. If data suggests, the analysis might be performed applying a logarithm scale instead.

The proportions of patients with at least a 5% body weight loss after 2 and 3 years compared to baseline will be analyzed using the methodology of Cochran-Mantel-Haenszel (using CMH option in PROC FREQ procedure, SAS version 8.2 or higher). Estimates for treatment effects and differences between treatment groups will be obtained along with 95% confidence intervals and p-values using this methodology with stratification for CV risk category and baseline hematuria. The same method will be repeated for the additional body weight endpoints: proportions of patients with at least a 10% body weight loss after 2 and 3 years.

The body weight analyses will be performed for all patients and also for the subgroup with patients taking insulin during the study excluded.

All body weight analyses will also be performed for the subgroup of patients with BMI greater than 30 separately.

Retinal laser and/or intraocular treatment due to development of and/or deterioration in diabetic retinopathy, all strokes, need for an increase in dose of current anti-diabetes medication or in addition of new anti-diabetes medication, initiation of insulin therapy in patients not receiving insulin therapy at baseline, major hypoglycemia, hospitalization for hypoglycemia and regression in albuminuria, will be examined using statistics according to analysis of proportions that will include 95% confidence intervals for treatment effects and for the comparison between treatments as well as nominal 2-sided p-values. Time to event analyses will also be performed.

12.2.6 Safety analyses

The number and percent of patients with adverse events, leading to discontinuation of IP, serious adverse events and adverse events of special interest will be summarized by system organ class and preferred term for each treatment group using terms coded by MedDRA. The assessment will include an evaluation of the incidence of bladder and breast cancers, liver injury and bone fractures. All events of possible malignancies (excluding non-melanoma skin cancer) and liver injury will be independently adjudicated, in addition to the cardiovascular endpoints.
Incidence rate ratios and corresponding confidence intervals will be provided using exact methods with Proc StatXact for the Mantel-Haenszel relative risk estimates for Bladder cancer and for Breast cancer.

Changes from baseline to each scheduled time point for each clinical laboratory test, including estimated GFR and estimated creatinine clearance and non-categorical vital sign measurements will be summarized by treatment group. In addition, the number and percent of patients with a marked abnormality in clinical laboratory tests will be summarized by treatment group.

For safety analyses other than the primary endpoint, summaries will be provided using both on-treatment observations and using all observations regardless of whether patients are on or off study treatment.

12.2.7 Considerations of incomplete follow-up

It is expected that complete information on the components of the primary composite endpoint (and as much as possible of the eCRF data for patients contacted by telephone) will be obtained for all treatment dropouts (patients who prematurely discontinue IP), unless they refuse any form of follow-up and withdraw consent or are lost to follow-up. Thus, event free treatment dropouts will not be censored before study closure (if not lost to follow-up/withdrawn consent) in the primary FAS analysis. Other points of censoring, e.g., last in-person visit, may be considered in sensitivity analyses.

The time-to-event analysis (Cox regression) relies on the assumption of non-informative censoring. To examine this assumption, presence of informative censoring will be assessed by comparing the event rates between subjects with incomplete follow-up and subjects with complete follow-up. Potential informative censoring will be investigated. The rates of study

dropouts will also be compared between treatment arms to assess potential differential dropouts.

Depending on the results of the above assessments concerning informative censoring, appropriate sensitivity analyses may be performed to assess the robustness of the primary analysis of treatment effect on the primary composite endpoint and all-cause mortality.

The options of sensitivity analyses may include, but are not limited to:

- Imputing expected number of events for withdrawn subjects using event rate similar to that observed in the study and allocating these residual events in different proportions to the treatment groups
- CV death replaced with all-cause mortality, including vital status information from patients who have withdrawn consent (or are lost to follow-up)
- Censoring at the last in-person visit for event free patients after permanent premature discontinuation of IP.

12.2.8 Interim analyses

A DMC will be appointed jointly by the Sponsors and the academic leadership of the study. The DMC will be responsible for safeguarding the interests of the patients in the outcome study by assessing the safety of the intervention during the trial, and for reviewing the overall conduct of the clinical trial. In addition, the DMC will have the responsibility to assess the efficacy data of the interim analysis and make recommendations based upon stopping guidelines. A detailed plan of interim monitoring for bladder cancer will be provided in the Statistical Analysis Plan (SAP) and the DMC Charter.

We plan a group sequential design with 2 interim analyses to assess the MACE and all-cause mortality. The analyses will take place at 1/3 and 2/3 of the primary events using an O'Brien–Fleming alpha-spending rule. The interim analyses will assess superiority of dapagliflozin to placebo for MACE because the study will only be considered for early termination if superiority is met. All-cause mortality is included as an endpoint to the interim analyses for an additional assessment of benefit. The first interim analysis will have a one-sided alpha level of 0.00095. The second interim analysis will have a one-sided alpha level of 0.00614. According to the O'Brien-Fleming spending rule this will leave a 1-sided alpha level of 0.023095 for the final analysis. At each interim analysis, MACE will be tested first at the specified alpha level, and if found to be statistically significant, all-cause mortality will then be assessed for significance at the same alpha level. If superiority is achieved for both endpoints, an action is triggered whereby the DMC will evaluate the CV data and safety data, including bladder cancers and liver events, to determine if benefit is unequivocal and overwhelming such that the DMC recommends ending the study.

With the exception of all-cause mortality, secondary endpoints will only be tested at the completion of the trial or if the decision is made to terminate the trial early. The alpha will be controlled for the overall Type I error across the primary and secondary endpoints and across

the interims and final analysis. The same alpha level used for MACE at the time of stopping the trial will also be used for testing the secondary endpoints according to the confirmatory testing procedure as explained in detail in Table 4.

If, outside of the 2 pre-specified interim efficacy analyses, the DMC feels compelled for safety concerns to examine efficacy data formally with consideration of stopping the trial early for overwhelming efficacy, then the alpha applied to such efficacy analyses would be determined according to the O'Brien-Fleming spending function, and subsequent alpha-levels for any remaining planned efficacy interim and final analyses would also be adjusted according to the O'Brien-Fleming spending function to maintain the control of the Type I error. Any unscheduled interim analysis would evaluate both MACE and all-cause mortality in the same way as for a scheduled interim analysis

The SEER rate for the general US population of 0.044% per person-year for bladder cancer may be conservative; higher bladder cancer rates could be observed in this trial. If the SEER rate is adjusted to reflect an increased risk in a diabetes population, an estimated annual rate of 0.06% could occur.

We assume that the rate of bladder cancers observed in this study will be 0.06%, which would correspond to a total of 46 bladder cancers.

Interim monitoring for bladder cancers is planned for the purposes of communicating potential signals with regulatory authorities. The accumulation of patients with bladder cancer would suggest 4 interim analyses at 8, 16, 24 and 32 events. The interim analysis would take place at approximately 26, 37, 46 and 55 months. The interim analyses would be assessed at an overall alpha-level of 0.10 with a Pocock spending rule. If an interim analysis is significant, the DMC would inform others according to a strict communication plan. The number of interim analyses for bladder cancers may be adjusted if the event rate is different than expected.

12.3 Determination of sample size

1390 MACE events will be required to have 85% power to demonstrate superiority of dapagliflozin to placebo if the true HR is 0.85, i.e., a 15% relative risk reduction, with a one-sided alpha of 2.31%. To achieve this number of MACE events, we have designed the study with the following condition. 17150 randomized patients will be required for the study, with an assumed annual event rate of 2.1% on placebo, and an annual study withdrawal rate of 1.0% over a 3-year accrual period and 3-year minimum follow-up. With above assumptions and 1390 MACE events it is estimated to have >99% power to test the hypothesis of non-inferiority H0:HR [dapa:placebo] $\geq$ 1.3 vs H1:HR < 1.3.

We anticipate approximately 770 events for the composite of CV death or hospitalization for heart failure, which would provide 87% power to detect a hazard ratio of 0.80 with a 1-sided alpha of 2.31%. The alpha levels at the final analysis will depend on the alpha spending

function, the observed number of events for each endpoint at interim and final analyses and the hierarchical testing procedure.

The final sample size will depend on multiple factors including the rate of accrual of primary endpoint events and rate of IP discontinuation. Therefore the sample size may be changed if planning assumptions are modified by blinded data review. The Executive Committee of the trial will monitor the aggregate event rate and rate of IP discontinuation and may alter the sample size, number of primary endpoints or duration of the trial in accordance with the goals of the trial. Such changes will be made in consultation with the Sponsor.

Assuming the rate of bladder cancer is 0.06% per person-year, 46 bladder cancers may be expected during the study. With 46 events, a relative risk of 2.28 can be ruled out with one-sided 97.5% confidence and 80% power under the hypothesis that the true relative risk is 1. In parallel, a difference in incidence rates of 0.049% could be ruled out using the same assumptions.

The SEER rate for the general US population of 0.044% per person-year for bladder cancer may be conservative; higher bladder cancer rates could be observed in this trial. If the SEER rate is adjusted to reflect an increased risk in a diabetes population, an estimated annual rate of 0.06% could occur. The rate observed for dapagliflozin in the complete Phase 2b and 3 programs was 0.16% per person-year. When those patients with baseline hematuria are screened out, an annual rate of 0.07% was found among the dapagliflozin-treated patients and 0.046% amongst all treated patients (dapagliflozin and comparator combined). Detection of early bladder cancers may be higher than for the general population (i.e., SEER) since this study proposal plans a more thorough assessment of hematuria following randomization than would be found in standard medical practice. Table 5 illustrates the levels of risk that can be ruled out at different event rates of bladder cancer.

Table 5 Levels of bladder cancer relative risks and incidence rate differences that can be ruled out under different assumptions

			One-sided 97.5% confidence level		
Event rate	Expected number of events	Power	True RR that can be ruled out	True rate diff that can be ruled out	Max value that can be observed and rule out true RR, rate diff[a]
Bladder cancers					
0.044%	34	80%	2.62	0.042%	1.33, 0.013%
0.06%	46	80%	2.28	0.049%	1.28, 0.015%
0.07%	54	80%	2.14	0.053%	1.26, 0.016%
0.16%	123	80%	1.66	0.080%	1.16, 0.024%

RR = relative risk; risk diff = absolute incidence rate difference

[a] The max values that can be observed and rule out the true RR and rate diff are the same for both confidence levels

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

12.4 Data monitoring committee

12.4.1 Clinical Event Adjudication Committee

An independent, blinded CEC will be appointed jointly by the Sponsors and the academic leadership of the study.

The CEC will adjudicate all primary and secondary CV endpoints. Investigators will report potential events via electronic case report forms (CRFs) in real time. Additionally, the clinical trial database will be searched at least monthly for other AEs, or laboratory data that might also indicate a potential event. Once a potential event has been identified, a complete package of information will be collected with the goal to send to the CEC within two weeks of identification. A packet would be considered complete after translation and would allow for assessment if all required data are present. The CEC reviewers would set a target to evaluate the complete package within four weeks of receipt.

All possible malignancies (excluding non-melanoma skin cancer), pre-defined liver enzyme elevations and all events of potential diabetic ketoacidosis will undergo adjudication.

The CEC will determine the probability that drug-induced liver injury (DILI) is the cause of liver related abnormalities, included but not limited to:

- Hepatic disorders leading to discontinuation from study treatment and/or death
- Significant liver laboratory abnormalities

Additional details are provided in the CEC charter.

12.4.2 Data Monitoring Committee (DMC)

An independent DMC will be appointed jointly by the Sponsors and the academic leadership of the study.

The DMC will be responsible for safeguarding the interests of the patients in the outcome study by assessing the safety of the intervention during the trial, and for reviewing the overall conduct of the clinical trial. They will review overall safety in the trial and specifically the incidence of bladder cancers and potential drug induced liver injury (DILI) cases. In addition, the DMC will have the responsibility to assess the efficacy data of the interim analysis and

decide if stopping guidelines are met. The DMC will have access to the individual treatment codes and will be able to merge these with the collected study data while the study is ongoing.

The DMC charter will be prepared to detail precise roles and responsibilities and procedures to ensure maintenance of the blinding and integrity of the study in the review of accumulating data and interactions with the Executive Committee.

12.5 Study organization

12.5.1 Committee organizations

In consideration of the large nature of this trial, several key groups will act as alliances to provide direction and guidance throughout this study. The Executive and Steering Committees focus mainly on the scientific aspects of the trial whereas the Operations Committee and Joint Working Group are study tactics and operational in nature.

All committee meetings, unless otherwise noted, are considered open in that others may join in a listening-only mode.

A joint governance process will be issued by members of the academic institutions and the Sponsors.

12.5.1.1 Executive Committee

The Executive Committee will be responsible for the overall design, conduct, and supervision of the study, including the development of the committee and any protocol amendments. The EC will make a recommendation to the Sponsor based on the information from the DMC. The Executive Committee membership will comprise designated academic leaders and members of the Sponsor.

12.5.1.2 Steering Committee

The Steering Committee will be responsible for providing clinical guidance on study implementation and conduct of the study, and interpretation of results. The Steering Committee will comprise designated members from among the Principal Investigators (PI) and recognized leaders in the field of diabetes and CV disease, and all members of the Executive Committee.

12.5.1.3 Strategy and Tactics Groups

The Strategy and Tactics Group will include key members from the academic leadership institutions for the study in addition to representatives from the Sponsors. This group is charged with developing strategies and tactics of key aspects of this study providing guidance in aspects of study operations.

12.5.1.4 Joint Working Group

The Joint Working Group will include key leaders of the study aspects from the academic institutions and the study Sponsors. The group, meeting frequently, will direct, on a daily level, all aspects of study operations.

12.5.2 Study Project Operational Procedures (TIMI)

For this study, a Project Operational Procedures (POP) manual was developed jointly between AstraZeneca, BMS, the TIMI study group and Hadassah Medical Center. Updates to the POP will be developed jointly between AstraZeneca, the TIMI study group and Hadassah Medical Center.

All procedures (aligned with Standard Operating Procedures), Operational Procedural Information and guidances will be described in detail in the POP. As such, the POP will supersede internal AZ documents where there is a case of overlapping procedures. Any compliance monitoring will be performed using the procedures, processes, or guidances listed in the POP.

The POP will be reviewed, discussed and signed by members of senior management of both the Sponsors and academic institutions.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and trial contacts

The PI is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such (see Section 6.4.5)**

In the case of a medical emergency, the Investigator may contact the TIMI Study Hotline.

The TIMI hotline # [redacted] **or** [redacted]

The treatment code may not be broken unless in an emergency situation when the appropriate management of the patient necessitates knowledge of the treatment allocation. In such an emergency, the Investigator will, if time and circumstances permit, contact the TIMI Hotline prior to breaking the treatment code. If the treatment code is broken, the date, time, and reason should be recorded and the Investigator should sign the record (see also Section 5.4.2).

For reporting of unsolicited SAE 30 days after end of study, see Section 6.4.4.

13.2 Overdose

Overdose is defined as the accidental or intentional ingestion of any dose of investigational product that is considered both excessive and medically important. For further dosing

information please refer to the IB. Once an Investigator decides that a particular occurrence is an overdose, it must be reported as a Serious Adverse Event. If an overdose is suspected, monitoring of vital functions as well as treatment as appropriate should be performed. It should be noted that even extreme doses are likely to be asymptomatic.

If an overdose on dapagliflozin occurs in the course of the study, then Investigators or other site personnel inform appropriate TIMI representatives **immediately or within 24 hours** of when he or she becomes aware of it.

13.3 Pregnancy

All outcomes of pregnancy should be reported to the TIMI Hotline.

If a patient becomes pregnant during the course of the study investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate TIMI representatives **immediately or within 24 hours** of when he or she becomes aware of it.

The PREGREP module in the eCRF 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 AZ DES using the same procedure and timelines as for SAE reporting. An AstraZeneca paper Pregnancy Outcome Report, part 2, is used to report the outcome of the pregnancy.

The same timelines apply when outcome information is available.

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Clinical Study Protocol Appendix A

Drug Substance	Dapagliflozin
Study Code	D1693C00001
Edition Number	Final 5.0
Date	25 Sep 2016
Protocol Dated	*12 November 2012*

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

DECLARE

Dapagliflozin Effect on CardiovascuLAR Events

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients with Type 2 Diabetes

---

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

I agree to the terms of this study protocol.

AstraZeneca Research and Development site representative

[redacted]

ASTRAZENECA SIGNATURE(S)

DECLARE

Dapagliflozin Effect on CardiovascuLAR Events

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients with Type 2 Diabetes

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AstraZeneca Research and Developmen
site representative

[redacted]

ASTRAZENECA SIGNATURE(S)

DECLARE

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---

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

I agree to the terms of this study protocol.

AstraZeneca Research and Development site representative

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

DECLARE

Dapagliflozin Effect on CardiovascuLAR Events

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients with Type 2 Diabetes

---

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

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

Centre No.:

Signature:

SIGNATURE OF CO-PRINCIPAL INVESTIGATOR

DECLARE

Dapagliflozin Effect on CardiovascuLAR Events

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients with Type 2 Diabetes

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Centre No.:

Signature: 

SIGNATURE OF CO-PRINCIPAL INVESTIGATOR

DECLARE

Dapagliflozin Effect on CardiovascuLAR Events

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Centre No.:

Signature:

AstraZeneca

Clinical Study Protocol Appendix B

Drug Substance	Dapagliflozin
Study Code	D1693C00001
Edition Number	Final 2.0
Date	*25 Sep 2016*

Appendix B
Additional Safety Information

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

Life threatening

'Life-threatening' means that the patient 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 patient'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).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study (e.g. elective hospital admissions) are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study. Elective hospitalizations meeting this definition should be reported on the hospitalization pages only. Elective revascularization without an associated clinical event (e.g. new or worsening illness or disease) should be recorded on the revascularization and AE form.

Important medical event or medical intervention

Medical and scientific judgment 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, hospitalization, disability or incapacity but may jeopardize the patient 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 anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- 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 patient 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 recognized 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	D1693C00001
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Date	*12 November 2012*

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

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

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

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

Clinical Study Protocol Appendix D	
Drug Substance	Dapagliflozin
Study Code	D1693C00001
Edition Number	Final 3.0
Date	25 Sep 2016

Appendix D
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 laboratory ALT and/or AST >3X ULN should be scheduled for a follow-up visit within 3 days, whenever possible, following receipt of the initial laboratory results, to obtain repeat central laboratory ALT, AST, TB and Alkaline Phosphatase (ALP). In the event that the repeat laboratory assessments cannot be obtained within 3 days, the Investigator is encouraged to discuss possible alternatives with the TIMI. 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 ≤ 2X ULN,** the patient's medical history, including details of risk factors for liver diseases, should be evaluated for potential underlying aetiologies. In addition, specialized blood sampling will be performed to evaluate liver function as well as identify potential causes of laboratory elevation(s). The Investigator should continue to monitor the patient's liver tests every 3 days following receipt of the prior laboratory results until the ALT and AST are ≤2X ULN or until ALT and AST are at or below baseline levels. The frequency of retesting can decrease to once a week or less if abnormalities stabilize and the patient is asymptomatic. Patients should remain on study medication unless confirmatory results indicate that a criterion for discontinuation has been met or continuing study medication would be otherwise contraindicated.

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

- ALT and/or AST are >3 x ULN **and** TB >2 x ULN

- ALT and/or AST are >5 x ULN confirmed over a period of 14 days or more

- ALT and/or AST are >8 x ULN

In each of these situations, study medication will be discontinued, the Sponsor notified and the End of Treatment Visit performed within 3 days of the confirmed laboratory results (see Section 5.8.1). At the End of Treatment Visit, medical history including details of risk factors for liver diseases (if not previously assessed) will be requested and additional blood sampling performed (Hy's law panel, see detailed below).

A referral consultation to a hepatologist or gastroenterologist (specializing in liver abnormalities) should be obtained.

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

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.

Guidance on Assessment of Hepatic Laboratory Abnormalities

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

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

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

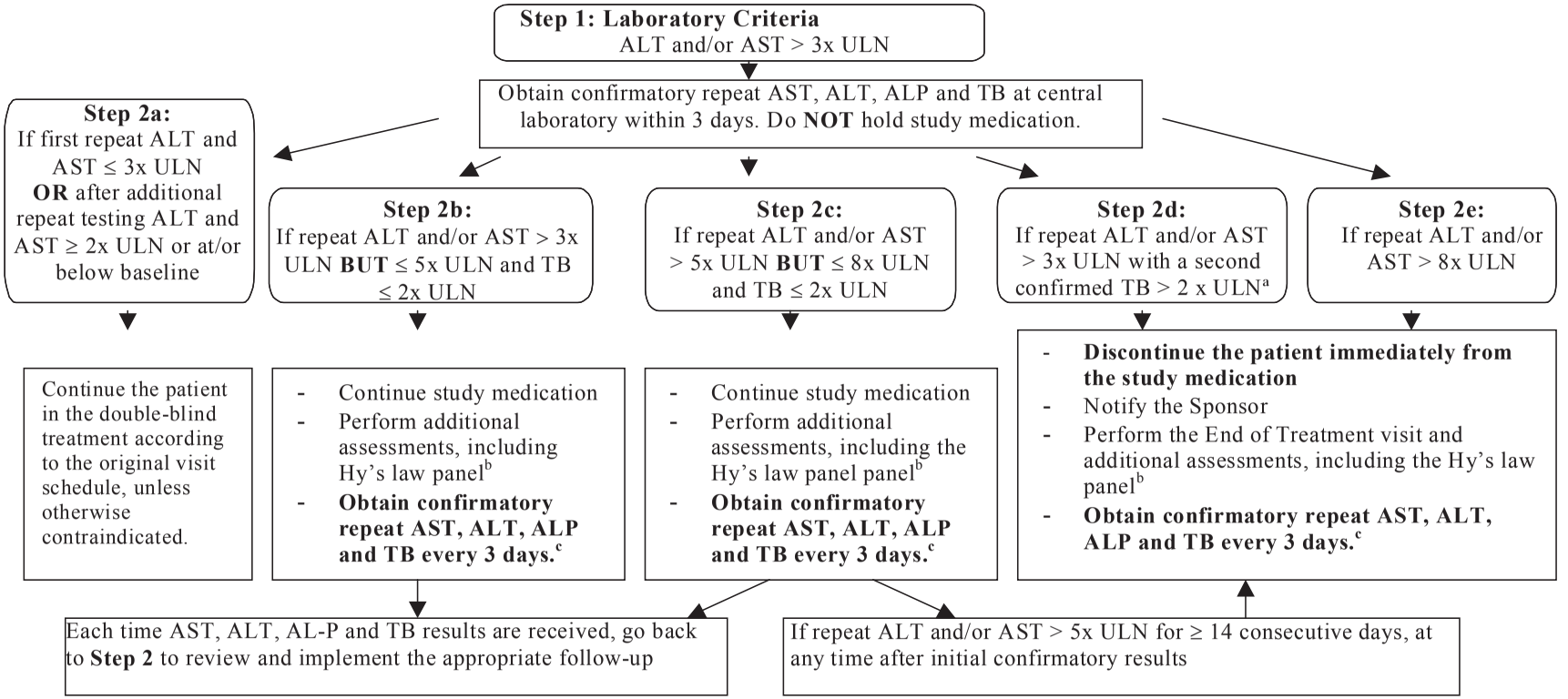
Hy's law Panel

For patients who are being monitored frequently as a result of confirmed AST and/or ALT >3X ULN, additional central laboratory tests should 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
- Cytomegalovirus (CMV) IgM Ab
- Herpes Simplex Virus (HSV) 1 and 2
- Ceruloplasmin
- Toxoplasmosis
- Alpha-1 antitrypsin

For specific details regarding the Hy's law 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 ≤ 2 x ULN at Step 1 should be followed according to Step 2b. Patients with an initial TB and confirmatory repeat TB > 2x ULN should be followed according to Step 2d.

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

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Clinical Study Protocol Appendix E	
Drug Substance	Dapagliflozin
Study Code	D1693C00001
Edition Number	Final 2.0
Date	19 December 2013

Appendix E
Disease State Definitions

DISEASE STATE DEFINITIONS

1. Type 2 Diabetes Mellitus (T2DM)

- Diagnosis of T2DM can be based on the following:
  - Prior documentation of type 2 diabetes AND/OR
  - Treatment with anti-hyperglycemic medications and/or diet AND/OR
  - ADA criteria: fasting >126 mg/dl (7.0 mmol/L) or HbA1C ≥6.5% or 2-h plasma glucose≥200 mg/dl (11.1 mmol/L) during an oral glucose tolerance test, or a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L) in patients with classic symptoms of hyperglycemia or hyperglycemic crisis. In the absence of unequival hyperglycemia, results should be confirmed by repeat testing.

2. Cardiovascular disease:

2.1 Established Vascular Disease

- Ischemic heart disease (any of the following):
  - Documented Myocardial Infarction
  - Percutaneous Coronary Intervention
  - Coronary Artery Bypass Grafting
  - Objective Findings of Coronary Stenosis (≥ 50%) in at least 2 coronary artery territories (ie, left anterior descending, ramus intermedius, left circumflex, right coronary artery) involving the main vessel, a major branch, or a bypass graft
- Cerebrovascular disease (any of the following):
  - Documented ischemic Stroke
    - Known transient ischemic attack, primary intracerebral haemorrhage or sub-arachnoid hemorrhage do not qualify.
  - Carotid stenting or endarterectomy

  Please note, transient ischemic attack, primary intracerebral haemorrhage or sub-arachnoid hemorrhage do not qualify
- Peripheral Arterial Disease (any of the following):

- peripheral arterial intervention, stenting or surgical revascularization
- lower extremity amputation as a result of peripheral arterial obstructive disease
- Current symptoms of intermittent claudication AND ankle/brachial index (ABI) < 0.90 documented within last 12 months

OR

2.2 Multiple Cardiac Risk Factors

No known cardiovascular disease AND

- Age ≥ 55 years in men and ≥ 60 in women

AND presence of at least 1 of the following additional risk factors

- Dyslipidemia (at least one of the following)
  - Low-density lipoprotein cholesterol (LDL-C) >130 mg/dl (3.36 mmol/L) within last 12 months
  - On lipid lowering therapy prescribed by a physician for hypercholesterolemia (ie LDL-C > 130 mg/dl (3.36 mmol/L)) for greater than 12 months. This should be verified by documentation of lab value LDL-C > 130 mg/dl (3.36 mmol/L).
- Hypertension (at least one of the following)
  - BP >140/90 mm/Hg at enrollment visit. The patient must have both an elevated systolic BP (> 140 mmHg) and an elevated diastolic BP (> 90 mmHg) on both measurements (see section 6.4.8.1)
  - On anti-hypertensive therapy prescribed by a physician for blood pressure lowering
- Tobacco use (5 cigarettes/day or more for at least 1 year at randomization)

Clinical Study Protocol Appendix F	
Drug Substance	Dapagliflozin
Study Code	D1693C00001
Edition Number	Final 1.0
Date	12 November 2012

Appendix F
ADA/EASD Treatment Algorithm for Antihyperglycemic Therapy in T2DM

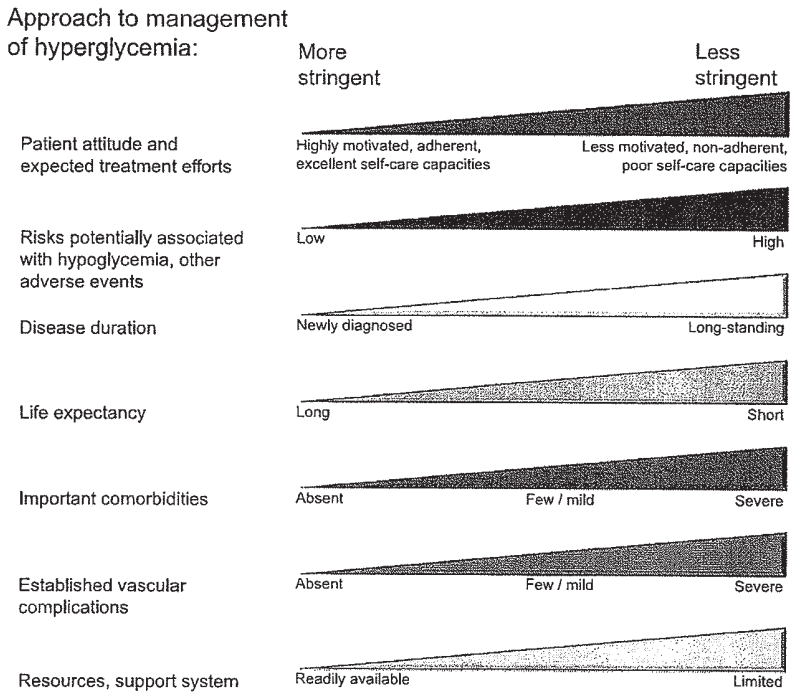


Figure 1—*Depiction of the elements of decision making used to determine appropriate efforts to achieve glycemic targets. Greater concerns about a particular domain are represented by increasing height of the ramp. Thus, characteristics/predicaments toward the left justify more stringent efforts to lower* HbA_{1c}*, whereas those toward the right are compatible with less stringent efforts. Where possible, such decisions should be made in conjunction with the patient, reflecting his or her preferences, needs, and values. This "scale" is not designed to be applied rigidly but to be used as a broad construct to help guide clinical decisions. Adapted with permission from Ismail-Beigi et al. (20).*

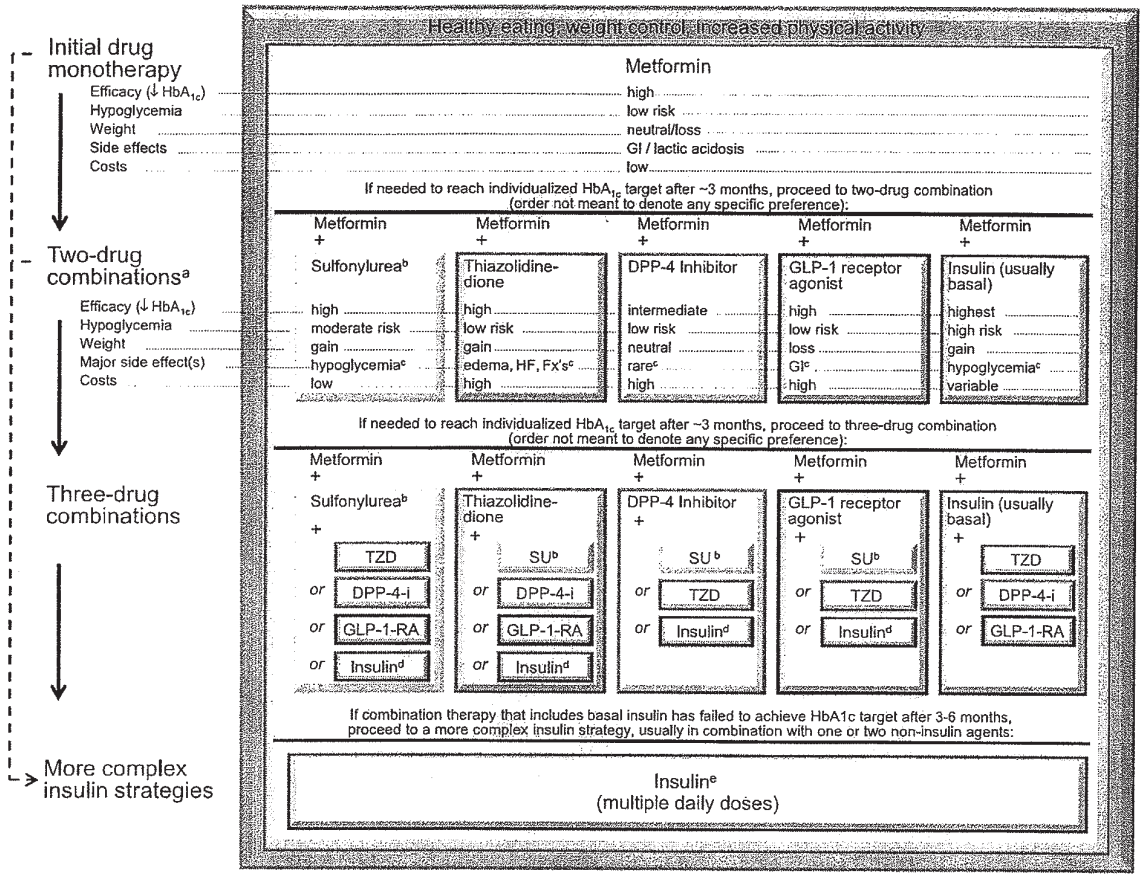


Figure 2—*Antihyperglycemic therapy in type 2 diabetes: general recommendations. Moving from the top to the bottom of the figure, potential sequences of antihyperglycemic therapy. In most patients, begin with lifestyle changes; metformin monotherapy is added at, or soon after, diagnosis (unless there are explicit contraindications). If the HbA_{1c} target is not achieved after ~3 months, consider one of the five treatment options combined with metformin: a sulfonylurea, TZD, DPP-4 inhibitor, GLP-1 receptor agonist, or basal insulin. (The order in the chart is determined by historical introduction and route of administration and is not meant to denote any specific preference.) Choice is based on patient and drug characteristics, with the over-riding goal of improving glycemic control while minimizing side effects. Shared decision making with the patient may help in the selection of therapeutic options. The figure displays drugs commonly used both in the U.S. and/or Europe. Rapid-acting secretagogues (meglitinides) may be used in place of sulfonylureas. Other drugs not shown (α-glucosidase inhibitors, colesevelam, dopamine agonists, pramlintide) may be used where available in selected patients but have modest efficacy and/or limiting side effects. In patients intolerant of, or with contraindications for, metformin, select initial drug from other classes depicted and proceed accordingly. In this circumstance, while published trials are generally lacking, it is reasonable to consider three-drug combinations other than metformin. Insulin is likely to be more effective than most other agents as a third-line therapy, especially when HbA_{1c} is very high (e.g., ≥9.0%). The therapeutic regimen should include some basal insulin before moving to more complex insulin strategies (Fig. 3). Dashed arrow line on the left-hand side of the figure denotes the option of a more rapid progression from a two-drug combination directly to multiple daily insulin doses, in those patients with severe hyperglycemia (e.g., HbA_{1c} ≥10.0–12.0%). DPP-4-i, DPP-4 inhibitor; Fx's, bone fractures; GI, gastrointestinal; GLP-1-RA, GLP-1 receptor agonist; HF, heart failure; SU, sulfonylurea. [a]Consider beginning at this stage in patients with very high HbA_{1c} (e.g., ≥9%). [b]Consider rapid-acting, nonsulfonylurea secretagogues (meglitinides) in patients with irregular meal schedules or who develop late postprandial hypoglycemia on sulfonylureas. [c]See Table 1 for additional potential adverse effects and risks, under "Disadvantages." [d]Usually a basal insulin (NPH, glargine, detemir) in combination with noninsulin agents. [e]Certain noninsulin agents may be continued with insulin (see text). Refer to Fig. 3 for details on regimens. Consider beginning at this stage if patient presents with severe hyperglycemia (≥16.7–19.4 mmol/L [≥300–350 mg/dL]; HbA_{1c} ≥10.0–12.0%) with or without catabolic features (weight loss, ketosis, etc.).*

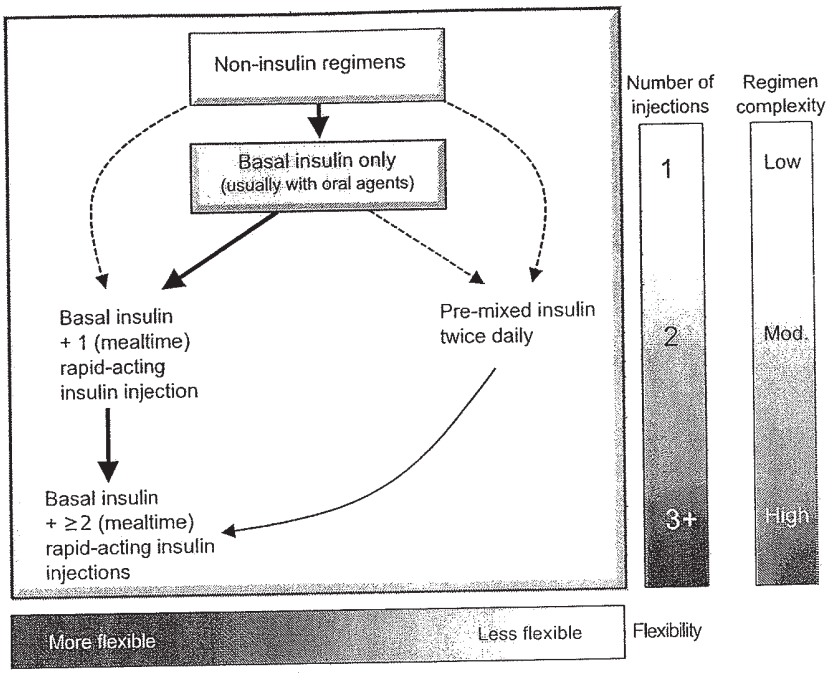
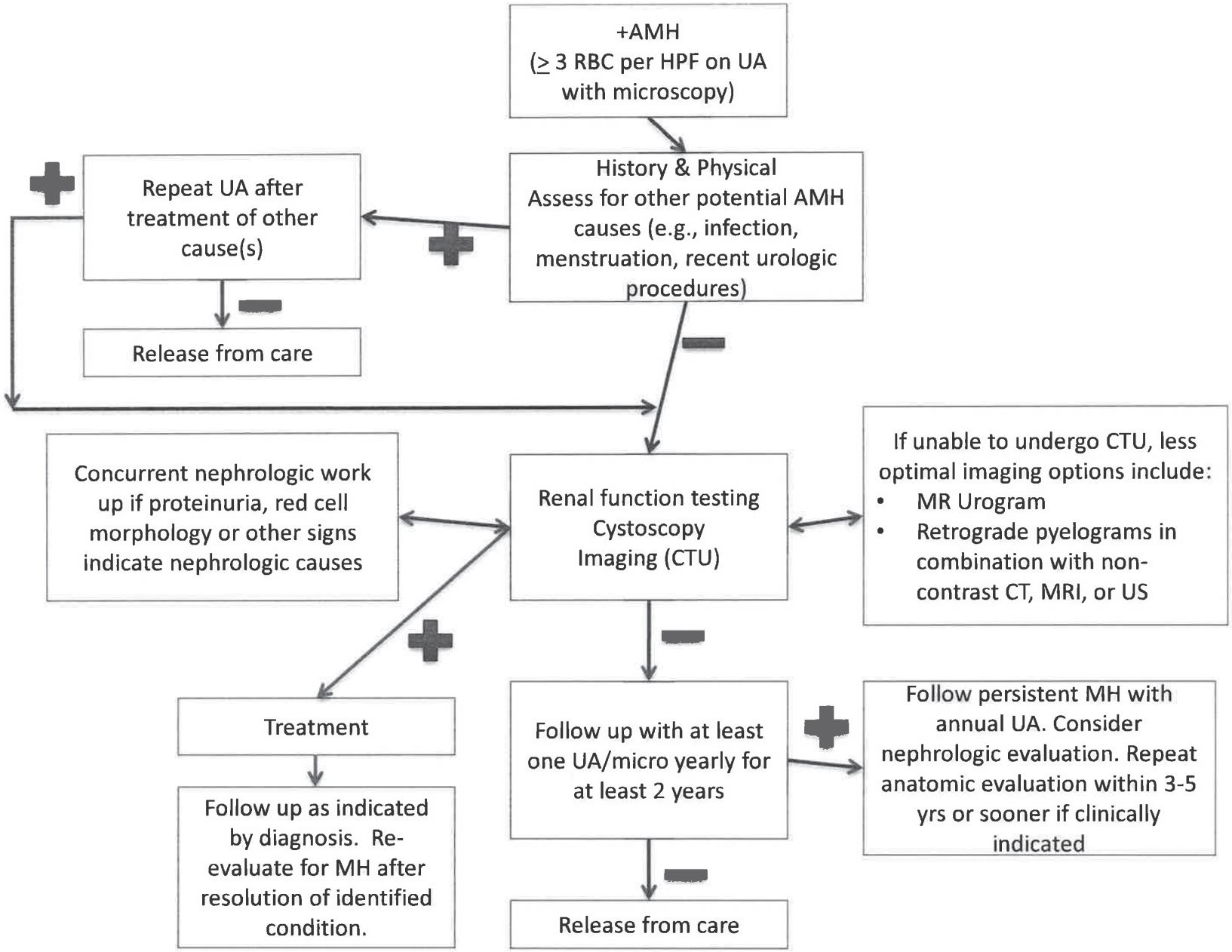


Figure 3—*Sequential insulin strategies in type 2 diabetes. Basal insulin alone is usually the optimal initial regimen, beginning at 0.1–0.2 units/kg body weight, depending on the degree of hyperglycemia. It is usually prescribed in conjunction with one to two noninsulin agents. In patients willing to take more than one injection and who have higher HbA_{1c} levels (≥9.0%), twice-daily premixed insulin or a more advanced basal plus mealtime insulin regimen could also be considered (curved dashed arrow lines). When basal insulin has been titrated to an acceptable fasting glucose but HbA_{1c} remains above target, consider proceeding to basal plus mealtime insulin, consisting of one to three injections of rapid-acting analogs (see text for details). A less studied alternative—progression from basal insulin to a twice-daily premixed insulin—could be also considered (straight dashed arrow line); if this is unsuccessful, move to basal plus mealtime insulin. The figure describes the number of injections required at each stage, together with the relative complexity and flexibility. Once a strategy is initiated, titration of the insulin dose is important, with dose adjustments made based on the prevailing glucose levels as reported by the patient. Noninsulin agents may be continued, although insulin secretagogues (sulfonylureas, meglitinides) are typically stopped once more complex regimens beyond basal insulin are utilized. Comprehensive education regarding self-monitoring of blood glucose, diet, exercise, and the avoidance of, and response to, hypoglycemia are critical in any patient on insulin therapy. Mod., moderate.*

Clinical Study Protocol Appendix G	
Drug Substance	Dapagliflozin
Study Code	D1693C00001
Edition Number	Final 1.0
Date	12 November 2012

Appendix G
AUA Recommendations For Evaluation of Asymptomatic Microscopic Hematuria



AstraZeneca

Clinical Study Protocol Appendix H

Drug Substance	Dapagliflozin
Study Code	D1693C00001
Appendix Edition Number	Final 3.0
Appendix Date	25 Sep 2016

Appendix H

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AstraZeneca

Clinical Study Protocol Appendix I	
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Appendix I
Biomarker Research

TABLE OF CONTENTS PAGE

1. BACKGROUND AND RATIONALE

Diabetes is a chronic disease with activation of multiple pathologic inflammatory, thrombotic, and metabolic pathways (Pradhan and Ridker 2002). Elevated levels of circulating pro-inflammatory and thrombotic biomarkers can successfully identify patients at particularly high risk of developing incident diabetes (Meigs et al. 2004; Festa et al. 2006). However, the potential for biomarkers to predict the risk for future macro and microvascular adverse outcomes in patients with established diabetes has yet to be realized. By way of analogy, in terms of atherosclerosis, circulating biomarkers have proven extremely valuable in helping define which patients are at high risk for developing incident cardiovascular disease as well as defining which patients with prevalent cardiovascular disease are at highest risk for adverse clinical outcomes (Nozaki et al 2009 and Sabatine et al 2012).Thus, diabetic subjects with risk factors for or with established cardiovascular disease are an ideal patient population in which to leverage circulating biomarkers for risk stratification.

Building on that concept, biomarkers that identify patients at higher risk for major adverse clinical outcomes can provide important insights in terms of tailoring therapy. Specifically, patients at higher risk for adverse events will, by definition, enjoy a greater *absolute* risk reduction for a given relative risk reduction from a therapy and hence require a smaller number needed to treat to prevent an adverse event. Moreover, patho-biologically relevant biomarkers may identify a specific subset of patients who enjoy a larger *relative* risk reduction with a given pharmaco-therapeutic intervention, and thus an even greater absolute risk reduction.

In addition to established biomarkers, new insights into mechanistic pathways and consequences of diabetes and atherothrombosis have fostered a steady pace of emergence of candidate novel cardiovascular and metabolic biomarkers. Using novel biomarkers that reflect the inflammatory, thrombotic, metabolic, and hemodynamic mediators of risk in subjects with diabetes and atherosclerotic disease, it may be possible to characterize noninvasively the participation of these different pathobiologic contributors in an individual subject and to monitor response to therapy (Morrow and Braunwald 2003). Thus, there is a tremendous opportunity to gain insight into pathobiology.

In terms of categories of biomarkers, those of interest for this study are broadly twofold-(1) those related to diabetes and metabolic disarray and its complications such as markers of glycation, metabolism, adiposity and renal dysfunction, and (2) those related to cardiovascular disease such as markers of atherosclerosis, ischemia, inflammation, thrombosis, hemodynamic stress and lipid dysregulation. A few select examples follow.

In terms of markers reflecting the vascular effects associated with glucose dysregulation, circulating advanced glycation products (AGEs), the soluble receptor for these AGEs (sRAGE), as well plasma phospholipid levels and ratios have been proposed as prognostic markers for vascular disease and heart failure. (Katakami et al 2006, Guo et al 2008 and Koyama et al 2008).

Central obesity is a major underlying factor in insulin resistance. Adipocytes produce inflammatory molecules and adipokines such as adiponectin, leptin, angiotensinogen and

resistin. These adipokines together play a major role in the development of atherosclerosis (Pittas et al 2004).

Increased serum cystatin C in the absence of explicit chronic kidney disease (CKD) has shown a graded association with increased cardiovascular disease (CVD) morbidity and mortality (Menon et al 2007).

Cardiac troponin is commonly used for diagnosis of acute myocardial infarction. More recently, however, the advent of high-sensitivity assays has now permitted quantification of troponin in stable individuals and the demonstration that higher levels of troponin are associated with an increased risk of cardiovascular mortality (Omland et al 2009).

Similarly, the natriuretic peptides (eg, BNP, ANP and their N-terminal prohormones) have been used to risk stratify patients with ACS, and now have also been shown to act as robust predictors of the short and long-term risk of cardiovascular death in patients with stable ischemic heart disease (Kragelund et al 2005 and Omland et al 2007).

Inflammation is central to atherothrombosis and insulin resistance and thus biomarkers that provide insight into the inflammatory processes that preceed and lead up to atherothrombosis such as oxidative stress, leukocyte recruitment and activation, and fibrous cap degradation offer predictive value. For example, high-sensitivity measurement of C-reactive protein (hs-CRP), an acute phase reactant and global barometer of inflammation, has been shown to predict risk of first MI in healthy cohorts (Ridker et al 2000 and Danesh et al 2004) and future coronary events in patients with stable CHD (Haverkate et al 1997 and Sabatine et al 2007). Enzymes such as lipoprotein-associated and secretory type II phospholipase A2 (Lp-PLA2 and sPLA2) that hydrolyze phospholipids to generate pro-atherogenic compounds are independent predictors of recurrent coronary events in stable patients (Koenig et al 2006, Sabatine et al 2007, Kugiyama et al 1999 and Mallat et al 2007).

Elevated circulating levels of several biomarkers of platelet activation, thrombosis, and endothelial dysfunction not only predict events, but may offer insight into which patients benefit the most from potentially cardioprotective therapy. For example, soluble CD40 ligand, (a marker of platelet activation and potential direct participant in plaque destabilization) and myeloid-related protein (MRP)-8/14 (discovered using transcriptomics to be upregulated during ACS) are independent predictors of cardiovascular events (Heeschen et al 2003) (Healy et al 2006 and Morrow et al 2008).

Finally, biomarkers may also help detect adverse safety signals with diabetes and other cardiovascular medications.

Thus, the evaluation of biomarkers in patients in this trial may provide important insight into pathobiology of diabetes and cardiovascular disease, improve our ability to risk stratify patients, and provide information that can be used to tailor therapy. This study may also provide additional insights into the possible mechanistic pathways leading to CV benefit with dapagliflozin.

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2. OBJECTIVES

1. To evaluate the value of individual biomarkers and a multi-marker approach for predicting major adverse cardiovascular outcomes in a diabetic population.

2. To evaluate whether diabetic patients identified at higher risk on the basis of biomarkers experience greater absolute and /or relative risk reduction in major adverse cardiovascular outcomes with dapagliflozin versus placebo.

3. To evaluate the change over time in biomarkers in patients with diabetes; to assess whether treatment with dapagliflozin alters this natural history; and to examine the correlation of change in biomarkers with subsequent clinical outcomes.

3. BIOLOGIC RESEARCH PLAN AND PROCEDURES

This appendix to the Clinical Study Protocol has been subjected to peer review according to AstraZeneca and Bristol-Myers Squibb standard procedures.

3.1 Selection of biologic research population

3.1.1 Study selection record

All patients in select countries will be asked to participate in this biologic 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.

3.1.2 Inclusion criteria

For inclusion in this biologic research, patients must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol.

3.1.3 Exclusion criteria

Exclusion from this biologic research may be for any of the exclusion criteria specified in the main study.

3.1.4 Discontinuation of patients from this biologic research

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

- Withdrawal of consent for biologic research: Patients may withdraw from this biologic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in the main Clinical Study Protocol.

3.2 Collection of samples for biologic research

All patients in participating countries will be asked to participate in this biologic research at Visit 2. If the patient agrees to participate, blood samples will be taken at Visit 2 (Randomization) and Visit 4 (month 6) in patients in select countries. Detailed procedures are described in the Laboratory Manual of Operations.

3.3 Coding and storage of samples

The processes adopted for the coding and storage of samples for biologic analysis are important to maintain patient confidentiality. The biomarker samples will be labeled (or "coded") with a study specific code. Samples do not carry any patient identifying information. Samples will be stored for a maximum of 20 years following the finalization of the CSR, after which they will be destroyed. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

3.4 Analytes

Categories of biomarkers of interest and select examples are listed below; specific biomarkers to be explored will depend on the totality of published data at the time analyses are ready to commence. Examples of categories and biomarkers are listed below.

Biomarkers of Inflammation and Atherothrombosis:

• hs-CRP

• phospholipases (eg, Lp-PLA2 and sPLA2)

• metalloproteinases (eg, PAPP-A, MMP-9, MMP-11)

• cytokines (eg, IL-1β, IL-1Ra, IL-6, IL-18, GDF-15, PlGF)

• chemotactic molecules (eg, MCP-1)

Glycation end products and associated receptors

• For example: AGE, sRAGE, RAGE

Biomarkers of Metabolic/Lipid Dysregulation/Insulin Resistance

• Adipokines (eg, adiponectin)

• Lipoproteins and modified/oxidized lipoproteins

• Lp(a)

Biomarkers of Oxidative Stress

• Myeloperoxidase

• ADMA and other arginine metabolism products

Biomarker of Renal Dysfunction

• For example: cystatin-C, FGF-23, NGAL

Biomarkers of Endothelial Function

• For example: VCAM-1, ICAM-1, vWF, E-selectin,

Biomarkers of Thrombosis

• For example: sCD40L

Biomarkers of Ischemia/Necrosis

• For example: cardiac troponin, FABP

Biomarkers of Hemodynamic Stress

• Natriuretic peptides (eg, BNP, ANP and their NT-prohormones)

• MR-adrenomedullin, C-terminal proendothelin 1, copeptin

• ST-2

• Galectin-3

As the field of biomarkers is rapidly evolving, future data may suggest a role of additional biomarkers in the risk for cardiovascular outcomes and the response to treatment, which may lead to additional exploratory research. In addition to analysis of existing biomarkers, proteomics and metabolomic analyses may be performed on samples to develop and test novel protein markers of cardiovascular outcomes.

Blood samples may be analyzed by the TIMI Study Group, AstraZeneca and potentially their collaborators and/or vendors. Samples will be stored for up to 20 years (or sooner as required by local regulations) and then destroyed.

4. ETHICAL AND REGULATORY REQUIREMENTS

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

Informed consent

The biologic component of this study is optional and the patient may participate in other components of the main study without participating in the biologic component. The principal investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue from the biologic aspect of the study at any time.

Patient data protection

AstraZeneca will not provide individual 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 biologic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the biologic 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 biologic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the biologic files would remain physically separate.

5. DATA MANAGEMENT

Biomarker data from the TIMI Biomarker Core Lab will be merged with the clinical database for statistical analysis.

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

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

6. STATISTICAL ANALYSIS PLAN

A sample size of 15,000 patients will provide 80% power to detect an odds ratio of ≥1.20 for the primary endpoint for patients above vs. those below the median level of a biomarker. This sample size will also provide approximately 80% power to detect interaction hazard ratios (the ratio of HRs for the benefit of dapagliflozin on the primary endpoint in those above and below the median of a biomarker) of ≤0.70 (assuming a treatment effect of 0.85 and a risk of 1.20 for the biomarker). These values are in keeping with risk estimates and interactions seen with other biomarkers and represent the thresholds of clinical importance. These calculations assume an event rate as outlined in the main protocol and that 10% of samples will be non-evaluable for a given biomarker, and uses a two-sided alpha threshold of 0.05 (no correction for multiple hypotheses testing as all analyses are exploratory).

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