
Clinical Study Protocol

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An exploratory Phase II/III, randomized, double-blind, placebo controlled, parallel design study to evaluate the efficacy, safety and pharmacodynamics of dapagliflozin and dapagliflozin in combination with saxagliptin in CKD patients with type 2 diabetes mellitus and albuminuria treated with ACEi or ARB

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

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

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5	18-Sep-2017		
Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

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This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

VERSION HISTORY

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PROTOCOL SYNOPSIS

An exploratory Phase II/III, randomized, double-blind, placebo controlled, parallel design study to evaluate the efficacy, safety and pharmacodynamics of dapagliflozin and dapagliflozin in combination with saxagliptin in CKD patients with type 2 diabetes mellitus and albuminuria treated with ACEi or ARB

International Co-ordinating Investigator

PPD



Target subject population

The target patients include, female or male aged ≥ 18 years at visit 1:

- With history of type 2 diabetes mellitus (T2DM) for more than 12 months with
 1. Inadequate glycemc control, defined as HbA1c $\geq 7.0\%$ and $\leq 11.0\%$ before randomization
- AND
2. Stable anti-diabetic treatment during the last 12 weeks prior to randomization
- With albuminuria (UACR 30 - 3500 mg/g)
 - With renal impairment, Estimated Glomerular Filtration Rate (eGFR) 25-75 mL/minute/1.73 m² before randomization
 - With stable angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) for at least 3 months prior to screening, where the dose of the ACE inhibitor or the ARB is considered appropriate for that patient and the patient has been stable and maintained on that dose for at least 4 weeks prior to study randomization.

Study site(s) and number of subjects planned

This study will be an international multi-centre study at approximately 100 clinical sites across North America, EU & ROW. It is planned to randomize a total of 450 patients (aim 150

patients per treatment). Each clinical site is expected to randomize at least 4 patients. Competitive enrolment will be applied.

Study period		Phase of development
Estimated date of first subject enrolled	Q3 2015	Phase II/III
Estimated date of last subject completed	Q2 2018	

Study design

This is an exploratory, phase II/III, randomized, double-blind, 3-arms, parallel group, placebo controlled, multi-national, multi-centre study to evaluate the efficacy, safety and pharmacodynamics of dapagliflozin and dapagliflozin in combination with saxagliptin in CKD patients with type 2 diabetes mellitus and albuminuria treated with ACEi or ARB.

The study consists of a 2-week screening period followed by a 4-week single-blind placebo lead-in period, 24 week double-blind placebo-controlled treatment and a 3-week follow-up period.

Objectives

Primary Objectives:	Outcome Measure:
<p>Primary objectives for the Saxagliptin/Dapagliflozin treatment arm</p> <ul style="list-style-type: none"> To compare the mean change from baseline in HbA1c between dapagliflozin 10 mg plus saxagliptin 2.5 mg and placebo, after 24 weeks of oral administration of double-blind treatment in patients with type 2 diabetes and CKD. To compare the mean percent change from baseline in urine albumin-to creatinine ratio (UACR) between dapagliflozin 10 mg plus saxagliptin 2.5 mg and placebo, after 24 weeks of oral administration of double-blind treatment in patients with type 2 diabetes and CKD. 	<ul style="list-style-type: none"> Change from baseline in HbA1c at Week 24 Percent change from baseline in UACR at Week 24
<p>Primary objective for the Dapagliflozin treatment arm</p> <ul style="list-style-type: none"> To compare the mean percent change from baseline in urine albumin-to creatinine ratio (UACR) between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment in patients with type 2 diabetes and CKD . 	<ul style="list-style-type: none"> Percent change from baseline in UACR at Week 24

Secondary Objectives:	Outcome Measure :
<p>Secondary objectives for the Saxagliptin/Dapagliflozin treatment arm:</p> <ul style="list-style-type: none"> • To compare the mean percent change from baseline in total body weight between dapagliflozin 10 mg plus saxagliptin 2.5 mg and placebo, after 24 weeks of oral administration of double-blind treatment. • To compare the mean change from baseline in fasting plasma glucose (FPG) between dapagliflozin 10 mg plus saxagliptin 2.5 mg and placebo, after 24 weeks of oral administration of double-blind treatment. • To compare the proportion of patients achieving a 30% reduction in UACR between dapagliflozin 10 mg plus saxagliptin 2.5 mg and placebo, after 24 weeks of oral administration of double-blind treatment. • To compare the proportion of patients achieving a reduction in HbA1c <7.0% between dapagliflozin 10 mg plus saxagliptin 2.5 mg and placebo, after 24 weeks of oral administration of double-blind treatment. • To compare the mean change from baseline in seated systolic blood pressure (SBP) between dapagliflozin 10 mg plus saxagliptin 2.5 mg and placebo, after 24 weeks of oral administration of double-blind treatment. 	<ul style="list-style-type: none"> • Percent change from baseline in total body weight at Week 24 • Change from baseline in FPG at Week 24 • 30% reduction in UACR at Week 24 • HbA1c < 7.0 % at Week 24 • Change from baseline in seated SBP at Week 24
<p>Secondary objectives for the Dapagliflozin treatment arm:</p> <ul style="list-style-type: none"> • To compare the mean percent change from baseline in total body weight between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment. • To compare the proportion of patients achieving a 30% reduction in UACR between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment. • To compare the mean 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. • 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. • To compare the mean change from baseline in fasting plasma glucose (FPG) between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment. • To compare the proportion of patients achieving a reduction in HbA1c <7.0% between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment. 	<ul style="list-style-type: none"> • Percent change from baseline in total body weight at Week 24 • 30% reduction in UACR at Week 24 • Change from baseline in seated SBP at Week 24 • Change from baseline in HbA1c at Week 24 • Change from baseline in FPG at Week 24 • HbA1c < 7.0 % at Week 24

Safety Objectives:	Outcome Measure :
<ul style="list-style-type: none">• To assess the proportion of patients discontinued from the study due to sustained increase in serum creatinine by ≥ 1.5 times baseline level (AKI stage 1).• To evaluate the safety and tolerability of dapagliflozin 10 mg once daily and dapagliflozin 10 mg plus saxagliptin 2.5 mg once daily in patients with type 2 diabetes and CKD .• To assess the mean change from baseline in eGFR after 24 weeks of oral administration of double-blind treatment between dapagliflozin 10 mg and placebo and between dapagliflozin 10 mg plus saxagliptin 2.5 mg and placebo.• To assess the mean change from baseline in eGFR at follow-up (3 weeks after treatment completion) between dapagliflozin 10 mg and placebo and between dapagliflozin 10 mg plus saxagliptin 2.5 mg and placebo.	<ul style="list-style-type: none">• Discontinuation from study due to sustained increase in serum creatinine ≥ 1.5 times baseline level• AEs• Vital Signs• Orthostatic Reactions• Physical Examination• Clinical Chemistry/Haematology Parameters• Change from baseline in renal function (eGFR) at Week 24• Change from baseline in renal function (eGFR) at Week 27

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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 be randomized to double-blind treatment in a 1:1:1 ratio to receive either:

- a) Dapagliflozin 10 mg tablet plus saxagliptin 2.5 mg tablet,
- b) Dapagliflozin 10 mg tablet plus saxagliptin 2.5 mg placebo tablet,
or
- c) Dapagliflozin 10 mg placebo tablet plus saxagliptin 2.5 mg placebo tablet, administered once daily for the 24-week double-blind treatment period and followed up for 3 weeks after the treatment period.

Investigational product, dosage and mode of administration

Dapagliflozin 10 mg alone or dapagliflozin 10 mg plus saxagliptin 2.5 mg will be administered orally once daily during the 24-week double-blind, treatment period.

Comparator, dosage and mode of administration

Placebo to match dapagliflozin 10mg and placebo to match saxagliptin 2.5mg 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

- Insulin, antihypertensive drugs, lipid lowering drugs, and oral anti-diabetic drugs (except SGLT2 inhibitors, GLP-1 agonists and DPP4 inhibitors) are allowed during the study. The dose should be kept constant throughout the entire study from start of run-in to end of follow-up (week 27).

- 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 inhibitor, GLP1 agonist and DPP4 inhibitors, for which there is either initiation or upward titration, in accordance with the approved label and conventional standards of care.
- The dose of any concomitant anti-hypertensive medication should be kept constant as far as possible throughout the entire study from start of run-in to the end of follow-up (week 27). However, in case of symptomatic hypotension or severe uncontrolled hypertension, anti-hypertensive treatment can be adjusted according to the Investigator's judgement.

Statistical methods

Multiplicity due to the two active treatment groups will be controlled by a Bonferroni adjustment, such that statistical significance will be determined according to a two-sided alpha level of 0.025. Within the saxagliptin 2.5 mg + dapagliflozin 10 mg treatment group the control of the alpha level in the testing of both co-primary endpoints (the percent change in urine albumin-to creatinine ratio (UACR) from baseline to 24 weeks and the change in HbA1c from baseline to 24 weeks) will require that each achieves statistical significance at the 0.025 level for a claim of superiority to placebo, and to proceed to a sequential comparison of secondary endpoints. Within the dapagliflozin 10 mg treatment group the control of the alpha level for the primary endpoint (the percent change in urine albumin-to creatinine ratio (UACR) from baseline to 24 weeks) will require the achievement of statistical significance at the 0.025 level for a claim of superiority to placebo, and to proceed to a sequential comparison of secondary endpoints. Parallel sequential testing strategies will be used for comparing each active treatment group to placebo for the secondary endpoints.

The analysis of the change in HbA1C from baseline to Week 24 will be based on a repeated measures model (RMM) including all scheduled time points following randomization up to and including week 24. The analysis of percent change in UACR from baseline to Week 24 will be conducted on the log-transformed UACR values using RMM.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ACEi	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin II receptor blocker
AE	Adverse event
ALK-P	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AKI	Acute Kidney Injury
AST	Aspartate Aminotransferase
AIx	Augmentation Index
BMI	Body Mass Index
BP	Blood Pressure
CABG	Coronary Artery Bypass Grafting
CCI	
CPP	Central Pulse Pressure
CKD	Chronic Kidney Disease
CRF	Case Report Form (electronic/paper)
CRO	Contract Research Organization
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
DNA	Deoxyribonucleic acid
DPP4	Dipeptidyl peptidase-4
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
eGFR	Estimated Glomerular Filtration Rate

Abbreviation or special term	Explanation
CCI	
EU	European Union
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
CCI	
GLP-1	Glucagon-like peptide-1
FFA	Free Fatty Acids
FPG	Fasting Plasma Glucose
FU	Follow-Up
Hb	Haemoglobin
HbA1C	Glycosylated Haemoglobin
HDL-C	High Density Lipoprotein Cholesterol
HF	Heart Failure
HIV	Human Immunodeficiency Virus
HN	High Normal
HOMA	Homeostatic Model Assessment
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
LDL-C	Low Density Lipoprotein Cholesterol
LOCF	Last Observation Carried Forward
LSLV	Last Subject Last Visit
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

Abbreviation or special term	Explanation
NYHA	New York Heart Association
OD	Once Daily
OAE	Other Significant Adverse Event
PI	Principal Investigator
PK	Pharmacokinetic
PPG	Post-Prandial Glucose
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTH	Parathyroid Hormone
CCI	[REDACTED]
RMM	Repeated Measures Model
ROW	Rest of the World
SAE	Serious adverse event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SGLT2	Sodium Glucose co-Transporter 2
SU	Sulfonylurea
T2DM	Type 2 Diabetes Mellitus
T2DN	Type 2 Diabetes Nephropathy
TB	Total Bilirubin
TG	Triglycerides
TIA	Transient Ischemic Attack
TZD	Thiazolidinedione
UACR	Urine albumin-to-creatinine ratio
UA	Uric Acid
ULN	Upper Limit of Normal
US	United States
UTI	Urinary Tract Infections
WBDC	Web Based Data Capture
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Dapagliflozin (Forxiga®, Farxiga®) 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. 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. Results from nonclinical- and clinical studies have shown that dapagliflozin can be used to promote urinary excretion of glucose as a well-tolerated and effective method of reducing blood glucose levels. Thus, treatment with an SGLT2 inhibitor may affect hyperglycaemia directly by increasing glucose excretion in the urine as well as indirectly by ameliorating underlying defects in glucose homeostasis in patients with T2DM.

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.

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. 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.

Saxagliptin (Onglyza®) is a highly potent, selective, reversible, and competitive dipeptidyl 1 peptidase 4 (DPP4) inhibitor. DPP4 is the enzyme responsible for the inactivation of Glucagon-like peptide-1 (GLP-1) and Gastric inhibitory polypeptide (GIP). By inhibiting the enzyme DPP4, saxagliptin potentiates active endogenous GLP-1 concentrations, augmenting the physiological mechanism of insulin secretion and decreasing glucagon release, thereby reducing postprandial and fasting glucose levels in patients with T2DM.

The results from the saxagliptin Phase IIb and III programs in over **CCI** patients support the oral dose of saxagliptin 2.5 and 5 mg once daily in a wide range of patients with T2DM, as either monotherapy, add-on combination therapy with metformin, a thiazolidinedione (TZD), a sulfonylurea (SU), insulin or initial combination therapy with metformin and the results from the Phase III studies confirmed clinically meaningful benefits on HbA1c, as well as fasting plasma glucose (FPG), postprandial glucose (PPG), insulin, C-peptide, and glucagon levels.

Diabetic subjects with renal impairment are of interest because diabetic nephropathy affects approximately 30% of patients with diabetes. In the United States, for instance, about 20% of individuals with diabetes have an estimated glomerular filtration rate (eGFR) lower than 60 ml/min/1.73m² (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. Safety and efficacy data in subjects with normal, mildly, and moderately impaired renal function have been collected in previous studies in the dapagliflozin and saxagliptin development program.

While saxagliptin 2.5 mg daily has been shown to be well tolerated and improve glucose control even in individuals with CKD stage ≥ 3 (Nowicki et al 2011), dapagliflozin's ability to inhibit renal glucose reabsorption declines with decreasing eGFR and in CKD3, urinary glucose excretion with dapagliflozin is about 50% lower than in patients with normal or mildly impaired renal function. In a previous study in CKD3, dapagliflozin 5 and 10 mg daily was well-tolerated but 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. Differential 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 limitations including, a very short placebo lead-in period, and a relatively large placebo effect in this study could potentially also have affected its generalizability 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 well-tolerated and effective in T2DM patients with reduced kidney function lending support to further studies in this population.

There is a growing body of evidence indicating that SGLT2 inhibition might be beneficial from a nephroprotective standpoint. This effect is thought to be achieved partly by mechanisms independent of overall blood pressure and blood glucose reductions. Such other mechanisms are thought to be reduced intra-glomerular pressure through an enhanced

tubuloglomerular feedback mechanism (De Nicola 2014 and Thomas 2014) as well as a reduced glucose and sodium transport over the proximal tubule cells (Pollock et al 1991 and Komala et al 2013)

Preclinical data in a mouse model of type 2 diabetes and obesity show similar reductions in renal inflammatory response after dapagliflozin treatment as has been seen with ARB treatment (Terami et al 2014 and Sato-Horiguchi et al 2012). Further, data from a type 2 diabetic nephropathy model have indicated that a combination therapy with SGLT2i and ACEI is more effective in lowering blood pressure and more nephroprotective than administration of either agent alone (Kojima et al 2013). Of notice, treatment with a SGLT2i in a type 1 diabetic nephropathy (eNOS knockout) rat model did not have any nephroprotective effect.

Preclinical data do also support nephroprotective effects of DPP4 inhibitors. Thus, in rodent models of T1 and T2DN, treatment with DPP4 inhibitors has been found to decrease renal injury markers such as albuminuria, fibrosis, inflammation and oxidative stress (Tanaka et al 2014). Even clinical data suggest nephroprotective effect of SGLT2 and DPP4 inhibitors as reduced urinary albumin excretion have been observed in T2DN trials with both these agents. (Scirica et al 2013).

Despite the glucose lowering effect of dapagliflozin is reduced in parallel with a declining renal function, reduced urinary albumin excretion has been found in patients with moderate renal impairment on top of RAAS blockade for up to 1 year (Sjöström et al 2015).

Although a causal relationship is debated, changes in albuminuria over time predicts mortality and both cardiovascular and renal outcomes significantly better than glucose status and blood pressure control in patients at a high cardiovascular risk (Schmieder et al 2014).

The combination of DPP-4 and SGLT2 inhibition has therefore been proposed as a promising future option for T2DM patients with CKD (Scherthaner et al 2014).

Rationale for study design, doses and control groups

This study will be performed as part of the clinical development program for dapagliflozin for treatment of T2DM. This study intends to evaluate the efficacy, safety and pharmacodynamics of dapagliflozin and dapagliflozin in combination with saxagliptin in CKD patients with type 2 diabetes mellitus and albuminuria treated with ACEi or ARB who have inadequate glycemic control, defined as HbA1c $\geq 7.0\%$ and $\leq 11.0\%$, and renal impairment (eGFR ≥ 25 to ≤ 75 ml/min/1.73 m²).

The pharmacodynamic effects of saxagliptin and dapagliflozin have previously been studied in patients with renal impairment. Saxagliptin 2.5mg once daily significantly reduced UACR and HbA1c (Mosenzon et al 2014, Nowicki et al 2011, Kohan et al 2014) and dapagliflozin reduced UACR and HbA1c albeit the effect on HbA1c was not statistically different from placebo (Kohan et al 2014). All these doses were well-tolerated in this population and the saxagliptin dose of 2.5 mg is currently in the approved label for treatment of subjects with moderate or severe renal impairment. Dapagliflozin 10mg once daily was chosen because the

overall safety has not been different from 5mg once daily and the long term albuminuria lowering effects are thought to be more robust. Because the anti-glycemic effect of dapagliflozin wanes with decreasing GFR, HbA1c is the primary endpoint in the dapagliflozin + saxagliptin arm and secondary in the dapagliflozin arm.

Patients will be randomized to 24 weeks treatment with dapagliflozin 10 mg, dapagliflozin 10 mg plus saxagliptin 2.5 mg or matching placebo. The study will be an international multi-centre study at approximately 100 centres in North America, EU & ROW. It is planned to randomize a total of 450 patients (150 patients per treatment arm). The study is powered to detect a difference of 0.42% in mean HbA1c and 35% difference in UACR between active treatment and placebo following 24 weeks of treatment.

Dapagliflozin 10 mg once daily, saxagliptin 2.5 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 II/III study requires a placebo group to determine efficacy of dapagliflozin and dapagliflozin plus saxagliptin 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 and investigator's judgement for the targeted CKD segments (i.e., eGFR ≥ 25 -75 ml/min/1.73 m², calculated using the MDRD formula or specific formulas for Japanese and Taiwanese see 5.2.1). The study consists of a 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 drugs are taken once daily in the morning. The main efficacy assessments will be performed at regular intervals and will include HbA1c, UACR, weight, waist circumference, 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, orthostatic reaction, renal function (change in s-creatinine), safety laboratory test, and AE monitoring.

1.2 Benefit/risk and ethical assessment

Risk category

Dapagliflozin and saxagliptin have global market approval and have been administered to thousands of T2DM patients. Details regarding potential risks associated with administration

of dapagliflozin once daily and saxagliptin once daily are provided in respective Investigator's Brochures.

Considering dapagliflozin's and saxagliptin's mechanism of action, the previous clinical experience with these compounds, 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

Details regarding potential risks associated with administration of saxagliptin and dapagliflozin are provided in the Investigator's Brochure (IB) for each medication.

Dapagliflozin:

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. Severe hypovolaemia can cause hypotension, reduced renal perfusion and, in worst cases, acute renal failure. 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, 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/ (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.

Saxagliptin:

Prior to approval, saxagliptin was evaluated in 6 pivotal Phase III, randomized, double-blind controlled trials. The majority of adverse events (AEs) reported in clinical studies have been of mild intensity and few have required treatment discontinuation. Post approval, the cardiovascular safety of saxagliptin was evaluated in 8280 patients with T2DM with high CV risk. When added to the standard of care, saxagliptin neither reduced nor increased the risk of the primary composite endpoint of CV death, myocardial infarction (MI), or ischemic stroke (Scirica et al 2013). However, in subgroups analysis, increased risk for hospitalization for heart failure was found in patients treated with saxagliptin.

Joint pain (arthralgia) was reported during post marketing use of saxagliptin, as well as other medicines from the same medicine group (DPP4 inhibitors). Patients experienced joint pain which could be severe in some cases. Some patients experienced relief of symptoms when the medication was discontinued. Some patients experienced recurrence of symptoms when restarting the same or another DPP4 inhibitor medication.

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 and saxagliptin therapy on glycemic control. This phase II/III study will evaluate these effects of dapagliflozin and dapagliflozin together with saxagliptin in T2DM patients with CKD. 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 10 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 saxagliptin 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 and none of the exclusion criteria and consent to take part in the study.

1.3 Study Design

This is an exploratory phase II/III study in patients with CKD (eGFR= 25-75 mL/minute/1.73m²), type 2 diabetes mellitus with micro- or macroalbuminuria (urine albumin-to-creatinine ratio (UACR) 30-3500 mg/g). The study is randomized, double-blind, placebo controlled and parallel group designed, multi-national, multi-centre study to evaluate pharmacodynamics of dapagliflozin 10 mg once daily (od) and dapagliflozin 10 mg once daily in combination with saxagliptin 2.5 mg once daily on top of background ACEi or ARB treatment. The study consists of a 2-week screening period followed by a 4-week single-blind placebo lead-in period, 24-week double-blind placebo-controlled treatment, and a 3-week follow-up period. Patients will be screened within two weeks before the lead-in period.

Patients will be stratified according to background anti-diabetes medication. All patients must have had a stable anti-diabetic treatment during the previous 12 weeks.

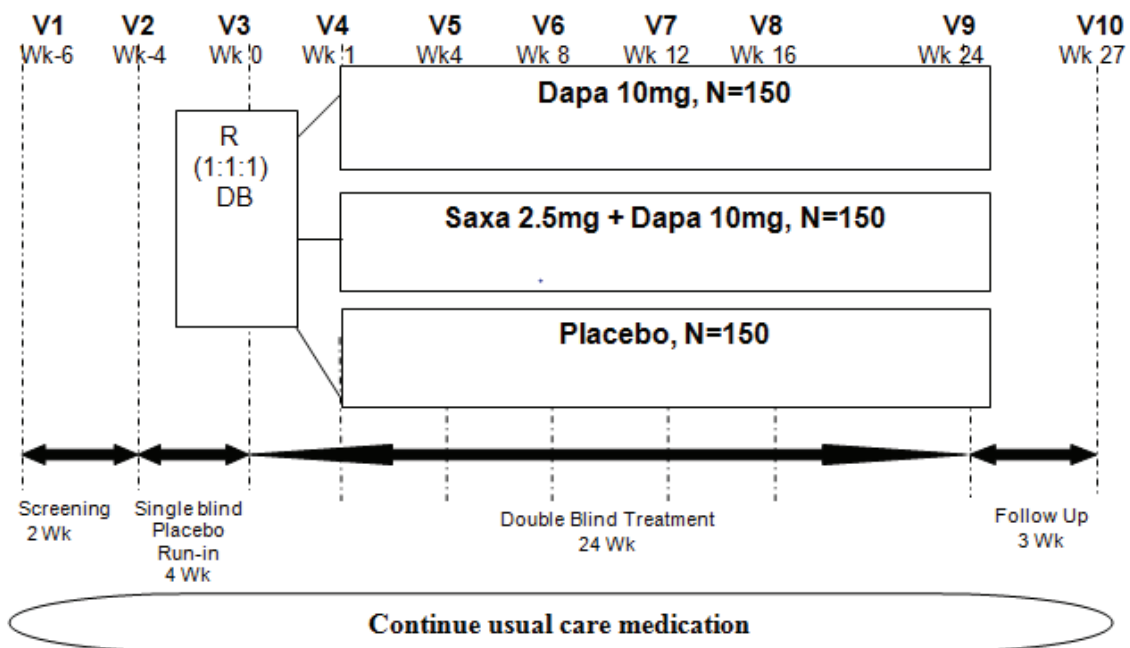
The study will be an international multi-centre study at approximately 100 clinical sites in North America, EU & ROW. It is planned to randomize a total of 450 patients (aim 150 patients per treatment). Each clinical site is expected to enrol at least 4 patients. Competitive enrolment will be applied. The study is primarily designed to investigate the effect of dapagliflozin alone or in combination with saxagliptin on HbA1c and UACR.

The main efficacy assessments will include HbA1c and morning spot urine albumin to creatinine ratio (UACR).

Safety assessments will be performed at regular intervals and will include physical examination, vital signs (including measured orthostatic reactions), renal function, body weight, safety laboratory test, hypoglycaemia and AE monitoring.

1.4 Study flowchart details

Figure 1 Study flow Chart



At Visit 1, patients will be screened for an HbA1c ($\text{HbA1c} \geq 7.0\%$ and $\leq 11.0\%$), eGFR level (eGFR 20-80 mL/minute/1.73m²) and micro or macroalbuminuria (UACR 30 – 3500 mg/g). Patients who meet these criteria will be enrolled and further examined for all inclusion and exclusion criteria. At Visit 2 (start of lead-in visit), patients will be examined for lab panel. If

the eGFR value (eGFR 25-75 mL/minute/1.73m²) meets the inclusion criteria at Visit 1 or 2 and none of the exclusion criteria are met the patients will enter a 4-week single-blind placebo lead-in period. At Visit 3, patients who meet all of the inclusion criteria and none of the exclusion criteria at Visit 1 and 2 spaces will be randomized to the 24-week double-blind placebo-controlled treatment period. The prescription of anti-diabetic and anti-hypertensive drugs, (including diuretics) should be kept constant throughout the entire 4-week lead in period. At randomization, patients will be stratified according to the pre-enrolment anti-hyperglycaemic therapy.

After either completion of the treatment period or permanent premature discontinuation of study medication, patients will enter a 3-week safety and sustained efficacy follow-up period without study medication. The follow-up visit (Visit 10) provides the opportunity to further evaluate changes in physical signs, symptoms or laboratory parameters that may be related to dapagliflozin with/without co-administration of saxagliptin. The total planned study duration from Visit 1 to the safety follow-up (Visit 10) will be 33 weeks.

Summary scheme for inclusion based on HbA1c, eGFR and UACR

- Visit 1: HbA1c 7.0%-11.0%, inclusive
 eGFR **20-80** mL/min/1.73 m², inclusive
 Single morning spot UACR 30-3500 mg/g, inclusive
- Visit 2: eGFR **25-75** mL/min/1.73 m², inclusive at Visit 1 or 2

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objectives:	Outcome Measure:
<p>Primary objectives for the Saxagliptin/Dapagliflozin treatment arm</p> <ul style="list-style-type: none"> • To compare the mean change from baseline in HbA1c between dapagliflozin 10 mg plus saxagliptin 2.5 mg and placebo, after 24 weeks of oral administration of double-blind treatment in patients with type 2 diabetes and CKD . • To compare the mean percent change from baseline in urine albumin-to creatinine ratio (UACR) between dapagliflozin 10 mg plus saxagliptin 2.5 mg and placebo, after 24 weeks of oral administration of double-blind treatment in patients with type 2 diabetes and CKD . 	<ul style="list-style-type: none"> • Change from baseline in HbA1c at Week 24 • Percent change from baseline in UACR at Week 24
<p>Primary objective for the Dapagliflozin treatment arm</p> <ul style="list-style-type: none"> • To compare the mean percent change from baseline in urine albumin-to creatinine ratio (UACR) between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment in patients with type 2 diabetes and CKD . 	<ul style="list-style-type: none"> • Percent change from baseline in UACR at Week 24

2.2 Secondary objectives

Secondary Objectives:	Outcome Measure :
<p>Secondary objectives for the Saxagliptin/Dapagliflozin treatment arm:</p> <ul style="list-style-type: none"> • To compare the mean percent change from baseline in total body weight between dapagliflozin 10 mg plus saxagliptin 2.5 mg and placebo, after 24 weeks of oral administration of double-blind treatment. • To compare the mean change from baseline in fasting plasma glucose (FPG) between dapagliflozin 10 mg plus saxagliptin 2.5 mg and placebo, after 24 weeks of oral administration of double-blind treatment. • To compare the proportion of patients achieving a 30% reduction in UACR between dapagliflozin 10 mg plus saxagliptin 2.5 mg and placebo, after 24 weeks of oral administration of double-blind treatment. • To compare the proportion of patients achieving a reduction in HbA1c <7.0% between dapagliflozin 10 mg plus saxagliptin 2.5 mg and placebo, after 24 weeks of oral administration of double-blind treatment. • To compare the mean change from baseline in seated systolic blood pressure (SBP) between dapagliflozin 10 mg plus saxagliptin 2.5 mg and placebo, after 24 weeks of oral administration of double-blind treatment. 	<ul style="list-style-type: none"> • Percent change from baseline in total body weight at Week 24 • Change from baseline in FPG at Week 24 • 30% reduction in UACR at Week 24 • HbA1c < 7.0 % at Week 24 • Change from baseline in seated SBP at Week 24

<p>Secondary objectives for the Dapagliflozin treatment arm:</p> <ul style="list-style-type: none"> • To compare the mean percent change from baseline in total body weight between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment. • To compare the proportion of patients achieving a 30% reduction in UACR between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment. • To compare the mean 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. • 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. • To compare the mean change from baseline in fasting plasma glucose (FPG) between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment. • To compare the proportion of patients achieving a reduction in HbA1c <7.0% between dapagliflozin 10 mg and placebo, after 24 weeks of oral administration of double-blind treatment. 	<ul style="list-style-type: none"> • Percent change from baseline in total body weight at Week 24 • 30% reduction in UACR at Week 24 • Change from baseline in seated SBP at Week 24 • Change from baseline in HbA1c at Week 24 • Change from baseline in FPG at Week 24 • HbA1c < 7.0 % at Week 24
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<p>CCI [REDACTED] [REDACTED]</p> <p>[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]</p>	<p>[REDACTED] [REDACTED] [REDACTED]</p>
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Each subject 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

For inclusion in the study subjects should fulfil the following criteria:

- 1 Provision of informed consent prior to any study specific procedures.
- 2 Female or male aged ≥ 18 years at Visit 1.

<< **(JP)** The following should be added if applicable. *For subjects aged <20 years and enrolled in Japan, a written informed consent should be obtained from the subject and his or her legally acceptable representative.* >> **(End JP)**

- 3 History of type 2 diabetes mellitus for more than 12 months.
- 4 Inadequate glycemic control, defined as HbA1c $\geq 7.0\%$ and $\leq 11.0\%$ measured at Visit 1.
- 5 Stable antidiabetic treatment during the last 12 weeks up to randomization.
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. A regimen of any approved oral anti-diabetic medication (except SGLT2 inhibitors, GLP-1 receptor agonists and DPP4 inhibitors) where no dose-changes have occurred during the last 12 weeks up to randomization.
 - b. Any insulin regimen is permitted as long as the dose is stable 12 weeks before randomization, changes $\pm 10\%$ are allowed ((average daily number of units during the 12 weeks compared to the average during the last week before randomization).).
- 6 Renal impairment defined as eGFR 20-80 mL/minute/1.73m² at Visit 1 to enter the lead-in period, 25-75 mL/minute/1.73m² at Visit 1 or Visit 2 for randomization (for eGFR calculation, see section 5.2.1).
- 7 Micro or macroalbuminuria (UACR 30 – 3500 mg/g or 3.34- 395.85 mg/mmol, inclusive) at Visit 1.
- 8 Patient must be receiving an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) for at least 3 months prior to screening, where the dose of the ACE inhibitor or the ARB is considered appropriate for that patient, and has been stable and maintained on that dose for at least 4 weeks prior to study randomization.
- 9 Body mass index between 20 and 45 kg/m² at visit 1.

3.2 Exclusion criteria

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

- 1 Pregnant (confirmed with positive pregnancy test) or breast feeding at Visit 2.

- 2 Women of childbearing potential (WOCBP) who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period.
- 3 Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) > 3X ULN at Visit 2.
- 4 Total Bilirubin (TB) >2 mg/dL (35 µmol/L) at Visit 2.
- 5 Serum Potassium (K) > 5.5 meq/L (5.5 mmol/L) at Visit 2.
- 6 Serum Calcium (Ca) <8 mg/dL or > ULN (<1.99 mmol/L or > ULN) at Visit2.
- 7 Documented history of positive serologic evidence of current infectious liver disease including hepatitis B surface antigen or anti-hepatitis C virus antibody at Visit 2. Subjects how have isolated positive anti-hepatitis B antibodies (i.e. indicating immunity to hepatitis B infection or previous vaccination) may be included.
- 8 History of ≥2 major hypoglycaemic events in the 3 months prior to enrolment visit (Visit 1), defined as symptomatic events requiring external assistance due to severe impairment in consciousness or behaviour and prompt recovery after glucose or glucagon administration.
- 9 Haemoglobin ≤9.0 g/dL (90 g/L) at Visit 2.
- 10 Patients with Type 1 DM, history of pancreatitis or pancreatic surgery
- 11 History of diabetes insipidus, diabetic ketoacidosis or hyperosmolar nonketotic coma.
- 12 Severe uncontrolled hypertension defined as systolic blood pressure (SBP) ≥ 180 mmHg and/or diastolic blood pressure (DBP) ≥ 110 mmHg at any visit up to randomization.
- 13 Any of the following CV/Vascular Diseases within 3 month prior to signing the consent at Visit 1:
 - a. Myocardial infarction.
 - b. Cardiac surgery or revascularization (CABG/PTCA).
 - c. Unstable angina.
 - d. Unstable heart failure (HF).
 - e. HF New York Heart Association (NYHA) Class III-IV.
 - f. Transient ischemic attack (TIA) or significant cerebrovascular disease.
 - g. Unstable or previously undiagnosed arrhythmia.
- 14 Significant hepatic disease, including, but not limited to, chronic active hepatitis and/or severe hepatic insufficiency.
- 15 Documented history of severe hepatobiliary disease or hepatotoxicity with any medication.
- 16 History of haemoglobinopathy, or chronic or recurrent haemolysis.

- 17 History of acute kidney injury requiring renal replacement therapy (dialysis or ultrafiltration) or any biopsy or imaging verifying intercurrent kidney disease other than diabetic nephropathy or diabetic nephropathy with nephrosclerosis.
- 18 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.
- 19 Malignancy within 5 years of the enrolment visit (Visit 1), with the exception of treated basal cell or treated squamous cell carcinoma.
- 20 Known immunocompromised status, including but not limited to, individuals who have undergone organ transplantation or who are positive for the human immunodeficiency virus.
- 21 History of unexplained microscopic or gross haematuria, or microscopic haematuria at Visit 2, confirmed by a follow-up sample at next scheduled visit.
- 22 Subjects who have contraindications to therapy as outlined in the saxagliptin and dapagliflozin Investigator Brochures or the local saxagliptin or dapagliflozin product label, including current treatment with potent cytochrome P4503A4/5 inhibitors (in countries where adjustment would be required by the local saxagliptin label).
- 23 Known allergies or contraindication to the contents of dapagliflozin, saxagliptin or placebo tablets.
- 24 History of drug-induced myopathy or drug-induced CK elevation.
- 25 Treatment with a SGLT2 inhibitor, GLP-1 agonist or DPP4 inhibitors at Visit 1 or 2.
- 26 Simultaneous treatment with both an ACEi and an ARB.
- 27 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.
- 28 A metformin dose which is outside the specified dose range for eGFR – 25-75 mL/minute/1.73m², according to local guidelines and/or investigator's judgement.
- 29 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 or patient suspected or with confirmed poor protocol or medication compliance.
- 30 Patients at risk for volume depletion as judged by the investigator.
- 31 Employees of AstraZeneca, or their immediate relatives. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
- 32 Administration of any other investigational drug or participation in any interventional clinical studies 30 days prior of planned screening to this study.
- 33 Poorly controlled diabetes including but not limited to marked polyuria and polydipsia with greater than 10% weight loss during the 3 months prior to visit 1.
- 34 Administration of weight loss medication.

3.3 Subject recruitment information

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3.4 Subject enrolment and randomization

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CCI

3.5 Procedures for handling incorrectly enrolled or randomized subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Subjects 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 need to be taken:

- The Investigator or monitor should inform the AstraZeneca study physician immediately, ensuring patient safety must always be the number one priority.
- 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 that whether to continue or discontinue the patient from study treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.
- 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.

3.6 Methods for assigning treatment groups

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[Redacted content]

3.8 Methods for unblinding

Individual treatment codes, indicating the treatment randomisation for each randomised subject, 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.

<<(JP) Replace the above paragraph with: Individual treatment codes, indicating the treatment randomisation for each randomised subject, will be available to the Investigator(s) or pharmacists, and the personnel who are independent to the study evaluation at the Patient Safety Department, AstraZeneca from the IVRS/IWRS.>> (End JP)

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

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

3.9 Restrictions

- All patients will visit the clinic fasting in the morning, 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 Visit 1). 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 prescribed.
- 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).

Donation of blood or blood products to a blood bank is not allowed during participation in the study. Prohibited and restricted concomitant medications are listed in Section 7.7.

3.10 Discontinuation of investigational product

Patients may be discontinued from IP in the following situations:

- Patient decision. The patient may, at any time, discontinue study treatment, without prejudice to further treatment. Patients who choose to discontinue study treatment are expected to continue in the study until the closing of the study.
- Safety reasons as judged by the Investigator, by or an AZ representative.
- Severe non-compliance to protocol as judged by the investigator and/or AZ

Subjects MUST discontinue study treatment (investigational or non-investigational treatment) for any of the following reasons:

- Any clinical AE, laboratory abnormality or inter current illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the subject.
- Pregnancy
- 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.
- Protocol-defined major hypoglycemia episodes.
- Liver criteria:

ALT and/or AST >3 times the upper limit of normal (ULN) and concomitant TB >2 times ULN confirmed at a repeated measurement at the central laboratory (which should be obtained within 3 days, whenever possible, following receipt of the initial laboratory results)

ALT and/or AST >8 times ULN confirmed at a repeated measurement at the central laboratory (which should be obtained within 3 days, whenever possible, following receipt of the initial laboratory results)

ALT and/or AST >5 times ULN confirmed at the central laboratory and sustained over a period of 14 days or more

(See Appendix D Algorithm on Management of Sustained Elevated Liver Safety Abnormalities for further details)

- Acute renal insufficiency or worsened chronic renal insufficiency based on sustained ≥ 1.5 times increase in baseline s-creatinine (see page 56 Discontinuation Guidelines due to Acute Kidney Injury).

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 (ie, excess physical activity, concurrent illness, or missed or delayed meal)

and/or

- Documented finger stick glucose values < 54 mg/dL (< 3.0 mmol/L).

3.10.1 Discontinuation Guidelines due to Protocol-Defined Major Hypoglycemia Episode or Recurrent Non-Major Hypoglycemia Episodes

Subjects will be discontinued from study medication if they experience severe and/or frequent hypoglycemia episodes, defined as more than one major episode or recurring non-major episodes in the event where the possibility of down-titration of insulin and/or oral anti-diabetic medication(s), (other than blinded study medication) and/or other contributing factors (e.g., excessive physical activity) have been evaluated and corrected. ***NOTE: Dose titration of blinded study medication is not permitted at any time during the study.***

- A Major Hypoglycemia Episode is defined as a symptomatic episode which meets **all** of the following criteria:
 - External (the 3rd party) assistance due to severe impairment in consciousness or behaviour.
 - Capillary or plasma glucose value of < 3 mmol/L (< 54 mg/dL)
 - Prompt recovery after glucose or glucagon administration
- Recurring Non-Major Episodes are defined as any recurrent hypoglycemia episodes, as determined by the Investigator, not meeting the definition of Major Episodes.

It is the Investigator's clinical assessment whether subjects who experience non-recurrent and non-major episodes of hypoglycemia should be discontinued from study medication.

3.10.2 Discontinuation Guidelines due to Acute Kidney Injury (AKI)

For patients with signs of deterioration in renal function, additional monitoring needs to be conducted. Any patients with ≥ 1.5 x baseline serum creatinine increase needs to be scheduled for a new serum creatinine test within 4 days whenever possible.

- If the new serum creatinine value is ≥ 1.5 x basal level, the patient should be evaluated for any suspected new, temporary and reversible cause of renal dysfunction, e.g. concurrent use of NSAIDs, antibiotics, or other medications known to affect creatinine clearance; volume depletion; urinary tract infection, and obstructive uropathy.
 - If there is no suspected cause of the acute drop in renal function, the subject must permanently discontinue study medication and the Sponsor is notified. The investigator will follow the subject until the event has resolved or stabilized.
 - If there is a suspect reversible cause, the following actions should be taken:
 - Study medication should be withheld.
 - The suspected cause of renal dysfunction should be identified and corrected.
 - Serum creatinine should be checked again after approximately one week:
 - ◆ If serum creatinine is still ≥ 1.5 x baseline level:
 - The subject must permanently discontinue study medication and the Sponsor is notified. The Investigator will follow the subject until the event has resolved or stabilized
 - ◆ If serum creatinine is < 1.5 x baseline level:
 - Study medication can be resumed.
 - Serum creatinine should be checked after approximately one week
 - The subject may continue in the study and will be followed according to the protocol. Additional monitoring of serum creatinine may be performed according to the local practice or Investigator's judgment.

3.10.3 Rescue Due to Lack of Glycemic Control in the Treatment Period

Rescue Medication

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 medication regimen. Rescue medication in this

protocol refers to any approved, appropriate anti-diabetic agent, except SGLT2-inhibitors, GLP-1 agonists or DPP4 inhibitors, 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.

During the 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.

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, except to start treatment with a SGLT2 inhibitor, a GLP1 agonist or a DPP4 inhibitor.

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 1 below), based upon central laboratory FPG and confirmatory, repeat FPG, have been established during the 24 week treatment period, starting at Week 4 and up to Week 24 visits, to determine eligibility for open-label rescue medication initiation/titration.

Table 1 Lack of Glycemic Control Criteria for Initiation of Open-Label Rescue Medication

Visit Label	Central Laboratory FPG
From Week 4 to Week 12 (excluding week 12)	FPG > 240 mg/dL (13.3 mmol/L)
From Week 12 to Week 24 (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 (within 5 days whenever possible) before being rescued to ensure that important trial 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 medication. Rescued patients will then continue in the treatment period according to their original visit schedule. 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, without repetition of rescue visits.

3.10.4 Guidelines with regard to changes in insulin dose

Each subject'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 subject 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 glycaemic control between the active treatment arms and the placebo arm. During the double-blind treatment period, a few subjects will experience poor glycaemic control, as measured by increased fasting plasma glucose measurements from the central laboratory during study visits. When glucose measurements exceed certain limits (as specified), the subject will be "rescued".

Up-titration in insulin dose is not allowed, unless fasting blood glucose rescue criteria is fulfilled or if insulin requirement has increased only temporarily, e.g., due to an infection and the increase in insulin dose is ≤ 10 percent of the baseline level after 1 week. If lasting increase in insulin dose is made i.e. the insulin dose is still >10 percent higher than the baseline level 1 week after up-titration, the subject shall be handled as administration of anti-diabetic rescue medication and be treated as "rescued" (i.e., the patient must complete the Week 24 visit procedures, as outlined in section 4.5.7 and the patient will continue in the treatment period according to their original visit schedule.

Down-titration of insulin is allowed only as necessary to prevent low blood glucose or hypoglycemia.

3.10.5 Procedures for discontinuation of a subject from investigational product

If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

At any time, subjects are free to discontinue investigational product or withdraw from the study (i.e., investigational product and assessments – see Section 3.11), without prejudice to further treatment. A subject that decides to discontinue investigational will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (See Section 6); *<<diary cards, questionnaires (e.g., for patient reported outcomes)>>* and all study drugs should be returned by the subject.

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 (Visit 9) procedures will be performed. Patients will then 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 subject is withdrawn from study, see Section 3.11.

3.11 Criteria for withdrawal

3.11.1 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 ‘Incorrect Enrolment’ (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.

3.11.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (investigational product 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 adverse events (AE). The Investigator will follow up AEs outside of the clinical study.

If a subject withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn subjects will not be replaced.

3.11.3 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.

3.12 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial subjects 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 subject at the time of discontinuation of follow-up must be recorded in the CRF. 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 subjects' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

4.1 Study flowchart details

At Visit 1 patients will be screened for an HbA1c ($\text{HbA1c} \geq 7.0\%$ and $\leq 11.0\%$), eGFR level (eGFR 20-80 mL/minute/1.73m²,) and micro- or macroalbuminuria (UACR 30 – 3500 mg/g). Patients who meet these criteria will be enrolled and further examined for all inclusion and exclusion criteria. At Visit 2 (start of lead-in visit), patients will be examined for lab panel. If the eGFR value is 25-75 mL/minute/1.73m² at Visit 1 or Visit 2 and all other inclusion and none of the exclusion criteria are met, the patients will enter a 4-week single-blind placebo lead-in period. At Visit 3, patients who meet all of the inclusion and none of the exclusion criteria at Visit 1 and 2 spaces will be randomized to the 24-week double-blind placebo-controlled treatment period. The prescription of anti-diabetic and anti-hypertensive drugs, (including diuretics) should be kept constant throughout the entire 4-week lead in period. At randomization, patients will be stratified according to pre-enrolment anti-hyperglycaemic therapy.

After either completion of the treatment period or permanent premature discontinuation of study medication, patients will enter a 3-week safety and sustained efficacy follow-up period without study medication. The follow-up visit (Visit 10 (FU)) provides the opportunity to further evaluate changes in physical signs, symptoms or laboratory parameters that may be related to dapagliflozin with/without co-administration of saxagliptin. The total planned study duration from Visit 1 to the safety follow-up (Visit 10) will be 33 weeks.

Summary scheme for inclusion based on HbA1c, eGFR and UACR

Visit 1: HbA1c 7.0%-11.0%, inclusive
 eGFR **20-80** mL/min/1.73 m², inclusive
 Single morning spot UACR 30-3500 mg/g, inclusive

Visit 2: eGFR **25-75** mL/min/1.73 m², inclusive, at Visit 1 or Visit 2.

4.2 Assessments schedule

Table 2 Study Planning and details procedure

Study period	Screening Period	Lead-in period	Randomization		Treatment period			Follow-up period		For details see Protocol Section
	1 ^a Non-fasting	2 ^{b,c} Fasting	3 ^{c,d,e} Fasting	4 ^{c,d,e} Fasting	5 ^{c,d,e} Fasting	6 ^{c,d,e} Fasting	7 ^{c,d,e} Fasting	8 ^{c,d,e} Fasting	9 ^{c,d,e} Fasting	
Visit number	-6	-4	0	1	4	8	12	16	24	27
Week	-6	-4	0	1	4	8	12	16	24	27
Day	-42 to -29	-28	1	8	29	57	85	113	169	190
Visit window	±5	±5	±0	±2	±5	±5	±5	±5	±5	±3

Written informed consent ^f	X										10.4
Demographics	X										4.3
Brief physical examination ^g	X			X	X		X			X	5.2.3
Full physical examination ^h			X						X		5.2.3
Weight and height ⁱ	X		X	X	X	X	X	X	X	X	5.1.4
Medical/surgical history	X										4.3
Inclusion/exclusion criteria	X ^j	X ^k	X ^l								3.1 & 3.2
12-lead ECG ^m		X									5.2.4
Randomisation to study treatment			X								3.4

Study period	Screening Period	Lead-in period	Randomization	Treatment period					Follow-up period	For details see Protocol Section	
	1 ^a Non-fasting	2 ^{b,c} Fasting	3 ^{c,d,e} Fasting	4 ^{c,d,e} Fasting	5 ^{c,d,e} Fasting	6 ^{c,d,e} Fasting	7 ^{c,d,e} Fasting	8 ^{c,d,e} Fasting	9 ^{c,d,e} Fasting		10 ^{c,d} Fasting
Visit number	-6	-4	0	1	4	8	12	16	24	27	
Week											
Day	-42 to -29	-28	1	8	29	57	85	113	169	190	
Visit window		±5	±0	±2	±5	±5	±5	±5	±5	±3	

Blood pressure and Heart Rate	X	X	X	X	X	X	X	X	X	X	5.1.6
Orthostatic blood pressure			X	X	X	X	X	X	X	X	5.2.5.1
Waist Circumference			X						X	X	5.1.7
Concomitant medication	X	X	X	X	X	X	X	X	X	X	7.7
Dietary and life-style advice		X	X	X	X		X	X	X		4.4
Dispense Glucose Meter and Supplies/Provide Instructions		X	X	X	X		X	X	X		5.1.11& 5.2.6.1
Pregnancy test (WOCBP only)	X	X	X	X	X	X	X	X	X	X	5.2.2
Dispensation of Study Medication		X	X				X				7
Drug accountability			X	X	X	X	X	X	X	X	7.6

Study period	Screening Period	Lead-in period	Randomization		Treatment period					Follow-up period	
			3 ^{c,d,e} Fasting	4 ^{c,d,e} Fasting	5 ^{c,d,e} Fasting	6 ^{c,d,e} Fasting	7 ^{c,d,e} Fasting	8 ^{c,d,e} Fasting	9 ^{c,d,e} Fasting	10 ^{c,d} Fasting	For details see Protocol Section
Visit number	1^a Non-fasting	2^{b,c} Fasting	3^{c,d,e} Fasting	4^{c,d,e} Fasting	5^{c,d,e} Fasting	6^{c,d,e} Fasting	7^{c,d,e} Fasting	8^{c,d,e} Fasting	9^{c,d,e} Fasting	10^{c,d} Fasting	
Week	-6	-4	0	1	4	8	12	16	24	27	
Day	-42 to -29	-28	1	8	29	57	85	113	169	190	
Visit window	±5	±5	±0	±2	±5	±5	±5	±5	±5	±3	






Urinalysis, dipstick		X	X	X	X	X	X	X	X	X		5.2.2
UACR, spot urine ^e	X		X	X	X	X	X	X	X	X		5.1.1
CGI			■	■	■	■	■	■	■	■		■
■			■	■	■	■	■	■	■	■		■
■			■	■	■	■	■	■	■	■		■
■			■	■	■	■	■	■	■	■		■
■			■	■	■	■	■	■	■	■		■
HbA1c	X		X	X	X	X	X	X	X	X		5.1.2
S-creatinine for eGFR calculation ^t	X	X	X	X	X	X	X	X	X	X		5.2.1
FPG		X	X	X	X	X	X	X	X	X		5.1.3
Assess FPG for Rescue			X	X	X	X	X	X	X	X		3.10.3
Fasting Serum Lipids (Total-C, LDL-C, HDL-C, TG, FFA)			X						X			5.1.12

Study period	Screening Period	Lead-in period	Randomization		Treatment period					Follow-up period	For details see Protocol Section				
			Fasting	3 ^{c,d,e}	Fasting	4 ^{c,d,e}	Fasting	5 ^{c,d,e}	Fasting			6 ^{c,d,e}	Fasting	7 ^{c,d,e}	Fasting
Visit number	1^a Non-fasting	2^{b,c} Fasting		3^{c,d,e} Fasting	4^{c,d,e} Fasting	5^{c,d,e} Fasting	6^{c,d,e} Fasting	7^{c,d,e} Fasting	8^{c,d,e} Fasting	9^{c,d,e} Fasting	10^{c,d} Fasting				
Week	-6	-4	0	1	4	8	12	16	24	27					
Day	-42 to -29	-28	1	8	29	57	85	113	169	190					
Visit window		±5	±0	±2	±5	±5	±5	±5	±5	±5	±3				

CCJ												
Parathyroid hormone (PTH)												
Hepatitis Screen Panel		X								X		5.2.2
												5.2.2

Assessment schedule footnotes

- 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) Visit 3 should occur ≤ 42 days from visit 1 the period from visit 2 to visit 3 must be at least 28 ±5 days. Note: The single-blind Lead-in study medication and all the central laboratory results from Visit 1 must have been received at the site prior to completing the entry into Visit2.
- c) Central Laboratory samples must be collected in a fasting state (at least 8 hours fasting (drinking water is allowed) prior to the study visit) and subjects should be seen between 6 AM and 10 AM. Subjects must refrain from tobacco, caffeine for 12 hours, and alcohol for 24 hours 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 on the day of the visits must be taken upon completion of study visit procedures.
- 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 (except ±2 days for Visit 4). Subjects will bring their glucose meter and study supplies to the site at all visits. Once a patient is randomised, all visits should be scheduled relative to Visit 3. Any slippage in time from one visit must not accumulate to affect other visits.

- e) Randomized subjects discontinuing study medication or requiring rescue should have Week 24 procedures done at the time of rescue or study medication discontinuation. All subjects who discontinue study medication will be asked to continue ordinary visit schedule, unless they entirely withdraw consent from the study. In subjects discontinuing the study due to AE/SAE, the Investigator will follow the subjects until the event has resolved or stabilized. In addition, subjects who prematurely discontinue from the study may be contacted after discontinuation from the study, to collect vital status information.
- f) The start of enrolment is defined by the signature of the Protocol-Specific Informed Consent Form by the prospective subject. When only the Protocol-Specific Informed Consent is signed, and all other enrolment visit procedures are completed at a later time. The date on which the Informed Consent Form is signed will serve to determine the date and window for the entry into start lead-in /Day -28 visit (Visit 2).
- g) A brief physical examination should include cardiovascular, lungs, abdomen, and extremities; and any organ systems pertinent to the subject's signs, symptoms, or adverse events.
- h) A full physical examination should include general appearance, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdomen, lymph nodes, extremities, neurological, skin, and musculoskeletal.
- i) Height only at Visit 1.
- j) Only HbA1c and s-Cr for eGFR calculation as well as single spot urine UACR (values at Visit 1).
- k) s-Cr for eGFR, standard lab and other IC/EC (values at Visit 2).
- l) Lab values from Visit 3 will only be used as baseline values for study entry and not for eligibility evaluating.
- m) The 12-lead ECG must be performed at Visit 2. The results from this ECG must be available, assessed, and initialled and dated by the Investigator prior to Visit 3.
- n) SAE should be collected from the time when the informed consent form is obtained from a patient
- o) For blood chemistry only HbA1c and s-Cr for eGFR calculation. The samples do not have to be collected in a fasting state.
- 
- 
- r) Urine Albumin-to-Creatinine ratio: At Visit 1, one spot urine sample from the first morning void portion around or on the visit day, but for all other visits one spot urine sample from each of three separate first morning void portions on days around the visit with one of the samples collected in the morning on the visit day.
- 
- t) Please see formulas for eGFR calculation in section 5.2.1. At Visit 1, a separate serum sample is collected for eGFR calculation but at all other visits, the serum creatinine value from the clinical chemistry panel is used.
- 
- 
- w) For participants in selected sites only.

4.3 Enrolment/screening period

Procedures will be performed according to the Study Plan Table 2.

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 Heart Rate), body weight & height
- Obtain specimen (blood) for HbA1c, creatinine for eGFR calculation
- Obtain morning urine sample for UACR
- Perform urine pregnancy test for women of child bearing potential. Serum pregnancy test (β hCG) is performed, if urine pregnancy test result is positive.
- Review concomitant medications & Serious Adverse events
- 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, antihypertensive drugs, lipid lowering drugs and anti-platelet drugs, the morning of their next visit and to refrain from tobacco/nicotine/ caffeine for 12 hours and alcohol for 24 hours, respectively prior to next visit

4.4 Single-blind placebo lead-in period (Visit 2)

At visit 2, HbA1c and eGFR level from blood sample obtained from Visit 1 will be checked. If the HbA1c is ≥ 7.0 and $\leq 11.0\%$ and the eGFR value is within the range (20-80 mL/min/1.73 m²), 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 12-lead ECG. ECG must be obtained and reviewed with no significant abnormalities prior to Randomization
- Obtain vital signs (seated BP and Heart Rate)
- Obtain blood samples for haematology and clinical chemistry
- Obtain specimens (blood) for creatinine for eGFR calculation, FPG and hepatitis screen panel
- Perform urine pregnancy test for women of child bearing potential. Serum pregnancy test (β hCG) is performed, if urine pregnancy test result is positive
- 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 selfmonitoring of blood glucose (see Section 5.2.6.1)
- Provide instruction on recording daily insulin and glucose values in the patient diary
- Dispense the study drug
- Obtain specimen for urinalysis
- Remind patient to bring study drug, diary and glucose meter to the next
- Schedule next visit
- Review concomitant medications and AEs including hypoglycaemic events
- Remind patient to be fasting and withhold the study medication, anti-diabetic medications, insulin, antihypertensive drugs, lipid lowering drugs and anti-platelet drugs, the morning of their next visit and to refrain from tobacco/nicotine/ caffeine for 12 hours and alcohol for 24 hours, respectively prior to next visit

4.5 Treatment period

Descriptions of the procedures for this period are included in the Study Plan Table 2. The specific requirements for the treatment period are mentioned below:

4.5.1 Visit 3, Randomization

At Visit 3, patients who meet all of the inclusion and none of the exclusion criteria, including HbA1c $\geq 7.0\%$ and $\leq 11.0\%$ measured at Visit 1, eGFR 25-75 mL/minute/1.73m² inclusive, at Visit 1 or Visit 2, and micro or macro-albuminuria (UACR 30–3500 mg/g, inclusive) at Visit 1, will be randomized to the 24 weeks double-blind treatment period.

- Perform complete physical examination.
- Measure body weight & waist circumference.
- Review and confirm the patient's eligibility for the study by assessing inclusion and exclusion criteria listed in Sections 3.1 and 3.2.
- Contact IVRS/IWRS to randomize patient and obtain study drug dispensing assignment number and dispense the study drug.
- Obtain vital signs (seated BP, orthostatic BP and Heart Rate).
- Perform arterial stiffness measurements (for participants in selected sites only).
- Obtain blood samples for haematology and clinical chemistry.
- Provide instruction on diet and life-style.
- Dispense blood glucose meter and supplies, provide instruction on their use and self-monitoring of blood glucose.
- Perform urine pregnancy test for women of child bearing potential. Serum pregnancy test (β hCG) is performed, if urine pregnancy test result is positive.
- Collect and assess compliance with study drug based on tablet count.
- Review concomitant medications and Adverse events (AEs & SAEs) and hypoglycaemic events.
- Obtain specimen (blood) for PTH and creatinine for eGFR calculation.
- Obtain plasma and serum specimens (blood) to freeze and store for future potential exploratory biomarker analysis.

- CCI [REDACTED]
[REDACTED]
[REDACTED]
- Obtain specimen for urinalysis, CCI [REDACTED]
[REDACTED]
- Obtain urine specimen for UACR (morning urine sample on 3 different days around the visit).
- CCI [REDACTED]
[REDACTED]
- Remind patient to be fasting and withhold the study medication, anti-diabetic medications, insulin, antihypertensive drugs, lipid lowering drugs and anti-platelet drugs, the morning of their next visit and to refrain from tobacco/nicotine/ caffeine for 12 hours and alcohol for 24 hours, respectively prior to next visit.

4.5.2 Visit 4, Treatment

- Perform brief physical examination
- Measure body weight
- Obtain vital signs (seated BP, Heart Rate and orthostatic BP)
- Obtain blood samples for haematology and clinical chemistry
- Review concomitant medications and adverse events including AEs, SAEs and hypoglycaemic events.
- Obtain specimen for urinalysis, CCI [REDACTED]
[REDACTED]
- Obtain specimen (blood) for FPG
- Remind patient to be fasting and withhold the study medication, anti-diabetic medications, insulin, antihypertensive drugs, lipid lowering drugs and anti-platelet drugs, the morning of their next visit and to refrain from tobacco/nicotine/ caffeine for 12 hours and alcohol for 24 hours, respectively prior to next visit

4.5.3 Visit 5, Treatment

- Perform brief physical examination
- Measure body weight

- Obtain vital signs (seated BP, orthostatic BP and Heart Rate)
- Review concomitant medications and adverse events (AEs & SAEs) and hypoglycaemic events.
- Provide instruction on diet and life-style
- Obtain blood samples for haematology and clinical chemistry
- Obtain blood samples for PK
- Dispense blood glucose meter and supplies, provide instruction on their use and self-monitoring of blood glucose.
- Perform urine pregnancy test for women of child bearing potential. Serum pregnancy test (β hCG) is performed, if urine pregnancy test result is positive.
- Collect and assess compliance with study drug based on tablet count.
- Obtain specimen for urinalysis. CCI [REDACTED]
- Obtain urine specimen for UACR (morning urine sample on 3 different days around the visit).
- Obtain specimen (blood) for HbA1c & FPG
- Assess FPG for Rescue
- Remind patient to be fasting and withhold the study medication, anti-diabetic medications, insulin, antihypertensive drugs, lipid lowering drugs and anti-platelet drugs, the morning of their next visit and to refrain from tobacco/nicotine/ caffeine for 12 hours and alcohol for 24 hours, respectively prior to next visit

4.5.4 Visit 6, Treatment

- Measure body weight
- Obtain vital signs (seated BP, orthostatic BP and Heart Rate)
- CCI [REDACTED]
- Obtain blood samples for haematology and clinical chemistry
- Perform urine pregnancy test for women of child bearing potential. Serum pregnancy test (β hCG) is performed, if urine pregnancy test result is positive

- Review concomitant medications and Adverse events (AEs & SAEs) and hypoglycaemic events
- Obtain specimen for urinalysis, CCI [REDACTED]
- Obtain urine specimen for UACR (morning urine sample on 3 different days around the visit)
- Obtain specimen (blood) for HbA1c, FPG
- Assess FPG for Rescue
- Remind patient to be fasting and withhold the study medication, anti-diabetic medications, insulin, antihypertensive drugs, lipid lowering drugs and anti-platelet drugs, the morning of their next visit and to refrain from tobacco/nicotine/ caffeine for 12 hours and alcohol for 24 hours, respectively prior to next visit

4.5.5 Visit 7, Treatment

- Perform brief physical examination
- Measure body weight
- Obtain vital signs (seated BP, orthostatic BP and Heart Rate)
- Review concomitant medications and Adverse events (AEs & SAEs) and hypoglycaemic events
- Provide instruction on diet and life-style
- Dispense blood glucose meter and supplies, provide instruction on their use and self-monitoring of blood glucose
- Perform urine pregnancy test for women of child bearing potential. Serum pregnancy test (β hCG) is performed, if urine pregnancy test result is positive
- Dispense the study drug
- Collect and assess compliance with study drug based on tablet count
- Obtain specimen for urinalysis, CCI [REDACTED]
- Obtain urine specimen for UACR (morning urine sample on 3 different days around the visit)

- Obtain specimen (blood) for haematology and clinical chemistry, HbA1c & FPG
- CCI
- Assess FPG for Rescue
- Remind patient to be fasting and withhold the study medication, anti-diabetic medications, insulin, antihypertensive drugs, lipid lowering drugs and anti-platelet drugs, the morning of their next visit and to refrain from tobacco/nicotine/ caffeine for 12 hours and alcohol for 24 hours, respectively prior to next visit

4.5.6 Visit 8, Treatment

- Measure body weight
- Obtain vital signs (seated BP, orthostatic BP and Heart Rate)
- Obtain blood samples for haematology and clinical chemistry
- Perform urine pregnancy test for women of child bearing potential. Serum pregnancy test (β hCG) is performed, if urine pregnancy test result is positive;
- Obtain specimen for urinalysis, CCI
- Obtain urine specimen for UACR (morning urine sample on 3 different days around the visit)
- Review concomitant medications and Adverse events (AEs & SAEs) and hypoglycaemic events
- Obtain specimen (blood) for HbA1c, FPG
- Assess FPG for Rescue
- Remind patient to be fasting and withhold the study medication, anti-diabetic medications, insulin, antihypertensive drugs, lipid lowering drugs and anti-platelet drugs, the morning of their next visit and to refrain from tobacco/nicotine/ caffeine for 12 hours and alcohol for 24 hours, respectively prior to next visit

4.5.7 Visit 9, End of Treatment/Discontinuation/Rescue

Randomized patients discontinuing study drug or requiring rescue should have Visit 9 (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 fully physical examination

- Measure body weight & waist circumference
- Obtain vital signs (seated BP, orthostatic BP and Heart Rate)
- At Visit 9/End of Treatment/Discontinuation: Perform arterial stiffness measurements (for participants in selected sites only). Not needed at Rescue Visit.
- Obtain blood samples for haematology and clinical chemistry
- Obtain blood samples for PK
- Provide instruction on diet and life-style
- Dispense blood glucose meter and supplies, provide instruction on their use and self-monitoring of blood glucose
- Perform urine pregnancy test for women of child bearing potential. Serum pregnancy test (β hCG) is performed, if urine pregnancy test result is positive
- Collect and assess compliance with study drug based on tablet count
- Review concomitant medications and Adverse events (AEs & SAEs) and hypoglycaemic events
- Obtain specimen (blood) for PTH and creatinine for eGFR calculation.
- Obtain plasma and serum specimens (blood) to freeze and store for future potential exploratory biomarker analysis.
- CCI [REDACTED]
[REDACTED]
[REDACTED]
- Obtain specimen for urinalysis, CCI [REDACTED]
[REDACTED]
- Obtain urine specimen for UACR (morning urine sample on 3 different days around the visit)
- CCI [REDACTED]
[REDACTED]
- Assess FPG for Rescue
- Remind patient to be fasting and withhold the study medication, anti-diabetic medications, insulin, antihypertensive drugs, lipid lowering drugs and anti-platelet

drugs, the morning of their next visit and to refrain from tobacco/nicotine/ caffeine for 12 hours and alcohol for 24 hours, respectively prior to next visit

4.6 Visit 10, Follow-up period

Descriptions of the procedures for this period are included in the Study Plan Table 2. 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 10) provides the opportunity to further evaluate changes in physical signs, renal function, symptoms or laboratory parameters that may be related to dapagliflozin or the combination of dapagliflozin and saxagliptin.

- Perform brief physical examination
- Measure body weight & waist circumference
- Obtain vital signs (seated BP, orthostatic BP and Heart Rate)
- Perform urine pregnancy test for women of child bearing potential. Serum pregnancy test (β hCG) is performed, if urine pregnancy test result is positive
- Review concomitant medications and Adverse events (AEs & SAEs) and hypoglycaemic events
- Obtain specimen for urinalysis, CCI [REDACTED]
- Obtain urine specimen for UACR (morning urine sample on 3 different days around the visit)
- Obtain specimen (blood) for haematology, and clinical chemistry, HbA1c, creatinine for eGFR calculation & FPG

5. STUDY ASSESSMENTS

CCI [REDACTED] will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms 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.

<< **(JP)** For Japan: replace *Clinical Study Agreement with applicable information* >> **(End JP)** The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

<< **(JP)**: The Principal Investigator/Investigator will record data on the observations, tests and assessments specified in the protocol on the <<*paper/electronic*>> CRFs provided by AstraZeneca. 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. >> **(End JP)**

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 and follow-up period, HbA1c and spot 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 unblinded value throughout the study. During the whole study, CCI [REDACTED] will be blinded to Investigator and to the Sponsor.

All glycemic efficacy objectives will be based on values measured by central laboratory. Any self-monitored plasma glucose measured by the patient and FPG measured by the site using glucose meter 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 UACR

Urinary albumin to creatinine ratio is the primary assessment for the determination of the anti-proteinuric efficacy. Morning spot urine sample (first morning void) will be collected for each study visit (except Visit 2 and 4) and analysed according to the procedures described in the Laboratory Manual. Note that three samples are needed for each visit, except Visit 1 (one sample).

5.1.2 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

5.1.3 FPG

FPG is a well-established measure of glycemic efficacy and will be analysed by a central laboratory according to the procedures described in the Laboratory Manual.

CCI

[REDACTED]

5.2 Safety assessments

Safety assessments will be performed at regular intervals and will include physical examination, vital signs (including measured orthostatic reactions), renal function (change in eGFR), body weight, safety laboratory test (clinical chemistry, haematology, blood ketones and UA), hypoglycaemia and AE monitoring.

5.2.1 eGFR

eGFR is calculated according to the following formulas:

- The general MDRD formula:
$$\text{eGFR (ml/min/1.73m}^2\text{)} = 175 \times (\text{standardized sCr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if Black})$$
 [Note: sCr reported in mg/dL]
- The MDRD formula adapted for Japanese:
$$\text{eGFR (ml/min/1.73m}^2\text{)} = 194 \times (\text{standardized sCr})^{-1.094} \times (\text{Age})^{-0.287} \times (0.739 \text{ if female})$$
 [Note: sCr reported in mg/dL]

To be considered Japanese, both parents and both sets of grandparents must be Japanese. The patient must be born in Japan, and must not have lived outside Japan for more than 5 years.

- The MDRD formula adapted for Taiwanese:

$$eGFR \text{ (ml/min/1.73m}^2\text{)} = 1.309 \times \text{the general MDRD}^{0.912}$$

To be considered Taiwanese, both parents and both sets of grandparents must be Taiwanese. The patient must be born in Taiwan, and must not have lived outside Taiwan for more than 5 years.

5.2.2 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 (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin (Hb)	S-Aspartate transaminase (AST)
B-Haematocrit	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
Urinalysis (dipstick)	S-Albumin
Urine blood (dipstick for haematuria screening and microscopy if dipstick is positive)	S-Total protein
Pregnancy test (Urine HCG pregnancy test for WOCBP (HCG minimum sensitivity of 25 IU/L), dipstick analysed at the study centre)	S-Uric acid
	S-Potassium
	S-Calcium, total
	S-Sodium
	S- Bicarbonate
	S- Chloride
	S- Magnesium
	S- Phosphorus

S- β HCG, if urine pregnancy test result is positive

P- Parathyroid Hormone (PTH)

P- 3-hydroxybutyrate

Hepatitis Screen Panel (Includes Hepatitis Bviral 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 subject shows an AST **or** ALT >3xULN **or** total Bilirubin > 2xULN please refer to Appendix D ‘Algorithm on Management of Sustained Elevated Liver Safety Abnormalities’, for further instructions.

5.2.3 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.

5.2.4 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.

5.2.5 Vital signs

5.2.5.1 Pulse and blood pressure

As BP is both efficacy and safety variable in this study, measurement of seated BP is described in Sections 5.1.6

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.

5.2.6 Other safety assessments

5.2.6.1 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 6.3.8. 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 plasma 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

5.2.6.2 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.

5.2.6.3 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 $\geq 10^5$ colony forming units/mL of bacteria, in a properly collected voided urine specimen, without signs or symptoms typically attributed to urinary tract infection (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, US Preventative Services Taskforce 2008 (USPSTF 2008)) nor Europe (European Association of Urology 2014 (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 haemoglobin but will not routinely report the results of urinary dipstick tests for leukocyte esterase as a screening test for pyuria in surveillance urine examinations.

5.2.6.4 Microscopic Haematuria

In the event that haematuria is observed during a patient's participation, the sponsors recommend standard of care in diagnosing the cause of the haematuria. This section presents

references and an example of standard of care evaluation of microscopic haematuria. Local standards of care should be followed.

Patients with repeated reports of microscopic haematuria 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 haematuria as three or more red blood cells per high-power microscopic field in urinary sediment from two or more properly collected urinalysis specimens (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 haematuria 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 haematuria, 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 haematuria as well as smoking history, occupational exposure to dyes or chemicals (such as benzenes or aromatic amines), visible haematuria, 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 (Greenwood M 1926). Results from any procedure or investigations should be reported on the eCRF.

5.2.6.5 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.

5.3 Other assessments---Not applicable

5.4 Pharmacokinetics

5.4.1 Blood sample collection

CCI
[Redacted text block]

5.4.2 Determination of drug concentration

CCI
[Redacted text block]

CCI [Redacted]
[Redacted]

[Redacted]
[Redacted]
[Redacted]

5.4.3 Storage and destruction of pharmacokinetic samples

CCI [Redacted]
[Redacted]
[Redacted]

[Redacted]
[Redacted]

[Redacted]
[Redacted]
[Redacted]
[Redacted]

[Redacted]
[Redacted]
[Redacted]

5.5 Pharmacodynamics

CCI [Redacted]
[Redacted]
[Redacted]

5.6 Pharmacogenetics (Not Applicable)

5.7 Biomarker analysis

Collection of additional blood and urine biological samples for potential future analysis are performed at visit 3 and visit 9 (Rescue and Discontinue visit, if applicable). The donation of these extra samples is optional and the subject needs separately informed consent. After collection, the samples are stored for potential future analysis for exploratory biomarkers to assess correlations with disease activity, effects of study drug, clinical outcomes and toxicity.

Storage, re-use and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with

biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

5.7.1 Labelling and shipment of biological samples

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

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

5.7.2 Chain of custody of biological samples

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

The Principal Investigator <<at each centre>> keeps full traceability of collected biological samples from the subjects 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.

Samples retained for further use are registered in the AstraZeneca Biobank during the entire life cycle.

5.7.3 Withdrawal of Informed Consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site

- Ensures that the subject and AstraZeneca are informed about the sample disposal.

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

5.8 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 sample	Total Volume (ml)
Haematology HbA1c	2	10	20 (approx.)
PK	6	3	18 (approx.)
Clinical chemistry, Electrolyte Panel , eGFR By MDRD, Lipid Panel, CCI [REDACTED] ^a	2.5 or 3.5 or 5 ^a	10	36 (approx.)
FPG	2	9	18 (approx.)
CCI [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED] [REDACTED] [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Parathyroid hormone	2	2	4 (approx.)

(PTH)			
Hepatitis Screen Panel	3.5	1	3.5 (approx.)
Total			161. ^{5c} (approx.)

- a. Request a part of these tests on each visit based on the assessment schedule.
- b. Exploratory biomarkers samples are optional and the subject needs separately informed consent.
- c. Refer to the central laboratory manual for the detailed sample collection volume.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (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 serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

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

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

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 9) and including the follow-up period (Visit 10).

SAEs will be recorded from the time of informed consent is obtained until the end of the study (Visit 10)

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 subject 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 Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

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

A guide to the interpretation of the causality question is found in Appendix B to the 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 summarized 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.

6.3.7 Hy's Law

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 5.2.6.2

6.3.8 Hypoglycemic events

A separate section in the eCRF will be used to document all reported episodes of hypoglycaemia (see Section 5.2.6.1). 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.

6.3.9 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 Adjudication 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.

6.3.10 Adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs (“preceding events”)

To ensure that data on amputations is systematically collected, amputations and underlying conditions relevant to amputation will be recorded on a specific eCRF page.

If any of these relevant events have occurred, relevant information must be provided (this will be collected on a dedicated eCRF page).

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 adverse events 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.

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 is the IB for the AstraZeneca drug.

6.5 Overdose

Overdose is defined as >100 mg for dapagliflozin or >40 mg for saxagliptin 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 1 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 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

There is no restriction on fathering children or donating sperm during the study.

6.7 Management of IP related toxicities

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.

6.8.1 Steering Committee---Not Applicable

6.8.2 Data Monitoring Committee---Not Applicable

6.8.3 Scientific Advisory Committee---Not Applicable

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Name	Manufacturer	IMP/NIMP	Role	Type	Mandatory or guidance?	Route of administration	Formulation	Comment
Dapagliflozin 10 mg	CCI	IMP		Drug	Mandatory	Oral	Film Coated Tablet	Green, plain, diamond shaped
Dapagliflozin 10 mg placebo	CCI	IMP		Placebo	Mandatory	Oral	Film Coated Tablet	Green, plain, diamond shaped
Saxagliptin 2.5 mg	CCI	IMP		Drug	Mandatory	Oral	Film Coated Tablet	Plain, yellow, biconvex, round
Saxagliptin 2.5 mg placebo	CCI	IMP		Placebo	Mandatory	Oral	Film Coated Tablet	Plain, yellow, biconvex, round

The tablets contain lactose, which may cause discomfort in lactose-intolerant individuals.

7.2 Dose and treatment regimens

The study consists of a 2-week screening period followed by a 4-week single-blind placebo lead-in period, a 24-week double-blind & double dummy placebo-controlled treatment, and a 3-week follow-up period. Doses of study drug on the day of the visits must be taken after completion of study visit procedures.

Treatment arm	Description	Investigational drugs/ treatments used in arm	Subject ratio
Main Treatment Arm Screening	Single blind placebo lead-in (4w)	Dapagliflozin 10 mg placebo + saxagliptin 2.5 mg placebo	100%
Randomized treatment arm 1	Dapagliflozin 10 mg group	Dapagliflozin 10 mg + saxagliptin 2.5 mg placebo	33%
Randomized treatment arm 2	Saxagliptin 2.5 mg + dapagliflozin 10 mg group	Dapagliflozin 10 mg + saxagliptin 2.5 mg	33%
Randomized treatment arm 3	Placebo group	Dapagliflozin 10 mg placebo + saxagliptin 2.5 mg placebo	33%

Treatment during single-blind lead-in period

During the 4-week (Visit 2-3) single-blind lead-in period eligible patient will be dispensed 1 bottle of placebo to match saxagliptin 2.5mg along with 1 bottle of placebo to match dapagliflozin 10mg. 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 & double dummy randomization period

At Visit 3, eligible patients will be randomized to double-blind, double dummy treatment of dapagliflozin 10mg, saxagliptin 2.5mg or placebos to match both active products. 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 any 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 3.9 First dose of study drug will be administered at the clinic by site staff.

7.3 Labelling

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

<<(JP) *Replace the above paragraph with the paragraph below:* Details are specified in the document explaining the reconstitution procedures and other handling procedures for the investigational products.>>(End JP)

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.

<<(JP) *Replace the second sentence of the paragraph above with:* A description of the appropriate storage conditions is specified in the document explaining the reconstitution procedures and other handling procedures for the investigational products.>>(End JP)

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 ($\geq 70\%$ and $\leq 130\%$) during the lead-in period. For patients with compliance between $\geq 70\%$ and $< 80\%$ or $> 120\%$ and $\leq 130\%$, 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.
- 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.

<< **(JP)** Replace content in this section with: Study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The Investigational Product Storage Manager is responsible for managing the study drug from receipt by the study site until the return of all unused study drug to AstraZeneca. AstraZeneca will provide the study documents ‘Procedures for drug accountability’ and ‘Procedures for drug storage’ which describes the specific requirements. The Investigator(s) is responsible for ensuring that the subject has returned all unused study drug.>> **(End JP)**

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 antidiabetic 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 renal impairment (eGFR 25-75mL/minute/1.73m ²) according to local guidelines and/or investigator's judgement 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.
Anemia treatment	Use of erythropoiesis stimulating agents including, but not limited to, erythropoietin epoetin alfa, epoetin beta, darbepoetin alfa, or methoxy-polyethylene-glycol-epoetin beta, are allowed provided the treatment has been ongoing for at least 6 months and the dose is unchanged from 3 months prior to Visit 1 and throughout the study.

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, Victoza (liraglutide) indicated for anti-obesity treatment, and/or phendimetrazine from 30 days prior to Visit 1 to end of study is not allowed.
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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 study from start of run-in to end of follow-up (week 27).

However, in case of hypotension, the dose of any anti-hypertensive medication can be reduced according to the Investigator's judgement.

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

Multiplicity due to the two active treatment groups will be controlled by a Bonferroni adjustment, such that statistical significance will be determined according to a two-sided alpha level of 0.025. Within the saxagliptin 2.5 mg + dapagliflozin 10 mg treatment group the control of the alpha level in the testing of both co-primary endpoints (the percent change in urine albumin-to creatinine ratio (UACR) from baseline to 24 weeks and the change in HbA1c from baseline to 24 weeks) will require that each achieves statistical significance at the 0.025 level for a claim of superiority to placebo, and to proceed to a sequential comparison of secondary endpoints. Within the dapagliflozin 10 mg treatment group the control of the alpha level for the primary endpoint (the percent change in urine albumin-to creatinine ratio (UACR) from baseline to 24 weeks) will require the achievement of statistical significance at the 0.025 level for a claim of superiority to placebo, and to proceed to a sequential comparison of secondary endpoints. Parallel sequential testing strategies will be used for comparing each active treatment group to placebo for the secondary endpoints.

8.2 Sample size estimate

With 142 subjects per treatment group with post-baseline measurements, there is 90% power to detect a difference of 0.42% in mean change from baseline in HbA1c between saxagliptin/dapagliflozin treatment group and placebo and, separately dapagliflozin treatment group and placebo at significance level of 0.025, using a two sided alpha and assuming a standard deviation (SD) of 1.0%. Assuming 5% of the subjects do not have a post-baseline assessment, a total of 450 subjects (150 subjects per treatment group) need to be randomized. The estimated sample size of 142 subjects per group will also yield 92% power to detect a 35% difference in UACR for each comparison at an alpha level of 0.025, assuming a SD = 80%. Based upon existing pooled data for dapagliflozin in treating patients with eGFR <60 ml/min/1.73 m² on ACEi/ARB the minimal detectable difference for this study is 0.27% for HbA1c and 21% for UACR

The significance level used to infer statistical significance for comparisons of primary and secondary endpoints will be 0.025, representing a two sided alpha level. Within the saxagliptin 2.5 mg + dapagliflozin 10 mg treatment group the control of the alpha level in the testing of both co-primary endpoints (the percent change in urine albumin-to creatinine ratio (UACR) from baseline to 24 weeks and the change in HbA1c from baseline to 24 weeks) will require that each achieves statistical significance at the 0.025 level for a claim of superiority to placebo, and to proceed to a sequential comparison of secondary endpoints. Within the dapagliflozin 10 mg treatment group the control of the alpha level for the primary endpoint (the percent change in urine albumin-to creatinine ratio (UACR) from baseline to 24 weeks) will require the achievement of statistical significance at the 0.025 level for a claim of superiority to placebo, and to proceed to a sequential comparison of secondary endpoints. Parallel sequential testing strategies will be used for comparing each active treatment group to placebo for the secondary endpoints. In all analyses p-values will be represent two-sided tests, and will not be adjusted for multiplicity.

8.3 Other statistical considerations

If superiority of is demonstrated within the saxagliptin 2.5 mg + dapagliflozin 10 mg treatment group the for each of the two primary endpoints (HbA1c and percent change from baseline UACR) at the 0.025 level and/or within the dapagliflozin 10 mg treatment group the for the primary endpoints (percent change from baseline UACR) at the 0.025 level then secondary endpoints will be compared separately between that treatment group and placebo at an alpha level of 0.025. Comparisons of secondary endpoints will be performed sequentially in the order prescribed in Section 2.2, and will cease for a given treatment group at the first instance a secondary endpoint dose not statistical significance in a secondary endpoint, or at the last comparisons, whichever occurs first. Superiority of a treatment to placebo will be inferred if statistical significance is demonstrated and greater improvement occurred with that treatment than placebo.

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Continuous secondary and exploratory endpoints that are statistically compared and are measured at multiple instances during the 24 week double-blind treatment period will be evaluated using repeated measures models (RMM) which will include measurements from all scheduled time points following randomization up to and including week 24. Primary, secondary, exploratory, and eGFR safety parameters within or at the end of 24 weeks double-blind treatment analysed in the model will exclude all post-treatment results subsequent to glycemic rescue. However, the effect of exclusion on estimates and differences will be evaluated in sensitivity analyses. Continuous secondary and exploratory endpoints that are statistically compared and are only measured at baseline and at the end of the 24 week double-blind treatment period will be evaluated using analysis of variance models (ANOVA).

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Analyses of secondary, safety, and exploratory categorical endpoints that represent proportions of subjects will be performed using a logistic regression model. The endpoints within or at the end of 24 weeks double-blind treatment analyzed in the model will exclude all post-treatment results subsequent to glycemic rescue. Details will be provided in the Statistical Analysis Plan.

8.4 Definitions of analysis sets

8.4.1 Enrolled Patients Data Set

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

8.4.2 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.

8.4.3 Full Analysis set

The Full Analysis Set which will consist of all randomized patients who take 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.

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).

8.4.4 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.

8.4.5 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. No formal statistics analysis will be made for the safety variables, only descriptive summaries.

8.4.6 PD analysis set---Not Applicable

8.4.7 PRO analysis set---Not Applicable

8.5 Outcome measures for analyses

8.5.1 Primary outcome variables

- The primary outcome variable will be the change from baseline in HbA1c (% saxagliptin/dapagliflozin versus placebo only) at Week 24.
- Percent change from baseline in UACR at Week 24.

8.5.2 Secondary outcome variables

Secondary outcome variables for the Saxagliptin/Dapagliflozin treatment comparisons:

- Percent change from baseline in body weight (kg) at Week 24.
- Change from baseline in FPG (mg/dL) at Week 24.
- 30% reduction in UACR at Week 24.

- HbA1c < 7.0 % at Week 24.
- Change from baseline in seated SBP (mmHg) at Week 24.

Secondary outcome variables for the Dapagliflozin treatment comparisons:

- Percent change from baseline in body weight (kg) at Week 24.
- 30% reduction in UACR at Week 24.
- Change from baseline in seated SBP (mmHg) at Week 24.
- Change from baseline in HbA1c (%) at Week 24.
- Change from baseline in FPG (mg/dL) at Week 24.
- HbA1c < 7.0 % at Week 24.

8.5.3 Safety outcome variables

Safety outcome variables will be:

- Discontinuation for a sustained increase in serum creatinine by ≥ 1.5 times baseline level (AKI stage 1).
- AEs.
- Changes from baseline in SBP (mmHg), DBP (mmHg), and heart rate (bpm).
- Changes from baseline in clinical chemistry/haematology parameters.
- Changes from baseline in the findings from physical examination.
- Changes from baseline in clinical laboratory test results.
- Change from baseline in eGFR at Week 24.
- Change from baseline in eGFR at Week 27.

8.5.4 Exploratory outcome variables

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8.6 Methods for statistical analyses

Analyses on the variables shown below will only include measurements obtained prior to or on the date of rescue medication for some analyses. For other efficacy variables and exploratory variables, measurements after rescue medication will not be excluded from the analyses.

- Change from baseline in HbA1c (%)
- Change from baseline in FPG (mg/dL)
- Proportion of patients with HbA1c < 7%

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Further details will be specified in the Statistical Analysis Plan (SAP).

8.6.1 Analysis of the primary variable (s)

The analysis of the change in HbA1C from baseline to Week 24 will be based on a repeated measures model (RMM) including all scheduled time points following randomization up to and including week 24. The analysis of percent change from baseline in UACR from baseline to Week 24 will be conducted on the log-transformed UACR values using RMM. Separate RMM models will be used to compare saxagliptin/dapagliflozin with placebo, and to compare dapagliflozin 10 mg alone with placebo. RMM represent a longitudinal repeated measures analysis using ‘direct likelihood’, and include patients in the Full Analysis Set who have a baseline measurement and at least one post-baseline measurement. Analyses on HbA1c will only include measurements prior to the administration of rescue medication. Measurements made following rescue administration will not be included in HbA1c analysis.

The SAS procedure PROC MIXED will be used for primary analyses. The primary analysis models will each 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. (In UACR analyses the natural logarithmic transformation will be applied to baseline UACR values prior to analysis.) 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 in HbA1c within each model for each treatment group as well as the difference in mean change between the saxagliptin/dapagliflozin treatment group and placebo will be calculated. P-value of the differences in Week 24 estimates between saxagliptin/ dapagliflozin and placebo will be calculated. For UACR, point estimates and 95% confidence intervals for the mean percent change in UACR within each treatment group will be obtained by exponentiation of model estimates, and differences in mean percent change will be similarly calculated. P-values of the differences in Week 24 percent change estimates between each treatment group (saxagliptin/dapagliflozin and, separately, dapagliflozin 10 mg only) and placebo from each model will be calculated.

8.6.2 Analysis of the secondary variable(s)

Comparisons of the secondary efficacy endpoints between dapagliflozin 10 mg and placebo will be performed only if the test for the primary UACR endpoint is significant. Secondary efficacy endpoints will only be compared between saxagliptin/dapagliflozin and placebo will only be performed if each comparison of both co-primary endpoints is significant. If statistical significance is achieved as prescribed above, then the secondary endpoints will be compared between that treatment (those treatments) and placebo in the order specified in Section 2.2. A sequential testing procedure will be employed for secondary comparisons in order to control the type I error rate at the 0.025 level. Statistical comparisons between each treatment and placebo will be only performed for a given secondary endpoint if all previous sequential tests for that comparison are also significant. Otherwise, the testing procedure will stop at the secondary endpoint that does not reach statistical significance.

The secondary endpoints percent change from baseline in total body weight at Week 24, change from baseline in FPG at Week 24, change from baseline in seated SBP at Week 24, and change from baseline in HbA1c at Week 24 (Dapagliflozin 10 mg) will be analyzed by RMM analyses, as described for the primary analyses.

The secondary analyses of proportions for subjects with at least a 30 percent reduction in UACR from baseline to Week 24 and, separately, proportions for subjects with an HbA1c of less than 7 percent at Week 24 will be analyzed using a logistic regression model with adjustment for randomization strata and baseline measurement.

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8.6.4 Interim analysis

Not Applicable

8.6.5 Exploratory analysis

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[REDACTED]

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[REDACTED]

[REDACTED]

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 subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject, including verification of informed consent of participating subjects. In case of withdrawal of Informed Consent for the use of the biological sample (biomarkers) the monitor should verify that the sample disposal has been done and has been reported to the subject, and that the sample disposal is verified and documented at site.
- 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.

<<(JP): Source data are any data generated as a result of the subject's inclusion in the study (including run-in and/or follow up related to the study) and includes all related medical examinations and other records. <<Original data recorded on the CRFs and regarded as source data are as follows:>> **(End JP)**

(JP) <<Add the following section:

9.2.2 Direct access to source data in Japan

The Head of the study site and the Principal Investigator/ Investigator will cooperate for monitoring and audit by AstraZeneca, and accept inspection by the IRB or regulatory

authorities. All study documents such as raw data will be open for direct access to source data at the request of the monitor and the auditor of AstraZeneca, the IRB, or regulatory authorities.

<<(JP) The monitor(s) will verify data from the CRFs against source data before the Principal Investigator signs the CRFs to ensure accuracy and completeness of documentation, and assure that the Principal Investigator has submitted the CRFs to AstraZeneca. If the Investigator wishes to amend the collected CRFs, the monitor will ensure that the Principal Investigator has recorded the amendment with signature and date and provided this to AstraZeneca.>>(End JP)

9.2.3 Study agreements

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

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

<<(JP) *Replace paragraphs above with paragraph below:* The Principal Investigator at each centre should comply with all the terms, conditions, and obligations of the Study Agreement with the Principal Investigator, or equivalent, for this study. In the event of any inconsistency between this CSP and the Study Agreement with Principal Investigator, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Study Agreement with Principal Investigator shall prevail. Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or any subjects are enrolled.>>(End JP)

9.2.4 Archiving of study documents

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

<<(JP) *Replace the above paragraphs with the paragraphs below:*

Study files. AstraZeneca will provide the Principal Investigator with a file in which to organise and retain all study-related documents. All study documents (including letters from AstraZeneca) should be retained in this file by the Principal Investigator. The monitor will regularly check the file to ensure that all relevant documents are retained. The contents of the file may be audited/inspected by AstraZeneca's auditor, regulatory authorities, or IRB.

Period of record retention. The study site (and the Principal Investigator) will retain the essential documents specified in the ICH GCP (e.g., source document such as medical records, contract, and signed consent form). Essential documents should be retained at the study site for at least 15 years following completion of the study, or per regulatory obligations if longer,

and thereafter destroyed only after agreement with AstraZeneca. However this is not always applied to those that are not preservable such as blood samples. In the event of any inconsistency between the above-mentioned contents and the contract with the study site, the contract shall prevail. These documents should be retained for a longer period however if needed by AstraZeneca, and the specific period and method of retention will be separately discussed between the study site and AstraZeneca. AstraZeneca should notify the head of the study site in writing when the study related records are no longer needed. The records should be managed by a responsible person appointed by the head of the study site.>>(End JP)

<<(JP) Add following section:

9.3 Study timetable and end of study

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

The study is expected to be started in Q3 2015 and to be ended by Q2 2018.

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

<<(JP) Replace the above with: Planned duration of the study: Study period: <<Month, Year-Month, Year>> (End JP)

<<(JP) Discontinuation or suspension of the whole study programme

If AstraZeneca decides to prematurely terminate or suspend the study, the Principal Investigator/Investigator, the head of the study site, and regulatory authorities should receive written notification of the reasons for the premature termination or suspension.

The Principal Investigator/Investigator will immediately notify the decision to the subjects, give appropriate medical treatment; take necessary measures, and record treatment or measures provided on the source documents.

Completion of the study

Upon terminating the study, the Principal Investigator/Investigator will report in writing the completion of the study as well as the summary of the results to the head of the study site in accordance with the study site’s rules. The head of the study site, who is informed of the termination by the Investigator, will provide a written notification of the results to the IRB and AstraZeneca. >>(End JP)

9.4 Data management by CCI

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

Data will be entered into the CCI [REDACTED] 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 Management of genotype data

Not Applicable

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/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

<<(JP) *Add the following:* The applicable regulatory requirements in Japan are ‘Good Clinical Practice for Trials on Drugs (MHLW Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications)>>(End JP)

10.2 Subject data protection

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

<<(JP) *Replace the above paragraph with this text:*

The Master Informed Consent Form will explain that:

- Study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation
- Patient data will be maintaining confidentiality in accordance with national data legislation
- For data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an IRB may require direct access to parts of the hospital or practice source records relevant to the study, including subjects’ medical history

All data computer processed by AstraZeneca will be identified by study code and enrolment code (E-code) (End JP)

10.3 Ethics and regulatory review

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

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

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

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

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

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

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

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

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

<<(JP) *Replace the above paragraphs with:*

An IRB should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The head of the study site will ensure the distribution of these documents to the applicable IRB, and the Principal Investigator to the Investigator and study site staff.

The opinion of the IRB should be given in writing. The head of the study site should submit a notification of direction/determination as well as a copy of the IRB written approval to AstraZeneca and the Principal Investigator before enrolment of any subject should into the study.

The IRB should approve all advertising used to recruit subjects for the study.

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

A valid contract between the study site and AstraZeneca should be signed before the Investigator can enrol any subject into the study. The protocol should be re-approved by the IRB annually.

The head of the study site should seek the opinion of the IRB with respect to the appropriateness of continuing the study at the study site at least once a year when the duration of the study exceeds one year. The Principal Investigator should submit progress reports to the IRB via the head of the study site at the time of the protocol re-approval.

Before enrolment of any subject into the study, the final study protocol, including the final version of the ICF, should be approved by the national regulatory authority with notification provided, according to local regulations. AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, IRB, the head of the study site and the Principal Investigator with safety updates/reports according to local requirements.

The head of the study site should submit a written report to the IRB providing the details of all safety relative information reported by AstraZeneca. >>(End JP)

10.4 Informed consent

The Principal Investigator(s) at each centre will:

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

<<(JP) Japan only:

- If any new information on the study medication becomes available which may influence the decision of the subject to continue the study, the Investigator(s) should inform the subject of such information immediately, record this in a written form, and confirm with the subject if he or she wishes to continue the participation in the study. In addition, if the Investigator(s) deem it necessary to revise the Informed Consent Form, they should revise it immediately (Refer to Section 10.5). The Investigator(s) should re-explain the subjects using updated Informed Consent Form even if although the subjects have already been informed of the new information

verbally. Written informed consent to continue participation in the study should be provided separately.>>(End JP)

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, National Co-ordinating Investigator, and the Principal 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 Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee 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 Principal Investigator(s). For distribution to Ethics Committee see Section 10.3.

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

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

<<(JP) *Replace the above paragraphs with:*

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca. If it is necessary for the study protocol to be amended, the amendment should be submitted to the Head of the Study Site and be approved by its IRB. If applicable, AstraZeneca should submit a notification to the regulatory authority before it is implemented. If a protocol amendment requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the centre's IRB should be notified. Approval of the revised Informed Consent Form by AstraZeneca and by the IRB is required before the revised form is used. If an administrative change is required, such a change should be notified to or approved by each IRB according to local requirements >> **(End JP)**

10.6 Audits and inspections

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

applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

<<(JP) All study data may undergo a reliability review and onsite-GCP inspection by the regulatory authorities. >>(End JP)

11. LIST OF REFERENCES

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12. APPENDIX A ADDITIONAL SAFETY INFORMATION

12.1 Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

These should usually be considered as serious.

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

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

Development of drug dependency or drug abuse

12.2 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there

is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

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

13. APPENDIX B INTERNATIONAL AIRLINE TRANSPORTATION ASSOCIATION (IATA) 6.2 GUIDANCE DOCUMENT

13.1 Labelling and Shipment of Biohazard Samples

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

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

14. APPENDIX C ALGORITHM ON MANAGEMENT OF SUSTAINED ELEVATED LIVER SAFETY ABNORMALITIES

14.1 Algorithm on Management of Sustained Elevated Liver Safety Abnormalities

The monitoring for liver safety will be performed using the serum levels of AST, ALT and TB (see [Figure 1](#) Sustained elevated liver safety abnormalities flow chart).

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

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

14.2 Patients must be Discontinued from the Study if an Initial and Repeat Confirmatory Laboratory Tests Meet any of the Following Criteria:

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

- ALT and/or AST are >5 x ULN for > 14 consecutive days, at any time after initial confirmatory results
- ALT and/or AST are >8 x ULN

In each of these situations, study medication will be discontinued, the Sponsor notified and the End of Treatment Visit performed within 3 days of the confirmed laboratory results (see Section 3.10 in the CSP).

At the End of Treatment Visit, medical history including details of risk factors for liver diseases (if not previously assessed) will be requested and additional blood sampling performed (Specialized Liver Panel and Liver Discontinuation Panel, see detailed below). Patient should also be scheduled for a Follow-up Visit (ie, procedures of Visit 10) 3 weeks after discontinuation of investigational product. A referral consultation to a hepatologist or gastroenterologist (specializing in liver abnormalities) should be obtained.

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

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

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

14.3 Guidance on Assessment of Hepatic Laboratory Abnormalities

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

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

- AE assessment
- Physical Examination for jaundice and other signs of liver diseases
- Review of relevant risk factors and current history focusing on possible causes of the increased ALT and/or AST and/or TB, including:
 - Use of suspect concomitant medication [including over-the-counter (ie, acetaminophen/paracetamol), herbal and vitamin preparations]

- Recent alcohol consumption or recreational drug/narcotic use
 - Recent unaccustomed physical exertion
 - Occupational or environmental exposure to hepatotoxins
 - Other conditions which may cause liver diseases or which may cause abnormal test results
- Specialized Liver Laboratory Panel (see below)

14.4 Specialized Liver Panel

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

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

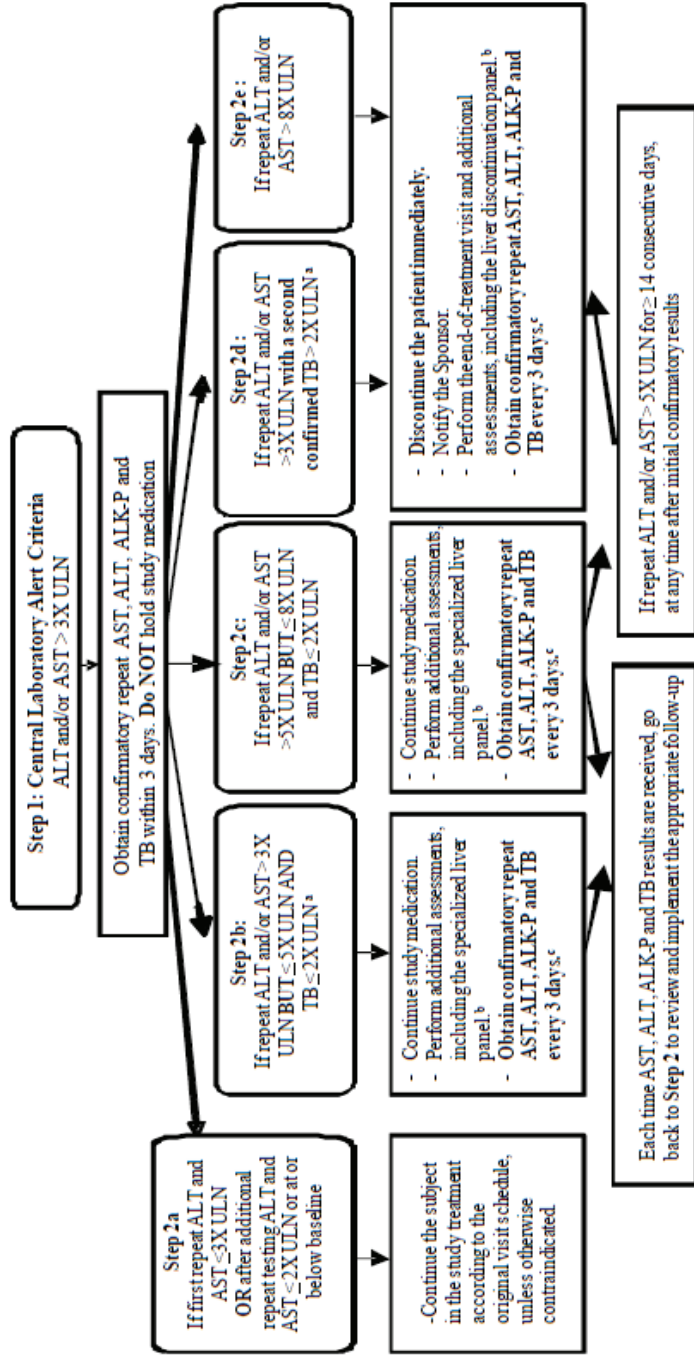
14.5 Liver Discontinuation Panel

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

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

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

Figure 1 Sustained elevated liver safety abnormalities flow chart



- a In patient with repeat ALT or AST > 3X ULN but ≤ 8X ULN, only patient with TB ≤ 2X ULN at Step 1 should be followed according to Step 2b.
 Patient with an initial TB and confirmatory repeat TB > 2X ULN should be followed according to Step 2d.
- b Please see text above in the Appendix for details on additional assessments to be performed (AE assessment, PE, review of current medical history including focused review to risk factors for liver diseases and collection of blood samples [specialized liver panel or liver discontinuation panel])
- c Confirmatory repeat AST, ALT, ALK-P and TB should be obtained every 3 days following receipt of prior laboratory results, until the ALT and AST are ≤ 2X ULN or until ALT and AST are at or below baseline levels. The frequency of retesting can decrease to once a week or less if abnormalities stabilize and the patient is asymptomatic.

15. APPENDIX D NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION

15.1 New York Heart Association (NYHA) Classification

The NYHA classification will be based on the following definitions:

Class I No limitation:

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

Class II Slight limitation of physical activity:

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

Class III Marked limitation of physical activity:

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

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

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