AstraZeneca

Statistical Analysis Plan

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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

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Study Statistician PPD [redacted] 6 Jun 2018
Date

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Global Product Statisticia PPD [redacted] 06 June 2018
Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACEi	Angiotensin-converting enzyme inhibitor
AIx	Augmentation Index
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ARB	Angiotensin II receptor blocker
AST	Aspartate Aminotransferase
AZRand	AZ Randomization system
BMI	Body Mass Index
BP	Blood Pressure
C	Conventional Units
CABG	Coronary Artery Bypass Grafting
CKD	Chronic Kidney Disease
CCI	[redacted]
CRA	Clinical Research Associate
CRF	Case Report Form (electronic/paper)
CRO	Contract Research Organization
CCI	[redacted]
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DKA	Diabetic ketoacidosis
DM	Diabetes Mellitus
DPP4	Dipeptidyl peptidase-4
eGFR	Estimated Glomerular Filtration Rate
EU	European Union
CCI	[redacted]
[redacted]	[redacted]

Abbreviation or special term	Explanation
FPG	Fasting Plasma Glucose
FU	Follow-Up
GLP-1	Glucagon-like peptide-1
CCI [redacted]	[redacted]
Hb	Haemoglobin
HbA1c	Glycosylated Haemoglobin
HDL-C	High Density Lipoprotein Cholesterol
HF	Heart Failure
HIV	Human Immunodeficiency Virus
Hr	Hour
[redacted]	CCI [redacted]
[redacted]	[redacted]
ICH	International Conference on Harmonisation
IP	Investigational Product
ITT	Intention to treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
CCI [redacted]	[redacted]
KG	Kilogram
LDL-C	Low Density Lipoprotein Cholesterol
LOCF	Last Observation Carried Forward
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MG	Milligram
MMRM	Mixed-effects Model Repeated Measures
MTP	Multiple testing procedure
[redacted]	CCI [redacted]
NYHA	New York Heart Association
OAD	Oral Anti-diabetic Drug

Abbreviation or special term	Explanation
OD	Once Daily
PK	Pharmacokinetic
CCI	[redacted]
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTH	Parathyroid Hormone
ROW	Rest of the World
IPD	Important Protocol Deviation
SAE	Serious adverse event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SGLT2	Sodium Glucose co-Transporter 2
SI	International System of Units
SU	Sulfonylurea
T2DM	Type 2 Diabetes Mellitus
T2DN	Type 2 Diabetes Nephropathy
TB	Total Bilirubin
TC	Total Cholesterol
TG	Triglycerides
TIA	Transient Ischemic Attack
TZD	Thiazolidinedione
UACR	Urine albumin-to-creatinine ratio
CCI	[redacted]
ULN	Upper Limit of Normal
US	United States
WOCBP	Women of childbearing potential

AMENDMENT HISTORY

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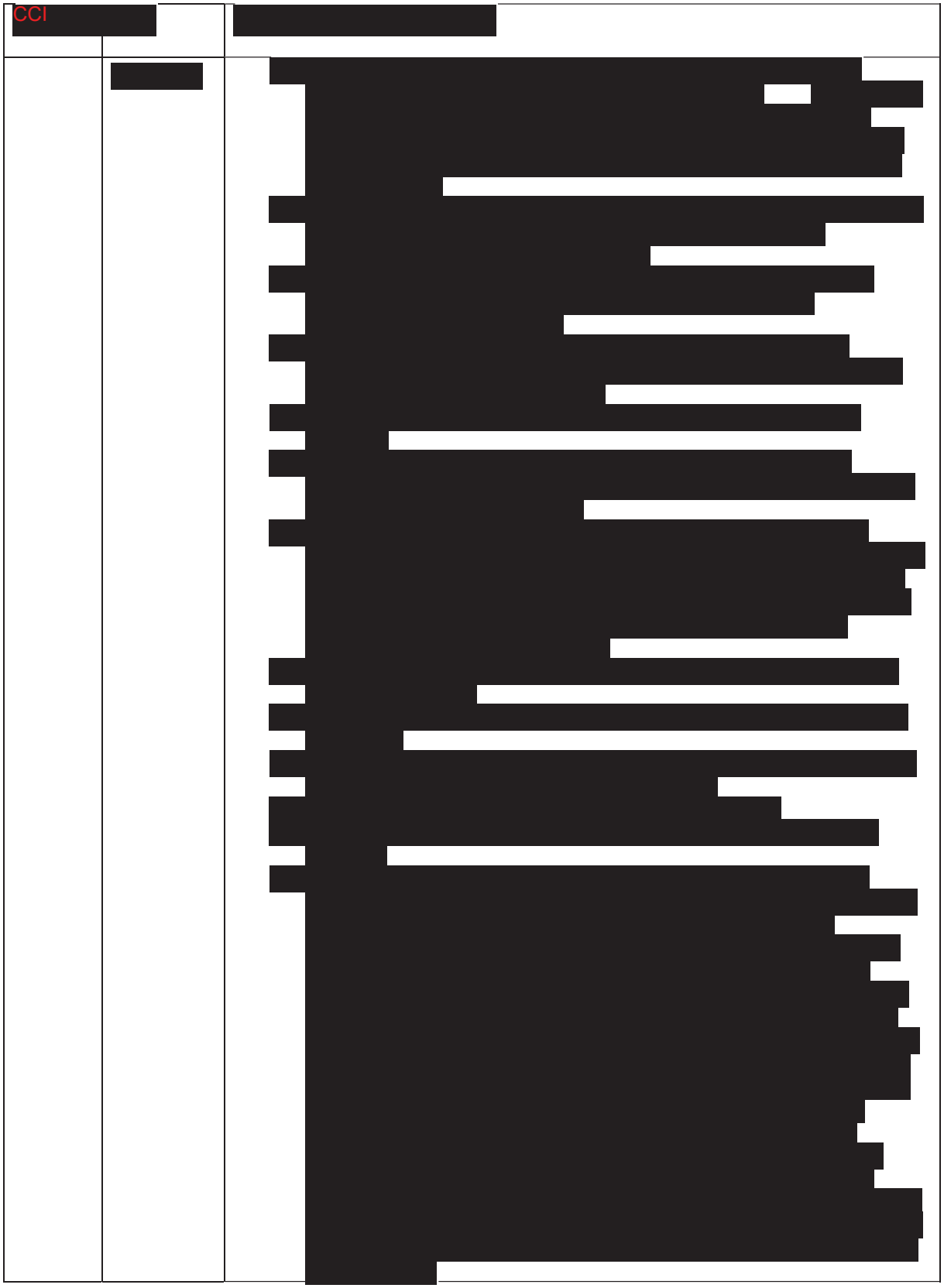
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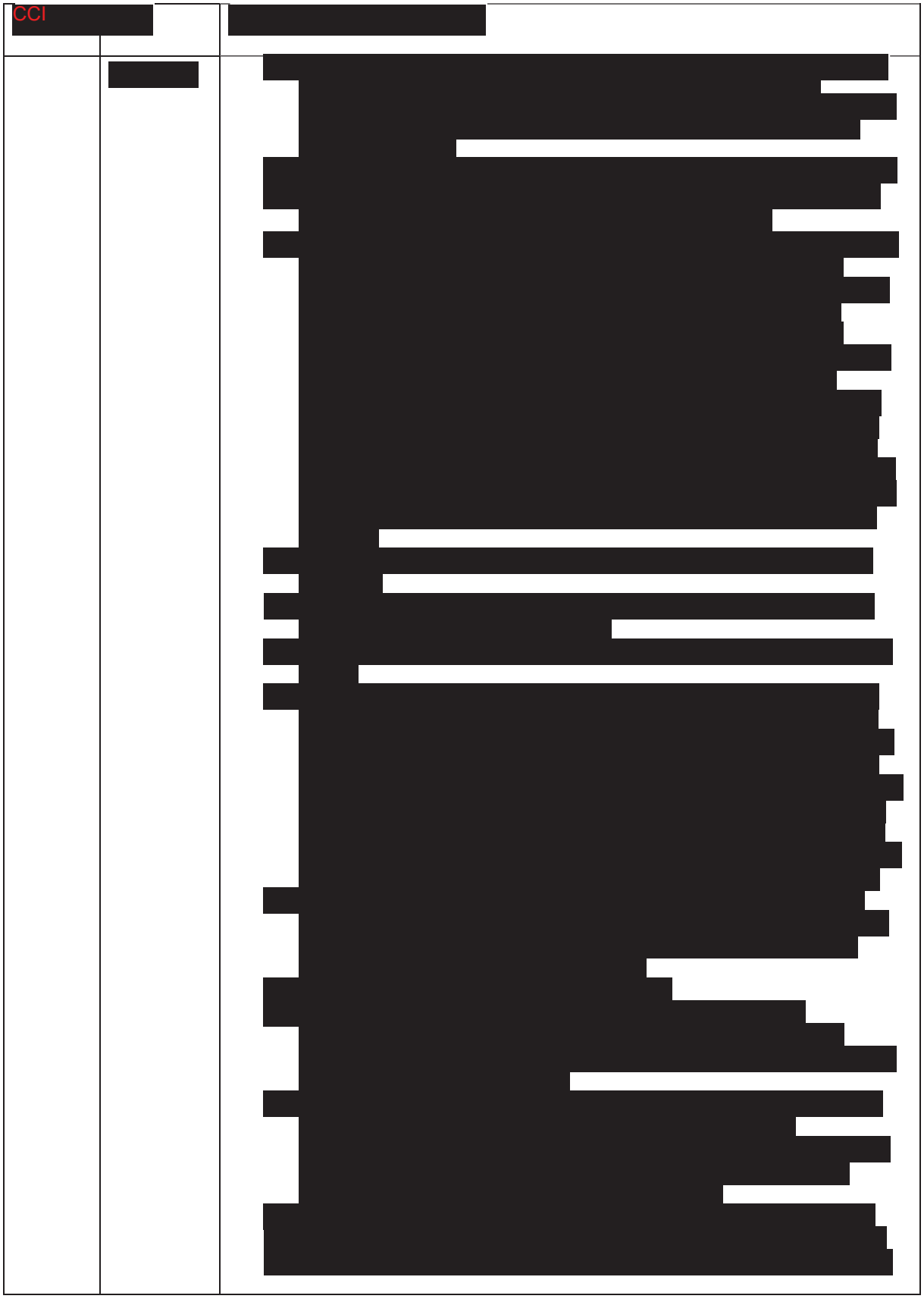

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1. STUDY DETAILS

1.1 Study Objectives

1.1.1 Primary Efficacy Objectives

The primary objectives of the study are:

1. To evaluate the efficacy of dapagliflozin 10 mg plus saxagliptin 2.5 mg versus placebo once daily in the CKD patients (mild-severe renal impairment; eGFR 25-75 mL/min/1.73 m^2) with type 2 diabetes mellitus and albuminuria treated with ACEi or ARB by comparison of:
    - Mean change from baseline in HbA1c at Week 24
    - Mean percent change from baseline in urine albumin-to-creatinine ratio (UACR) at Week 24
2. To evaluate the efficacy of dapagliflozin 10 mg versus placebo once daily in the CKD patients with type 2 diabetes mellitus and albuminuria treated with ACEi or ARB by comparison of:
    - Mean percent change from baseline in UACR at Week 24

1.1.2 Secondary Efficacy Objectives

The secondary objectives of the study are:

1. To evaluate the efficacy of dapagliflozin 10 mg plus saxagliptin 2.5 mg versus placebo once daily after 24 weeks of oral administration of double-blind therapy in the CKD patients with type 2 diabetes mellitus and albuminuria treated with ACEi or ARB by ordered comparison of:
    - Mean percent change from baseline in total body weight at Week 24
    - Mean change from baseline in FPG at Week 24
    - Proportion of patients achieving ≥30% reduction in UACR at Week 24
    - Proportion of patients achieving a reduction in HbA1c <7.0% at Week 24
    - Mean change from baseline in seated SBP at Week 24
2. To evaluate the efficacy of dapagliflozin 10 mg versus placebo once daily after 24 weeks of oral administration of double-blind therapy in the CKD patients with type 2 diabetes mellitus and albuminuria treated with ACEi or ARB by ordered comparison of :

- Mean percent change from baseline in total body weight at Week 24
- Proportion of patients achieving ≥30% reduction in UACR at Week 24
- Mean change from baseline in seated SBP at Week 24
- Mean change from baseline in HbA1c at Week 24
- Mean change from baseline in FPG at Week 24
- Proportion of patients achieving a reduction in HbA1c <7.0% at Week 24

1.1.3 Safety Objectives

The safety objectives include:

- To assess the proportion of patients discontinued from study medication due to sustained increase in serum creatinine ≥1.5 times baseline level (AKI stage 1) for dapagliflozin 10 mg, dapagliflozin 10 mg plus saxagliptin 2.5 mg, and placebo once daily in the CKD patient with type 2 diabetes and albuminuria treated with ACEi or ARB
- To evaluate the safety and tolerability of dapagliflozin 10 mg and dapagliflozin 10 mg plus saxagliptin 2.5 mg once daily in the CKD patients with type 2 diabetes mellitus and albuminuria treated with ACEi or ARB
- To evaluate the effect of dapagliflozin 10 mg, dapagliflozin 10 mg plus saxagliptin 2.5 mg versus placebo once daily on renal function in the CKD patients with type 2 diabetes and albuminuria treated with ACEi or ARB by assessment of mean change from baseline in eGFR at Week 24
- To evaluate the effect of dapagliflozin 10 mg, dapagliflozin 10 mg plus saxagliptin 2.5 mg versus placebo once daily on renal function in the CKD patients with type 2 diabetes and albuminuria treated with ACEi or ARB by assessment of mean change from baseline in eGFR at Week 27

1.1.4 Exploratory Objectives

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1.1.5 Pharmacokinetics Objectives

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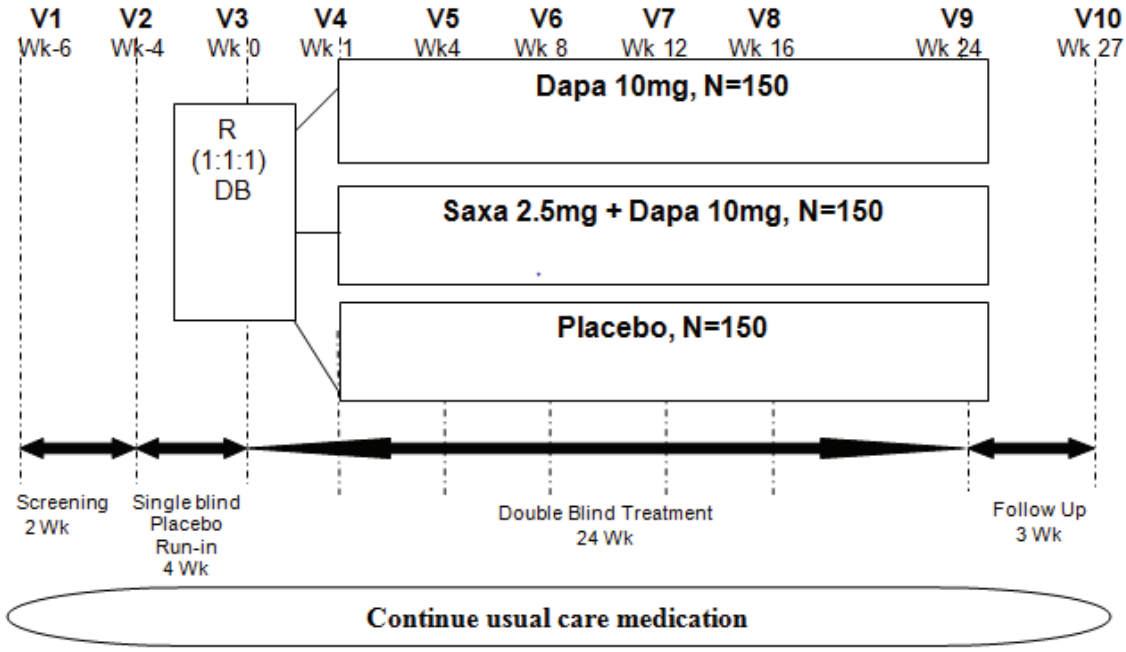
1.2 Study design

This is an exploratory phase II/III study, randomized, double-blind, placebo controlled, multi-national, multi-centre study to evaluate the efficacy and safety and pharmacodynamics of dapagliflozin 10 mg once daily (od) and dapagliflozin 10 mg od in combination with saxagliptin 2.5 mg od in patients with CKD, type 2 diabetes 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. Patients will be randomized to 24-week treatment with dapagliflozin 10 mg, dapagliflozin plus saxagliptin 2.5 mg or matching placebo after the placebo lead-in period. Figure 1 illustrates details on timing of visits. Table 1 Study Planning and detail provides details schedule of study procedures.

The study will be run at approximately 100 clinical sites in North America, EU and ROW.

Figure 1 Study flow chart



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

Table 1 Study Planning and detailed schedule

Study period	**Screening Period**	**Lead-in period**	**Randomization**	**Treatment period**						**Follow-up period**	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	±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
Blood pressure and Heart Rate	X	X	X	X	X	X	X	X	X	X	5.1.6

Study period	Screening Period	Lead-in period	Randomization	Treatment period						Follow-up period	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	±0	±2	±5	±5	±5	±5	±5	±3	
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		4.4
Dispense Glucose Meter and Supplies/Provide Instructions		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	5.2.2
Dispensation of Study Medication		X	X				X				7
Drug accountability			X		X		X		X		7.6
Adverse event review (AEs and SAEs)	X[n]	X	X	X	X	X	X	X	X	X	6

Study period	Screening Period	Lead-in period	Randomization	Treatment period						Follow-up period	
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	For details see Protocol Section
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	±3	
Hypoglycaemic events		X	X	X	X	X	X	X	X	X	5.2.6.1
Blood samples for haematology and clinical chemistry	X[o]	X	X	X	X	X	X	X	X	X	5.2.2
CCI											
Urinalysis, dipstick		X	X	X	X	X	X	X	X	X	5.2.2
UACR, spot urine[r]	X		X		X	X	X	X	X	X	5.1.1

Study period	Screening Period	Lead-in period	Randomization	Treatment period						Follow-up period	
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	For details see Protocol Section
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	±3	
CCI [redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HbA1c	X		X		X	X	X	X	X	X	5.1.2
S-creatinine for eGFR calculation[t]	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		3.10.3
Fasting Serum Lipids (Total-C, LDL-C, HDL-C, TG, FFA)			X						X		5.1.12
CCI [redacted]			[redacted]						[redacted]		[redacted]

Study period	Screening Period	Lead-in period	Randomization	Treatment period						Follow-up period	
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	For details see Protocol Section
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	±3	
Arterial stiffness assessment[w]			X			X			X		
Parathyroid hormone (PTH)			X						X		5.2.2
Hepatitis Screen Panel		X									5.2.2

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 1The 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.

p) PK blood sample is collected in the morning before dosing of the study medication

C [redacted]

r) Urine Albumin-to-Creatinine ratio: At Visit 1, one spot urine sample from one morning void portion around or on the visit day, but for all other visits one spot urine sample from each of three separate morning void portions on days around the visit with one of the samples collected in the morning on the visit day.

C [redacted]

t) Please see formulas for eGFR calculation in section 4.1.1.4. 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.

C [redacted]

C [redacted]

w) Selected countries and sites only.

Screening Period (V1 to V2, 2 weeks)

All patients will provide informed consent prior to undergoing any study procedures. At Visit 1, patients will be screened for an HbA1c (HbA1c ≥7.0% and ≤11%), eGFR level (eGFR 20 – 80 mL/minute/1.73m^2) and micro or macroalbuminuria (UACR 30 – 3500 mg/g or 3.34-395.85 mg/mmol inclusive). Patients who meet these criteria will be enrolled and further examined for all inclusion and exclusion criteria.

Placebo Lead-in Period (V2-V3, 4 weeks)

At Visit 2 (start of lead-in visit), HbA1c and eGFR from Visit 1 will be evaluated, and a blood sample will be collected for qualifying eGFR. If the eGFR value (eGFR 25 – 75 mL/minute/1.73m^2) meets the inclusion criteria at Visits 1 or 2 and all other inclusion criteria are met 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 will be randomized to the 24-week double-blind placebo-controlled treatment period.

Summary scheme for inclusion based on HbA1c, eGFR and UACR is outlined in Table 2.

Table 2 Summary of the algorithm for inclusion based on HbA1c, UACR and eGFR

Visit	Algorithm
Samples obtained at Visit 1	HbA1c 7.0 - 11%, inclusive
	eGFR 20-80 mL/min/1.73 m^2, inclusive
	Single morning spot UACR 30-3500 mg/g, inclusive
Sample obtained at Visit 1 or Visit 2	eGFR 25-75 mL/min/1.73 m^2, inclusive

Double Blind Treatment Period (V3 to V9, 24 weeks)

Following completion of the lead-in phase, eligible patients will enter the 24-week double blind treatment phase. The dose of Oral Anti-diabetic Drugs (OADs), insulin, antihypertensive drugs, lipid lowering drugs and anti-platelet drugs should be kept constant throughout the entire 24-week treatment period.

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

Patients with lack of glycemic control during the 24-week treatment period may be eligible to receive open-label rescue medication in addition to their blinded treatment in order to treat ongoing hyperglycemia. Rescue medication refers to any approved, appropriate anti-diabetic agent, except SGLT2-inhibitors, GLP-1 agonists or DPP4 inhibitors.

Pre-specified glycemic criteria (see Table 3), 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 3 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)

Irrespective of study visit number, patients who meet rescue criteria in the treatment period must first complete the Week 24 visit procedures 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.

Follow-up Period (V9 to V10, 3 weeks)

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. In accordance with ITT principles all subjects that discontinue treatment will be strongly encouraged to remain in the study and undergo all scheduled clinical assessments through Visit 10 (Week 27).

The total planned study duration from Visit 1 to the safety follow-up (Visit 10) will be 33 weeks.

1.2.1 Treatment Assignment

The randomization codes will be computer generated by CCI [redacted] and loaded into the IVRS/IWRS database. Randomization codes will ensure approximate balance (1:1:1) between the three treatment arms (dapagliflozin

10 mg, dapagliflozin 10 mg + saxagliptin 2.5 mg or matching placebo, once daily) within each anti-diabetic medication stratum.

Randomization will be done via IVRS/IWRS at Visit 3. The IVRS/IWRS will allocate randomization codes centrally as patients become eligible for randomization.

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

1) Insulin-based regimen: Patients receiving insulin alone or in combination with any other anti-hyperglycemic medication.
2) Metformin-based regimen: Patients receiving metformin alone or in combination with any other anti-hyperglycemic medication except insulin.
3) Sulfonylurea (SU)-based regimen: Patients receiving a SU alone or in combination with any other anti-hyperglycemic medication except insulin and metformin.
4) Thiazolidinedione (TZD)-based regimen: Patients receiving a TZD alone or in combination with any other anti-hyperglycemic medication except insulin, metformin, or a SU
5) Other regimen: Patients receiving either any anti-hyperglycemic medication(s) not described by strata 1-4, or no background anti-hyperglycemic medication.

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

1.2.2 Blinding and Unblinding

1.2.2.1 Blinding

The investigator, AstraZeneca personnel, and patients will remain blinded to treatment allocation throughout the entire study period. The database used for the analysis of the double-blind data of the study will be locked after all patients have terminated the study. In order to protect the integrity of the treatment period of the study, the patients and investigators will not have access to the individual treatment assignments until the study has completed.

Unless otherwise specified, to maintain integrity of the study, HbA1c values and urinary glucose values will be blinded on laboratory reports to investigators for all visits except visit 1, visit 2 and visit 3. FPG value will be reported as an unblinded value throughout the study. During the whole study Hs-troponin will be blinded to Investigator.

Until the completion of the entire study, no member of the study team at AstraZeneca, at the investigational centres or any CRO handling data will have access to the randomisation scheme, with the exceptions of personnel generating the randomisation scheme as well as relevant persons at Pharmaceutical Development Supply Chain at AstraZeneca or their designee, where the information is needed to package study medication, the Patient Safety data entry site and the CRO companies providing the IVRS/IWRS and carrying out the packaging and labelling of investigational products. Patients and investigators will remain blinded throughout the study. The treatment codes and results will be kept strictly within CCI to safeguard the integrity of the blind of the investigators and patients, and hence to minimize any possible bias in data handling.

The exception is for those personnel analysing the PK data. The randomisation code will be provided to ensure that only samples from patients who were on the relevant active study treatment are analysed. The randomization list will be kept in a secure location until the end of the study, and pharmacokinetic data will not be transferred to the sponsor until the clinical database is locked.

1.2.2.2 Unblinding

Blinding is critical to the integrity of this clinical trial. However, in the event of a medical emergency, during which knowledge of the identity of the investigational product is critical to the patient's management, procedures are in place to have the blind broken for an individual patient. A separate procedure is in place for unblinding in case of expedited safety reporting to regulatory authorities.

Unmasked HbA1c, urinary glucose, CCI values will be transferred from the Central Lab to the external clinical database vendor between “Clean File” and “Database Lock”. Unblinding of treatment data will also occur in the clinical database after “Database Lock”. The unblinded clinical database will not be available to the study team until after database lock. The locked database will be unblinded for reporting purposes.

1.3 Sample size estimation

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 for saxagliptin/dapagliflozin treatment group versus placebo and dapagliflozin treatment group versus placebo at significance level of 0.025, using a two-sided alpha and assuming a standard deviation (SD) of 1.0% (see Table 4). 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 m^2 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 from baseline to 24 weeks in UACR 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 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. The active treatment groups will be compared to placebo in separate sequential testing in the order described in Section 1.1 which will be conducted in parallel to each other. In all analyses p-values will represent two-sided tests, and will be reported at the nominal level.

Table 4 Number of Patients

Total Enrolled Patients (per group)	1125 (375)	Assuming 60% screen failure rate
Total Randomized Patients (per group)	450 (150)	Assuming 5% is not evaluable
Total Number of Evaluable Patients (per group)	426 (142)	Number of patients with valid data needed to provide adequate power

2. ANALYSIS SETS

2.1 Definition of Analysis Sets

2.1.1 Enrolled Patients Set

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

2.1.2 Lead-in Patients Set

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

2.1.3 Randomized Analysis Set

All patients assigned a randomization code by the IVRS/IWRS system will be included in the analysis set.

The Randomized Analysis Set will be used in the summary of demographic baseline characteristics, and sensitivity analyses regardless of rescue and/or treatment discontinuation.

2.1.4 Full Analysis Set

The Full Analysis Set will consist of all randomized patients who take at least one dose of double-blind study drug during double-blind period and have a non-missing efficacy baseline value and at least one post-baseline value for any of the efficacy variables (i.e., HbA1c, UACR, weight, FPG or SBP).

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

2.1.5 Per Protocol Analysis Set

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

The PP Analysis set will only be applied if the PP Analysis set has a minimum of 10% fewer patients than the Full Analysis Set after the removal of complete exclusions due to important protocol deviations in dapagliflozin 10 mg, dapagliflozin 10 mg + saxagliptin 2.5 mg or matching placebo treatment group. In that case, only the primary efficacy endpoint of change from baseline in HbA1c and percent change from baseline in UACR will be analysed using the PP Analysis set. Demographics, and baseline diabetes characteristics will be summarized using the PP Analysis set if necessary.

2.1.6 Safety Analysis Set

The Safety Analysis Set will consist of all patients who received at least one dose of double-blind study drug during double-blind treatment period. The Safety Analysis 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 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.

2.1.7 PK Analysis Set

The PK Analysis Set will include all patients who received at least one dose of dapagliflozin 10 mg and saxagliptin 2.5 mg or dapagliflozin 10 mg, and have at least one reportable PK plasma concentration during the study.

2.2 Protocol Deviations

AstraZeneca uses ICH E3 terminology for protocol deviations, which are all important deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment.

2.2.1 Protocol Deviation Monitoring

During study conduct, protocol deviations will be closely monitored and identified from two sources:

- CCI monitoring – deviations will be automatically derived from the database via edit checks and must be reported as a protocol deviation in CCI by the Site Monitor. Some protocol deviations which do not have corresponding data checks must be manually checked in Rave and must be reported as a protocol deviation in CCI by the Site Monitor.

- Statistical programmed protocol deviation – These are deviations generated by execution of programs written using the predefined deviator descriptions in the SAP Appendix A.

The reports or information collected from CCI monitoring report will be reviewed and assessed periodically during study conduct by AZ/vendor study team and documented in EXCEL spreadsheet, with study id, patient id, PD collection date, PD free text term, PD coded term, PD source, major or minor criteria, and comments.

In the case of a discrepancy (e.g. statistical programming shows patient is 100% compliant with study drug but CCI monitoring report shows patient is non-compliant), the statistical programming from the clinical database will be considered as the definitive source.

A decision will be made prior to unblinding the study to determine which protocol deviations may significantly affect the study outcome and should be excluded completely or partially from the Per Protocol Analysis.

2.2.2 Protocol Deviation Reporting

The criteria for all major and minor protocol deviations will be provided in a separate protocol deviation document from the SAP. Protocol deviations that the study team considers to be important will be tabulated or listed in CSR.

Protocol deviations that may affect the study outcome significantly and the interpretability of the study results are defined as important protocol deviations (IPD). The criteria for important protocol deviations are given in Appendix A of the SAP.

Patients having IPD (Appendix A) will be summarized by treatment group and overall. Separate listings of all patients with important protocol deviations will also be produced.

The details of instruction of programming for IPD would be described in a separate document from the SAP.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Primary Efficacy Variables

The primary outcome variables are:

1. Change from baseline in HbA1c (%) (dapagliflozin 10 mg plus saxagliptin 2.5 mg versus placebo only) at Week 24.

2. Percent change from baseline in UACR (mg/g) at Week 24.

3.2 Secondary, Safety and Exploratory Variables

3.2.1 Secondary Efficacy Variables

Secondary outcome variables are:

1. Percent change from baseline in body weight (kg) at Week 24.

2. Change from baseline in FPG (mg/dL) at Week 24.

3. ≥30% reduction in UACR at Week 24.

4. HbA1c < 7.0 % at Week 24.

5. Change from baseline in seated SBP (mmHg) at Week 24.

6. Change from baseline in HbA1c (%) at Week 24 (dapagliflozin 10 mg versus placebo only)

3.2.2 Safety Variables

Safety outcome variables are:

- Incidence of AEs (including SAEs, Hypoglycemic AEs, other significant AEs, AEs of interest, deaths, adjudicated Diabetic ketoacidosis (DKA) AEs and Hepatic AEs).
- Treatment discontinuation for a sustained increase in serum creatinine by ≥1.5 times baseline level (AKI stage 1).
- Changes from baseline in vital signs (including measured orthostatic reactions).
- Changes from baseline in clinical chemistry/haematology/urinalysis parameters.
- Changes from baseline in the findings from physical examination at the end of the double-blind treatment.
- Change from baseline in eGFR at Week 24.
- Change from baseline in eGFR at Week 27.

3.2.3 Exploratory Efficacy Variables

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- [redacted]
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- [redacted]
- CCI [redacted]
- [redacted]
- [redacted]

CCI

[redacted]

4. ANALYSIS METHODS

The primary analysis of the change in HbA1c from baseline to Week 24 will be based on a mixed model repeated measures (MMRM) analysis using the FAS, and will include all available data at scheduled time points following randomization up to and including Week 24. Analyses for HbA1c will only include measurements on or prior to the administration of rescue medication or treatment discontinuation, (whichever occurs first). Measurements of

HbA1c made following rescue administration or treatment discontinuation will not be included in primary and secondary efficacy analyses, but will be included in sensitivity analysis regardless of rescue and/or treatment discontinuation.

The primary analysis of percent change from baseline in UACR to Week 24 will be conducted on the change from baseline in log-transformed UACR values [$\log_e$(post) - $\log_e$(pre)] using the FAS, and will also include all available data at scheduled time points following randomization up to and including Week 24 using MMRM. MMRM represents a longitudinal repeated measures analysis using a 'direct likelihood' method. Analyses for UACR will only include measurements on or prior to the treatment discontinuation. Measurements of UACR made following IP discontinuation will not be included in primary and secondary efficacy analyses, but will be included in sensitivity analysis regardless of rescue and/or treatment discontinuation.

An additional analysis to support primary analysis will be repeated with the 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) on the Per Protocol Analysis Set. The sensitivity analysis in the Per Protocol Analysis Set will be applied to primary efficacy endpoints only if there is more than 10% difference in the number of patients in any treatment group from the corresponding number in the Full Analysis Set.
Additional sensitivity analyses (including Multiple Imputation based on Retrieved Dropouts (MI-RD), Washout Imputation and the Tipping Point imputation) will be performed to address the impact of missing data, treatment discontinuation or initiation of rescue.

The effect of multiplicity on the Type 1 error due to the multiple comparisons of two active treatment groups with a common placebo group will be controlled by a Bonferroni adjustment, see section 4.3.

4.1 General principles

CCI [redacted] will be used in all analyses. The primary analysis for the change in HbA1c, percent change in UACR from baseline to Week 24 will be based on longitudinal repeated measures analysis (Section 4.1.2 of the SAP). An unstructured matrix for the within-subject error variance covariance will be used. The denominator degrees of freedom will be calculated according to the Kenward-Roger method.

In case of non-convergence of the preferred model or memory space issues the following back-up models are defined:

- The first backup model is the same as the preferred model but the Kenward- Roger method will be replaced by Satterthwaite approximation.
- The second backup model is the same as the preferred model but without the term for baseline measurement-by-week interaction.

The second back-up model will only be provided if the first back-up model does not converge or has memory issues.

The model will provide least-squares mean estimates, standard errors and 2-sided 95% confidence intervals for mean change at all time points within and between treatments.

All statistical comparisons of primary and secondary efficacy variables will be based on separate 2-sided sequential test procedures (for the dapagliflozin/saxagliptin versus placebo; and dapagliflozin versus placebo) with an alpha level of significance of 0.025 required to infer statistical significance, unless otherwise specified. All analyses will report nominal p-values. No other correction to the reported p-values will be made for the analysis of secondary measures. Where appropriate, interval estimates at a nominal 95% level of confidence will be presented.

Descriptive statistics for continuous data will include n, mean, median, standard deviation, minimum and maximum value. Descriptive data for categorical data will include n, frequency, and percentage.

Efficacy analyses will be based on the Full Analysis Set except the sensitivity analysis which will be based on the Per Protocol Analysis Set and/or Randomized Analysis Set as described in section 4.4.6.3. The Safety Analysis Set will be used for analysis of all safety and tolerability variables.

An additional analysis to support primary analysis will be repeated with the primary variable (change from baseline in HbA1c, percent change from baseline in UACR, MMRM) at week 24 on the per-protocol analysis set. The sensitivity analysis in the Per Protocol Set will be applied to primary efficacy endpoints only if there is more than 10% difference in the number of patients in any treatment group from the corresponding number in the Full Analysis Set.

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[redacted]

4.1.1 Definition of Study Variables

Individual listings should contain both day of randomization as well as day of first dose. Safety assessments will be performed at regular intervals and will include physical examination, vital signs (including measured orthostatic reactions), renal function (change in eGFR), safety laboratory test (clinical chemistry, haematology and urinalysis), SAEs, Hypoglycemic AEs, other significant AEs, AEs of interest, deaths, adjudicated diabetic

ketoacidosis (DKA) AEs, Hepatic AEs and treatment discontinuation for a sustained increase in serum creatinine by ≥1.5 times baseline level (AKI stage 1).

4.1.1.1 Baseline Values

For most efficacy variables, the baseline value will be the last non-missing value on or prior to the date of the first dose of double-blind study medication.

The protocol specifies that except screening (Visit 1), at all other visits one spot urine sample is to be collected from each of three separate first morning void on days around the visit with one of the samples collected in the morning on the visit day. Accordingly, in the statistical analysis, the baseline value for Urine Creatinine, Urine Albumin and UACR will be the average of the three available non-missing measurements on or prior to the date of the first dose of double-blind study medication. Specifically, the average will be derived based on the samples grouped by the visit date, regardless of the number of samples associated with a visit date. Note there could be fewer or more than three samples associated with a visit date. If there are more than one sample collected on the same date, the earliest sample will contribute to the average. If there are more than one sample collected on the same time at the earliest of the day, all samples will contribute to the average. The last average value available for a visit day on or prior to the date of the first dose of double-blind study medication will be considered as baseline. The urine sample(s) at screening (Visit 1) will not be included in the baseline average.

The baseline value of each safety laboratory test or physical exam endpoint is defined as the last assessment (either numerical or character value) on or prior to the date of the first dose of double-blind study medication, with exception of systolic blood pressure, diastolic blood pressure and heart rate for which the average of the last three SBP, DBP and pulse assessments collected prior to the administration of double-blind medication will be used.

4.1.1.2 Change and Percent Change from Baseline

Change from baseline to any randomized treatment period Week t is defined as follows:

$$Change = \ Measurement\ at\ Week\ t\ - Baseline$$

Percent change from baseline to any randomized treatment period Week t is defined as follows:

$$Percent\ change = \frac{Measurement\ at\ Week\ t\ - Baseline}{\text{Baseline}} \times 100$$

4.1.1.3 Derivation of Efficacy Variable at Rescue/Premature Treatment Discontinuation

In efficacy analyses, for premature treatment discontinuation, details refer to section 4.5.2.

For rescue, the below glycemic parameters will only include measurements obtained prior to or on the date of rescue medication administration. An exception would be sensitivity

analysis, where the analysis is performed on data regardless of rescue or IP discontinuation (see Section 4.4.7). For all the below endpoints, analysis will be performed excluding assessments collected post-rescue or treatment discontinuation, whichever occurs first:

a) Change from baseline in HbA1c (%).

b) Change from baseline in FPG (mg/dL).

c) Proportion of patients with HbA1c <7 % (LOCF)

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For all other efficacy variables, measurements after rescue medication will not be excluded from the analyses. Patients rescued or not completing the treatment period should have all Week 24 visit procedures done at the time of IP discontinuation or rescue.

4.1.1.4 eGFR

eGFR by MDRD will be calculated for Japanese and Taiwanese patients using nationality-specific MDRD equations, and that for all other nationalities the general MDRD equation will be used. eGFR is calculated according to the following formulas:

The general MDRD formula:

> eGFR (ml/min/1.73m^2) = 175 x (standardized sCr)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if Black) [Note: sCr reported in in mg/dL]

The MDRD formula for Japanese subgroup:

> eGFR (ml/min/1.73m^2) = 194 x (standardized sCr)$^{-1.094}$ x (Age)$^{-0.287}$ x (0.739 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:

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

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.

The protocol-specified assessment of eGFR at Screening, start of placebo Lead-in, Day 1, Week 24 and Week 27 will be calculated by the central lab. The Sponsor will calculate eGFR for Weeks 1, 4, 8, 12, 16 in order to characterize the eGFR change over time. These additional eGFR values will be derived programmatically, outside the data provided by the central lab.

4.1.2 Longitudinal Repeated Measures Analysis

4.1.2.1 Longitudinal Repeated Measures Analysis for Change from Baseline

For changes from baseline to Week 24 in all continuous efficacy parameters (e.g. HbA1c, FPG, seated SBP, and body weight etc.) CCI [redacted], analyses will be based on a longitudinal repeated measures analysis using "direct likelihood". CCI [redacted]. The preferred model for this analysis will include the fixed categorical effects of treatment, week, randomization stratification factor (i.e. anti-diabetic treatment strata), and treatment-by-week interaction, as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction. A common model will be used in analysis that includes change from baseline values for the dapagliflozin 10 mg plus saxagliptin 2.5 mg group, the dapagliflozin 10 mg group, and the placebo group.

The mixed model will provide least-squares mean estimates, standard errors and 2-sided 95% confidence intervals within each treatment group. The differences in least-squares means, 2-sided 95% confidence intervals and p-value of the differences in week 24 visit estimates between each active treatment group and placebo will be presented as well.

4.1.2.2 Longitudinal Repeated Measures Analysis for Percent change from Baseline

Unless otherwise specified, for all percent changes from baseline to Week 24 in efficacy parameters (e.g. percent change from baseline UACR, percent change from baseline in body weight (kg)), analyses will use the longitudinal repeated measures analysis; the difference between the natural logarithmically transformed post-treatment and baseline values [$\log_e$(post) – $\log_e$(baseline)] will serve as the continuous response variable for each model. A common model will be used in analysis that includes log-change from baseline values for the dapagliflozin 10 mg plus saxagliptin 2.5 mg group, the dapagliflozin 10 mg group, and the placebo group.

For percent change from baseline in efficacy parameters (UACR, body weight (kg)), the analysis model will include the fixed categorical effects of treatment, week, randomization stratification factor (i.e. anti-diabetic treatment strata), and treatment-by-week interaction, as

well as the continuous fixed covariates of $\log_e$(baseline) and $\log_e$(baseline)-by-week interaction.

Exponentiation of estimates based on differences on a natural logarithmic scale will be performed prior to reporting, and geometric values (e.g., estimates, standard errors, differences and standard errors, and 95% confidence limits) will be converted to percentages prior to reporting, and reported on a percentage scale. See Table 5 for more details.

Table 5 Formulae Used to Transform Back the Results from ANCOVA Model or Longitudinal Model onto the Original Scale

Quantity	***Computation method***
Geometric mean of the Week *t* to baseline ratio	exp(mean change from baseline in natural logarithm)
Mean percent change from baseline	100 × [exp(mean change from baseline in natural logarithm) – 1]
Standard error of mean percent change from baseline	100 × exp(mean change from baseline in natural logarithm) × standard error of mean change from baseline in natural logarithm – or, equivalently – 100 × Geometric mean of the Week *t* to baseline ratio × standard error of mean change from baseline in natural logarithm
Lower confidence limit for mean percent change from baseline	100 × [exp(lower confidence limit for mean change from baseline in natural logarithm) – 1]
Upper confidence limit for mean percent change from baseline	100 × [exp(upper confidence limit for mean change from baseline in natural logarithm) – 1]
Adjusted geometric mean of the Week *t* to baseline ratio	exp(Adjusted mean change from baseline in natural logarithm)
Adjusted mean percent change from baseline	100 × [exp(Adjusted mean change from baseline in natural logarithm) – 1]
Standard error of adjusted mean percent change from baseline	100 × exp(Adjusted mean change from baseline in natural logarithm) × standard error of mean change from baseline in natural logarithm – or, equivalently – 100 × adjusted geometric mean of the Week *t* to baseline ratio × standard error of mean change from baseline in natural logarithm
Lower confidence limit for adjusted mean percent change from baseline	100 × [exp(lower confidence limit for adjusted mean change from baseline in natural logarithm) – 1]
Upper confidence limit for adjusted mean percent change from baseline	100 × [exp(upper confidence limit for adjusted mean change from baseline in natural logarithm) – 1]

Quantity	*Computation method*
Adjusted geometric mean of the Week t to baseline ratio achieved with each dapagliflozin treatment arm relative to that achieved with Control, expressed as a percent difference. Please note that for the SAS output, a shorter text will be used: Adjusted GM of Week t/Baseline for each dapagliflozin treatment arm relative to Control, in % difference.	100 × (((adjusted mean percent change for dapagliflozin treatment arm +100)/(adjusted mean percent change for Control +100)) – 1) – or, equivalently – 100 × (exp(difference in adjusted mean change from baseline between dapagliflozin treatment arm and Control in natural logarithm) – 1)

4.1.3 Analysis of Covariance

4.1.3.1 ANCOVA Model for Change from Baseline

Unless otherwise specified, when an analysis of covariance (ANCOVA) model is used to analyse a continuous variable (e.g. 24-hour urine glucose etc.), the model will represent the change from baseline to Week 24 (LOCF) and will include the fixed main effects of treatment group, anti-diabetic treatment strata at randomization, and the baseline measurement as a covariate. A common model will be used in analysis that includes change from baseline values for the dapagliflozin 10 mg plus saxagliptin 2.5 mg group, the dapagliflozin 10 mg group, and the placebo group.

The ANCOVA will present least squares (LS) mean estimates and 2-sided 95% confidence intervals (CIs) for mean changes from baseline within and between treatments.

4.1.3.2 ANCOVA Model for Percent Change from Baseline

Unless otherwise specified, for analyses of parameters in terms of percent change from baseline at Week t (e.g. percent change from baseline in lipid parameters), ANCOVA analysis will be performed on the difference between natural logarithmically transformed value at the end of treatment and at baseline [$\log_e$(post) – $\log_e$(baseline)], and will include fixed terms for treatment and anti-diabetic treatment strata at randomization, and the log-transformed baseline value as a covariate. A common model will be used in analysis that includes log-change from baseline values for the dapagliflozin 10 mg plus saxagliptin 2.5 mg group, the dapagliflozin 10 mg group, and the placebo group.

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Least squares estimates and differences and the corresponding 95% confidence intervals obtained from the model output will be used to generate estimates of (geometric) mean percent change. Where applicable, the t-statistic corresponding to the Type III sums of squares for the differences in the least squares means will be used to obtain p-values for treatment group comparisons. CCI [redacted]

Table 5 details the formulae that will be used to transform back the results from the ANCOVA model to obtain the values reported in the tables.

4.1.4 Handling of Dropouts or Missing Data for Efficacy Analyses

The primary estimand will be the treatment difference at Week 24 if all subjects had remained in the trial and received treatment as planned, and prior to rescue medication for HbA1c. In order to address the impact of missing data, initiation of rescue therapy, and premature treatment discontinuation on the primary efficacy analysis, the analysis of the primary efficacy endpoints UACR and HbA1c will be repeated in ITT estimand sensitivity analyses.

For the assessment of efficacy, interpretation of results in the presence of missing data depends on the missing data mechanism assumptions as well as on the use of data collected after initiation of rescue therapy or premature study treatment discontinuation in the analysis. In this study, the primary efficacy analysis is performed using an MMRM which assumes MAR, and based on data collected up to initiation of rescue (for HbA1c and other glycemic related variables see section 4.1.3 for details) or premature study treatment discontinuation, whichever occurs first.

Three additional methods of sensitivity analyses will be performed. These are Multiple Imputation based on Retrieved Dropouts (MI-RD), Washout Imputation, and Tipping Point Analysis based on Randomized Set.

In multiple imputation a common (fixed) seed value CCI [redacted], and 1000 simulations will be performed. The detailed analysis plan and implementation of these methods are described in Sections 4.1.4.2., 4.1.4.3 and 4.1.4.4 to, respectively.

To address the impact of missing data on primary efficacy analysis, the amount of missing data, the distribution of missing data among treatment groups, and the reasons for missing data will be examined. The proportion of patients with missing HbA1c and UACR assessments will be summarized by treatment group, scheduled time point during the double-blind treatment period, and categories of missing causes if applicable. In addition, spaghetti plots of mean UACR and HbA1c profiles over time will be provided for each treatment to assess the patterns of missing UACR and HbA1c assessments, with patients grouped according to the time of the last assessment prior to rescue or treatment discontinuation.

4.1.4.1 Last Observation Carried Forward (LOCF)

Unless otherwise specified, when an analysis of covariance (ANCOVA) model is used to analyse a continuous variable, analyses will be based on measurements at the time point Week 24. If no measurement is available at that time point Week 24, the last available post-baseline measurement will be carried forward (LOCF). For patients who started rescue medication prior to Week 24, their last post-baseline measurement taken prior to or on the date of the first dose of rescue medication will be used, if applicable

4.1.4.2 Multiple Imputation based on Retrieved Drop-outs (MI-RD)

In MI-RD, all patients in the randomized set who have a baseline assessment (regardless of rescue or treatment discontinuation) will be included in the analysis. Based on status of whether the patients have early treatment discontinuation and whether the assessment is available at Week 24, the population will be categorized as 4 subpopulations within each treatment group as described in.
Table 6

The main steps of the implementation of MI-RD are described below.

Step 1: Impute missing data for patients without HbA1c at Week 24 using a regression model imputation based on data from patients who discontinued treatment but had HbA1c assessment at Week 24 within that treatment group. The HbA1c baseline will be used as explanatory variable for imputation. If, for each (protocol-defined) visit where there is at least 1 patient with a last on-treatment assessment and is missing a Week 24 HbA1c value, there are (at that same visit) sufficient numbers of patients with a last on-treatment assessment that subsequently discontinued treatment but have a Week 24 HbA1c value, then the missing Week 24 HbA1c values will be imputed from the non-missing Week 24 HbA1c values within each treatment group. Otherwise, if there are sufficient numbers of patients that discontinued treatment but have a Week 24 HbA1c value (regardless of last protocol-defined visit "on-treatment") then missing Week 24 HbA1c values will be imputed from the patients that have discontinued treatment but have Week 24 HbA1c values within each treatment group. The imputation population and process are described in.
Table 6 Imputation will be done within each treatment group.

Step 2: Analyse the multiple imputed HbA1c change from baseline at Week 24 using ANCOVA model. Combine estimates obtained from multiple imputed datasets based on Rubin's combination rules (Little R., Rubin D.B. 2002).

The sensitivity analysis as described in steps 1 and 2 will be performed similarly for UACR endpoint.

The MI-RD approach requires a sufficient number of patients who discontinued treatment but had HbA1c assessment at Week 24 in each treatment. If there is not a sufficient number of patients to do the analysis, then this approach will not be implemented.

Table 6 Patterns for Imputation of Missing UACR/HbA1c data at Week 24 with the MI-RD approach

Subpopulations (patterns) considered in the imputation process	Imputation at Week 24
Subpopulation 1: Patients who were on treatment (and prior to rescue for HbA1c) with UACR/HbA1c at Week 24.	No action
Subpopulation 2: Patients who discontinued treatment (or post-rescue for HbA1c) by Week 24 but had UACR/HbA1c assessments at Week 24.	No action
Subpopulation 3: Patients who discontinued treatment (or post-rescue for HbA1c) by Week 24 without UACR/HbA1c assessments at Week 24.	Use data from Subpopulation 2 patients to estimate imputation model within each treatment group.
Subpopulation 4: Patients who did not discontinue treatment prematurely (or prior to rescue for HbA1c) but without UACR/HbA1c assessments at Week 24 (patients lost to follow-up).	Use data from Subpopulation 2 patients to estimate imputation model within each treatment group.

4.1.4.3 Washout Imputation

In washout-imputation, all patients in the randomized set who have a baseline assessment (regardless of rescue or treatment discontinuation) will be included in the analysis. This imputation method will only impute missing HbA1c values at Week 24 for the active treatment using multiple imputation regression with randomization strata and baseline HbA1c as the predictors. Missing Week 24 HbA1c values will be imputed from the non-missing Week 24 HbA1c values within the placebo group. This approach ignores any earlier post-baseline changes in the HbA1c values when predicting missing Week 24 values and will impute all patients similar to an average placebo patient. ANCOVA will be used as the analysis method.

The main steps of the implementation of the washout imputation are described below.

Step 1: Impute Week 24 missing data for patients in the active treatment using regression model multiple imputation based on data from the placebo arm. For patients in placebo arm missing data at any time point will be imputed assuming MAR mechanism. The variables used as explanatory variables for imputation include Randomization strata and baseline.

Step 2: Analyse the multiple imputed data at Week 24 using ANCOVA model. Combine estimates obtained from multiple imputed datasets based on Rubin's combination rules (Little R., Rubin D.B. 2002).

The sensitivity analysis as described in steps 1 and 2 will be performed similarly for UACR endpoint.

4.1.4.4 Tipping Point Analysis

The specific MNAR assumption that will be considered in this framework is that patients from the experimental treatment arm who discontinue study treatment prematurely or who initiate a rescue therapy would have, on average, their efficacy values post-rescue/post-treatment discontinuation worse by some amount delta compared to efficacy values of similar patients who continue with the study treatment and do not require rescue therapy. Delta is considered a sensitivity parameter representing a degree of departure from the MAR assumption. The aim of the Tipping Point Analysis is to find a "tipping point" corresponding to a value of delta where the study conclusion of a non-inferior treatment effect would no longer hold. An interpretation of clinical plausibility of the assumption underlying the tipping point will be provided.

The tipping point approach based on multiple imputation of values at time points after treatment discontinuation or initiation of rescue can be performed with a specified adjustment (referred to as delta adjustment or shift) applied to values imputed under an MAR-based imputation model for the appropriate subset of patients. In order to find a tipping point, a series of imputations will be performed with increasing values of delta.

For the HbA1c co-primary endpoint which is a continuous variable, an additive delta adjustment (a shift) will be used as follows:

$$Y_{i(adj)}^{(m)} = Y_{i(imp)}^{(m)} + \delta,$$

whereas for the UACR co-primary endpoint which is a continuous variable analysed the natural logarithmic scale, a multiplicative delta adjustment (a shift) will be used as follows:

$$\log[Y_{i(adj)}^{(m)}] = \log[Y_{i(imp)}^{(m)}] + \log[1+\delta],$$

where:

- $Y_{i(imp)}^{(m)}$ are values imputed using a MAR-based imputation model in the m^{th} imputed dataset, m=1,…,M (number of imputations)
- δ is a mean shift (delta adjustment) parameter for adjusting imputed values

The main steps in the implementation of the Tipping Point Analysis are described below.

Step 1: Investigate missing data patterns in the source data (containing observed values prior to initiation of rescue therapy or premature study treatment discontinuation). If missing data have both monotone and non-monotone patterns, use a multivariate regression imputation model and the Markov chain Monte Carlo (MCMC) method to partially impute non-monotone data under the MAR assumption. The variables used as explanatory variables for imputation include treatment, randomization strata, baseline, and post-baseline results at each time point.

As a result, each imputed dataset will only have a monotone missing data pattern.

Step 2: Impute remaining monotone missing data using an MAR-based regression imputation model for all patients who discontinued study treatment prematurely or initiated a rescue therapy. Apply a shift (an additive delta adjustment) to imputed values of patients in the experimental treatment arms. The variables used as explanatory variables for imputation include treatment, randomization strata, baseline, and post-baseline results at each time point. Separate tipping point analyses will be performed for each active treatment, with the delta adjustment restricted to the active arm being evaluated in the analysis.

Imputations with delta adjustment described above will be performed with varying values of delta in order to perform a series of analyses with progressively larger values of delta until a tipping point is reached. A tipping point will correspond to the smallest value of delta for which the primary hypothesis (non-inferiority) is no longer hold.

Step 3: At each level of delta, analyse each of multiple imputed datasets using an ANCOVA model used for the LOCF analyses. Combine estimates obtained from multiple imputed datasets based on Rubin's combination rules.

Step 4: Using 95% upper CI, find the tipping point, ie, the value of delta parameter for which the primary non-inferiority hypothesis is no longer held.

Separate tipping point analyses will be performed for HbA1c and UACR. Similar analyses following Steps 1 through 4 will be performed for HbA1c and UACR using the Randomized Analysis Set which includes data following rescue or treatment discontinuation.

4.1.5 Summaries of Continuous Endpoints

Descriptive statistics will be used to present efficacy and safety variables. For continuous variables, n, mean, standard deviation (or standard error), median, minimum, and maximum will be presented by visit when applicable. For demographic, baseline, disease, renal characteristics, and study treatment exposure and compliance descriptive summaries will also include 25th and 75 percentiles (first and third quartiles).

The changes from baseline will be summarized for relevant efficacy and safety (e.g., eGFR) parameters and will include 95% CIs for means. The percent changes from baseline will be summarized for selected lab parameters and will include 95% CIs for means.

4.1.6 Proportion of Patients with Pre-defined Characteristics

Secondary (30% reduction in UACR and HbA1c <7%) and exploratory analyses of variables that represent the proportions of subjects *with a pre-defined characteristic* at Week 24 LOCF will be analysed using the logistic regression model when there are at least 5 responders on average by treatment group. For proportion of responders (eg, meeting HbA1c/UACR criteria), estimates, confidence intervals, and tests will be obtained using logistic regression model with adjustment for baseline variable(s) and pooled randomization strata (as needed) to accommodate composite endpoints (eg, adjustment for baseline HbA1c/UACR and pooled

randomization strata, baseline SBP and pooled randomization strata, etc.). A common model will be used in analysis that includes pre-defined characteristics for the dapagliflozin 10 mg plus saxagliptin 2.5 mg group, the dapagliflozin 10 mg group, and the placebo group.

For proportional analysis using the logistic regression model (as needed), the pooled randomization strata will be used as the adjustment factor. If required, patients with randomization strata in (Metformin-based regimen, SU-based regimen, TZD-based regimen, and Other regimen will be pooled together as in one strata group called as "oral antidiabetic medications".

The difference in response rate for the dapagliflozin 10 mg plus saxagliptin 2.5 mg versus placebo, and (separately) dapagliflozin versus placebo will be displayed along with standard error and the 95% confidence intervals. P-values will be calculated if applicable. Raw proportions will also be displayed by treatment group. When there are less than 5 responders on average by treatment group, the unadjusted (and difference) proportions, exact 95% confidence interval, and p-values from the Fisher's exact test (when applicable) will be provided. Although p-values will be generated for exploratory endpoints, statistical significance will not be inferred and claims will not be made.

4.1.7 Summaries of Shifts from Baseline in Categorical Variables

Changes from baseline in certain categorical variables will be summarized using shift tables. Frequencies and percentages of patients within each treatment group will be generated for levels of cross-classifications of baseline and the on-treatment value of the variable. The on-treatment value can be either the value at a certain time point, (for example, laboratory tests) or the minimum/maximum value in the direction of toxicity, which has been observed during a study period. Treatment group differences will not be assessed in summaries of shifts.

4.1.8 Kaplan-Meier Curve and Estimates for Time-To-Event Analyses

Kaplan-Meier plots (Kaplan EL and Meier P 1958) will be used to generate product-limit estimates of probabilities for the freedom from rescue at each time rescue occurs by treatment for the 24-week double-blind period. Survival curves representing the proportions of patients who were not rescued will be displayed by treatment group in a survival plot. The last rescue will be carried-forward to Week 24.

Additionally, a summary table will accompany the plot and will display the Kaplan-Meier estimates of the cumulative proportion (with 95% CI calculated based on Greenwood's method when applicable (Greenwood M 1926)) of patients with event at specific time points by treatment group. If the estimated lower bound of 95% CI is below 0 or the estimated upper bound of 95% CI is over 1, then it will be restricted to 0 or 1 respectively. Unless otherwise specified, the plot will be presented only when there are at least 5 events in one treatment group.

A summary table of the cumulative proportion of patients at each treatment visit during the double blind treatment period up to Week 24 will be produced for all patients who were

rescued for failing to maintain adequate glycemic control during this period. This summary table will also display the cumulative proportion of these rescued patients who also had an increase in insulin dose of >10%.

4.2 Hypotheses

Unless otherwise indicated, the following hypotheses refer to alternative hypotheses. For tests of superiority, null hypotheses presuppose no difference between the treatment groups with respect to the parameter of interest.

4.2.1 Primary objective and hypotheses

The primary objective of this study is to evaluate the efficacy of dapagliflozin 10 mg plus saxagliptin 2.5 mg versus placebo and dapagliflozin 10 mg versus placebo in the treatment of CKD patients with type 2 diabetes mellitus and albuminuria treated with ACEi or ARB. The primary hypotheses are as follows:

- Dapagliflozin 10 mg plus saxagliptin 2.5 mg per day is superior to placebo in improving (reducing) the mean HbA1c from baseline to Week 24
- Dapagliflozin 10 mg plus saxagliptin 2.5 mg per day is superior to placebo in improving (reducing) the mean percent change from baseline in UACR to Week 24
- Dapagliflozin 10 mg per day is superior to placebo in improving (reducing) the mean percent change from baseline in UACR to Week 24

4.2.2 Secondary efficacy objectives and hypotheses

In order to evaluate the efficacy of dapagliflozin 10 mg plus saxagliptin 2.5 mg versus placebo and, separately, dapagliflozin 10 mg versus placebo in the treatment of CKD patients with type 2 diabetes mellitus and albuminuria treated with ACEi or ARB, the hypotheses will be tested sequentially as described in Section 4.3. The secondary hypotheses are as follows:

- Dapagliflozin (10 mg and, separately, 10 mg plus saxagliptin 2.5 mg) per day is superior to placebo in reducing the mean percent change from baseline in total body weight at Week 24
- Dapagliflozin (10 mg and, separately, 10 mg plus saxagliptin 2.5 mg) per day is superior to placebo in reducing the mean change from baseline in FPG at Week 24
- Dapagliflozin (10 mg and, separately, 10 mg plus saxagliptin 2.5 mg) per day is superior to placebo in the proportion of patients achieving ≥ 30% reduction in UACR at Week 24
- Dapagliflozin (10 mg and, separately, 10 mg plus saxagliptin 2.5 mg) per day is superior to placebo in the proportion of patients achieving a reduction in HbA1c <7.0% at Week 24

- Dapagliflozin (10 mg and, separately, 10 mg plus saxagliptin 2.5 mg) per day is superior to placebo in reducing the mean change from baseline in seated SBP at Week 24

- Dapagliflozin 10 mg per day is superior to placebo in reducing the mean HbA1c (%) from baseline to Week 24

4.3 Multiple testing procedure (MTP)

In order to account for the testing of dapagliflozin 10 mg plus saxagliptin 2.5 mg versus placebo, and dapagliflozin 10 mg versus placebo for the single primary (dapagliflozin 10 mg) or two co-primary (dapagliflozin 10 mg plus saxagliptin 2.5 mg) endpoints, a Bonferroni procedure for groups of hypotheses will be applied.

Type 1 error will be maintained at a two-sided 0.05 level using in inferential testing using the Bonferroni method to control for multiplicity. According to a Bonferroni adjustment, such that statistical significance will be determined according to a two-side 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 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 in the order specified in Section 1.1.2. Within the dapagliflozin 10 mg treatment group the control of the alpha level for the primary endpoint (the percent change in 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 in the order specified in Section 1.1.2. Parallel sequential testing strategies following the prescribed unique order for each set of secondary comparisons specified in Section 1.1.2 will be used for comparing each active treatment group to placebo for the secondary endpoints, and the separate statistical comparisons of each active treatment to placebo will each require (a two-sided) alpha level of 0.025 in order to claim superiority to placebo.

4.4 Analysis methods

4.4.1 Patient Disposition

All patients enrolled (who signed informed consent) will be summarized. The disposition of patients for the lead-in period, the double-blind treatment period and the whole study which include follow-up period will be summarized.

The summary of status in the lead-in period will include all patients receiving at least one dose of study drug (placebo) during the lead-in period. The summary of status in the double-blind treatment period will include all patients in Randomized Data Set. The number and percent of patients who entered, completed and discontinued, with the reasons for discontinuation will be summarized for each period (lead-in, double-blind treatment and the whole study which includes follow-up period). Summaries of double-blind and the whole study which includes follow-up period will be made by treatment group and overall.

A listing of patients who discontinued from the lead-in period and from the double-blind treatment period will be provided.

Patients enrolled, entered lead-in, randomized, and treated will be summarized by country and study site. Randomized treatment assignment will be summarized by country and study site.

4.4.2 Demographic and Baseline Characteristic Variables

Demographic and other baseline characteristics, including diabetes-related characteristics and renal function characteristics will be summarized by treatment group and overall, using the All Randomized Set.

Demographic and baseline characteristics are listed in Table 7. Diabetes related baseline characteristics are listed in Table 8. Renal function characteristics will be summarized based on the assessment corresponding to the qualifying eGFR value at enrolment and, separately, at baseline. The qualifying eGFR value will be the first eGFR at Visit 1 or Visit 2 that met the criterion for randomization (eGFR 25 - 75 mL/min/1.73 m^2). The UACR value at the qualifying visit will correspond to Visit 1 and be summarized in the Enrolment Renal Characteristics summary as well. Renal function characteristics are listed in Table 9.

Table 7 Demographic and baseline characteristics

Characteristic	Summarized as	Categories
Gender	Categorical	Male, Female
Age	Categorical and Continuous	< 65 yrs ≥ 65 yrs
Female Age	Categorical	≤ 50 yrs > 50 yrs
Race	Categorical	White Black or African American Asian Native Hawaiian or Other Pacific Islander American Indian or Alaska Native Other
Ethnicity	Categorical	Hispanic or Latino Not Hispanic or Latino
Body weight	Continuous	--
Waist Circumference	Continuous	--

Characteristic	Summarized as	Categories
Body Mass Index	Categorical and Continuous	< 25 kg/m^2 ≥ 25 kg/m^2 ≥ 27 kg/m^2 ≥ 30 kg/m^2
Geographic Region	Categorical	As defined in Appendix B

Table 8 Diabetes-Related Baseline Characteristics

Characteristic	Summarized as	Categories
Duration of type 2 diabetes	Categorical and Continuous	< 3 yrs ≥ 3 and ≤ 10 yrs > 10 yrs
HbA1c	Categorical and Continuous	<8% ≥8-<9% ≥9-<10% ≥10%
HbA1c	Categorical and Continuous	
FPG	Categorical and Continuous	<110 mg/dL ≥110 - <150 mg/dL ≥150 - <200 mg/dL ≥200 - <240 mg/dL ≥240 - <300 mg/dL ≥300 mg/dL
pre-enrolment anti-hyperglycemic therapy	Categorical	Insulin-based regimen SU-based regimen TZD-based regimen Metformin-based regimen other regimen

Table 9 Baseline and Enrolment Renal Function Characteristics

Characteristic	Summarized as	Categories
eGFR at Enrolment	Categorical and Continuous	< 25 mL/min/1.73 m^2 ≥ 25 and ≤ 75 mL/min/1.73 m^2 > 75 mL/min/1.73 m^2

Characteristic	Summarized as	Categories
eGFR at Baseline	Categorical and Continuous	< 30 mL/min/1.73 m^2 ≥ 30 and <45 mL/min/1.73 m^2 ≥ 45 and <60 mL/min/1.73 m^2 ≥ 60 and < 90 mL/min/1.73 m^2 ≥ 90 mL/min/1.73 m^2
Calculated urinary UACR	Categorical and Continuous	< 30 mg/g ≥30 and ≤ 300 mg/g > 300 and <3500 mg/g ≥ 3500 mg/g

All summaries of continuous characteristics will be based on non-missing observations. Summary statistics including mean, median, SD, the first and third quartiles will be calculated. For categorical characteristics, percent will be calculated out of the total number of patients in the data set, overall and by treatment group (ie, each denominator includes the number of patients with missing/unknown values for the endpoint).

4.4.3 Specific and General Disease Histories

The numbers and percent of patients with diabetes complications history, general medical history findings and surgical history will be summarized both overall and by body system for each treatment group using Randomized Analysis Set.

For these displays, percent will be calculated out of the total number of patients in the data set, overall and by treatment group (i.e., each denominator includes the number of patients with missing/unknown values for the endpoint).

The specific disease history and general medical history will be presented in listings for each patient in the All Randomized Set.

4.4.4 Current and Concomitant Medications

Current and concomitant medications will be summarized using the Safety analysis set by drug class (anatomic class and therapeutic class), generic drug name and treatment group, as defined by the AstraZeneca Drug Dictionary most current at time of database lock. A summary will be produced for each of the following:

- all current medication
- all concomitant medication
- all concomitant diuretic medication
- all concomitant ARB and/or ACE-I medication
- all concomitant anti-hypertensive medication
- all concomitant insulin medication
- all concomitant non-insulin antidiabetic medication

Current medications are defined as medications with a start date prior to the first day of double-blind treatment period and without a stop date prior to the consent date, i.e. current medication will be any medication with at least 1 dose taken on or after the day of consent date up to the day prior to the first dose of study medication.

Concomitant medication during the double-blind treatment period is defined a medication with either

- a recorded medication start date falling within the double-blind treatment period, or
- a recorded medication start date prior to the first day of study medication during the double-blind treatment period without any recorded medication stop date prior to the start of the double-blind treatment period.

This means that concomitant medications for the double-blind treatment period will be any medication taken from start of the double-blind treatment period up to the end of the double-blind treatment period. Concomitant medications will include all rescue medication administered during the double-blind treatment period.

Missing and partial date handling of start and stop dates of previous, current and concomitant medications, is described in Section 4.5.3.

4.4.5 Compliance with Study Medication and Extent of Exposure

Percent treatment compliance is calculated during the double-blind treatment period for the blinded study medication. Percent compliance is defined as the number of tablets taken, divided by the number of tablets that should have been taken. A patient is considered compliant if percent compliance is between 80% and 120%, inclusive. The number of tablets that should have been taken is calculated as (date of the last investigational dose - date of 1st investigational dose during randomized treatment period + 1), times the prescribed daily dose. Total number of tablets taken is the difference between total number of tablets dispensed minus total number of tablets returned over the entire randomized treatment period. All dates and tablets counts data are to be taken from the “Drug Accountability” or DA module in CRF.

The number and percent of patients compliant with double-blinded study drug during the double-blind treatment period will be summarized for the Safety Analysis Set.

Extent of exposure is defined as the number of days between the start and the end dates of study therapy, where the start date of study therapy is the date of the first dose of investigative or comparator treatment, and the end date of study therapy is the last known dose of investigative or comparator treatment during the double-blind randomized treatment period,ie,

Extent of exposure=Last dosing date - First dosing date + 1.

Extent of exposure to the investigational product will be summarized using Safety Analysis Set for the double-blind treatment period regardless of rescue and prior to rescue respectively, presenting the numbers and percents of patients with an extent of exposure within the

following day ranges by treatment group: 1 to 14, 15 to 28, 29 to 42, 43 to 56, 57 to 84, 85 to 112, 113 to 168, and ≥169 days. Also the mean, SD, median and range of extent of exposure to study medication will be presented by treatment group.

Extent of exposure for the investigational product during the double-blind treatment period will be summarized and listed by patient. Additionally, a listing of randomization scheme and a listing of patients by batch number of investigational product will be produced.

Also, rescue medication usage (number of patients taking rescue medication) will be summarized by treatment group based on CRF records. A by patient listing for rescue medication usage will be presented for all rescued patients during double-blind treatment period.

4.4.6 Efficacy Variables

4.4.6.1 Primary Analysis for Change from Baseline in HbA1c (%) at Week 24

The primary analysis for the change from baseline in HbA1c at Week 24 will be based on the Full Analysis Set using a longitudinal repeated measures analysis with a 'direct likelihood' method (see Section 4.1.2). In addition to the primary analysis the 3-way interaction term baseline-by-week-by-treatment will be used as a model check to assess if there is statistically significant treatment effect across visits which differs in dependency on baseline values. A common model will be used in analysis that includes change from baseline values for the dapagliflozin 10 mg plus saxagliptin 2.5 mg group, the dapagliflozin 10 mg group, and the placebo group. The contrast of interest is the treatment difference between dapagliflozin 10 mg plus saxagliptin 2.5 mg and placebo. The overall experiment type I error rate will be set to 0.05. Statistical inference will be made from separate comparisons of each treatment group with placebo at a two-sided statistical significance level of 0.025. The p-values from the primary analyses will be controlled using the MTP defined in section 4.3.

A pair-wise difference between least-square means for both dapagliflozin 10 mg plus saxagliptin 2.5 mg treatment group and placebo treatment group as well as dapagliflozin 10 mg and placebo group will be calculated and nominal 95% confidence intervals will be constructed. Point estimates of change from baseline for each treatment group will also be presented together with corresponding 95% confidence intervals. The comparison of change from baseline to Week 24 for HbA1c between dapagliflozin 10 mg and placebo from the common model will be evaluated as a secondary comparison (if allowed) under the sequential testing procedure.

Descriptive statistics will also be presented for each visit for HbA1c and change from baseline in HbA1c. All available data for patients in the Full Analysis Set will be summarized.

This analysis will be accompanied by a Figure of "HbA1c Adjusted Mean Change from Baseline over Time 24-Week double-blind treatment period (prior to rescue/IP discontinuation)", observed cases.

4.4.6.2 Primary Analysis for Percent Change from Baseline in UACR at Week 24

For the primary analyses of percent change from baseline in UCAR at Week 24, UACR values will first be transformed to logarithms and the results will be expressed as geometric mean percent changes from baseline. A longitudinal repeated measures model of the logarithms of the post-baseline to baseline ratios will be used (see Section 4.1.2). In addition the 3-way interaction term log-baseline UACR-by-week-by-treatment will be used as a model check to assess if there is statistically significant treatment effect across visits which differs in dependency on baseline values. A common model will be used in analysis that includes change from baseline values on the natural logarithmic scale for the dapagliflozin 10 mg plus saxagliptin 2.5 mg group, the dapagliflozin 10 mg group, and the placebo group. The p-values from the primary analyses will be controlled using the MTP defined in Section 4.3.

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 (see Table 5 for more details). P-values of the differences in Week 24 percent change estimates between each treatment group (saxagliptin/dapagliflozin and dapagliflozin) and placebo will be calculated.

Descriptive statistics will also be presented for each visit for percent change from baseline in urine albumin-to-creatinine ratio (UACR). All available data for patients in the Full Analysis Set will be summarized.

This analysis will be accompanied by a Figure "Adjusted Percent Change from Baseline in UACR over Time 24-Week double-blind treatment period", observed cases.

4.4.6.3 Sensitivity Analysis on the Primary Efficacy Endpoints at Week 24

To assess the robustness of the primary efficacy analysis, and to compare the results with previous studies, the sensitivity analyses on the primary efficacy endpoints will be carried out using the following approaches:

- Repeat of the primary analyses for the Per Protocol Set (if warranted), utilizing the longitudinal repeated measures methodology on the change from baseline in HbA1c and, separately, percent change from baseline in UACR described in Section 4.1.2. HbA1c measurements will be analysed by including values prior to rescue or treatment discontinuation. UACR measurements will be analysed by including values prior to treatment discontinuation.

  Note the sensitivity analysis using the Per Protocol Set will be applied to primary efficacy endpoints only if there the Per Protocol Set has a minimum of 10% fewer patients in any treatment group than in the Full Analysis Set for that treatment group.

- Repeat of the primary analyses for the Randomized Set who have a baseline assessment regardless of rescue or treatment discontinuation utilizing ANCOVA at Week 24 on the change from baseline in HbA1c and, separately, percent change from baseline in UACR endpoints within the framework of MI-RD imputation described in Section 4.1.4.2.

- Repeat of the primary analyses for the Randomized Set who have a baseline assessment regardless of rescue or treatment discontinuation utilizing ANCOVA at Week 24 on the change from baseline in HbA1c and, separately, percent change from baseline in UACR endpoints within the framework of Washout-imputation described in Section 4.1.4.3.

- Repeat of the primary analyses for the Randomized Set who have a baseline assessment regardless of rescue or treatment discontinuation utilizing ANCOVA at Week 24 on the change from baseline in HbA1c and, separately, percent change from baseline in UACR endpoints within the framework of the Tipping Point analysis described in Section 4.1.4.4.

- Repeat of the primary analyses for the Full Analysis Set who have a baseline assessment excluding data after rescue or treatment discontinuation utilizing ANCOVA at Week 24 on the change from baseline in HbA1c and, separately, percent change from baseline in UACR endpoints within the framework of the Tipping Point analysis described in Section 4.1.4.4.

Summaries and analyses supporting the primary efficacy objective are presented in Table 10.

Table 10 Summary of analysis to meet primary efficacy objectives

Analysis type	Estimand	Missing Data Assumption	Imputation Method	Analysis set
Repeated measures mixed model of ΔHbA1c to Week 24 (prior to rescue or treatment discontinuation) [a1]	Difference in outcome HbA1c improvement at Week 24 prior to rescue or treatment discontinuation.	MAR	No imputation	FAS [a1]/ PP [b]
Repeated measures mixed model of ΔHbA1c to Week 24 (regardless of rescue or treatment discontinuation)	Difference in outcome HbA1c improvement at Week 24 regardless of rescue or treatment discontinuation.	MAR	No imputation	FAS
Repeated measures mixed model of Δlog(UACR) to Week 24 in UACR [a2] (prior to treatment discontinuation)	Difference in outcome percent UACR improvement at Week 24 prior to treatment discontinuation.	MAR	No imputation	FAS [a2]/ PP [b]
Repeated Measures mixed model of Δlog(UACR) to Week 24 (regardless of treatment discontinuation)	Difference in outcome percent UACR improvement at Week 24 regardless of treatment discontinuation.	MAR	No imputation	FAS
ANCOVA of ΔHbA1c to Week 24 from MI-RD imputation (regardless of rescue or treatment discontinuation)	Difference in outcome HbA1c improvement at Week 24 regardless of rescue or treatment discontinuation.	MNAR	Observed and Imputed values	RAND
ANCOVA of Δlog(UACR) to Week 24 from MI-RD imputation (regardless of treatment discontinuation)	Difference in outcome percent UACR improvement at Week 24 regardless of treatment discontinuation.	MNAR	Observed and Imputed values	RAND

Analysis type	Estimand	Missing Data Assumption	Imputation Method	Analysis set
ANCOVA of ΔHbA1c to Week 24 from washout imputation (regardless of rescue or treatment discontinuation)	Difference in outcome HbA1c improvement at Week 24 regardless of rescue or treatment discontinuation.	MNAR	Observed and Imputed values	RAND
ANCOVA of Δlog(UACR) to Week 24 from washout imputation (regardless of treatment discontinuation)	Difference in outcome percent UACR improvement at Week 24 regardless of treatment discontinuation.	MNAR	Observed and Imputed values	RAND
ANCOVA of ΔHbA1c to Week 24 from Tipping Point analysis[c1] (prior to rescue or treatment discontinuation)	Difference in outcome HbA1c improvement at Week 24 prior to rescue or treatment discontinuation.	MNAR	Observed and Imputed values	FAS
ANCOVA of Δlog(UACR) to Week 24 from Tipping Point analysis[c1] (regardless of treatment discontinuation)	Difference in outcome percent UACR improvement at Week 24 regardless of treatment discontinuation.	MNAR	Observed and Imputed values	RAND
ANCOVA of ΔHbA1c to Week 24 from Tipping Point analysis[c2] (prior to rescue or treatment discontinuation)	Difference in outcome HbA1c improvement at Week 24 prior to treatment discontinuation.	MNAR	Observed and Imputed values	FAS
ANCOVA of Δlog(UACR) to Week 24 from Tipping Point analysis[c2] (regardless of treatment discontinuation)	Difference in outcome percent UACR improvement at Week 24 regardless of treatment discontinuation.	MNAR	Observed and Imputed values	RAND

LOCF = Last Observation carried Forward; ΔHbA1c=change from baseline in HbA1c; ΔUACR=percent change from baseline in UACR; PP=Per Protocol; FAS = Full analysis set; RAND = Randomized analysis set

[a1] The primary analysis is for (dapagliflozin 10 mg plus saxagliptin 2.5 mg versus placebo)

[a2] The primary analysis is for (dapagliflozin 10 mg plus saxagliptin 2.5 mg versus placebo) and (dapagliflozin 10 mg versus placebo)

[b] The sensitivity analysis on PP will be applied to primary efficacy endpoint only if there is at least a 10% difference in number of patients from FAS in any treatment group.

[c1] The analysis is for (dapagliflozin 10 mg plus saxagliptin 2.5 mg versus placebo)

[c2] The analysis is for (dapagliflozin 10 mg versus placebo)

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CCI [redacted]

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4.4.6.5 Secondary efficacy analysis at Week 24

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 both comparison of co-primary endpoints are significant. If statistical significance is achieved as described above, then the secondary endpoints will be compared between that treatment and placebo in the order specified:

a. Dapagliflozin 10 mg plus saxagliptin 2.5 mg versus placebo:

- Percent change from baseline in total body weight
- Change from baseline in fasting plasma glucose (FPG)
- Proportion of patients achieving > 30% reduction in UACR

- Proportion of patients achieving a reduction in HbA1c <7.0%
- Change from baseline in seated SBP

b. Dapagliflozin 10 mg versus placebo:

- Percent change from baseline in total body weight
- Proportion of patients achieving > 30% reduction in UACR
- Change from baseline in seated SBP
- Change from baseline in HbA1c
- Change from baseline in fasting plasma glucose (FPG)
- Proportion of patients achieving a reduction in HbA1c <7.0%

All secondary efficacy analyses will be performed using the Full Analysis Set.

To preserve the family-wise Type I error rate at 0.05, independent comparisons between each active treatment and placebo will utilize a sequential testing procedure across secondary comparisons as described in section 4.3. Each pair-wise comparison with placebo will be performed at a (two-sided) alpha level of 0.025. Statistical comparisons between a treatment and placebo will be only performed for a given secondary endpoint if all previous sequential tests for that treatment are also significant. Otherwise, the testing procedure will stop at the secondary endpoint that does not reach statistical significance.

The following secondary endpoints will be analysed using a longitudinal repeated measures model (see Section 4.1.2), which is similar to the primary efficacy analyses.

- 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
- Change from baseline in HbA1c at Week 24 (only for Dapagliflozin 10 mg)

All pair-wise differences between least-square means for dapagliflozin 10 mg plus saxagliptin 2.5 mg and placebo, as well dapagliflozin 10 mg and the placebo will be calculated and nominal 95% confidence intervals will be constructed. P-values will be presented at the nominal level, and statistical inference will be made when warranted as described in Section 4.3. Descriptive statistics will be presented for each variable at each visit and for change from baseline. All available data in the FAS will be included in analysis.

The following secondary endpoints will be analysed using the logistic regression model with adjustment for randomization strata and baseline measurement described in Section 4.1.6 of the SAP:

- Proportion of subjects achieving a therapeutic glycemic response defined as HbA1c < 7% at Week 24 (LOCF)
- Proportion of patients achieving at least 30% reduction in UACR from baseline to Week 24 (LOCF)

In analysis of proportions, all subjects in the Full Analysis Set that are missing a secondary endpoint value will be considered as having failed to achieve the desired level of improvement.

For analysis using the logistic regression model, the pooled randomization strata will be used as the adjustment factor. The insulin-based regimen strata will remain unchanged, however non-insulin strata may be combined (Metformin-based regimen, SU based regimen, TZD-based regimen, and other regimen strata) into a pooled strata called "oral antidiabetic medications" for dichotomous endpoints with few events. The estimated odds ratio with pre-defined response characteristic for the dapagliflozin/saxagliptin to the placebo group, and dapagliflozin treatment to the placebo group will be displayed along with standard error and the 95% confidence intervals.

Descriptive statistics (frequency tabulations) will be presented for each visit. Data based on last observation carried forward (LOCF) will be summarized

CCI [redacted]

- CCI [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

- [redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

4.4.7 Analysis supporting safety and tolerability

The Safety Analysis Set will be used for all safety analyses, including all data after rescue during the double-blind treatment period.

Sensitivity analyses on data collected prior to rescue during the double-blind treatment period will be performed for selected Adverse Events (AEs) as described in multiple sub-sections under Section 4.4.7.4.

Safety analyses will be conducted on the double-blind treatment period and follow-up period.

AEs within 4 days or SAEs within 30 days post last double-blind study medication, which are considered in the double-blind treatment period, will not be counted as AEs or SAEs during the follow-up period.

Unless otherwise specified, the safety analyses of changes from baseline to a specific time point in safety variables (e.g., laboratory parameters and vital signs) will only include patients from the Safety Analysis Set who have data available for both the baseline and the time point under consideration.

Safety data that collected before the start of double-blind treatment will not contribute to summaries but will be listed.

4.4.7.1 Change from baseline in eGFR at Week 24 and Week 27

The analysis of covariance (ANCOVA) described in Section 4.1.3 of the SAP will be used to compare the mean change from baseline in eGFR between dapagliflozin 10 mg versus placebo, as well between dapagliflozin 10 mg plus saxagliptin 2.5 mg versus placebo at Week 24.

The longitudinal repeated measures analysis described in Section 4.1.2 of the SAP will be used to examine the mean change from baseline in eGFR, and estimated mean change from baseline in eGFR will be compared between dapagliflozin 10 mg and placebo, and separately, between dapagliflozin 10 mg plus saxagliptin 2.5 mg and placebo at Week 27.

The analysis of change from baseline in eGFR will be performed using the Safety Analysis Set.

Common models will be used in analysis that includes change from baseline values for the dapagliflozin 10 mg plus saxagliptin 2.5 mg group, the dapagliflozin 10 mg group, and the placebo group.

All pair-wise differences between least-square means for dapagliflozin/saxagliptin versus placebo, and dapagliflozin versus placebo will be calculated and nominal 95% confidence intervals will be constructed.

The adjusted proportions, standard errors, confidence levels will be displayed.Descriptive statistics will be presented for each visit for eGFR and change from baseline in eGFR. All available change from baseline data from the Safety Analysis Set will be included in analysis.

CCI [redacted]

4.4.7.2 Treatment Discontinuation for a sustained increase in serum creatinine by ≥1.5 times baseline level (AKI stage 1).

Potential events of treatment disconsolation due to sustained AKI will be reviewed and events will be determined prior to unblinding the study.

The methodology of logistic regression model with adjustment for randomization strata and baseline creatinine level will be used to compare:

- Percent of patients who discontinued the double-blind treatment period for a sustained increase in serum creatinine by ≥1.5 times baseline level (AKI stage 1)

The estimated odds ratio of dapagliflozin/saxagliptin to placebo, and, separately, the odds ratio of dapagliflozin to placebo will be displayed along with standard error and the 95% confidence intervals.

The adjusted proportions, standard errors, confidence levels will be displayed.

Data based on last observation carried forward (LOCF) will be summarized.

4.4.7.3 Proportion of patients with rescue events

Descriptive statistics (frequency tabulations) of cumulative proportion of rescued patients will be presented for each visit. Data based on last observation carried forward (LOCF) will be summarized.

4.4.7.4 Adverse events

Adverse Events (AEs) will summarized for the Safety Analysis Set, and will be classified by Primary System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA). All adverse events will be coded using the latest available version of MedDRA by the database lock.

Unless otherwise specified, no statistical tests will be performed to compare AE rates between treatment groups. This policy was adopted to recognize the lack of power and the potential for misleading interpretation based on repeated statistical tests which increase the family-wise Type I error level.

Counting rules for adverse events are described in Section 4.5.4.

In summaries by system organ class (SOC) and preferred term (PT), AEs will be sorted by decreasing frequency of each PT and SOC, within SOC, according to the Dapagliflozin 10 mg

plus saxagliptin 2.5 mg group. In summaries by PT, AEs will be sorted by decreasing frequency of PT according to the Dapagliflozin 10 mg group plus saxagliptin 2.5 mg group.

AEs within 4 days or SAEs within 30 days post last double-blind study medication, which are considered in the double-blind treatment period, will not be counted as AEs or SAEs during the follow-up period. Missing AE onset dates will be imputed as defined in Section 4.5.3.1.

Separate pages to capture events of hypoglycemia are contained within the CRF. Hypoglycemia or treatment discontinuation due to hypoglycemia would not be reported on an AE CRF page unless the event fulfilled criteria for an SAE in which case an SAE form would be completed. Hypoglycemia and DKA events that are reported as SAEs will be included in all summaries of AEs or SAEs. Separate summaries will be provided including hypoglycemia events reported on the hypoglycemia CRF page (see Section 4.4.7.4.6 Adverse events of interest).

4.4.7.4.1 All Adverse Events

All adverse events (serious and non-serious) with onset during the double-blind treatment period will be summarized by system organ class, preferred term and treatment group, for both the primary and sensitivity safety analyses.

The patient incidence of Related AEs, Deaths, SAEs and DAEs will be summarized. SAE of DKA and SAE of hypoglycemia will be included in all AE summaries. Hypoglycemic events that were reported on separate eCRF pages will be summarized separately.

The patient and event incidence of most common AEs (reported in at least 2% and 5% of the patients in any treatment group) will be presented by PT and treatment group. For most common AEs reported in at least 5% for any treatment group the number of AEs will also be reported.

In addition, following summaries will be provided for the double-blind treatment period. These summaries will exclude hypoglycemic AEs that are not reported as SAEs:

- Proportion of patients with adverse events in subgroups of patients defined by age category (< 65 and ≥ 65 yrs), gender, race and female age category (≤ 50 and > 50 years).
- Adverse events by system organ class, preferred term, intensity and treatment group.
- Adverse events related to study medication by system organ class, preferred term and treatment group.

All AEs occurring during the study (including the placebo lead-in period, double-blind treatment and the follow-up period) will be listed.

4.4.7.4.2 Deaths

All deaths recorded on the status page, the AE page, or SAE page (with a death date, cause of death, outcome or SAE categorization present) of the CRF will be considered a death in the analyses. Any deaths that occur during the study will be described in depth as narrative in the CSR. A listing of all deaths that occur during the study will be produced.

4.4.7.4.3 Serious adverse events

SAEs (including DKA and hypoglycemic events) with an onset from Day 1 of double-blind treatment up to and including 30 days after the last dose date in the double-blind treatment period will be considered as occurring during the double-blind treatment period.

SAEs (including DKA and hypoglycemic SAEs) occurring during the double-blind treatment period will be summarized by SOC, PT and treatment group. In addition, the proportion of patients with related SAEs will be presented by SOC, PT and treatment group.

A listing of all SAEs will be produced, displaying all SAEs (including pre-treatment events) that occurred during the study.

4.4.7.4.4 Related adverse events

The patient incidence of related AEs will be presented by SOC, PT and treatment group. This summary will exclude hypoglycaemic AEs.

4.4.7.4.5 Adverse events leading to treatment discontinuation (DAE)

AEs that led to treatment discontinuation during the double-blind treatment period will be summarized by SOC, PT and treatment group.

When summarizing AEs leading to treatment discontinuation, no upper cut-off day windows (i.e. 4 days and 30 days from last dosing date in double-blind treatment period for AEs and SAEs respectively) are applied. For double-blind period analyses, the only upper cut-off date is the last date of the double-blind treatment period.

In addition, a patient listing of treatment discontinuation due to AEs will be provided, displaying all events that led to treatment discontinuation that occurred during the study.

4.4.7.4.6 Adverse events of interest

Separate summaries will be provided for the following adverse events of interest. To identify each type of adverse event of interest in this section, a list of preferred terms will be selected, reviewed and finalized prior to the database lock and unblinding of the database. Adverse events of interest summaries will include events with onset after rescue medication administration.

Unless otherwise specified, AEs and SAEs of interest with an onset from Day 1 of double-blind treatment up to and including 4 days and 30 days respectively, after the last dose date in

the double-blind treatment period will be considered as occurring during the double-blind treatment period.

4.4.7.4.6.1 Hypoglycaemia

Separate pages to capture events of hypoglycemia are contained within the CRF.

Hypoglycemic events with an onset from Day 1 of the double-blind treatment period up to and including 4 days (SAE up to 30 days) after the last dose date in the double-blind treatment period will be considered as occurring during the double-blind treatment period. The proportion of patients with hypoglycemic events will be tabulated by treatment group in the double-blind treatment period. Both primary and sensitivity safety analyses will be performed. Hypoglycemic events will be categorized using the following classes:

- Major episodes of hypoglycemia - defined as symptomatic episodes requiring external (3rd party) assistance due to severe impairment in consciousness or behaviour, with a capillary or plasma glucose value < 3 mmol/L (< 54 mg/dL), and prompt recovery after glucose or glucagon administration,

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

- Other episodes of hypoglycemia - defined as episodes reported by the investigator that are suggestive of hypoglycemia but do not meet the above criteria.

When summarizing hypoglycemic events leading to treatment discontinuation no upper cut-off day windows are applied.

A listing of patients will be produced and it will display all hypoglycemic events with an onset on or after the start date of double-blind treatment period.

4.4.7.4.6.2 All other AEs of interest

For this study, the categories for all other AEs of interest are listed below:

- Genital Infection

- Urinary-tract Infection

- Volume depletion (including hypotension, dehydration, and hypovolemia)

- Renal Impairment/Renal Failure

- Bone Fractures

- Hepatic events

- Diabetic ketoacidosis events
- Amputations

Those adverse events of interest, with the exception of Hepatic events, DKA events and amputations will be defined based on lists of preferred terms. The lists will be reviewed and finalized prior to database lock and unblinding of the database. Hepatic events and DKA events and amputations will be identified through CRF module "Clinical Endpoints and Events of Special Interest".

For each category, the number and percentage of patients with the event will be summarized by PT and treatment group.

Adverse events of interest summaries will include all data from the double-blind treatment period, including data after rescue for rescued patients.

DKA events will be adjudicated and DKA events will be summarized by treatment group based on the adjudicated result. Also, that data collected on the signs, symptoms, and risk factors for DKA events will be included in listings of DKA events.

4.4.7.4.6.3 Hepatic event adjudication committees

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 followed by repeat testing where TB is added and >2x ULN and AST/ALT >3x ULN also confirmed by repeat testing (within 14 days of the AST and/or ALT elevation);
- AST and/or ALT >10x ULN.

Events reviewed by the hepatic event adjudication committees will be listed.

4.4.7.5 Clinical laboratory tests evaluation

Unless otherwise specified, laboratory data obtained after the start of study medication dosing up to and including 4 days (30 days for liver function laboratory test) after the last double-blind dosing date will be considered as obtained during the double-blind treatment period. Laboratory data obtained from the day after the last study medication + 4 days (30 days for liver function laboratory test) up to the last visit date of the follow-up period will be considered as obtained during the follow-up period.

For liver safety, a summary of proportion of patients with elevated liver test including Hy's law (see Appendix C for definition) will be provided for the double-blind treatment period. In

addition, a summary of proportion of patients with elevated liver test and/or reported AE of hepatic disorder will also be provided for the double-blind treatment period. A

All scheduled laboratory evaluations are performed by central laboratories. All laboratory evaluations performed by central laboratories will be included in summary tables.

Laboratory parameters will be presented in international system units, except for those listed in Table 12, which will be presented in conventional units (C) and international system units (SI).

Table 12 SI and C units

Test name	SI unit	C unit
FPG	mmol/L	mg/dL
FFA	mmol/L	mg/dL
Cholesterol (incl. LDL and HDL)	mmol/L	mg/dL
Triglycerides	mmol/L	mg/dL
Urate	umol/L	mg/dL
Urine glucose excretion	Arbitrary units	Arbitrary units
Total Bilirubin	umol/L	mg/dL
Serum creatinine	umol/L	mg/dL
Urine creatinine	mmol/L	mg/dL
Urine albumin	mg/L	g/dL
Phosphate	mmol/L	mg/dL

Note: UACR will be presented as C and not SI

4.4.7.5.1 Marked laboratory abnormalities

Laboratory abnormalities will be evaluated based on marked abnormality (MA) criteria. Appendix C (Laboratory Abnormality Criteria) lists the pre-defined criteria for MAs. If both the baseline and on-treatment values of a parameter are beyond the same MA limit for that parameter, then the on-treatment value will be considered a MA only if it is more extreme (farther from the limit) than was the baseline value. If the baseline value is beyond the low, and the on-treatment value is beyond the high MA limit (or vice-versa), then the on-treatment value will be considered a MA. If the baseline value is not beyond either MA limit, and the post-baseline value is beyond either MA limit, then the post-baseline value will be considered MA.

Laboratory MAs occurring during the double-blind treatment period will be summarized by treatment group for primary and sensitivity safety analysis. The directions of changes (high or low) in MAs will be indicated in the tables. Separate summaries will be provided for marked laboratory abnormalities including and excluding data after the administration of rescue medication.

Additionally, for each patient with a MA for a parameter, all the patient's values of that parameter over the double-blind treatment period and the follow-up period will be listed.

4.4.7.5.2 Changes from baseline values for selected laboratory parameters over time

All analyses of laboratory data will use observed data regardless of rescue. Visit windows are provided in Section 4.5.1 in order to link each laboratory test to a scheduled visit. Change from baseline during the double-blind treatment period and the follow-up period for selected laboratory parameters will be summarized by treatment group, presenting n's, means, medians, minimum, maximum, SEs:

Haematology parameters:

- haemoglobin
- haematocrit
- red blood cell (RBC) count
- white blood cell (WBC) count
- platelet count

Serum/plasma Chemistry parameters:

- aspartate aminotransferase (AST)
- alanine aminotransferase (ALT)
- alkaline phosphatase
- total bilirubin
- blood urea nitrogen (BUN) BUN will be calculated by the external laboratory.
- electrolytes - sodium, potassium, bicarbonate, chloride, magnesium, calcium
- total protein and albumin
- TC, LDL-C, HDL-C, TG, and FFA
- Uric Acid
- CCI [redacted]
- creatinine, serum (Scr)

- Estimated GFR (changes from baseline) based on serum creatinine, using a specific equation for Japanese, modified MDRD equation for Taiwanese and the general MDRD equation for others
- Phosphorus
- Parathyroid Hormone (PTH)
- CCI [redacted]

Urine parameters:

- CCI [redacted]
- [redacted]
- [redacted]
- [redacted]
- Calculated UACR
- CCI [redacted]
- [redacted]
- [redacted]

4.4.7.5.3 Additional Laboratory Data Summaries

Shift Tables for Electrolytes (Sodium, Potassium, Calcium, Phosphate, and Magnesium) Categories

Shift tables of Safety Data Set patients with electrolytes values in categories of low, normal, and high (based on normal range of central laboratory) will be summarized by treatment group using the highest (for sodium, calcium, phosphate, and magnesium) and lowest (for sodium, potassium, and calcium) values (regardless of rescue) obtained during the double-blind treatment period.

CCI [redacted]

4.4.7.6 Electrocardiograms

The 12-lead ECG is performed at Visit 2 only. Listings of ECG interpretations will be generated on request.

4.4.7.7 Vital signs

Unless otherwise specified, vital signs and other physical data obtained after the start of study medication dosing up to 4 days (inclusive) after the last double-blind dosing date will be considered as obtained during the double-blind treatment period. Vital signs and other physical data obtained from the day after the last study medication + 4 days (exclusive) up to the last visit date of the follow-up period will be considered as obtained during the follow-up period.

Visit windows are provided in Section 4.5.1 in order to link each vital sign measurement to a scheduled visit.

The values and changes from baseline for systolic and diastolic blood pressures and heart rate will be summarized by treatment group at each scheduled visit using descriptive statistics (using available data regardless of rescue for patients in Safety Data Set). The baseline value of systolic blood pressure, diastolic blood pressure and heart rate will be calculated as the average of the last three SBP, DBP and pulse assessments collected on or prior to the administration of double-blind medication.

Number and percentages of patients with orthostatic hypotension (fall in systolic blood pressure of > 20 mmHg or diastolic blood pressure of > 10 mmHg (supine to standing)) will be summarized by treatment group at each scheduled visit using available data regardless of rescue in Safety Data Set. All observations regardless of distance to the target in each scheduled visit window will be used for the summary of orthostatic hypotension.

Changes from baseline in BMI, and waist circumference, will be summarized presenting n's, means, medians, minimums, maximums, and SEs, at each scheduled visit during the double-blind treatment period and the follow-up period.

4.4.7.8 Physical examinations

Physical examination changes from baseline to end of treatment will be summarized by treatment and body system using findings from full physical examinations by shift tables for the Safety Analysis Set.

The proportion of patients with abnormal physical examinations at each visit will be displayed by treatment group and overall.

4.4.7.9 Pregnancy Test Results

A by-patient listing of pregnancy test results will be provided using Safety Data Set.

4.5 Conventions

4.5.1 Visit Compliance

Patients do not always adhere strictly to the visit timing in the protocol. Therefore, the designation of visits during the double-blind treatment period and follow-up period will be based on the day of evaluation relative to the reference start date rather than the nominal visit recorded in the CRF.

To assign a measurement to a Week t during a study period, the first step consists of selecting all measurements falling within this study period as defined below. To further determine the Week t measurement, mutually exclusive relative day windows are used.

The day windows are defined to provide derived visits that correspond to the post-baseline time points specified in the protocol. As already stated, some restrictions may exist on some laboratory assessments to be included in efficacy analyses. These restrictions will be reflected in the day ranges. For example, since no HbA1c is to be collected at Week 1, the windows for HbA1c will only start at Week 4. No Week 1 windowing will be defined.

For each visit, a window will be defined such that the lower and upper bounds of each window is generally the midpoint between 2 consecutive study visits. The visit windows and applicable study day ranges are presented below in Table 13.

Table 13 Visit windows for efficacy data and safety data

Visit	**Target Day****	**Adjusted windows for analyses**				
		HbA1c **UACR**** **Spot Urine Glucose/Creatinine Ratio**	**Vital Signs, SBP** **Weight** **BMI, FPG** **Safety Laboratory**	**Fasting Serum Lipids** **Uric acid** **Waist circumference, full physical examination**	**Arterial stiffness assessment**	**PK blood sample**
Baseline	1	≤1	≤1	≤1	≤1	≤1
Week 1	8		2-18*			
Week 4	29	2-43*	19-43*			22-36*
Week 8	57	44-71*	44-71*		2-113*	
Week 12	85	72-99*	72-99*			57-113*
Week 16	113	100-141*	100-141*			
Week 24	169	142-Last day of DB period	142- Last day of DB period	2- Last day of DB period	114- Last day of DB period	141- Last day of DB period

Visit	Target	Adjusted windows for analyses				
Follow-up Week 27	190	Day 1 of FU period- Last day of FU period	Day 1 of FU period- Last day of FU period	Day 1 of FU period- Last day of FU period		

* before the last day of DB period.

**For Urine Creatinine, Urine Albumin and UACR, the visit date used to group the samples will apply.

For some efficacy parameters, the use of double-blind treatment observations is specified in Section 4.5.2. This section defines the last day after treatment for which these observations are included in the visit window.

Day 1 of the double-blind treatment period is the start date of double-blind study medication. Day 1 of the follow-up period is the day after the last visit in double-blind study medication. The last visit in double-blind treatment period is on the day after the last dose of the study medication.

For assignment of data to time points using the visit windows, study day will be defined as follows:

(Date of assessment - Date of first dosing) + 1.

In case of multiple observations within a single visit window, the following rules apply:

- If there are two or more observations within the same visit window, the observation closest to the target day will be used in the analysis
- If two observations are equidistant from the target day and the ties are on different sides of the target day, the observation with the earlier assessment date will be used in the analysis
- If two observations are equidistant from the target day and the ties located on the same sides of the target day (i.e. more than one observation for the same day but different time), the observation with the earlier (if the assessment day is equal or larger than the target day) or later (if the assessment day is smaller than the target day) assessment time will be used in the analysis
- If two or more observations are collected on the same day, all non-missing but with no collection time associated with at least one of them, the average of the observations will be used in the analysis.

- If two or more observations are collected on the same day and time, and they are same closest to the target day, the average of the observations will be used in the analysis.

If a visit window does not contain any observation, then the data will be missing for that visit.

The protocol specifies that except screening (Visit 1), at all other visits one spot urine sample is to be collected from each of three separate first morning void on days around the visit with one of the samples collected in the morning on the visit day. Accordingly, in the statistical analysis, CCI [redacted] and UACR values will be the average of the three available non-missing measurements. Specifically, the average will be derived based on the samples grouped by the visit date, regardless of the number of samples associated with a visit date. Note there could be fewer or more than three samples associated with a visit date. If there are more than one sample collected on the same date, the earliest sample will contribute to the average. If there are more than one sample collected on the same time at the earliest of the day, all samples will contribute to the average. The average value closest to the target day in each visit window will be used in summary and analysis.

4.5.2 Post-Dosing Observations

While double blind treatment period efficacy observations will be listed regardless of whether the patient was taking blinded study drug, observations will be summarized only when the following rules are satisfied:

- HbA1c, body weight, BMI and waist circumference will be summarized only if measured on or before the 8th day after the last double-blind drug dosing date.
- FPG, UACR, SBP, eGFR, CCI [redacted] ill be summarized only if measured on or before the 1st day after the last double-blind drug dose date.
- Lipids and other exploratory parameters (if available) will be summarized only if measured on or before the 4th day after the last double-blind drug dose date.

For sensitivity analysis all data will be included regardless of treatment discontinuation of the study treatment.

4.5.3 Missing values

Instances of variables with a large proportion of missing values will be documented in the CSR. For listings of efficacy and safety measures, missing values will be represented as not reported.

If the date Type 2 diabetes was diagnosed is partially missing, the following rules will take effect:

- Missing day, but month and year are present: the day will be imputed as the 15th day of the month.
- Missing day and month, but year is present: the day and month will be imputed as 30 June of the year (provided that the imputed date is less than the consent date).
- Missing year, but day and month are present: No imputations will occur, and the subject will be excluded from all summaries related to duration of Type 2 diabetes.
- Missing day, month and year: No imputations will occur, and the subject will be excluded from all summaries related to duration of Type 2 diabetes.
- If any such imputed date falls after the consent date, then the diagnosis date will be taken as equal to the consent date.

These durations, even if partially imputed, will be listed. However, only the portion of the date of diagnosis actually observed, rather than imputed dates, will be displayed in listings.

4.5.3.1 Assignment of Dates to Adverse Events and Laboratory Assessments

In case of missing dates and/or times imputation rules will be applied as follows:

For AEs, a missing or incomplete onset date will be imputed according to the following conventions:

1. If the onset date for an AE is missing or incomplete, an imputed date will be derived to slot the event to an appropriate analysis period. This derived date will not be reported in summary tables or listings.

   Exception: No dates will be imputed for SAEs. Every effort will be made to determine the actual onset date for the event or to obtain a reliable estimate for the onset date from the investigator.

2. If an onset date is missing, the derived onset date will be calculated as the first non-missing valid date from the following list (in order of precedence):

- First active study medication date
- Consent date
- Visit date corresponding to the visit at which the event was reported.
- If a valid non-missing date is not available for any of these dates, the derived onset date will be set to missing.

3. If an onset date is incomplete, the derived onset date will be calculated using the following algorithm:

- Calculate a surrogate date as the first non-missing valid date from the following list (in order of precedence):

  – First active study medication date

  – Consent date

  - Visit date corresponding to the visit at which the event was reported
  - If a valid non-missing date is not available for any of these dates, the surrogate date will be set to missing.

- Based on the information provided, set the derived date to the earliest possible date. If only a year is provided, set the derived date to January first of that year. If a year and month is provided, set the derived date to the first day of that month.

- If the surrogate date is non-missing then:
  - If the derived date is on or after the surrogate date use the derived date as calculated
  - If the derived date is before the surrogate date and the surrogate date is consistent with the partial data provided for the onset date, use the surrogate date as the derived date
  - If the derived date is before the surrogate date and the surrogate date is not consistent with the partial data provided for the onset date then set the derived onset date to be the latest possible date based on the partial onset date information provided. If only a year is provided, set the derived date to December 31st of that year. If a year and month is provided, set the derived date to the last day of that month.

- If all three dates used to determine the surrogate date are missing, then based on the information provided, set the derived date to the earliest possible date. If only a year is provided, set the derived date to January first of that year. If a year and month is provided, set the derived date to the first day of that month.

4.5.3.2 Missing Dates Assessment for Concomitant Medications

Start and stop dates for all concomitant medications are collected on the CRF. However, in case of missing or partial information in these dates, the following rules will be used:

If start date is missing or partial:

- if month is missing, use January (01)
- if day is missing, use the 1st (01)
- if year is missing, use year of the entry visit (consent date for those missing entry visit)
- if entire date is missing, use consent date

If stop date is missing, partial or “continuing:”

- if month is missing, use December (12)
- if day is missing, use the last day of the month under consideration

- if year or the entire date is missing or if "continuing", we leave the date as missing.

Imputed dates will not appear on the tables of non-study medication.

Imputed dates will be reviewed within the study team and agreed by the study team prior to the study being unblinded.

4.5.4 Counting Rules for Adverse Events

1) Where a patient has the same AE, based on preferred terminology, reported multiple times in a single analysis period, the patient will only be counted once at the preferred terminology level in AE frequency tables.

2) When a patient has the same AE, based on preferred terminology, reported multiple times in a single analysis period, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

- **Relationship to study medication**: Related events will take precedence over unrelated events in determining the event to include in summary tables.
- **Intensity of event:** More intense events will take precedence over less intense events in determining the event to include in summary tables. Missing intensity will be considered the least intense event.
- **Onset date and time:** Earlier onset date-time events will take precedence over later onset date-time events in determining the event to include in summary.

3) When reporting AEs by intensity, in addition to providing a summary table based on the event selection criteria detailed above, summary tables will also be provided based on the most intense event during the analysis period - independent of relationship to study medication. For these tables, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

- Intensity of event
- Onset date

4.5.5 Fasting State

For fasting serum lipids (Total-C, LDL-C, HDL-C, TG, FFA) and uric acid, fasting plasma glucose [redacted] only assessments documented with the patient in fasting state will be summarized and listed. The patient will be determined to be fasting using the response to the question "Was the patient fasting?" in the Central Lab Data Transfer Specification. If the response is not marked, the patient is assumed not fasting.

4.5.6 Duration of Type 2 Diabetes

Duration of Type 2 diabetes is calculated as the number of years from Type 2 diabetes diagnosis date to informed consent date:

(consent date - diagnosis date +1) / 365.25.

The duration of diabetes will be included in the baseline diabetes characteristics listing.

4.5.7 BMI

The body mass index (BMI) will be presented and used for classification in the weight tables. The BMI is defined as:

$$\text{BMI} = (\text{weight in kilograms})/(\text{height in meters})^2$$

BMI values will not be rounded to whole integers.

4.5.8 Strip Sign for Selected Laboratory Data

For selected laboratory test values that have been received with an operator sign as a part of the result (>, ≥, <, or ≤), a process to strip the operator sign will be applied and the resulting numeric values will be used for data analysis. The raw value with operator will remain as such on the CRF (or in the electronic record) and in the database.

The applicable laboratory tests and applicable operator signs are listed in Appendix D. Additional laboratory parameters can be approved to be added in strip sign plan later along the progress of this study. Unless otherwise specified, for laboratory parameters not included in any statistical analyses, operator signs will not be stripped and the value will counted as missing.

4.5.9 Missing Insulin Dose

For patients who took insulin before or during the study, the mean total insulin dose should be collected in the CRF which includes the dosing values with start and end dosing date. If there are missing dosing values or date gaps during the insulin treatment period, linear interpolation will be used to fill in the missing doses or missing days. The interpolated values will be used to determine if the increase of >= 10% increase in insulin occurred for those patients.

5. INTERIM ANALYSES

N/A

6. CHANGES OF ANALYSIS FROM PROTOCOL

No changes of analysis from the latest version of protocol

7. REFERENCES

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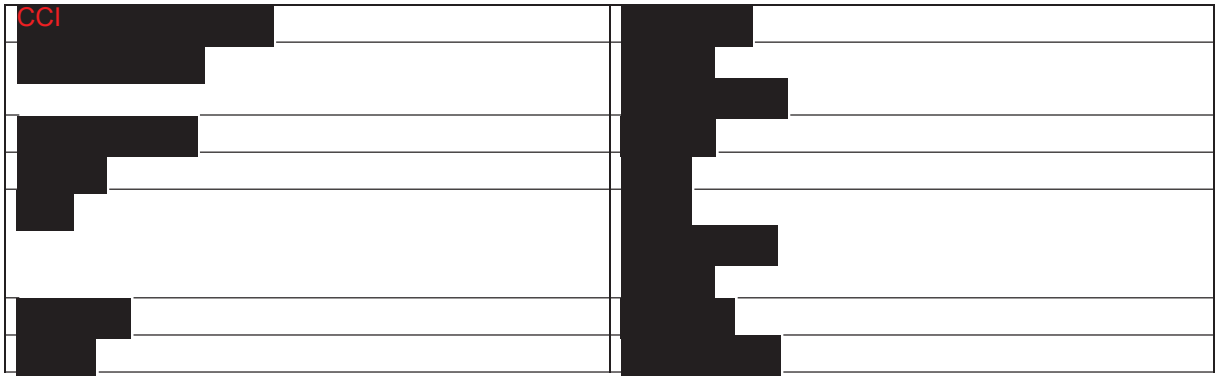
8. APPENDICES

Appendix A Criteria for Assessing Important Protocol Deviations

Number	Important Protocol Deviations (IPD) Criteria
[redacted]	[redacted]

Appendix B Geographic Regions



CCI [redacted]

[redacted]

[redacted]	[redacted]	[redacted]	
		[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]		[redacted]

		CCI	

Appendix D Laboratory Tests in Strip Sign Plan

Lab tests in strip sign plan*	Test Code	Operator Sign & Limit of Quantification
Albumin-to-Creatinine Ratio	ABCRR	<
CCI [redacted]	[redacted]	[redacted]
Parathyroid Hormone, Intact	PTHI	<
Thyroid Stimulating Hormone	TSH	<
CCI [redacted]	[redacted]	[redacted]
Fatty Acids, Free	FFA	<
CCI [redacted]	[redacted]	[redacted]
Bilirubin, Total	TBILI	<
Fibrinogen	FIBR	>
CCI [redacted]	[redacted]	[redacted]
Potassium, Serum	K	>
* Additional laboratory parameters can be added in strip sign plan along the progress of this study.		