AstraZeneca

Clinical Study Protocol

Drug Substance	Dapagliflozin
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A Multicenter, Double-Blind, Placebo-Controlled, Parallel Group, Randomized, Phase III study to Evaluate the Glycemic Efficacy and Renal Safety of Dapagliflozin in Patients with Type 2 Diabetes Mellitus and Moderate Renal Impairment (CKD 3A) who have Inadequate Glycemic Control

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VERSION HISTORY

Version 4.0, 17 January 2017

Changes to the protocol are summarised below:

Protocol Synopsis (Study site(s) and number of patients planned) and Section 9.3 (Study timetable and end of study): The estimated date of last patient completed has been updated considering the extension of recruitment timelines.

List of abbreviations and definition of terms: Updated to include the acronym DKA (Diabetic ketoacidosis)

Section 3.2 (Exclusion criteria): Exclusion criteria number 39 has been updated to include rapid or short acting insulin.

Although the inclusion criteria number 05 has clearly been stating that 'Long acting or intermediate acting insulin and mixed insulins are permitted' which means that rapid or short acting insulin were not allowed - this change to the exclusion criteria was made to provide more clarity about the exclusion of these types of insulin.

Section 5.2.5.6: This new section has been added to include information about the reporting and adjudication of diabetic ketoacidosis events in the study.

Version 3.0, 01 April 2016

Changes to the protocol are summarised below:

Title page: Included EudraCT number for reference.

Protocol Synopsis (Study site(s) and number of patients planned) and Section 9.3 (Study timetable and end of study): The estimated date of last patient completed has been updated considering the extension of recruitment timelines.

Protocol Synopsis (Study site(s) and number of patients planned), Sections 1.2 (Rationale for study design, doses and control groups) and 1.4 (Study Design): The estimated site number has been updated, as additional countries have been included in the study.

Protocol Synopsis (Target patient population), Sections 1.2 (Rationale for study design, doses and control groups), 1.4 (Study Design), 3.10.1 (Screen failures), Table 1 (Study Plan and Timing of Procedures), 4.2.2 (Visit 3, Lead-in), 4.3.1 (Visit 4, Randomization): These sections/Table have been updated appropriately, due to the modification of inclusion/exclusion criteria.

Sections 3.1 and 3.2 (Inclusion/Exclusion criteria):

- HbA1c has been removed from V3 and the eGFR criterion modified, to facilitate randomization into the study
- Exclusion criteria no. 24 has been introduced in order to exclude patients with rapid worsening of renal function (as part of the modified eGFR criterion).
- Exclusion criteria no. 47 (48, in the current version), has been modified to allow re-enrolment (one single time), provided that the patient had previously not been randomized in the study.

Sections 3.8 (Restrictions) and 5.11 (Volume of blood): Blood volume has been updated (reduced by 2 mL to 61 mL) due to removal of HbA1c testing at Visit 3.

8.5.1 (Analysis of the primary variable (s)): This section is updated, to include a sensitivity analysis to evaluate the effect of baseline (continuous) eGFR on the results obtained in primary analysis. This will be assessed by the addition of a single term for baseline eGFR to the primary analysis model.

Section 9.2 (Monitoring of the study): Deleted the text related to withdrawal of informed consent for biological samples, as it is not applicable in the study**.**

Version 2.0, 20 January 2016

Changes to the protocol are summarised below:

Protocol Synopsis (Study site(s) and number of patients planned), Sections 1.2 (Rationale for study design, doses and control groups) and 1.4 (Study design): Additional sites and country/ies are considered to be included in the study, in order to meet the recruitment targets. Hence, the number of sites is updated and the regions are mentioned in place of country names to avoid multiple updates to protocol due to addition of countries in future.

Protocol Synopsis, Sections 2.3 and 2.4 (Safety and Exploratory Objectives): These sections of the protocol have been updated to clarify the objectives and definitions of outcomes, and to correct the typographical error of the term ‘albuminuria’.

Protocol Synopsis (Statistical Methods): Eliminated unnecessary wording.

Table of contents:

- The heading of section 6.3.7 (Hy’s Law) has been deleted, hence the numbers of subsequent sections are modified accordingly, and the table of contents is updated.
- Some of the section headings and all the appendices numbers are updated as per the

new clinical study protocol template that has been used for authoring this document. Appendix A (Signatures) of the previous edition of protocol is no longer part of the appendices.

List of abbreviations and definition of terms: Updated to reflect the addition or deletion of terminologies and to rearrange the list alphabetically.

Section 1.3 (Benefit/risk and ethical assessment): Updated the section to include the potential risk of diabetic ketoacidosis and the action required to be taken from the investigator if any patients present with signs and symptoms consistent with diabetic ketoacidosis.

Section 3.1 (Inclusion criteria): The upper limit of BMI range has been increased to 45 kg/m^2, to enhance recruitment into the study. The medical team cannot see any risk by increasing the BMI to 45 kg/m^2.

Sections 3.2 (Exclusion criteria) and 7.7 (Concomitant and other treatments):

- The investigator's judgement may differ from the local guidelines on the metformin dose range for moderate renal impairment (eGFR 30 – 59 mL/minute/1.73m^2, MDRD formula), hence the criterion (#37) and text related to restrictions on metformin in section 7.7 are modified by including 'or' to allow this difference.

- Criterion #38 has been updated to explicitly state that ongoing treatment with GLP-1 agonist is an exclusion criterion.

Section 3.3 (Patient enrolment and randomization): In #3, section numbers are updated (Section 3.1 and 3.2) to provide reference to the specific sections (3.1 and 3.2).

Sections 3.10 (Criteria for withdrawal) and 9.2 (Monitoring of the study): Lost to follow-up, has been added as one of the withdrawal criteria CCI [redacted] An additional point is included under Section 9.2 to emphasise sites to be compliant with study procedures to avoid lost to follow up.

Section 4 (Table 1: Study plan and timing of procedures):

- Day 0 has been changed to Day 1 - to be consistent with other Dapagliflozin clinical study protocols and industry standard. This change (day numbers) is cascaded to the subsequent visits.

- The section numbers are updated in the table, due to the deletion of heading of section 6.3.7 (Hy's Law)

- In the footnote 'c', 'must' has been changed to 'should' – to emphasise on the timing of visit.

Sections 4.2.1 (Visit 2, Start of lead-in), 5.1 (Efficacy assessments) and 5.2.5.1 (Self-monitored FPG and hypoglycemic events): The sample specimen has been corrected to state 'blood glucose' instead of 'fasting plasma glucose' – as the patients are instructed to measure the blood glucose whenever they have symptoms suggestive of hypoglycaemia – hypolgycemia symptoms need not always occur at fasting state.

Section 4.4 (Follow-up period, Visit 9): The typographical error related to study period has been corrected from 'treatment' to 'follow up'.

CCI [redacted]

Section 5.2.1 (Laboratory safety assessments), Table 3: Deleted 'U-Hb/Erythrocytes' – as dipstick for blood would be sufficient to confirm haematuria.

Section 5.2.5.2 (Hepatic events (Hepatic Adjudication Committee)): Corrected the inconsistency in limits of AST, ALT and TB, with other sections and deleted the reference to Appendix D (Algorithm on Management of Sustained Elevated Liver Safety Abnormalities.)

Section 6.3.7 (Hy's Law): Deleted the text referring to Hy's law, as it is not applicable for the study.

Section 7.7 (Concomitant and other treatments): The trade name 'Victoza' for liraglutide has been removed as it was non-relevant. The procedure for dose reduction of oral antidiabetics and insulin, and continued participation in the study following the dose reduction has been clarified.

Sections 8.3.3 (Full Analysis set), 8.3.4 (Per protocol analysis set) and 8.3.5 (Safety analysis set): Added details to definition of Full Analysis Set and corrected typographical errors.

Sections 8.4.3 (Safety outcome variables) and 8.4.4 (Exploratory outcome variables): Deleted time references from outcome variable descriptions

Sections 8.5 (Methods for statistical analyses), 8.5.1 (Analysis of the primary variable (s)) and 8.5.2 (Analysis of the secondary variable(s)): These sections are updated, to clarify the primary analyses and sensitivity analyses, CCI [redacted] and to simplify text.

Section 8.5.6 (Exploratory analysis): CCI [redacted] to change the analysis of proportions to the current analysis convention, and to simplify text.

Section 11 (List of references): Deleted the references of Tsiatis et al 2008 and Zhang et al 2008, due to changes made in section 8.5.6.

Version 1.0, 25 March 2015
Initial creation

AstraZeneca

PROTOCOL SYNOPSIS

A Multicenter, Double-Blind, Placebo-Controlled, Parallel Group, Randomized, Phase III study to Evaluate the Glycemic Efficacy and Renal Safety of Dapagliflozin in Patients with Type 2 Diabetes Mellitus and Moderate Renal Impairment (CKD 3A) who have Inadequate Glycemic Control

International Co-ordinating Investigator

PPD

Study site(s) and number of patients planned

This study will be conducted at approximately 100 centres from countries across North America and European regions. It is expected that approximately 302 patients will be randomized into the study.

Study period		Phase of development
Estimated date of first patient enrolled	Q2 2015	Phase III
Estimated date of last patient completed	Q4 2017	

Study design

This is a confirmatory, phase III, randomized, double-blind, 2-arm, parallel group, placebo-controlled, multi-national, multi-centre study to evaluate the clinical efficacy and safety of dapagliflozin in patients with type 2 diabetes and Chronic Kidney Disease (CKD) stage 3A. The study consists of 2-week screening period with a 4-week single-blind placebo lead-in period and a 24-week double-blind placebo-controlled treatment period followed by 3-week of follow-up period.

Objectives

Primary Objective:	Outcome Measure:
To compare the mean change from baseline in HbA1c between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment in patients with type 2 diabetes and CKD stage 3A.	Change from baseline in HbA1c at Week 24

Secondary Objective:	Outcome Measure :
To compare the percent change from baseline in total body weight between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment.	Percent change from baseline in total body weight at Week 24
To compare the change from baseline in fasting plasma glucose (FPG) between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment.	Change from baseline in FPG at Week 24
To compare the change from baseline in seated systolic blood pressure (SBP) between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment.	Change from baseline in seated SBP at Week 24

Safety Objective:	**Outcome Measure :**
To examine eGFR changes during the study and 3-week post-treatment for dapagliflozin 10 mg and placebo.	Change in eGFR from baseline to end of treatment and 3-week post-treatment
To assess the proportion of patients discontinued from study medication because of worsening renal insufficiency (defined as patients reaching confirmed eGFR levels <30 mL/min/1.73 m^2) between dapagliflozin 10 mg and placebo.	Proportion of patients discontinued from study medication due to worsening renal insufficiency (<30 mL/min/1.73 m^2) at the end of treatment
To evaluate the safety and tolerability of dapagliflozin 10 mg once daily in type 2 diabetes and CKD stage 3A.	AEs /Serious Adverse Events (SAEs) Vital signs Physical examination Clinical chemistry parameters

Exploratory Objective:	**Outcome Measure :**
CCI [redacted]	

Exploratory Objective:	Outcome Measure :
CCI	

Exploratory Objective:	Outcome Measure :
CCI	

Exploratory Objective:	Outcome Measure :
CCI [redacted]	

Target patient population

The target patients include, Female or male aged ≥18 years and <75 years:

- With history of type 2 diabetes mellitus (T2DM) for more than 12 months with inadequate glycemic control, defined as HbA1c ≥7.0 and ≤11% at screening and stable anti-diabetic treatment during the last 12 weeks prior to randomization
- With moderate renal impairment; CKD 3A; Estimated Glomerular Filtration Rate (eGFR) 45 – 59 mL/minute/1.73m^2, MDRD-formula, before randomization (at Visit 1, or Visit 2, or Visit 3)

Duration of treatment

The study will start with a 2-week screening period. Eligible patients will enter a 4-week single-blind placebo lead-in period and then randomized to double-blind treatment in a 1:1

ratio to receive dapagliflozin 10 mg or matching placebo for a period of 24-week. Patients will be followed up for 3-week after the double-blind treatment period.

Investigational product, dosage and mode of administration

- Dapagliflozin 10 mg will be administered orally once daily during the 24-week double-blind treatment period

Comparator, dosage and mode of administration

- Matching placebo for dapagliflozin 10 mg will be administered orally once daily during the 4-week single-blind placebo lead-in period and the 24-week double-blind treatment period

Other treatments

- Oral Anti-diabetic Drugs (OADs) except SGLT2 inhibitors, insulin, anti-hypertensive drugs, lipid lowering drugs and anti-platelet drugs are allowed during the study and the dose should be kept constant throughout the entire 24-week double-blind treatment period

- Patients may receive open-label rescue medication added on to, but not as a replacement for their current study drug regimen. Rescue medication in this protocol refers to any approved, appropriate anti-diabetic agent, except SGLT2 inhibitors, for which there is either initiation or upward titration, in accordance with the approved label and conventional standards of care

Statistical methods

The sample size for this study was selected to be consistent with the research hypotheses. The study has a single primary endpoint for which the overall probability of a Type 1 error (Family-wise error rate) will be strictly controlled at no more than 0.05. The sample size for this study is governed by providing adequate power for the primary comparison to achieve statistical significance; namely, for the change from baseline in HbA1c. Significance levels are expressed in terms of two-sided alternatives; however, all tests in practice will be performed against one-sided alternatives using one-half the significance levels reported here.

From post-hoc results of similar clinical studies (Study MB102029, Study D1690C00018, and Study D1690C00019) when patients meeting eGFR entry criteria like those in this current study were selected, the mean placebo-corrected change from baseline in HbA1c after 24 weeks of treatment for the current study is estimated to be -0.3% for dapagliflozin 10 mg.

The present study seeks to detect a treatment difference over placebo in change from baseline HbA1c at Week 24 of -0.3% with high statistical power (80%). Given patients will be randomized with equal probability to dapagliflozin or placebo, it follows that 286 patients (143 per group) will provide 80% power to detect a difference in average placebo-corrected change from baseline in HbA1c at Week 24 of -0.3% (Δ = -0.3%) at a (two-sided) significance level =0.05. If 5% of randomized patients fail to qualify for inclusion in the full

analysis set due to missing baseline and/or all post-randomization values for this primary endpoint, then a total of 151 randomized patients are required for each treatment group. Therefore, with respect to the primary study endpoint, 302 randomized patients in total are needed for the study.

Assuming a common standard deviation (SD) of 0.9% in change from baseline HbA1c this sample size provides 80% power to detect a placebo-corrected difference in average change from baseline in HbA1c between dapagliflozin and placebo at a (two-sided) significance level of 0.05. If the primary comparison in mean change from baseline in HbA1c at Week 24 does not achieve statistical significance at an unadjusted alpha level of 0.05, then secondary comparisons will not be performed. Otherwise, secondary endpoint comparisons between dapagliflozin and placebo will be performed at an unadjusted alpha (Type I error) level of 0.05, with a sequential testing procedure of secondary endpoints used to control the alpha level for multiplicity.

A sample size of 143 evaluable patients per treatment group (dapagliflozin and placebo) provides 75 percent assurance that a statistically significant difference between dapagliflozin and placebo in mean change from baseline to Week 24 in HbA1c will be observed for the primary study endpoint.

The primary endpoint of changes from baseline to Week 24 will be evaluated using a mixed effects model with repeated measures (MMRM).

Changes from baseline to Week 24 in the secondary study endpoints (total body weight, FPG, and seated SBP) will be separately evaluated using MMRM.

A sequential testing procedure will be employed in comparisons of primary and secondary efficacy parameters. The ratio of the difference in LSM estimates (dapagliflozin versus placebo) to the corresponding standard error (e.g., the test statistic) will be tested first for the primary endpoint (HbA1c) at a two-sided alpha level of 0.05. If statistical significance is achieved and the difference indicates the dapagliflozin group experienced greater improvement in the primary endpoint at Week 24 than placebo, then superiority of dapagliflozin doses to placebo will be inferred, and secondary endpoints will be sequentially tested at a two-sided alpha level of 0.05. Otherwise, testing will cease. Comparisons of secondary endpoints between dapagliflozin and placebo will be performed using a sequential test procedure. Each test will be performed at an alpha level of 0.05, and the order of testing will follow the order that the secondary endpoints are listed in Section 8.4.2 of this protocol. Testing will cease at the first secondary endpoint for which superiority of dapagliflozin to placebo cannot be inferred, or the last secondary endpoint comparison is performed, whichever occurs first.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse Event
ALK-P	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUA	American Urological Association
BMI	Body Mass Index
BP	Blood Pressure
CKD	Chronic Kidney Disease
CRF	Case Report Form
CRO	Contract Research Organization
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DILI	Drug-Induced Liver Injury
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
eGFR	Estimated Glomerular Filtration Rate
EU	European Union
CCI	[redacted]
FPG	Fasting Plasma Glucose
FU	Follow-Up
GCP	Good Clinical Practice
GLP-1	Glucagon-like Peptide-1
GMP	Good Manufacturing Practice

Abbreviation or special term	Explanation
GRand	Global Randomization system
Hb	Haemoglobin
HbA1C	Glycosylated Haemoglobin
CCI	
HF	Heart Failure
HIV	Human Immunodeficiency Virus
HN	High Normal
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IRB	Institutional Review Board
IP	Investigational Product
KG	Kilogram
CCI	
LOCF	Last Observation Carried Forward
LSM	Least Square Mean
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MG	Milligram
MMRM	Mixed Effects Model With Repeated Measures
NOINT	No-Intercept
NYHA	New York Heart Association
OAD	Oral Anti-diabetic Drug
PI	Principal Investigator
PPG	Post-Prandial Glucose
PTH	Parathyroid Hormone
RMM	Repeated Measures Model
RPD	Relevant Protocol Deviation

Abbreviation or special term	Explanation
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
sCr	Serum Creatinine
SD	Standard Deviation
SGLT2	Sodium Glucose Co-Transporter 2
SU	Sulfonylurea
T2DM	Type 2 Diabetes Mellitus
TB	Total Bilirubin
CCI [redacted]	
TIA	Transient Ischemic Attack
TZD	Thiazolidinedione
CCI [redacted]	
ULN	Upper Limit of Normal
US	United States
UTI	Urinary Tract Infection
WBDC	Web Based Data Capture
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Dapagliflozin (Forxiga®) is a stable, reversible, highly selective, and orally active inhibitor of human renal sodium glucose co-transporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption in the kidney (Maranghi et al 2015). Dapagliflozin's mechanism of action results in the direct and insulin-independent elimination of glucose by the kidneys. Traditionally, the presence of glucose in the urine has been seen as a sign of poor glycemic control and, thus, something to be avoided. Familial renal glucosuria in humans, however, due to genetic mutations that reduce the function of SGLT2, is associated with life-long glucosuria that is generally asymptomatic (Santer et al 2010). Results from nonclinical- and clinical studies have shown that dapagliflozin can be used to promote urinary excretion of glucose as a safe and effective method of reducing blood glucose levels (Plosker et al 2014).

Dapagliflozin's mechanism of action reduces plasma glucose regardless of the patient's insulin sensitivity and β-cell secretory function. Because this mechanism is independent of insulin secretion or insulin action, this approach to anti-diabetic therapy provides an opportunity to achieve clinically important glycemic efficacy with a comparatively low risk of hypoglycemia. This insulin-independent mechanism is also potentially applicable to a broad spectrum of patients. In addition, the excretion of glucose may promote weight loss or prevent weight gain, as a consequence of calorie loss, a potential benefit for many patients with T2DM (Maranghi et al 2015).

The dapagliflozin clinical development program was designed to demonstrate the safety and efficacy of dapagliflozin in a wide range of patients with T2DM. The program included both placebo-controlled and active comparator studies in drug-naïve patients at an early stage of disease and patients who require additional therapy after failure to reach adequate glycemic control with their current regimen. Dapagliflozin's pharmacodynamic effect of glucosuria is detected almost immediately (within 1 hour post-dose), is maintained through 2 years of treatment, and results in reductions in Fasting Plasma Glucose (FPG), Post-prandial Glucose (PPG), and HbA1c (glycosylated haemoglobin). Treatment with dapagliflozin, with its unique mechanism of action, results in a persistent loss of glucose with associated calories in the urine, resulting in a consistent and maintained reduction of the total body weight, in addition to the improved glycemic control (Bolinder et al 2014). The weight loss is predominantly a result of a reduction in fat mass, visceral adipose tissue, and subcutaneous adipose tissue in T2DM. Dapagliflozin also has a mild diuretic effect, which in combination with weight loss, has the potential to reduce blood pressure (BP).

Diabetic patients with moderate renal impairment are of interest because diabetic nephropathy affects approximately 30% of patients with diabetes (Sheen et al 2014). In the Unites States, for instance, about 20% of individuals with diabetes have an eGFR lower than 60 ml/min/1.73m^2 (chronic kidney disease, CKD stage ≥3). As diabetic patients progress from normal to diminished renal function over the natural history of their disease, there is a medical need for safe and effective oral anti-diabetic therapy. Several existing anti-diabetic agents are

contraindicated in this population, are associated with increased risk of hypoglycemia, or have not been adequately studied in these patients (SDCD 2014). Safety and efficacy data in patients with normal, mildly, and moderately impaired renal function have been collected in previous studies in the dapagliflozin development program.

Notably, dapagliflozin's ability to inhibit renal glucose reabsorption declines with decreasing eGFR. Urinary glucose excretion is about 50% lower in patients with T2DM treated with dapagliflozin having CKD stage 3, as compared with patients with normal or mildly impaired renal function. Such eGFR dependence is expected given the fall in filtered glucose load with worsening CKD stage. In a previous study, dapagliflozin did not have a significant impact on glycemic control in patients with more advanced CKD, although there was a modest decrease in HbA1c and FPG in patients with a GFR of 45–59 ml/min (Kohan et al 2014). However, that study suffered from several limitations. The use of insulin-based regimens in almost two-thirds of patients, often with sliding scale administration, made accurate capture of insulin dosing difficult. Unmeasured differential behaviour with respect to sliding scale and other adjustments of insulin between placebo and dapagliflozin could have blunted the apparent efficacy of dapagliflozin. A second limitation was the relatively small size of the study, which was powered for a 0.6% change in HbA1c, and therefore limited in its ability to demonstrate smaller glycemic effects and thus, the study may be considered underpowered and subject to type 2 error. Other factors such as a very short placebo lead-in period and a relatively large placebo effect in this study could potentially also have affected and obscured the interpretation of the data. In other clinical studies, which did not suffer from the limitations described above, SGLT2-inhibitors have been shown to be safe and effective in T2DM patients with moderate renal impairment lending support to further studies in this specific patient segment (Yale et al 2013, Barnett et al 2014).

1.2 Rationale for study design, doses and control groups

This study will be performed as part of the clinical development program for dapagliflozin for the treatment of T2DM. This study intends to compare efficacy and safety of dapagliflozin with placebo in the treatment of patients with T2DM who have inadequate glycemic control, defined as HbA1c ≥7.0% and ≤11%, and moderate renal impairment (eGFR 45 to 59 ml/min/1.73 m^2). SGLT2-inhibition has been shown to improve glycaeimic control in T2DM patients with renal impairment. Based on these results, it is anticipated that after 24 weeks of daily oral administration of dapagliflozin 10 mg or placebo, there will be a greater mean reduction from baseline in HbA1c achieved with dapagliflozin compared to placebo in patients with T2DM and moderate renal impairment who have inadequate glycemic control on their current anti-diabetic regimen. A standard dapagliflozin dose for treatment of T2DM (10 mg dapagliflozin once daily) has been selected for this study and is expected to provide efficacy in reducing hyperglycemia while mitigating the potential for AEs, based on previous clinical experience. In addition to improved glycemic control in patient treated with dapagliflozin 10 mg, it is anticipated that a decrease in body weight and BP will provide additional benefit to the patients.

This is a confirmatory, phase III, randomized, double-blind, 2-arm, parallel group, placebo-controlled, multi-national, multi-centre study to evaluate the clinical efficacy and safety of

dapagliflozin in patients with type 2 diabetes and CKD stage 3A (eGFR 45-59 mL/min/1.73 m^2). Patients will be randomized to 24 weeks' treatment with dapagliflozin 10 mg or matching placebo. The study will be an international multi-centre study at approximately 100 centres from countries across North America and European regions. It is planned to randomize a total of 302 patients (151 patients per treatment arm). The study is powered to detect a change of 0.3% in HbA1c between active treatment and placebo following 24 weeks of treatment.

Dapagliflozin 10 mg once daily or matching placebo will be added to usual care of patients who have inadequate glycemic control on their existing therapies. This double-blind randomized phase III study requires a placebo group to determine efficacy of dapagliflozin in a specific patient segment in order to discriminate effects caused by the study treatment from effects caused by other factors. All patients in the study are protected from harm by rescue criteria, which call for withdrawal from the study if the patient shows evidence of inadequately controlled disease.

Randomization will be stratified by pre-enrolment anti-hyperglycemic therapy (long/intermediate-acting and mixed insulin regimen, metformin-based regimen, sulfonylurea (SU)-based regimen, thiazolidinedione (TZD)-based regimen, and other regimen). Any patients on metformin treatment need to have a dose suitable according to local guidelines or investigator's judgement for the full CKD 3 segment (i.e., eGFR 30 - 60 ml/min/1.73 m^2, calculated using the MDRD formula).

The study consists of 2-week screening period, a 4-week single-blind placebo lead-in period, a 24-week double-blind placebo-controlled treatment period, and a 3-week follow-up (FU) period. The study drug is taken once daily in the morning.

The main efficacy assessments will be performed at regular intervals and will include HbA1c, weight, CCI FPG, seated BP and heart rate. During the double-blind treatment period, HbA1c and urinary glucose values will be blinded to the Investigator and to the Sponsor. These values will be provided to the Investigator after the study has been completed. FPG value will be reported as an un-blinded value throughout the study.

The main safety assessments will be performed at regular intervals and will include physical examination, vital signs, renal function (change in eGFR), safety laboratory test, and AE monitoring.

1.3 Benefit/risk and ethical assessment

Risk category

Dapagliflozin has global market approval and has been administered to thousands of T2DM patients globally. Details regarding potential risks associated with administration of dapagliflozin once daily are provided in the Investigator's Brochure.

Considering dapagliflozin's mechanism of action, the previous clinical experience with dapagliflozin, the study's design features (including the inclusion, exclusion, and

discontinuation criteria), and the planned safety procedures, participation in this study presents a minimal, and thus acceptable, risk to the individual patients that will be included.

Potential risks

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

Based on the mechanism of action of dapagliflozin and results of animal and clinical studies, there may be a potential risk for this compound to cause hypovolaemia or electrolyte imbalance. As a precaution, patients who, in the judgment of the Investigator, may be at risk for dehydration or volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics, should have careful monitoring of their volume status. In patients already receiving dapagliflozin who develop conditions that may cause hypovolaemia or electrolyte imbalance, decisions to interrupt or discontinue dapagliflozin therapy and management of patients should be based on clinical judgment.

Higher proportions of patients with marked laboratory abnormalities of hyperphosphatemia were reported in dapagliflozin vs. placebo but the clinical meaning of this is unclear.

Hepatic laboratory markers were assessed in all the clinical studies with dapagliflozin. In the pooled analyses, the proportion of patients with elevated liver function tests was similar in the dapagliflozin and comparator groups and no clinically meaningful or consistent mean changes from baseline in liver function tests were observed in the dapagliflozin and placebo groups across the Phase IIb and III clinical studies. One patient had a SAE reported as drug-induced acute hepatitis that was later diagnosed as most comparable with autoimmune hepatitis.

There have been postmarketing reports of ketoacidosis, including diabetic ketoacidosis (DKA), in patients with type 1 and type 2 diabetes mellitus taking dapagliflozin and other SGLT2 inhibitors, although a causal relationship has not been established. Dapagliflozin is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with dapagliflozin who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise, and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL). If ketoacidosis is suspected, discontinuation or temporary interruption of dapagliflozin should be considered and the patient should be promptly evaluated.

Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (eg, type 1 diabetes, history of pancreatitis, or pancreatic surgery), insulin

dose reduction, reduced caloric intake, or increased insulin requirements due to infections, illness or surgery and alcohol abuse. Dapagliflozin should be used with caution in these patients.

No study procedure will put patients at a risk beyond those ordinarily encountered during the performance of routine medical examinations or routine tests.

Protection against risks

This study has been designed with appropriate measures in place so as to monitor and minimize any of the potential health risks to participating patients. In order to ensure the safety of all patients participating in this study, AstraZeneca will conduct a real-time review of all safety information from all ongoing clinical dapagliflozin studies as they become available. Safety signal detection will include the integration of all available sources of safety information, including clinical study data, AE reports, pre-clinical data, epidemiological studies and literature reports, to identify and characterize unrecognized safety risks or changes in those which are currently expected Adverse Drug Reactions. Any information that may affect the benefit-risk profile of dapagliflozin will be immediately communicated to relevant Health Authorities and appropriate actions will be taken regarding the clinical program as needed. Thus real-time, active safety surveillance will be conducted during the entire duration of this study. In addition, all dapagliflozin studies are subject to a carefully designed patient risk management plan that includes the temporary and if necessary permanent discontinuation of investigational product (IP) in individual patients in whom a potential health risk or a laboratory abnormality of clinical concern has been identified.

Potential benefits to patients

All patients will receive counselling on dietary and life-style modifications. Global phase II and phase III studies have established the effect of dapagliflozin therapy. This phase III study will evaluate these effects of dapagliflozin in T2DM patients with moderate renal impairment (CKD3A). In this study, the dose of dapagliflozin (10 mg) was chosen to provide efficacy in reducing hyperglycemia while mitigating the risk for AEs, based on previous clinical experience. In addition, dapagliflozin is expected to help decrease body weight (or prevent weight gain) as well as help lower BP especially in patients with elevated baseline BP. Patients are also expected to receive some benefit in the form of increased medical care/attention when participating in study procedures, which includes at least 9 clinical visits.

Informed consent and alternatives to participation

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

Conclusion

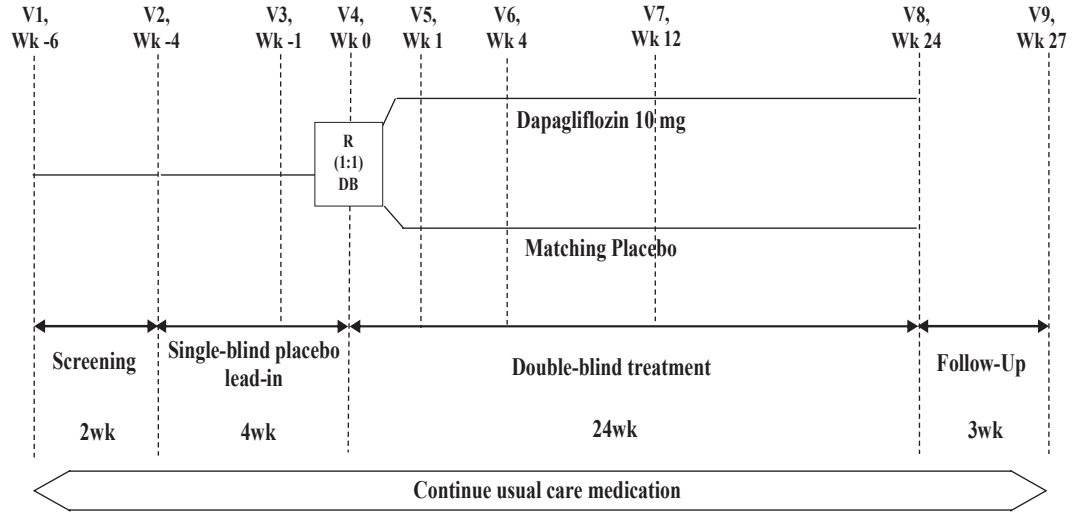
Considering the pre-clinical and clinical experience with dapagliflozin and the precautions included in the study protocol, participation in this study presents a minimal and thus acceptable risk to patients who meet the inclusion/exclusion criteria and consent to take part in the study.

1.4 Study Design

This is a confirmatory, phase III, randomized, double-blind, 2-arm, parallel group, placebo-controlled, multi-national, multi-centre study to evaluate the clinical efficacy and safety of dapagliflozin in patients with type 2 diabetes and CKD stage 3A. The study consists of 2-week screening period, a 4-week single-blind placebo lead-in period, a 24-week double-blind placebo-controlled treatment period, and a 3-week follow-up period. Patients will be randomized to 24 weeks treatment with dapagliflozin 10 mg or matching placebo after the placebo lead-in period. The study will be an international multi-centre study at approximately 100 centres from countries across North America and European regions.

The study comprises of 9 visits: enrolment visit (Visit 1), Start of lead-in (Visit 2), Lead-in (Visit 3), randomization visit (Visit 4), Treatment period (Visit 5-7), end of treatment visit (Visit 8), and a follow-up visit (Visit 9). For details on timing of visits, see Figure 1 below.

Figure 1 Study flow Chart



R = Randomization, DB = Double-blind, V = Visit, Wk = Week

At Visit 1, all potentially eligible patients will provide informed consent, undergo screening for HbA1c, eGFR level and other applicable inclusion/exclusion criteria. Visit 1, can be completed over multiple visits, provided all procedures have been completed, with the results reviewed, prior to Visit 2. Patients at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics should have careful monitoring of their volume status. At Visit 2 (start of lead-in), patients will be examined for HbA1c, and eGFR

level, from blood sample obtained from Visit 1. If the HbA1c is ≥7.0% and ≤11% and the eGFR value is within the range of 40-65 mL/min/1.73 m^2 (MDRD-formula), patients will enter a 4-week single-blind placebo lead-in period. Blood samples will be collected for standard lab values (and eGFR level). At Visit 2 and Visit 3, eGFR will be measured. At Visit 4, patients who meet all of the inclusion and none of the exclusion criteria, including the eGFR value within the range of 45-59mL/min/1.73 m^2 at Visit 1, or Visit 2, or Visit 3[1], and the standard lab values (from Visit 2) will be randomized to the 24 weeks double-blind treatment period. The dose of Oral Anti-diabetic Drugs (OADs), insulin, anti-hypertensive drugs, lipid lowering drugs and anti-platelet drugs should be kept constant throughout the entire 24-week treatment period. At randomization, patients will be stratified according to pre-enrolment anti-hyperglycemic therapy.

After either completion of the treatment period or discontinuation from treatment, patients will enter a 3 weeks safety follow-up period without study drug. At the follow-up visit (Visit 9 (FU)) any changes in physical signs, renal function (i.e., changes in eGFR), symptoms or laboratory parameters that may be related to dapagliflozin will be evaluated. The total planned study duration from Visit 1 to the safety follow-up (Visit 9) will be 33 weeks.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	**Outcome Measure:**
To compare the mean change from baseline in HbA1c between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment in patients with type 2 diabetes and CKD stage 3A.	Change from baseline in HbA1c at Week 24

2.2 Secondary objectives

Secondary Objective:	**Outcome Measure :**
To compare the percent change from baseline in total body weight between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment.	Percent change from baseline in total body weight at Week 24

[1] Summary of the algorithm for inclusion based on HbA1c and eGFR:

Sample obtained at Visit 1:	HbA1c ≥7.0% and ≤11%
	eGFR 40-65 mL/min/1.73 m^2, MDRD-formula
Samples obtained at Visit 1, or Visit 2, or Visit 3:	eGFR 45-59 mL/min/1.73 m^2, MDRD-formula

To compare the change from baseline in FPG between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment.	Change from baseline in FPG at Week 24
To compare the change from baseline in seated SBP between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment.	Change from baseline in seated SBP at Week 24

2.3 Safety objectives

Safety Objective:	**Outcome Measure :**
To examine eGFR changes during the study and 3-week post-treatment for dapagliflozin 10 mg and placebo.	Change in eGFR from baseline to end of treatment and 3-week post-treatment
To assess the proportion of patients discontinued from study medication because of worsening renal insufficiency (defined as patients reaching confirmed eGFR levels <30 mL/min/1.73 m^2) between dapagliflozin 10 mg and placebo.	Proportion of patients discontinued from study medication due to worsening renal insufficiency (<30 mL/min/1.73 m^2) at the end of treatment
To evaluate the safety and tolerability of dapagliflozin 10 mg once daily in type 2 diabetes and CKD stage 3A.	AEs /SAEs Vital signs Physical examination Clinical chemistry parameters

2.4 Exploratory objectives

Exploratory objectives are to determine whether treatment with dapagliflozin compared with placebo when added to current background therapy in patients with T2DM and CKD3A will have effect on the following parameters.

Exploratory Objective:	**Outcome Measure :**
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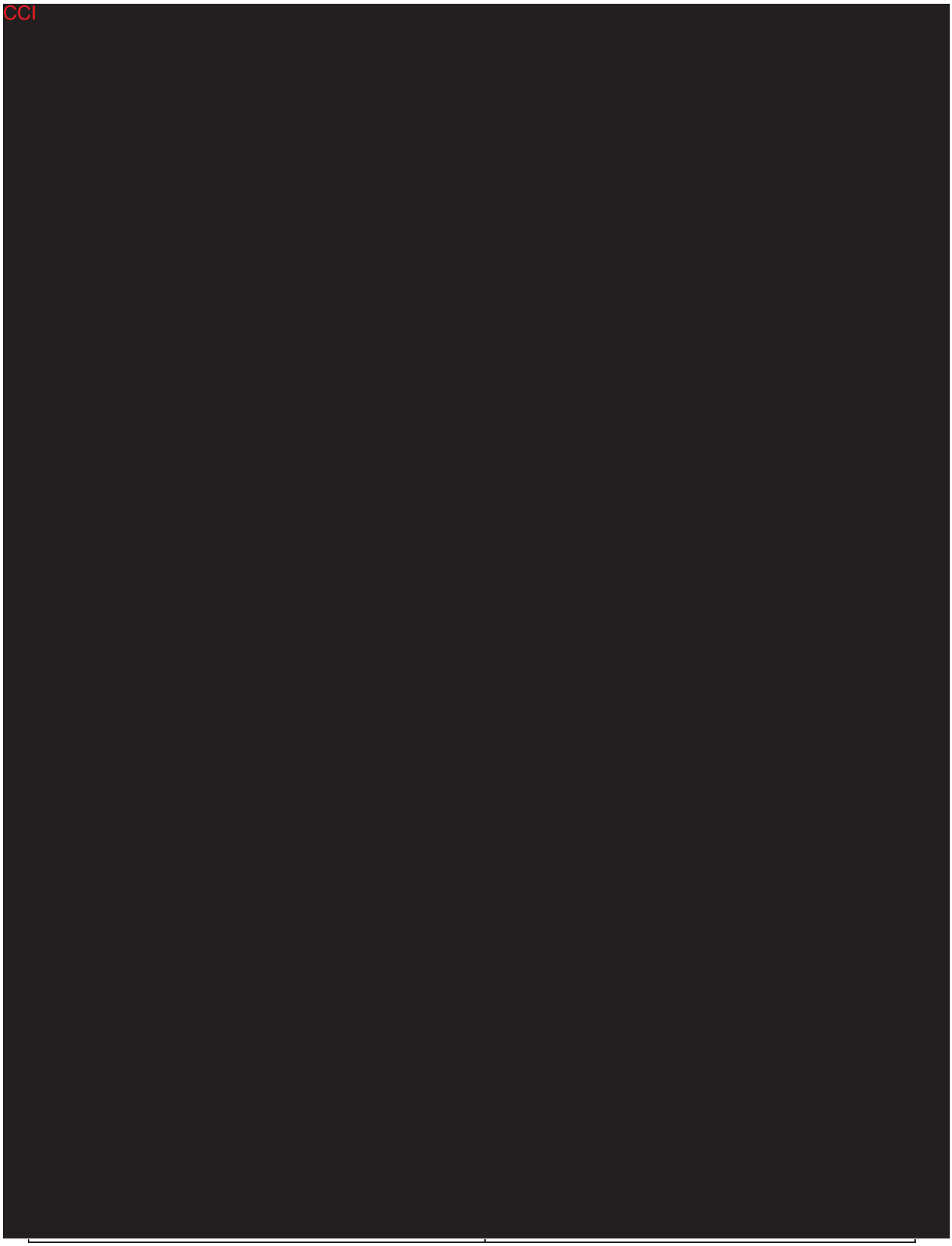

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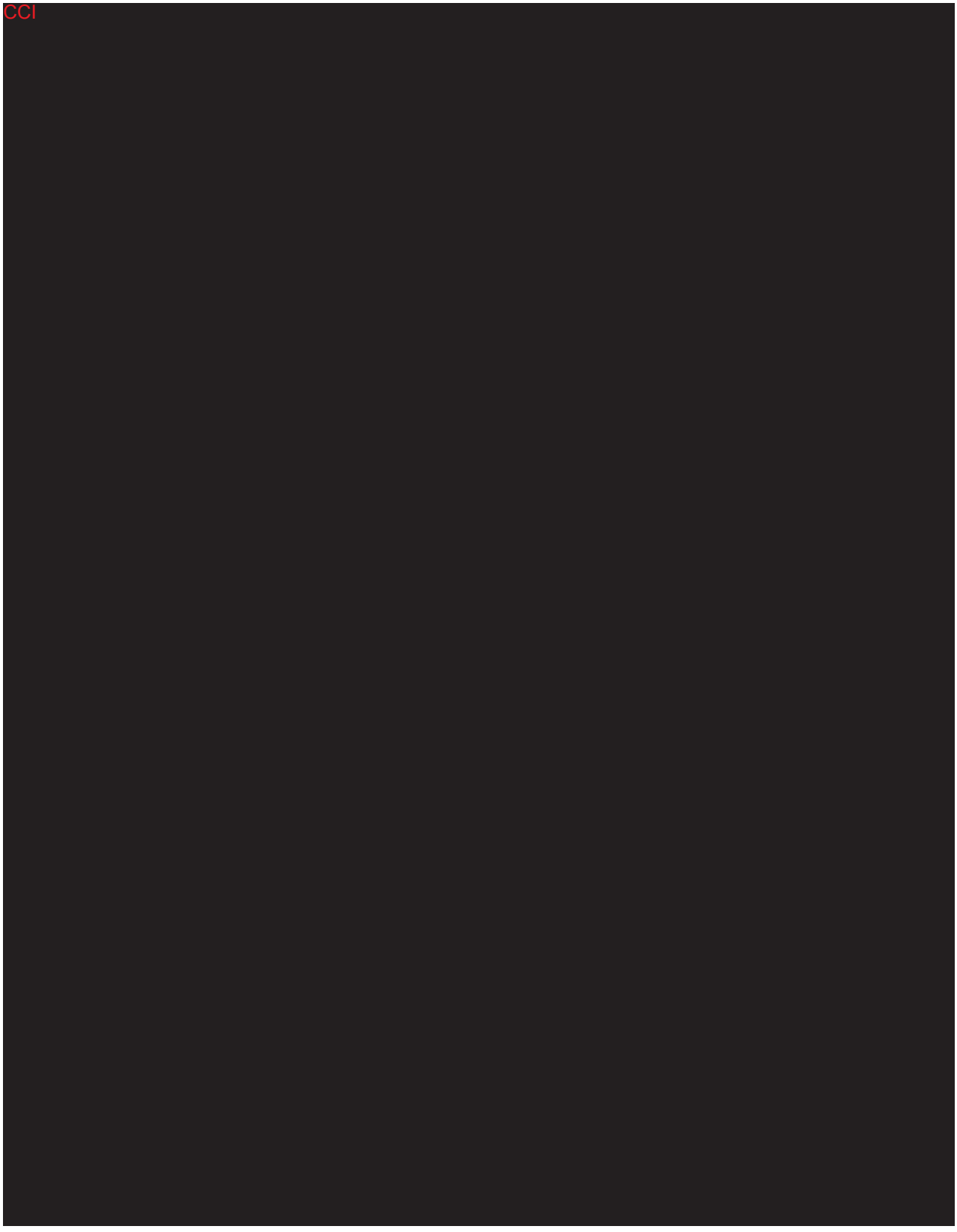

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3. PATIENT SELECTION, ENROLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

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.

3.1 Inclusion criteria

Patients should meet all inclusion criteria at the time of randomization. If at the time of enrolment (Visit 1) or start of lead-in (Visit 2) it is known that the patient will not meet criteria after a successful lead-in period, they should not be entered into single-blind placebo lead-in.

For inclusion in the study, patients should fulfil the following criteria:

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

2. Female or male aged ≥18 years and <75 years.

3. History of T2DM for more than 12 months.

4. Inadequate glycemic control, defined as HbA1c ≥7.0% and ≤11% measured at screening (value from blood sample obtained at Visit 1) for patient to be randomized.

5. Stable anti-diabetic treatment regimen, defined as stable diet and exercise therapy alone or in combination with any or both of the two following alternatives:

   - A regimen of any approved oral anti-diabetic medication (except SGLT2-inhibitors) where no dose-changes have occurred during 12 weeks before randomization.

   - Long acting or intermediate acting insulin and mixed insulin permitted as long as the dose is stable during last 12 weeks before randomization, changes ± 10% are allowed (in relation to number of units at randomization). For example, if the patient is taking 50 units/day of insulin at randomization, the total daily doses in the past 12 weeks should not have exceeded 55 units, or been less than 45 units. However, occasional exceptions (≤ one day/week) during this time period are permitted.

6. Renal impairment: CKD 3A

   - eGFR* 40 – 65 mL/minute/1.73 m^2 at Visit 2 (value from blood sample obtained at Visit 1) to enter the lead-in period.

   - eGFR* 45 – 59 mL/minute/1.73 m^2 at Visit 1, or Visit 2, or Visit 3 for randomization.

   *according to the re-expressed abbreviated (four-variable) MDRD Study equation, using central laboratory measurements of serum creatinine (sCr). [eGFR (mL/min/1.73m^2) = 175 x (standardized sCr)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if Black)] [Note: sCr reported in mg/dL]

7. Body mass index (BMI) between 18 and 45 kg/m^2, inclusive at Visit 1.

3.2 Exclusion criteria

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

Sex and Reproductive Status

1. Women of childbearing potential (WOCBP) who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period.

2. Women who are pregnant or breastfeeding.

3. Women with a positive pregnancy test on enrolment or prior to study drug administration.

Central Laboratory Test Findings (from blood samples obtained at Visit 2)

4. Aspartate Aminotransferase (AST) >3X ULN.

5. Alanine Aminotransferase (ALT) >3X ULN.

6. Total Bilirubin (TB) >2 mg/dL (35 μmol/L).

7. Serum Potassium (K) >5.5 meq/L (5.5 mmol/L).

8. Serum Calcium (Ca) <8 mg/dL or > ULN (<1.99 mmol/L or > ULN).

9. Positive for hepatitis B surface antigen.

10. Positive for anti-hepatitis C virus antibody.

11. Hemoglobin ≤9.0 g/dL (90 g/L).

Target Disease Exceptions

12. History of diabetes insipidus.

13. Symptoms of poorly controlled diabetes that would preclude participation in this study including but not limited to marked polyuria and polydipsia with greater than 10% weight loss during the three months prior to signing the consent at visit 1, or other signs and symptoms.

14. History of diabetic ketoacidosis or hyperosmolar nonketotic coma.

15. History of ≥2 major hypoglycemic events in the 3 months prior to enrolment, defined as symptomatic events requiring external assistance due to severe impairment in consciousness or behaviour, with blood glucose level <3.0 mmol/L, <54 mg/dL (plasma glucose level <3.5 mmol/L, <63 mg/dL) and prompt recovery after glucose or glucagon administration.

Medical History and Concurrent Diseases

CV/Vascular diseases:

16. Severe uncontrolled hypertension defined as SBP ≥180 mmHg and/or DBP ≥110 mmHg at any visit up to randomization.

Any of the following CV/Vascular Diseases within 3 months of prior to signing the consent at visit 1:

17. Myocardial infarction.

18. Cardiac surgery or revascularization (CABG/PTCA).

19. Unstable angina.

20. Unstable heart failure (HF).

21. HF New York Heart Association (NYHA) Class IV.

22. Transient ischemic attack (TIA) or significant cerebrovascular disease.

23. Unstable or previously undiagnosed arrhythmia.

Renal Diseases:

24. Rapid worsening of renal function from Visit 1 to Visit 3 defined as >25% decrease in eGFR* from Visit 1 to Visit 3.

    *according to the re-expressed abbreviated (four-variable) MDRD Study equation, using central laboratory measurements of serum creatinine (sCr). [eGFR (mL/min/1.73m^2) = 175 x (standardized sCr)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if Black)] [Note: sCr reported in mg/dL]

25. History of any biopsy or imaging verifying intercurrent kidney disease (such as glomerular nephritis or sign of renal artery stenosis) other than diabetic nephropathy or diabetic nephropathy with nephrosclerosis.

26. History of renal transplant.

27. Hemodialysis, ultrafiltration therapy, or peritoneal dialysis within 6 months prior to signing the consent at visit 1.

Hepatic Diseases:

28. Significant hepatic disease, including, but not limited to, chronic active hepatitis and/or severe hepatic insufficiency.

29. Documented history of hepatotoxicity with any medication.

30. Documented history of severe hepatobiliary disease.

Hematological and Oncological Diseases/Conditions:

31. History of hemoglobinopathy, or chronic or recurrent hemolysis.

32. Donation of blood or blood products to a blood bank, blood transfusion, or participation in a clinical study requiring withdrawal of > 400 mL of blood during the 6 weeks prior to signing the consent at visit 1.

33. Malignancy within 5 years of the enrolment visit (with the exception of treated basal cell or treated squamous cell carcinoma).

34. Known immunocompromised status, including but not limited to, individuals who have undergone organ transplantation or who are positive for the human immunodeficiency virus (HIV).

35. History of unexplained microscopic or gross hematuria, or microscopic hematuria at visit 2.

Allergies and Adverse Drug Reactions:

36. Known allergies or contraindication to the contents of dapagliflozin or placebo tablets. The tablets contain lactose and may cause discomfort in some individuals.

Prohibited Treatments and/or Therapies:

37. Long term treatment with glucocorticoids (two temporary periods of no longer than 10 days each are allowed during the study); topical or inhaled corticosteroids are allowed.

38. A metformin dose which is outside the specified dose range for moderate renal impairment (eGFR 30– 59 mL/minute/1.73m^2, MDRD formula) according to local guidelines or investigator's judgement.

39. Ongoing treatment with any SGLT2-inhibitor, GLP-1 analogue, or rapid/short acting insulins at screening.

40. History of bariatric surgery or lap-band procedure.

41. Administration of sibutramine, phentermine, orlistat, rimonabant, benzphetamine, diethylpropion, methamphetamine, liraglutide indicated for anti-obesity treatment, and/or phendimetrazine, within 30 days prior to signing the consent at visit 1.

Other Exclusion Criteria:

42. Any unstable endocrine, psychiatric, or rheumatic disorders as judged by the Investigator.

43. Patient is, in the judgment of the Investigator, unlikely to comply with the protocol or has any severe concurrent medical or psychological condition that may affect the interpretation of efficacy or safety data.

44. Patient who, in the judgment of the Investigator, may be at risk for dehydration or volume depletion due to co-existing conditions.

45. Patient with any condition which, in the judgment of the Investigator, may render the patient unable to complete the study or which may pose a significant risk to the patient.

46. Patient is currently abusing alcohol or other drugs or has done so within the last 6 months prior to signing the consent at visit 1.

47. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

48. Previous randomization in the present study.

    Note: Re-enrolment of a patient who has not previously been randomized to double-blind treatment in the study is allowed one single time only.

49. Participation in another clinical study with an IP during the last 30 days prior to signing the consent at visit 1.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study patients and to ensure that the results of the study can be used. It is imperative that patients fully meet all eligibility criteria.

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrolment and randomization

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

The Investigator(s) will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed. Patient is considered enrolled in the study after she/he has signed the informed consent form (ICF).

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3. Determine patient eligibility. See Section 3.1 and 3.2

4. Assign eligible patient unique randomization code, by accessing IVRS or IWRS, see Section 3.5. Patient is considered randomized in the study after this assignment.

Patients entering the single-blind placebo lead-in period

At the time of entry into the single-blind placebo lead-in period, the site will contact the IVRS/IWRS in order that lead-in medication can be assigned and dispensed.

Patient who does not meet the eligibility criteria is considered as screen failure in the study. These patients will be terminated from the study and registered as Screen Failure by using IVRS/IWRS. See section 3.10.1.

Patients entering the double-blind treatment period

Following completion of the single-blind lead-in period, patients eligible for double-blind treatment will be randomly assigned to one of the two treatment arms by the IVRS/IWRS in a 1:1 ratio (dapagliflozin 10 mg: matching placebo) using a randomization schedule.

If a patient discontinues/withdraws from the study, then his/her enrolment/randomization code cannot be reused.

3.4 Procedures for handling incorrectly enrolled or randomized patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study drug. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the following steps to be taken:

(a) The Investigator or monitor should inform the AstraZeneca study physician immediately, ensuring patient safety must always be the number one priority.

(b) Study Treatment must be discontinued in all cases where continued treatment is deemed to pose a safety risk to the patient. A discussion should occur between the AstraZeneca study physician and the investigator, a decision may be reached whether to continue or discontinue the patient from study treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

(c) In those cases where continuation of study therapy is judged not to present a concern related to safety and disease management, the rationale for continuing study therapy must be clearly documented. The patient should continue follow up in accordance with defined study procedures.

3.5 Methods for assigning treatment groups

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Randomization codes will be generated to ensure approximate balance (1:1) between the two treatment arms (dapagliflozin 10 mg or matching placebo, once daily).

Randomization will be done via IVRS/IWRS at Visit 4. The IVRS/IWRS will allocate randomization codes sequentially through central randomization as patients become eligible for randomization.

Randomization will be stratified by pre-enrolment anti-hyperglycemic therapy. The following 5 strata will be defined:

1. Insulin-based regimen: Patients receiving insulin alone or in combination with any other anti-hyperglycemic medication

2. Metformin-based regimen: Patients receiving metformin alone or in combination with any other anti-hyperglycemic medication except insulin

3. SU-based regimen: Patients receiving a SU alone or in combination with any other anti-hyperglycemic medication except insulin and metformin

4. TZD-based regimen: Patients receiving a TZD alone or in combination with any other anti-hyperglycemic medication except insulin, metformin, or a SU

5. Other regimen: Patients receiving either any anti-hyperglycemic medication(s) not described by strata 1-4, or no background anti-hyperglycemic medication.

For each patient randomized the IVRS/IWRS will provide the investigator with a unique Kit ID number matching the treatment arm assigned to the patient. Following randomization, the first dose of study drug will be administered to the patient after completion of study visit procedures. At randomization and subsequent dispensing visit the patient should always be provided medication with the Kit ID(s) allocated by the IVRS/IWRS. If a patient receives the incorrect randomized treatment at any time during the study, the centre must immediately notify the AstraZeneca representative and IVRS/IWRS contact and this must be corrected as soon as discovered after discussing with study physician.

3.6 Methods for ensuring blinding

The study has a single-blind placebo lead-in period of 4 weeks from Visit 2, where patients will be blinded to treatment. Other members at AstraZeneca, investigational centres or any Contract Research Organization (CRO) handling data will be aware of the placebo treatment during this period.

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

Until the completion of the 24-week randomized treatment period, no member of the study team at AstraZeneca, at the investigational centres or any CRO handling data will have access to the randomization scheme, with the exception of AstraZeneca personnel generating the randomization scheme as well as relevant persons at Pharmaceutical Development Supply Chain at AstraZeneca or their designee, where the information is needed to package study drug, the Patient Safety data entry site and the CRO companies providing the IVRS/IWRS and

carrying out the packaging and labelling of investigational products. Patients and investigators will remain blinded past the 24-week randomized treatment period.

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

3.7 Methods for unblinding

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

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP 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.

3.8 Restrictions

- All patients will visit the clinic fasting in the morning (except for Visits 1 and 5), between 6 a.m. to 10 a.m.
- Patients will be instructed to abstain from all food and beverages for 8 hours prior to each clinic visit (except for Visits 1 and 5). Drinking water is allowed
- Patients should not drink alcohol within 24 hours prior to each visit and should not use tobacco/nicotine within 12 hours prior to each visit
- Patients should bring all their medications and IP to the site
- Anti-hypertensive medication can be taken with a glass of water after completion of BP and body weight measurements
- Medications including IP should be taken after visit samples and examinations have been performed. Anti-hyperglycemic drugs should be taken in connection with a meal
- Antiepileptic drugs and antibiotics shall be taken as required

- Women must immediately contact the Investigator if they suspect they might be pregnant and if they have changed or plan to change their birth control method.

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

As up to approximately 61 mL of blood will be drawn from each patient during the entire duration of the clinical study (excluding extra blood samples taken at unscheduled, specialized liver/liver discontinuation visits, serum pregnancy test), patients should be instructed to abstain from donating any blood during the clinical study and for 12 weeks following their last study visit.

Prohibited and restricted concomitant medications are listed in Section 7.7.

3.9 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 treatment, without prejudice to further treatment. Patients who choose to discontinue study treatment are expected to continue in the study until the end of the study
- AEs, ie, any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the patient
- Severe non-compliance with the study protocol as judged by the investigator and/or AstraZeneca
- Pregnancy
- Incorrectly enrolled patients (see Section 3.4)
- Lost to FU, patient fails to return for study visits and cannot be reached with reasonable, repeated attempts.
- Termination of the study by AstraZeneca.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

3.9.1 Study specific discontinuation criteria

- 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 C Algorithm on Management of Sustained Elevated Liver Safety Abnormalities for further details)

- Protocol-defined recurrent major hypoglycemia episodes
- Acute renal insufficiency or worsened chronic renal insufficiency based on repeat eGFR values (eGFR<30 mL/minute/1.73m^2). The re-test should be scheduled within 4 days, whenever possible.

Discontinuation guidelines for protocol-defined major hypoglycemia episodes

Patients should not be discontinued from any treatment phase based on single episodes of hypoglycemia or symptoms of hypoglycemia unless clinically indicated. The assessment of a single finger stick or laboratory glucose value should not be the sole assessment used to determine patient discontinuation for hypoglycemia.

Clinical indications for discontinuation because of hypoglycemia may include the following:

- Multiple occasions of episodes outlined below that, in the opinion of the Investigator, indicate that continued treatment with study therapy is not in the best interest of the patient. This includes, but is not limited to:
  - Symptoms suggestive of hypoglycemia (e.g., sweating, shakiness, increased heart rate, confusion, dizziness, light-headedness, or hunger) in the absence of environmental factors known to contribute to hypoglycemia (i.e., excess physical activity, concurrent illness, or missed or delayed meal) and/or
  - Documented finger stick glucose values <54 mg/dL (<3.0 mmol/L).
- A patient may also be discontinued from the study because of severe hypoglycemia, as determined by the Investigator.

Discontinuation Guidelines for Acute Renal Insufficiency or Worsened Chronic Renal Insufficiency

For patients with signs of deteriorating renal function, additional monitoring needs to be conducted. Any patients with a calculated eGFR<30 mL/minute/1.73m^2 will be scheduled for a re-test within 4 days whenever possible. The eGFR is calculated based on the re-expressed abbreviated (four-variable) MDRD Study equation, using central laboratory measurements of sCr. [eGFR (mL/min/1.73m^2) = 175 x (standardized sCr)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if Black)] *[Note: sCr reported in mg/dL]*

If, at the re-test, the eGFR ≥30 mL/minute/1.73m^2, the patient can resume normal visit schedule.

If, at the re-test, the eGFR <30 mL/minute/1.73m^2, the patient should be discontinued from IP and the patient's renal function should continue to be monitored according to the judgment of the Investigator.

3.9.2 Procedures for discontinuation of a patient from IP

A patient that decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. Diaries and all study drugs should be returned by the patient.

All patients who discontinue study drug will be asked to remain in the study for FU and complete all scheduled study visits through Week 27. At the time of discontinuation the Week 24 procedures will be performed. Patients will not receive double-blind study drug during this follow-up period (and use of SGLT2-inhibitors should be restricted), but will complete all scheduled study visits and procedures. Patients unable or unwilling to return for scheduled visits as part of follow-up will have the opportunity to receive follow-up via telephone calls placed by the site mainly to review safety and concomitant medications. The only exception to this procedure is when a patient withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a patient is withdrawn from study, see Section 3.10.

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as 'Eligibility criteria not fulfilled' (i.e., patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomized patients). Patients can be re-enrolled one single time, but they cannot be re-randomized.

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (IP and assessments), without prejudice to further treatment.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AE the reason for withdrawal must be entered on the appropriate electronic case report form (eCRF) page. If possible, they will be seen and assessed by an Investigator(s). The Investigator will follow up AEs outside of the clinical study. The patient will return diaries and all study drugs.

If a patient withdraws from participation in the study, then his/her enrolment/randomization code cannot be reused. Withdrawn patients will not be replaced.

3.10.3 Lost to follow-up

Patient fails to return for study visits and cannot be reached with reasonable, repeated attempts.

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. Every effort will be made to ensure that the patient continues to return to the clinic for study visits and to avoid "lost to follow-up" during the conduct of the study. The study staff should make diligent attempts to contact patients who fail to return for study visits by using institutional databases, patient's health professionals, and any other means that comply with country and local laws and regulations. After the first missed visit, patients who are considered temporarily lost to follow-up will have 2 documented telephone contact attempts and 1 certified letter in an effort to contact patients

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, study patients are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the patient at the time of discontinuation must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Study Plan detailing the procedures

Study Period	**Screening period**	**Lead-in period**		**Treatment period**					**Follow-up period**	**For details see Protocol Section**
Visit	**Enrolment**	**Start of lead-in**	**Lead-in**	**Random-ization**	**Treat-ment**	**Treat-ment**	**Treat-ment**	**End of Treatment/ Discontinuat-ion/Rescue**	**Follow-up**	
Visit Number (Fasting/Non-fasting)	**1**[a] Non-fasting	**2**[b] Fasting	**3**[c] Fasting	**4**[c,d] Fasting	**5**[c,d,e] Non-fasting	**6**[c,d,e] Fasting	**7**[c,d,e] Fasting	**8**[c,d,e] Fasting	**9** Fasting	
Week	**-6**	**-4**	**-1**	**0**	**1**	**4**	**12**	**24**	**27**	
Day	**-42 to -29**	**-28**	**-7**	**1**	**8**	**29**	**85**	**169**	**190**	
Visit Window		**± 3**	**± 3**	**± 0**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	
Signed and Dated Informed consent[f]	X									10.4
Inclusion/Exclusion Criteria	X	X		X[g,h]						3.1 and 3.2
Allocation of E-code via IVRS/IWRS	X									3.3
Randomization to study treatment via IVRS/IWRS				X						3.3 and 3.5
Demographics	X									4.1
Medical and Surgical History	X									4.1
Brief Physical Examination[i]	X			X		X	X		X	5.2.2
Complete Physical Examination[j]		X						X		5.2.2
Height	X									5.1.3
Weight	X	X	X	X	X	X	X	X	X	5.1.3

Study Period	**Screening period**	**Lead-in period**		**Treatment period**					**Follow-up period**	**For details see Protocol Section**
Visit	**Enrolment**	**Start of lead-in**	**Lead-in**	**Random-ization**	**Treat-ment**	**Treat-ment**	**Treat-ment**	**End of Treatment/ Discontinuat-ion/Rescue**	**Follow-up**	
Visit Number (Fasting/Non-fasting)	**1**[a] Non-fasting	**2**[b] Fasting	**3**[c] Fasting	**4**[c,d] Fasting	**5**[c,d,e] Non-fasting	**6**[c,d,e] Fasting	**7**[c,d,e] Fasting	**8**[c,d,e] Fasting	**9** Fasting	
Week	**-6**	**-4**	**-1**	**0**	**1**	**4**	**12**	**24**	**27**	
Day	**-42 to -29**	**-28**	**-7**	**1**	**8**	**29**	**85**	**169**	**190**	
Visit Window		**± 3**	**± 3**	**± 0**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	
CCI [redacted]				X	X	X	X	X		5.1.6
Seated BP and Pulse	X	X	X	X	X	X	X	X	X	5.1.5.1
Orthostatic BP and Pulse				X	X	X	X	X	X	5.2.4.1
12-lead ECG[k]		X								5.2.3
Hepatitis Screen Panel		X								5.2.1
Blood samples for Safety Laboratory Panel[l]		X		X		X	X	X	X	5.2.1
Blood samples for HbA1c	X			X		X	X	X	X	5.1.1
Blood samples for S-Creatinine (eGFR calculation)	X	X	X	X		X	X	X	X	5.1.9
Blood samples for FPG				X		X	X	X	X	5.1.2
Assess FPG for Rescue						X	X			4.3.3.1
CCI [redacted]		X		X				X	X	5.1.10
CCI [redacted]				X				X	X	5.2.1
Pregnancy test[m]	X	X	X	X	X	X	X	X	X	5.2.1

Study Period	**Screening period**	**Lead-in period**		**Treatment period**					**Follow-up period**	**For details see Protocol Section**
Visit	**Enrolment**	**Start of lead-in**	**Lead-in**	**Random-ization**	**Treat-ment**	**Treat-ment**	**Treat-ment**	**End of Treatment/ Discontinuat-ion/Rescue**	**Follow-up**	
Visit Number (Fasting/Non-fasting)	**1**[a] Non-fasting	**2**[b] Fasting	**3**[c] Fasting	**4**[c,d] Fasting	**5**[c,d,e] Non-fasting	**6**[c,d,e] Fasting	**7**[c,d,e] Fasting	**8**[c,d,e] Fasting	**9** Fasting	
Week	**-6**	**-4**	**-1**	**0**	**1**	**4**	**12**	**24**	**27**	
Day	**-42 to -29**	**-28**	**-7**	**1**	**8**	**29**	**85**	**169**	**190**	
Visit Window		**± 3**	**± 3**	**± 0**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	
Urinalysis (dipstick and spot urine collection)		X		X		X	X	X	X	5.2.1
Timed urine sample collection (24-hours)				X				X		5.1.7
Dietary and life-style advice		X		X		X	X	X		4.2.1
Dispense Glucose Meter and/or Supplies (including diaries) /Provide Instructions		X	X	X	X	X	X	X		5.1.8 and 5.2.5.1
Review of diaries			X	X	X	X	X	X	X	5.1.8 and 5.2.5.1
Dispensation of Study Medication via IVRS/IWRS		X		X		X	X			7
Return of Study Medication and accountability				X		X	X	X		7.5 and 7.6
Adverse event review (AEs and SAEs)[n]	X	X	X	X	X	X	X	X	X	6
Hypoglycemic events review		X	X	X	X	X	X	X	X	5.2.5.1 and 6.3.7
Concomitant medication	X	X	X	X	X	X	X	X	X	7.7

[a] Screening procedures, indicated under Visit 1, can be completed over multiple visits, provided all procedures have been completed, with the results reviewed, prior to Visit 2.

[b] Patients must have their Visit 2 completed within 14 days following Visit 1. Visit window of ±3 for Visit 2 corresponds to the randomization visit (Visit 4). Note: The single-blind lead-in study medication and the central laboratory results from Visit 1 must have been received at the site prior to completing the entry into Visit 2.

[c] Central Laboratory samples must be collected in a fasting state (at least 8 hours of fasting prior to the study visit) except visit 5, and patients should be seen between 6 a.m. and 10 a.m. Patients must refrain from tobacco/nicotine for 12 hours and alcohol for 24 hours, respectively prior to study visits. Ensure to collect all fasting blood samples prior to the morning dose(s) of blinded study medication. Doses of study medication and other concomitant medications on the day of the visits must be taken upon completion of study visit procedures. (See Section 3.8)

[d] Double-blind treatment period visits must be scheduled according to the randomization visit date (Day 1), with a protocol-allowed visit window of ±5 days. Patients will bring their glucose meter and study supplies to the site at all visits. Any slippage in time from one visit must not accumulate to affect other visits.

[e] Randomized patients discontinuing study medication or requiring rescue should have Week 24 procedures done at the time of anti-diabetic rescue or study medication discontinuation. All patients who discontinue study medication will be asked to continue ordinary visit schedule, unless they entirely withdraw consent from the study. In patients discontinuing the study due to AE/SAE, the Investigator will follow the patients until the event has resolved or stabilized.

[f] The signature of the ICF by the prospective patient should be obtained at Visit 1. When only the Informed Consent is signed, and all other screening visit procedures are completed.

[g] eGFR value for inclusion is based on eGFR value between 45 – 59 mL/minute/1.73 m^2 at Visit 1, or Visit 2, or Visit 3.

[h] Lab values for inclusion will be based on results from Visit 2 and Visit 3. Lab values from Visit 4 will be used as baseline values for study entry.

[i] A brief physical examination should include cardiovascular (CV), lungs, abdomen, and extremities; and any organ systems pertinent to the patient's signs, symptoms, or AEs.

[j] A complete physical examination should include general appearance, head, eyes, ears, nose, throat, neck, CV, lungs, abdomen, lymph nodes, extremities, neurological, skin, and musculoskeletal.

[k] The 12-lead ECG must be performed at Visit 2. The results from this ECG must be available, assessed, and initialed and dated by the Investigator prior to Visit 4.

[l] Includes Hematology and Clinical chemistry. Please refer to Table 3

[m] Only for WOCBP. Blood sample will be collected for serum βHCG test, only if urine test is positive.

[n] SAEs will be collected from the time of informed consent and AEs will be collected from the start of the placebo lead-in (Visit 2).

4.1 Enrolment/screening period (Visit 1 to Visit 2)

Procedures will be performed according to the Study Plan Table 1.

At enrolment, obtain written informed consent prior to any study procedure or change in medical therapy required by the protocol. Consenting patients are assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be enrolled in the study.

The below assessments to be performed for all consented patients at Visit 1:

- Contact IVRS/IWRS to obtain unique patient enrolment number
- Review and confirm the patient's eligibility for the study by assessing inclusion and exclusion criteria listed in Sections 3.1 and 3.2.
- A standard patient medical, medication and surgical history will be obtained with the review of selection criteria
- Record demography (including sex, age, race and ethnic group)
- Perform brief physical examination
- Obtain vital signs (seated BP and pulse), body weight and height
- Obtain specimen (blood) for HbA1c
- Obtain specimens (blood) for S-Creatinine for eGFR calculation
- Perform urine pregnancy test for women of child bearing potential. Serum pregnancy test (βhCG) is performed, if urine pregnancy test result is positive
- Review concomitant medications
- Schedule the entry into lead-in visit between 06.00 a.m. and 10.00 a.m.
- Remind patient to be fasting and withhold anti-diabetic medications, insulin, anti-hypertensive drugs, lipid lowering drugs and anti-platelet drugs, the morning of their next visit and to refrain from tobacco/nicotine for 12 hours and alcohol for 24 hours, respectively prior to next visit

4.2 Single-blind placebo lead-in period (Visit 2 to Visit 4)

4.2.1 Visit 2, Start of lead-in

At visit 2 patients will be examined for HbA1c and eGFR level from blood sample obtained from Visit 1. If the HbA1c ≥7.0 and ≤11.0% and the eGFR value is within the range 40-65 mL/min/1.73 m^2 (MDRD-formula), then patients will enter a 4-week single-blind placebo

lead-in period. At the lead-in visit, the patient's current dietary and life-style will be reviewed. Patients will be instructed on diet and life-style in accordance with the local Diabetes guidelines or ADA guidelines by a qualified member of the study staff beginning with the lead-in visit. The below procedures will be performed during the visit for the eligible patients:

- Review and confirm the patient's eligibility for the study by assessing inclusion and exclusion criteria listed in Sections 3.1 and 3.2.
- Perform complete physical examination and body weight
- Obtain vital signs (seated BP and pulse)
- Perform 12-lead ECG. ECG must be obtained and reviewed with no significant abnormalities prior to Randomization
- Obtain specimens (blood) for hepatitis screen panel, safety laboratory panel including S-Creatinine for eGFR calculation, CCI [redacted]
- Perform urine pregnancy test for women of child bearing potential. Serum pregnancy test (βhCG) is performed, if urine pregnancy test result is positive
- Obtain specimen for urinalysis (dip stick and spot urine collection)
- Contact IVRS/IWRS to register visit and obtain study drug dispensing bottle assignment number and dispense study drug bottle
- Have patient to take their first dose of lead-in period study drug
- Provide instruction on diet and life-style
- Dispense blood glucose meter and supplies, provide instruction on their use and self-monitoring of blood glucose (see Section 5.2.5.1)
- Provide instruction on recording daily insulin doses and glucose values (when symptoms suggestive of hypoglycaemia) in the patient diary
- Remind patient to be fasting and withhold study drug and other anti-diabetic medications, insulin, anti-hypertensive drugs, lipid lowering drugs and anti-platelet drugs, the morning of their next visit and to refrain from tobacco/nicotine for 12 hours and alcohol for 24 hours, respectively prior to next visit
- Remind patient to bring study drug, diary and glucose meter to the next scheduled visit
- Review concomitant medications and SAEs from Visit 1.

4.2.2 Visit 3, Lead-in

- Obtain vital signs (seated BP and pulse) and body weight
- Obtain specimens (blood) for S-Creatinine for eGFR calculation
- Perform urine pregnancy test for women of child bearing potential. Serum pregnancy test (βhCG) is performed, if urine pregnancy test result is positive
- Dispense blood glucose meter supplies and diary (if required)
- Review diary and calculate mean total daily dose of insulin (see Section 5.1.8)
- Review concomitant medications
- Assess AEs including hypoglycemic events (see Section 6.3.7)
- Remind patient to be fasting and withhold study drug and other anti-diabetic medications, insulin, anti-hypertensive drugs, lipid lowering drugs and anti-platelet drugs, the morning of their next visit and to refrain from tobacco/nicotine for 12 hours and alcohol for 24 hours, respectively prior to next visit

4.3 Treatment period

Descriptions of the procedures for this period are included in the Study Plan Table 1. The specific requirements for the treatment period are mentioned below:

4.3.1 Visit 4, Randomization

At Visit 4, patients who meet all of the inclusion and none of the exclusion criteria, including the eGFR value between 45-59 mL/min/1.73 m^2 at Visit 1, or Visit 2, or Visit 3 - will be randomized to the 24 weeks double-blind treatment period.

- Perform brief physical examination
- Measure body weight and CCI [redacted]
- Obtain vital signs (seated and orthostatic BP and pulse)
- Obtain specimen (blood) for safety laboratory panel including S-Creatinine for eGFR calculation

CCI [redacted]

- Perform urine pregnancy test for women of child bearing potential. Serum pregnancy test (βhCG) is performed, if urine pregnancy test result is positive

- Obtain specimen for urinalysis (dip stick and spot urine collection)
- Timed urine sample collection (24-hours) (see Section 5.1)
- Contact IVRS/IWRS to randomize patient and obtain study drug dispensing bottle assignment number and dispense the study drug bottle
- Patient will be administered his/her first dose of the double-blind treatment at site
- Provide dietary and life-style advice
- Dispense glucose meter supplies and diary (if required)
- Review diary and calculate mean total daily dose of insulin for baseline (see Section 5.1.8)
- Collect and assess compliance with lead-in period study drug based on tablet count (see Section 7.5)
- Review concomitant medications and AEs including hypoglycemic events
- Remind patient to withhold study drug and other anti-diabetic medications, insulin, anti-hypertensive drugs, lipid lowering drugs and anti-platelet drugs, the morning of their next visit and to refrain from tobacco/nicotine for 12 hours and alcohol for 24 hours, respectively prior to next visit

4.3.2 Visit 5, Treatment

- Measure body weight CCI [redacted]
- Obtain vital signs (seated and orthostatic BP and pulse)
- Perform urine pregnancy test for women of child bearing potential. Serum pregnancy test (βhCG) is performed, if urine pregnancy test result is positive
- Dispense glucose meter supplies and diary (if required)
- Review diary and calculate mean total daily dose of insulin (see Section 5.1.8)
- Review concomitant medications and AEs including hypoglycemic events
- Remind patient to be fasting and withhold study drug and other anti-diabetic medications, insulin, anti-hypertensive drugs, lipid lowering drugs and anti-platelet drugs, the morning of their next visit and to refrain from tobacco/nicotine for 12 hours and alcohol for 24 hours, respectively prior to next visit

4.3.3 Visit 6, Treatment

- Perform brief physical examination
- Measure body weight and [redacted]
- Obtain vital signs (seated and orthostatic BP and pulse)
- Obtain specimens (blood) for safety laboratory panel including S-Creatinine for eGFR calculation
- Obtain specimen (blood) for HbA1c and FPG
- Assess FPG for rescue (see Section 4.3.3.1 for details)
- Perform urine pregnancy test for women of child bearing potential. Serum pregnancy test (βhCG) is performed, if urine pregnancy test result is positive
- Obtain specimen for urinalysis (dip stick and spot urine collection)
- Contact IVRS/IWRS and obtain study drug dispensing bottles assignment number and dispense the study drug bottles
- Collect and assess compliance with study drug based on tablet count (see Section 7.5)
- Provide dietary and life-style advice
- Dispense glucose meter supplies and diary (if required)
- Review diary and calculate mean total daily dose of insulin (see Section 5.1.8)
- Review concomitant medications and AEs including hypoglycemic events
- Remind patient to be fasting and withhold study drug and other anti-diabetic medications, insulin, anti-hypertensive drugs, lipid lowering drugs and anti-platelet drugs, the morning of their next visit and to refrain from tobacco/nicotine for 12 hours and alcohol for 24 hours, respectively prior to next visit

4.3.3.1 Rescue Medication Due to Lack of Glycemic Control in the Treatment Period

Patients with lack of glycemic control during the 24-week treatment period may be eligible to receive open-label rescue medication in addition to their blinded treatment in order to treat ongoing hyperglycemia. Patients may receive open-label rescue medication added on to, but not as a replacement for, their current study drug regimen. Rescue medication in this protocol refers to any approved, appropriate anti-diabetic agent, except SGLT2-inhibitors, for which there is either initiation or upward titration, in accordance with the approved label and

conventional standards of care. Open-label rescue medication is to be titrated as needed to obtain adequate glycemic control. Patients who received a first rescue medication, who subsequently fulfil lack of glycemic control criteria, may have other rescue medications added or substituted, according to Investigator judgment.

During the 24-week double-blind treatment period, all rescue decisions will be based on central laboratory FPG and confirmatory FPG results. If patients meet the protocol-specified glycemic criteria based on FPG, they will be recommended for open-label rescue medication.

Between scheduled visits, the patients will be asked to check their blood glucose if they develop symptoms suggestive of hyperglycemia. The sections and tables listed below define the lack of glycemic control criteria. Glucometers will be provided by AstraZeneca. The patients will receive instructions for the use of the glucometer according to the manufacturer's instructions. Patients will be instructed to contact the investigator if they experience a hyperglycemic event in order to schedule an extra visit for central laboratory FPG and if needed, a confirmatory, repeat FPG.

Patients in the follow-up phase will not need to adhere to the protocol defined rescue criteria, and may have their anti-diabetic regimen adjusted at the Investigator's discretion.

The sections and tables listed below define the lack of glycemic control criteria for initiation of open-label rescue medication.

Protocol-Defined Lack of Glycemic Control Criteria for Initiation of Open-Label Rescue Medication

Pre-specified glycemic criteria (see Table 2 below), based upon central laboratory FPG and confirmatory, repeat FPG, have been established during the 24-week double-blind treatment period, from Week 4 and up to Week 24 visits, to determine eligibility for open-label rescue medication initiation/titration.

Table 2 Lack of Glycemic Control Criteria for Initiation of Open-Label Rescue Medication

Visit Label	Central Laboratory FPG
From Week 4 (Visit 6) to Week 12 (Visit 7) (excluding Week 12)	FPG >240 mg/dL (13.3 mmol/L)
From Week 12 (Visit 7) to Week 24 (Visit 8) (excluding Week 24)	FPG >200 mg/dL (11.1 mmol/L)

Patients with a central laboratory FPG value meeting the lack of glycemic control criterion at a pre-specified visit will be scheduled for a follow-up visit (within 3 - 5 days) to obtain a second central laboratory FPG value and review the patient's glucose meter readings. If the repeat central laboratory FPG value still meets the criterion, the patient will receive rescue medication.

Irrespective of study visit number, patients who meet rescue criteria in the treatment period must first complete the Week 24 visit procedures before receipt of open-label anti-diabetic rescue medication to ensure that important study endpoint measurements are collected.

Following completion of the Week 24 "Rescue" visit, rescued patients will be administered open-label rescue medication in addition to their blinded study drug. Rescued patients will then continue in the treatment period according to their original visit schedule. Patients who received a first open-label anti-diabetic rescue medication, who subsequently fulfill lack of glycemic control criteria described in the Table 2 above, may have other rescue medications added or substituted, according to Investigator judgment, without repetition of rescue visits.

Patients with a central laboratory FPG value >200 mg/dL (11.1 mmol/L) at Week 24 (Visit 8), will not be considered as rescued for efficacy analysis.

Guidelines with regard to changes in insulin dose

Each patient's baseline insulin therapy should remain unchanged wherever possible throughout the double-blind treatment period. The stable insulin regimen aims to continue insulin as it was being used by the patient at enrollment and lead-in, with no changes to insulin type and with as few changes in insulin dosage as possible. A stable insulin regimen is pivotal, because it makes it possible for the study to measure any differences in glycemic control between the dapagliflozin treatment arm and the matching placebo arm. Down-titration of insulin will be allowed only as necessary to prevent low blood glucose or hypoglycemia. During the double-blind treatment period, a few patients will experience poor glycemic control, as measured by increased FPG measurements from the central laboratory during study visits. When glucose measurements exceed certain limits (as specified in Table 2 above), the patient will be ''rescued''.

During the double-blind treatment period, if up-titration of insulin dose is >10% (lasting more than 7 consecutive days) in comparison to the mean daily insulin dose at baseline, the patient shall be handled as administration of anti-diabetic rescue medication (i.e., the patient must complete the Week 24 visit procedures, as outlined in section 4.3.5) and the patient will continue in the treatment period according to their original visit schedule. Patients must record the daily dose of insulin in the diary provided (minimum of 80% of days with a value) and review any changes in insulin doses with their investigator, either at regularly scheduled visits, or via telephone calls between visits. Patients required to be rescued, shall be called for an unscheduled visit within 5 days, to complete the Week 24 procedures.

Any insulin dose changes (even if more than ±10% of the mean daily insulin dose at baseline) is not considered as an up or down titration as long the insulin dose change is not for a period of more than 7 consecutive days. For example, dose changes due to known changes in physical activity or food intake will not be registered as up or down titration as long as the insulin dose is back to the previous dose after the change. Similarly, if insulin requirement has increased temporarily, e.g., due to an infection, it will not be considered an up-titration even if the insulin dose increase is more than 10% of the baseline mean daily insulin dose, as

long as such an increase is for a period of not more than 7 consecutive days and the insulin dose is expected to return to the baseline level once the precipitating condition has resolved.

4.3.4 Visit 7, Treatment

Perform the same assessments as detailed in visit 6 (see Section 4.3.3).

4.3.5 Visit 8, End of Treatment/Discontinuation/Rescue

Randomized patients discontinuing study drug or requiring rescue should have Visit 8 (Week 24) procedures done at the time of rescue or study drug discontinuation. All patients who discontinue study drug will be asked to continue ordinary visit schedule, unless they entirely withdraw consent from the study.

- Perform complete physical examination
- Measure body weight CCI [redacted]
- Obtain vital signs (seated and orthostatic BP and pulse)
- Obtain specimen (blood) for safety laboratory panel including S-Creatinine for eGFR calculation

CCI [redacted]

- Perform urine pregnancy test for women of child bearing potential. Serum pregnancy test (βhCG) is performed, if urine pregnancy test result is positive
- Obtain specimen for urinalysis (dip stick and spot urine collection)
- Timed urine sample collection (24-hours) (see Section 5.1)
- Collect and assess compliance with study drug based on tablet count
- Provide dietary and life-style advice
- Dispense glucose meter supplies and diary (if required)
- Review diary and calculate mean total daily dose of insulin
- Review concomitant medications and AEs including hypoglycemic events
- Remind patient to be fasting and withhold anti-diabetic medications, insulin, anti-hypertensive drugs, lipid lowering drugs and anti-platelet drugs, the morning of their next visit and to refrain from tobacco/nicotine for 12 hours and alcohol for 24 hours, respectively prior to next visit

4.4 Follow-up period, Visit 9

Descriptions of the procedures for this period are included in the Study Plan Table 1. The specific requirements for the follow up period are mentioned below:

After completion of Week 24 visit, patients will enter a 3-week safety follow-up period without study drug. The follow-up visit (Visit 9) provides the opportunity to further evaluate changes in physical signs, renal function (i.e., changes in eGFR), symptoms or laboratory parameters that may be related to dapagliflozin.

- Perform brief physical examination
- Measure body weight
- Obtain vital signs (seated and orthostatic BP and pulse)
- Obtain specimen (blood) for safety laboratory panel including S-Creatinine for eGFR calculation

CCI

- Perform urine pregnancy test for women of child bearing potential. Serum pregnancy test (βhCG) is performed, if urine pregnancy test result is positive
- Obtain specimen for urinalysis (dip stick and spot urine collection)
- Review diary and calculate mean total daily dose of insulin
- Review concomitant medications and AEs including hypoglycemic events

5. STUDY ASSESSMENTS

The Rave® Web Based Data Capture (WBDC) system will be used for data collection and query handling.

The investigator will ensure that data on the observations, tests, and assessments specified in the protocol are recorded on the eCRF provided by AstraZeneca as specified in the study protocol and in accordance with the instructions provided. The CRF will be accompanied with "Instructions for the investigator", which should be followed. These instructions provide guidance for the recording of study data in the CRF including how to change data incorrectly recorded.

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.

5.1 Efficacy assessments

Blood and urine samples will be obtained at specified time points for laboratory evaluations. The central laboratory for this study will perform the analysis of all scheduled laboratory tests and will provide reference ranges for these tests. The detailed methods for specimen collection, handling, processing, shipping, and storage will be supplied in the Investigator's Laboratory Manual provided by the Central Laboratory. All clinical laboratory tests will be performed by the Central Laboratory or designated reference laboratory.

During the double-blind treatment period, HbA1c and urinary glucose values will be blinded to the Investigator and to the Sponsor. These values will be provided to the Investigator after the study has been completed. FPG value will be reported as an un-blinded value throughout the study.

All glycemic efficacy objectives will be based on values measured by central laboratory. Any self-monitored blood glucose measured by the patient and FPG measured by the site using glucometer will be used only for safety purposes. [Note: The patients will be asked to check their blood glucose only if they develop symptoms suggestive of hypoglycemia or hyperglycemia and to record hypoglycemia symptoms in the patient diary.]

5.1.1 HbA1c

HbA1c is the primary assessment for the determination of glycemic efficacy and will be analysed by a central laboratory according to the procedures described in the Laboratory Manual which will be distributed to each study site during site initiation.

5.1.2 FPG

FPG is a well established measure of glycemic efficacy and considered to be an acceptable secondary endpoint. FPG will be analysed by a central laboratory according to the procedures described in the Laboratory Manual which will be distributed to each study site during site initiation.

5.1.3 Weight and height

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

5.1.4 BMI

BMI is a calculated ratio between weight and height (weight / height2, where weight is measured in kg, and height in metres) and will be computed by AstraZeneca.

5.1.5 Vital signs

5.1.5.1 Seated blood pressure and pulse

Pulse and BP measurements must be taken consistently throughout the study. Pulse and BP should be recorded using the same equipment at each visit. Use only the right or the left arm when measuring these parameters. Document which arm was used, along with the observer's initials. The same arm should be used at all visits for each position. At each study visit, BP and pulse measurements should be obtained prior to blinded study drug administration. Pulse and BP will be measured thrice (1 minute apart) before any blood sampling is done after the patient has been sitting and resting for least 5 minutes. BP readings should be taken while the patient is in a comfortable seated position with the arm supported at the level of the heart. All three readings must be recorded in eCRF. For study analyses, the average of the three BP and pulse readings will be used.

CCI

[redacted]

5.1.8 Insulin dose

The daily insulin dose will be recorded in patient diary by patient and the mean daily dose is calculated by investigator. The calculated mean daily insulin dose is an average daily insulin use from the last visit.

5.1.9 eGFR

eGFR is calculated according to the MDRD formula): GFR (mL/min/1.73m^2) = 175 x (standardized sCr)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if Black)] [Note: sCr reported in mg/dL]

CCI

[redacted]

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in the Study Plan (see Section 4). Additional safety samples may be collected for analysis at local laboratory, if clinically indicated at the discretion of the investigator.

The detailed methods for specimen collection, handling, processing, shipping, and storage will be supplied in the Investigator's Laboratory Manual provided by the Central Laboratory.

The following laboratory variables will be measured:

Table 3 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	**Clinical Chemistry [serum (S) or plasma (P)]**
B-Haemoglobin (Hb)	S-Aspartate transaminase (AST)
B-Hematocrit	S-Alanine transaminase (ALT)
B-Red blood cell count	S-Alkaline phosphatase (ALK-P)
B-White blood cell count	S-Bilirubin, total
B-Platelet count	S-Blood Urea Nitrogen
	S-Creatinine
Urine analysis (dipstick)	S-Albumin
Blood (Microscopy if dipstick positive for blood)	S-Total protein
Pregnancy test (Urine HCG pregnancy test for WOCBP (HCG minimum sensitivity of 25 IU/L), dipstick analyzed at the study centre)	CCI
	S-Potassium
Urine analysis (spot urine)	S-Calcium, total
Creatinine	S-Sodium
Albumin	S- Bicarbonate
CCI	S- Chloride
Glucose (The quantitative urinary glucose values must not be disclosed during the double-blind phase (i.e., Visit 4 to 8) to maintain the blindness.)	S- Magnesium
	S- Phosphorus
	P- Parathyroid Hormone (PTH)
	S- 25-hydroxy-vitamin D
	S- βHCG, if urine pregnancy test result is positive
	Hepatitis Screen Panel (Includes Hepatitis B viral antibody IgM, Hepatitis B surface antigen and Hepatitis C virus antibody).

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

NB. In case a patient shows an AST and/or ALT ≥3xULN and TB ≥ 2xULN, please refer to Appendix C "Algorithm on Management of Sustained Elevated Liver Safety Abnormalities", for further instructions.

5.2.2 Physical examination

A brief physical examination should include the CV system, lungs, abdomen, and extremities, and any organ system pertinent to the patient's signs, symptoms, or AEs. The patient should always be evaluated for the presence of oedema. A complete physical examination should include general appearance, head, eyes, ears, nose, throat, neck, CV system, lungs, abdomen, lymph nodes, extremities, neurological system, skin, and musculoskeletal system. The patient should always be evaluated for the presence of oedema.

5.2.3 ECG

A 12-lead ECG will be taken after the patient has been lying down resting for at least 5 minutes. The ECG will be evaluated by the investigator and entered as 'Normal' or 'Abnormal' in the eCRF. If the ECG is evaluated as "Abnormal" the investigator should document the specific abnormality.

5.2.4 Vital signs

5.2.4.1 Blood pressure and pulse

As BP is both efficacy and safety variable in this study, measurement of seated BP is described in Sections 5.1.5.

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

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

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

5.2.5 Other safety assessments

5.2.5.1 Self-monitored blood glucose and hypoglycemic events

The patients will be asked to check their blood glucose when they develop symptoms suggestive of hypoglycemia and to record specific symptoms in a hypoglycemia/blood glucose diary. Any results collected in the diary will be reviewed by the investigator at each visit. The investigator is responsible for questioning the patient about all symptoms reported in the diary and for determining if they meet the clinical definition of hypoglycemia. Only symptoms and/or blood glucose values that meet the definition of hypoglycemia should be reported on the hypoglycemia eCRF pages see Section 6.3.7. Glucometers will be provided by AstraZeneca.

Patients will be instructed to contact the investigator anytime they experience a hypoglycemic event. Hypoglycemic events must be recorded in the diary anytime a patient experiences either of the following:

- Signs and symptoms of hypoglycemia (regardless of blood glucose value by finger stick)
- Blood glucose value by finger stick <63 mg/dL (3.5 mmol/L) (regardless of symptoms).

Data to be collected for each hypoglycemic event:

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

The patient diary will be reviewed and added to the patient's source record. A new diary for the next period will be handed over to the patient if needed

5.2.5.2 Hepatic events (Hepatic Adjudication Committee)

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

- Hepatic events timely related to death (within 30 days before death)
- AST and/or ALT >3x ULN and TB >2x ULN (within 14 days of the AST and/or ALT elevation
- AST and/or ALT >10x ULN

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

5.2.5.3 Asymptomatic bacteriuria

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

During enrolment, treatment and follow up of patients in this study, the investigator may discover a patient with asymptomatic bacteriuria. Asymptomatic bacteriuria is defined as the presence of ≥105 colony forming units/mL of bacteria, in a properly collected voided urine specimen, without signs or symptoms typically attributed to urinary tract infection (UTI). Asymptomatic bacteriuria is prevalent among diabetic women, and is associated with pyuria in 70% of cases. Neither guidelines from the US (Nicolle et al 2005, USPSTF 2008) nor Europe (EAU 2014) recommend screening for, or treatment of, asymptomatic bacteriuria in non-pregnant diabetic patients. In this study, the central laboratory will report urinary dipstick test results for hemoglobin but will not routinely report the results of urinary dipstick tests for leukocyte esterase as a screening test for pyuria in surveillance urine examinations.

5.2.5.4 Microscopic Hematuria

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

Patients with repeated reports of microscopic hematuria in 2 or more properly collected urine samples need to have follow-up for this result according to standard of care. The American Urological Association defines microscopic hematuria as three or more red blood cells per high-power microscopic field in urinary sediment from two or more properly collected urinalysis specimens (AUA, Grossfeld et al 2001). These Best Practice guidelines have been evaluated by Jung in a study of 772000 patients (Jung et al 2011).

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

Patients who lack other explanation for their hematuria, or who have risk factors for significant urologic disease, will need a urological evaluation and should be referred to an urologist. Risk factors for significant urological disease include unexplained microscopic hematuria as well as smoking history, occupational exposure to dyes or chemicals (such as benzenes or aromatic amines), visible hematuria, age >40 years, previous urologic history, history of irritative voiding symptoms, history of UTI, analgesics or phenacetin abuse, history of pelvic irradiation, or cyclophosphamide use (AUA, Greenwood M 1926). Results from any procedure or investigations should be reported on the eCRF.

5.2.5.5 Volume Depletion

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

5.2.5.6 Potential events of Diabetic Ketoacidosis

All potential events of DKA will be recorded in the eCRF and submitted to an independent DKA Adjudication Committee. The DKA Committee T2DM will assess available information on each potential DKA event and will classify the event in accordance with the definitions in the DKA Adjudication Charter T2DM.

The DKA Adjudication Committee will be kept blinded to the study drug treatment received by each patient with a potential DKA event in the clinical study. A separate DKA Adjudication Manual will define and describe the procedures for the collection of DKA information, handling, adjudication criteria and reporting of these events/cases.

5.3 Other assessments – Not Applicable

5.4 Pharmacokinetics – Not Applicable

5.5 Pharmacodynamics – Not Applicable

5.6 Pharmacogenetics – Not Applicable

5.7 Biomarker analysis – Not Applicable

5.8 Storage, re-use and destruction of biological samples

After the analyses are complete the samples will be either completely consumed during the analytical process or disposed of after the analysis.

5.9 Labelling and shipment of biological samples

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

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

5.10 Chain of custody of biological samples

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

The PI at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

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

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

5.11 Volume of blood

The total volume of blood that will be drawn for each patient in this study is listed in the Table 4 below. The collection of additional samples is performed locally at the discretion of the investigator and recorded appropriately, thus requiring additional sample volumes.

Table 4 Volume of blood to be withdrawn from each patient

Assessment	Sample Volume (mL)	No. of samples	Total volume (mL)
Clinical chemistry CCI [redacted]	2.5	8	20
CCI [redacted]	2.5	3	7.5
Haematology HbA1c	2	7	14
FPG	2	5	10
Hepatitis screen panel	3.5	1	3.5

[2] Combined in 1 sample with Clinical Chemistry

Assessment	Sample Volume (mL)	No. of samples	Total volume (mL)
Parathyroid Hormone (PTH)	2	3	6
Total			**61**

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 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.

6.2 Definitions of serious adverse event

A SAE is an AE occurring during any study phase (i.e., lead-in, treatment, washout, FU), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/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 jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix A to the Clinical Study Protocol (CSP).

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

AEs will be collected from the start of the placebo lead-in period throughout the treatment period (Visit 2 to 8) and including the follow-up period (Visit 9).

SAEs will be recorded from the time of informed consent is obtained until the end of the study (Visit 9).

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collect for each AE;

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

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death

- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Description of AE.

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

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

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 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. 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 when it satisfies the criteria shown in Section 6.2.

6.3.4 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 A to the CSP.

6.3.5 Adverse events based on signs and symptoms

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

6.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the CSR. 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 are clinically significant, fulfil 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., anaemia versus low Hb 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.

Pre-defined liver enzyme elevations will undergo adjudication. The definitions of the events to be adjudicated are provided in the Hepatic Adjudication Manual. For all events identified for adjudication, the Investigator will complete the appropriate eCRF pages and provide source documentation as detailed in the Hepatic Adjudication Manual. See also Section 5.2.5.2.

6.3.7 Hypoglycemic events

A separate section in the eCRF will be used to document all reported episodes of hypoglycaemia (see Section 5.2.5.1). Hypoglycemic episodes should also be reported on the AE eCRF page if the event fulfils protocol criteria for a SAE (see Section 6.2).

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

- Minor hypoglycemic event, defined as either a symptomatic episode with a capillary or plasma glucose measurement <63 mg/dL (<3.5 mmol/L) regardless of need for external assistance or an asymptomatic capillary or plasma glucose measurement below 63 mg/dL (3.5 mmol/L), that does not qualify as a major episode.

6.4 Reporting of serious adverse events

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 CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by designated back-up procedures.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

6.5 Overdose

Overdose is defined as more than 100 mg of dapagliflozin per day. Dapagliflozin has been well tolerated at doses of up to 500 mg per day in single dose testing in healthy volunteers and up to 100 mg per day in repeat dose testing for 14 days in healthy volunteers and patients with T2DM. If an overdose is suspected, monitoring of vital functions as well as treatment as appropriate should be performed

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.6.1 Maternal exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP 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 the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

6.6.2 Paternal exposure – Not Applicable

6.7 Management of IP related toxicities – Not Applicable

Dose reductions of IP are not permitted in the study.

6.8 Study governance and oversight

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance this could involve amendments to the study protocol and letters to Investigators.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Dapagliflozin 10 mg	Green, plain, diamond shaped, film coated 10 mg tablet	CCI [redacted]
Matching placebo for dapagliflozin 10 mg	Green, plain, diamond shaped, film coated tablet	CCI [redacted]

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

7.2 Dose and treatment regimens

The study consists of a 4-week single-blind placebo lead-in period, a 24-week double-blind placebo-controlled treatment period, and a 3-week follow-up period. The study drug is taken orally once daily in the morning. Doses of study drug on the day of the visits must be taken upon completion of study visit procedures.

Treatment during single-blind lead-in period

During the 4-week (Visit 2 to Visit 4) single-blind lead-in period eligible patients will receive 1 bottle containing 35 tablets of placebo matching dapagliflozin 10 mg. First dose of lead-in period study drug will be administered at the clinic by site staff. Subsequent doses should be taken once daily in the morning.

Treatment during double-blind randomization period

At Visit 4, eligible patients will be randomized to double-blind treatment of dapagliflozin 10 mg or matching placebo. The study drug should be taken once daily in the morning and at approximately the same time of the day during the study period. Nevertheless prior to each clinical visit patients should be instructed not to take any medication at morning and to abstain from all food and beverages for 8 hours; however, drinking water is allowed. On the day of study visit, study drug and other concomitant medications will be taken, after completion of study visit procedures. Except anti-hypertensive medication (see Section 3.8)

First dose of study drug will be administered at the clinic by site staff.

Table 5 Drug Dispensing Scheme

Visit ID	No. of bottles to dispense of dapagliflozin 10 mg or matching placebo[a]
Visit 1 (Enrolment)	N/A
Visit 2 (Start of Lead-in)	1 bottle (placebo)
Visit 3 (Lead-in)	N/A
Visit 4 (Randomization)	1 bottle (dapagliflozin or placebo)
Visit 5 (Treatment)	N/A
Visit 6 (Treatment)	2 bottles (dapagliflozin or placebo)
Visit 7 (Treatment)	3 bottles (dapagliflozin or placebo)
Visit 8 (Study Completion)	N/A
Visit 9 (Study Follow-Up)	N/A

[a] Each bottle contains 35 tablets.

7.3 Labelling

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

7.4 Storage

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

7.5 Compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the CRF.

Each time study drug is dispensed, compliance will be reinforced. When study drug is returned, compliance will be assessed based on returned tablet counts. Tablet counts will be recorded in the eCRF. Patients should demonstrate good compliance with the administration of study drug (≥70% and ≤130%) during the lead-in period. For patients with compliance between ≥70% and < 80% or > 120% and ≤130%, the Investigator should ensure that there are no systematic factors which may result in unacceptable compliance with study drug during the treatment period of the study. Such cases should be discussed with the study physician prior to randomization. During double-blind treatment period, patients judged to be non compliant (defined as taking less than 80% or more than 120% of the prescribed dose of study drug) may continue in the study, but should be counselled on the importance of taking their study medication and applicable concomitant medications as prescribed.

7.6 Accountability

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

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

The investigator is responsible for making sure:

- That the IP is handled and stored safely and properly (see Section 7.4).
- That the IP is only dispensed to study patients in accordance with this protocol.

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

At the termination of the Clinical Study or at the request of AstraZeneca, the investigator will either return any unused IP to AstraZeneca or its designate, or destroy IP 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 AstraZeneca or its designate, the study site personnel or the AstraZeneca monitor will account for all received IP received at the site, unused IP and for appropriate destruction. Certificates of delivery, destruction and return should be signed and archived.

7.7 Concomitant and other treatments

Changes in concomitant medication should be avoided during study participation, with the exception of situations defined in this protocol, but medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigators, who must decide if the patient should remain in study or need to be dismissed from study due to patient's safety or interference with study objectives.

The administration of all medication must be recorded in the appropriate sections of the electronic CRF. The specific type of medication (trade or generic name), the indication for use, dosages, and the dates of usage should be reported.

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

Restricted Medication/Class of drug:	**Usage:**
Metformin	A metformin dose which is outside the specified dose range for moderate renal impairment (eGFR 30– 59 mL/minute/1.73m^2, MDRD formula) according to local guidelines or investigator's judgment, is not allowed.

Teriparatide, bisphosphonates and/or calcitonin	Treatment with teriparatide, bisphosphonates and/or calcitonin are allowed provided the dose has not changed within 30 days prior to enrolment.

Prohibited Medication/Class of drug:	**Usage:**
Antiviral drugs	Treatment for HIV and/or use of antiviral drugs (delavirdine, indinavir, nelfinavir, ritonavir, saquinavir) is not allowed
Glucocorticoids (long term treatment)	Long term treatment with glucocorticoids (equivalent to oral prednisolone ≥10 mg (betamethasone ≥1.2 mg, dexamethasone ≥1.5 mg, hydrocortisone ≥40 mg) is not allowed, (two temporary periods of no longer than 10 days each are allowed during the study); topical or inhaled corticosteroids are allowed.
Weight loss medication	Use of weight loss medication, including but not limited to sibutramine, phentermine, orlistat, rimonabant, benzphetamine, diethylpropion, methamphetamine, liraglutide indicated for anti-obesity treatment, and/or phendimetrazine, within 30 days of the enrolment visit, is not allowed.

Rescue/Supportive Medication/Class of drug:	**Usage:**
Open label rescue medication	See Section 4.3.3.1

Guidelines with regard to standard of care and other therapy

During the duration of the study period, standard of care for each patient should be kept unchanged to the largest extent as possible, according to the judgment of the Investigator.

Specifically, the dose of OADs, insulin, anti-hypertensive drugs, lipid lowering drugs and anti-platelet drugs should be kept constant throughout the entire 24-week treatment period.

If dose of OADs and insulin is reduced according to the investigator discretion, patient should still continue in the study with double blind treatment and the dose changes must be recorded in the appropriate sections of the electronic CRF.

7.7.1 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and well being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF.

7.8 Post Study Access to Study Treatment – Not Applicable

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

- All personnel involved with the analysis of the study will remain blinded until database lock and protocol violators identified.
- Analyses will be performed by AstraZeneca or its representatives.
- Refer to SAP for details.
- All personnel involved with the analysis of the study will remain blinded until database lock and protocol violators are identified. Analyses will be performed by AstraZeneca or its representatives.

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to first patient randomized and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data (this is the expectation for the pivotal studies).

8.2 Sample size estimate

The primary endpoint is the change from baseline in HbA1c at Week 24. From post-hoc results of similar clinical studies (Study MB102029, Study D1690C00018, and Study D1690C00019) when patients meeting eGFR entry criteria like those in this current study were selected, the mean placebo-corrected change from baseline in HbA1c after 24 weeks of treatment for the current study is estimated to be -0.3% for dapagliflozin 10 mg.

Assuming a common standard deviation (SD) of 0.9% in the primary endpoint, 143 patients per treatment group with both baseline and at least one post-baseline HbA1c measurement will provide 80% power to detect a treatment difference of 0.3% in the primary endpoint at a two-sided significance level =0.05, using a two-sample t-test. Assuming that 5% of randomized patients fail to qualify for inclusion in the full analysis set due to missing baseline and/or all post-randomization values for this primary endpoint, a total of 302 randomized patients (151 per treatment group) are needed for the study.

8.3 Definitions of analysis sets

8.3.1 Enrolled Patients Data Set

The Enrolled Patients Data Set includes data collected from all patients who signed informed consent.

8.3.2 Lead-in Patients Data Set

The Lead-in Patients Data Set includes data collected from all patients who took at least one dose of lead-in medication.

8.3.3 Full Analysis set

The primary efficacy analysis will be performed on the Full Analysis Set, which will consist of all randomized patients who took at least one dose of double-blind study drug during the short term double-blind period and have a non-missing baseline value and at least one post-baseline efficacy value (HbA1c, total body weight, FPG, and SBP).

When the Full Analysis Set is used, patients will be presented in the treatment group to which they were randomized at the start of the short term double-blind treatment period (even if the treatment they received was different).

8.3.4 Per Protocol Analysis Set

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

Relevant Protocol Deviations (RPDs), used to determine complete or partial data exclusion for the short term double-blind treatment period due to prohibited concomitant treatment, are listed in section 7.7. Any further protocol deviations for a particular study will be specified in the study-specific SAP.

8.3.5 Safety Analysis Set

The Safety Analysis Data Set will consist of all patients who received at least one dose of double-blind study drug during the short term double-blind treatment period. The Safety Analysis Data Set will include any patient who accidentally received double-blind study drug but was not randomized in the study.

All analyses using the Safety Analysis Data Set will be presented by randomized treatment group, except in cases where information was available which indicated that a patient received a different treatment for the entire course of their participation in the double-blind treatment period of the study. In this case, the safety data for those patients will be presented by the treatment actually received. In case a patient never received the treatment as assigned by randomization, then the safety data for that patient will be presented by the first treatment received.

8.3.6 PK analysis set – Not Applicable

8.3.7 PRO analysis set – Not Applicable

8.4 Outcome measures for analyses

8.4.1 Primary outcome variable

The primary outcome variable will be the change in HbA1c (%).

8.4.2 Secondary outcome variables

Secondary outcome variables will be:

- Percent change from baseline in body weight (kg).
- Change from baseline in FPG (mg/dL).
- Change from baseline in seated SBP (mmHg).

8.4.3 Safety outcome variables

Safety outcome variables will be:

- Numbers and proportions of patients experiencing AEs and, separately, marked laboratory abnormalities.
- Changes from baseline in eGFR (mL/min)
- Proportions of patients discontinued from study drug due to worsening renal insufficiency (eGFR<30 mL/min/1.73m^2) during treatment.
- Changes from baseline in SBP (mmHg), DBP (mmHg), and heart rate (bpm).
- Changes from baseline in the findings from physical examination.
- Changes from baseline in clinical laboratory test results.

8.4.4 Exploratory outcome variables

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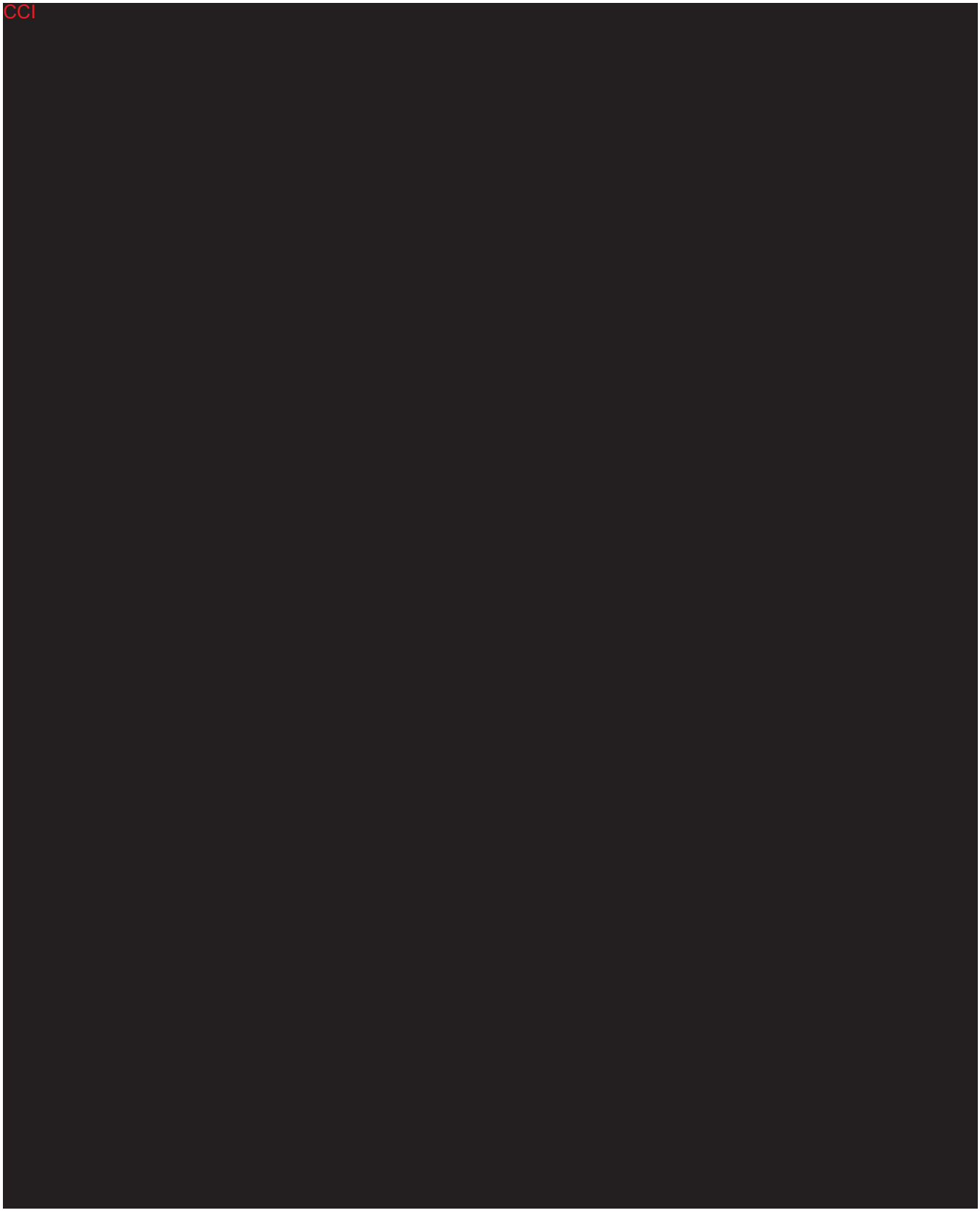

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8.5 Methods for statistical analyses

Unless otherwise specified, analyses of efficacy endpoints will only include measurements prior to the administration of rescue medication.

8.5.1 Analysis of the primary variable (s)

The primary endpoint is the changes from baseline in HbA1c at Week 24. The primary analysis of the primary endpoint will be based on a mixed effects model with repeated measures (MMRM) using 'direct likelihood', including patients in the Full Analysis Set who have a baseline measurement and at least one post-baseline measurement. The primary analysis will only include measurements prior to the administration of rescue medication. Measurements made following rescue administration will not be included in analysis.

The SAS procedure PROC MIXED will be used for the primary analysis. The primary analysis model will include the fixed categorical effects of treatment, week, randomization stratification factor (i.e. anti-diabetic treatment strata) and treatment-by-week interaction as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction. An unstructured matrix for the within-patient error variance-covariance will be used. The denominator degrees of freedom will be calculated according to the Kenward-Roger method. A number of back-up models will be defined in the statistical analysis plan in case of non-convergence of the preferred model or other issues. Point estimates and 95% confidence intervals for the mean change within each treatment group as well as the difference in mean change between the dapagliflozin and placebo will be calculated. P-value of the differences in week 24 visit estimates between dapagliflozin and placebo will be calculated.

A variety of sensitivity analyses will be specified in the Statistical Analysis Plan to assess the robustness of the primary analysis results, including a sensitivity analysis of the effect of baseline eGFR on the results obtained in primary analysis as well as sensitivity analyses which include all data pre- and post-rescue. In order to assess the robustness of the primary analysis results on the missing data assumptions, the amount of missing data, the distribution of missing data among treatment groups, and the reasons for missing data will be examined. If substantial amount of missing data is observed or if imbalance occurs amongst the treatment

groups, additional sensitivity analyses, including those based on alternative missing data assumptions, may be performed.

8.5.2 Analysis of the secondary variable(s)

A sequential testing procedure will be employed among the primary endpoint and secondary endpoints in order to control the type I error rate at the 0.05 level. The tests for the secondary efficacy endpoints will be performed only if the test for the primary endpoint is significant, in which case the secondary endpoints will be tested in the order that they appear in the objectives section of the protocol synopsis. Statistical tests will be only performed for a given secondary endpoint if all previous sequential tests for that comparison between dapagliflozin and placebo are also significant. Otherwise, the testing procedure will stop at the secondary endpoint that does not reach statistical significance.

The secondary endpoints, i.e, percent change from baseline in total body weight (using logarithmic transformation) at Week 24, change from baseline in FPG at Week 24, change from baseline in seated SBP at Week 24, and percent change from baseline in total body weight (using logarithmic transformation) at Week 24, will be analyzed using a MMRM, similar to the one used for the primary analysis of the primary endpoint.

CCI [redacted] MRM analysis will performed on the difference between natural logarithmically transformed values at end of treatment and at baseline, and will include terms for treatment, week, and the interaction between treatment and week, as well as the log-transformed baseline value and the interaction between week and log-baseline value.

8.5.3 Subgroup analysis

As part of the exploratory objectives, subgroup analyses for the primary endpoint and key secondary endpoints (percent change from baseline in body weight at Week 24 and change from baseline in seated SBP) will be performed for the following subgroups:

- Baseline HbA1c ≥8.5%, ≥7.5% and <8.5%, and <7.5%,
- Baseline BMI <25 kg/m^2, and ≥65 yrs

Additionally, subgroup analyses of the primary endpoints may be performed for the following subgroups. Further details will be provided in the SAP.

- Race of Black or African American, White, Asian, Other
- Age of <65, and ≥65 yrs
- Gender of Male, Female
- Anti-diabetic therapy of long/intermediate-acting and mixed insulin regimen, SU-based regimen, TZD-based regimen, metformin-based regimen and other regimen

- Country/region
- Other subgroups

8.5.4 Interim analysis – Not Applicable

8.5.5 Sensitivity analysis

Refer to section 8.5.1

8.5.6 Exploratory analysis

Exploratory analysis on continuous exploratory endpoints will be evaluated using a MMRM, similar to the one used for the primary analysis of the primary endpoint. Exploratory subgroup analysis will include additional covariates and interaction terms for the subgroup variables.

Exploratory analyses of variables that represent proportions of patients will be performed using the logistic regression with adjustment for randomization strata and baseline measurement.

Exploratory analyses of time-to-event variables will be performed using Kaplan-Meier plots accompanied by a tabular summary.

8.5.7 Analysis of safety variables

Safety analyses will be performed using descriptive statistics. Dichotomous safety variables will be summarized by treatment as counts and percentages. Categorical safety variables will be separately summarized by treatment as counts and percentages by category. Continuous safety variables will be summarized by treatment using descriptive statistics. Comparisons between dapagliflozin 10 mg and matching placebo will not be made for safety variables, and inferential testing will not be performed.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

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

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

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

9.2 Monitoring of the study

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

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (e.g., clinic charts)
- Ensure site is compliant with study procedures to avoid “lost to follow-up” as listed in Section 3.10

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

9.2.1 Source data

Refer to the CSA for location of source data.

9.2.2 Study agreements

The PI at each/the centre 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 CSP and the CSA, the terms of CSP 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 AstraZeneca and the PI should be in place before any study-related procedures can take place, or patients are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 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 2015 and to end by Q4 2017.

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

9.4 Data management by AstraZeneca or delegate

Data management will be performed by CCI the AZ Data Management Centre, according to the Data Management Plan.

Data will be entered into the WBDC system Rave at the study site. Trained site staff will be entering the data as specified in the protocol and according to the eCRF instructions. Data entered into the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. The data will then be Source Data Verified, reviewed, queried and updated as needed

AEs and medical/surgical history will be classified according to the terminology of the latest version the MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the Medical Coding Team at the Data Management Centre.

The PI is responsible for signing the eCRF and this may be delegated to a trained Investigator.

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. The Data Management Plan will also clarify the roles and

responsibilities of the various functions and personnel involved in the data management process.

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. A copy of the eCRF will be archived at the study site when the study is completed.

Serious Adverse Event (SAE) Reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory(ies) internal or external to AstraZeneca.

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 the clinical database. Data Management will assure that the data collection tool for IVRS are tested and validated. External data reconciliation will be done with the clinical database as defined in the Data Management Plan.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

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

10.2 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.

10.3 Ethics and regulatory review

An Ethics Committee (EC)/Institutional Review Board (IRB) should approve the final study protocol, including the final version of the ICF 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 EC/IRB, and to the study site staff.

The opinion of the EC/IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The EC/IRB should approve all advertising used to recruit patients for the study.

AstraZeneca 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 EC/IRB annually.

Before enrolment 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.

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

AstraZeneca will provide Regulatory Authorities, EC/IRB and PIs with safety updates/reports according to local requirements.

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

10.4 Informed consent

The PI(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed 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 ICF that is approved by an EC/IRB.

10.5 Changes to the protocol and informed consent form

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

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 CSP).

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

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each PI. For distribution to EC/IRB see Section 10.3.

If a protocol amendment requires a change to a centre's ICF, AstraZeneca and the centre's EC/IRB 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 EC/IRB.

10.6 Audits and inspections

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

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Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.