AstraZeneca

Clinical Study Protocol	
Drug Substance	Dapagliflozin
Study Code	D1683C00008
Edition Number	5.0
Date	14 Feb 2019

A Multicenter, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Therapy with Dapagliflozin added to Saxagliptin in Combination with Metformin compared to Therapy with Placebo added to Saxagliptin in Combination with Metformin in Asian Subjects with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin and Saxagliptin

(DS Navigation)

PPD

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

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
Version 1.0	02 Jun 2015	NA	NA
Version 2.0	16 Jan 2018	NA	NA
Version 3.0	29 Jun 2018	NA	NA
Version 4.0	29 Sep 2018	NA	NA
Version 5.0	14 Feb 2019	NA	NA
Administrative Change No.	**Date of Administrative Change**	**Local Administrative Change No.**	**Date of Local Administrative Change**
NA	NA	NA	NA

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

VERSION HISTORY

Version 5.0, 14 Feb 2019	
Section	**Summary of change**
Protocol Synopsis	Updated planned site numbers in China and study period. In the last paragraph, the open-label safety analysis set was modified to the open-label treated subjects analysis set to be consistent with section 8.3.3. Added that efficacy analyses will be performed and removed 'by stratum' to make it clear.
1.2 Rationale for study design, doses and control groups 1.3 Benefit/risk and ethical assessment	Specified that the combination of dapagliflozin 10 mg and saxagliptin 5 mg has been studied initially in 3 phase III trials in the fifth paragraph. (Ketoacidosis): "although a causal relationship has not been established" was removed based on the most current data. (Potential benefit to patient): Minor editorial errors were updated to make it clear.
3.3 Subject enrolment and randomization 3.6 Methods for ensuring blinding 3.8.2 Other restrictions	In the fifth paragraph, replaced 'patient' with 'subject'. Clarified when FPG would be un-blinded and how masked values would be shared. Clarified that MTT is only applicable for subjects in China. In the last bullet, replaced 'woman' with 'women'. Replaced 'and' with 'or'.
3.9.1 Procedures for discontinuation of a subject from investigational product	Only kept 16 weeks as sustained period of time for eGFR< 60mL/min/1.73m^2 to avoid misleading.
Table 1 Study Design for Stratum A & Stratum B	Footnote e and 5 were modified to specify that medication after ETD will be under care and direction of the investigator. Footnote l and 12 were modified to clarify when blood sample of FPG should be collected. Footnote n and 14 were updated to reflect that MTT is only applicable

	for subjects in China.
4.3.1 Randomization (Day 1) 4.3.3 Week24/Rescue/Early Treatment Discontinuation visit	Clarified that MTT is only applicable for subjects in China. Replaced '&' with 'and'. Specified that medication after ETD will be under care and direction of the investigator. Clarified that MTT is only for subjects in China. Replaced 'WK24' with 'Week24'.
5.1 Efficacy assessments 5.1.2.1 Postprandial glucose (PPG) at 120 minutes	The section was updated to be consistent with section 3.6. Clarified that MTT is only applicable for subjects in China. MTT procedures were modified to reflect that administration of meal supply is about 10 minutes to allow some flexibility. Clarified that PPG is only for subjects in China.
8.2 Sample size estimate 8.3 Definitions of analysis sets 8.3.1 Efficacy analysis sets 8.5.2 Analysis of the secondary variable(s) 8.5.6 Exploratory Analysis (if applicable) 8.5.7 Safety analysis	Modified 'Chinese subjects' to 'subjects in China' to make it clear. The open-label safety analysis set was modified to the open-label treated subjects analysis set to be consistent with section 8.3.3. Added that efficacy analyses will be performed. The definition of ITT analysis set was updated so that the ITT analysis set will include all randomized subjects who received at least one dose of double-blind study medication during the double-blind treatment period. Clarified that MTT is only applicable for subjects in China. The section was updated to reflect that AUC of glucose during MTT will be analysed based on data of subjects in China and analyses of the mean change from baseline for continuous endpoints will be performed using an MMRM or ANCOVA method depending upon the availability of repeated measurements for the endpoint. The open-label safety analysis set was modified to the open-label treated subjects analysis set to be consistent with section 8.3.3. Removed 'by stratum' to make it clear.

8.6 China cohort	Added selected exploratory objectives to clarify the scope of China cohort.
12.1 Further guidance on the definition of a serious adverse event (SAE)	Replaced 'iv' with 'IV'.
Version 4.0, 29 Sep 2018	
Section	**Summary of change**
Protocol Synopsis Exploratory Objectives	Update planned site numbers. Updated to mean percent change from baseline of fasting serum lipids as one of the exploratory variables.
Statistical methods	Move the sentence of "In this trial, Chinese subjects will constitute about 80% of the total number of subjects." to downstream paragraph to avoid potential confusions. Add the word "about" before planned numbers of allocated subjects in China and other countries to allow flexibility. Clarify the design that subjects with low HbA1c entering open-label will be limited according to stratum. Clarify safety analyses for the double-blinded treatment period
1.4 Study design	Excluded Week 24 in rescue criteria as recue is not applicable for Week 24 visit.
3.2 Exclusion criteria 3.9.1 Procedures for discontinuation of a subject from investigational product	Clarify the design that subjects with low HbA1c entering open-label will be limited according to stratum. Updated to align with the latest dapa PSSR.
Table 1 Study Design for Stratum A & Stratum B	"Assess FPG for rescue" deleted for WK 24 in the table and footnotes as recue is not applicable for Week 24 visit. In footnotes l and 12, clarify the reason for not requirement of FPG blood collection at Visit 5, WK24/ETD if MTT was performed at the

	same visit.
Table 2 Lack of glycaemic control criteria for initiation of rescue medication	Excluded Week 24 for rescue medication and reworded to clear the boundaries of the visit labels.
4.3.2 Double-blind treatment period (Week 6, 12, 18) and 4.4.3 WK24/Rescue/Early Treatment Discontinuation Visit	Reworded to exclude rescue in Week 24 in visit narratives.
5.2.1.3 eGFR	Typo corrected in eGFR formula.
5.2.1.4 Urinalysis	Urine glucose deleted to avoid risk of treatment unblinding.
5.2.3 ECG	Clarify that details of microscopic urinalyses should refer to laboratory manual. Added description on how to handle abnormal findings based on ECG.
6.1.1 Adverse events of special interest	"Fracture" added to be consistent with global pivotal study.
6.3.6 Adverse events based on examinations and tests	Added reference instructions on AE handling and safety analyses for ECG.
6.3.7 Hypoglycaemia	Replaced the wordings of “Plasma glucose concentration” with “glycemia level” and update “plasma glucose” to “blood glucose” since sources of glycemia value are not limited to plasma glucose, also include SMBG and CGM based on ADA guideline.
8.2 Sample size estimate	Updated to align with synopsis.
8.3.1 Efficacy analysis sets	Clarified the description of per protocol analysis set to align with iPD definition in new SOP.
8.3.3 Open-label safety analysis sets	Analysis set name updated to allow further efficacy analysis.
8.5.3 Subgroup Analysis	Specify time periods for duration of T2DM.
8.5.6 Exploratory Analysis	

(if applicable) 8.5.7 Safety analysis 8.5.8 Methods for multiplicity control 8.6 China Cohort 10.5 Changes to the protocol and informed consent form	Clarify that ITT will be used for exploratory analysis. Clarify safety analyses for the double-blinded treatment period Clarify more details on multiplicity control for hierarchical testing. Added section 8.6 for China cohort as a China led study. Deleted administrative change as it is not applicable any more based on current SOP.
Version 3.0, 29 Jun 2018	
Section	**Summary of change**
Multiple	Correct typos & hyperlinks, cross-references, update abbreviation list, change "patient(s)" to "subject(s)" and AstraZeneca House style. Rephrasing to increase readability and clear possible confusions.
Title page Version History	Add details of previous two versions and study name "DS Navigation" Correct date of version 1.0.
Protocol Synopsis Investigational Product, dosage and mode of administration Statistical methods	Update site number and study phase. Add details regarding Double-Dummy treatment. Rephrasing due to unclear wording on capping.
1.4 Study design Figure 1	Delete unclear wordings on capping.
3.1 Inclusion Criteria	Move open-label treatment period subject inclusion criteria on HbA1c of both Stratum A and Stratum B from exclusion criteria. Update pregnancy test details to clarify serum pregnancy test at screening and urine pregnancy test at randomization, and remove the sensitivity information regarding to urine pregnancy test. Specify acceptable method of birth control.

3.2 Exclusion Criteria	Specify the exclusion criteria for historical use of SGLT2 inhibitors. Add the exclusion criteria for historical over-the-counter weight loss medication. Add the exclusion criteria for abnormal finding in ECG. Update the hypersensitivity reaction related to study treatment and their excipients based on PSSR requirement. Reword eligibility check based on microscopic hematuria urinalysis to allow re-test.
3.3 Subject enrolment and randomization 3.6 Methods for ensuring blinding	Clarify the re-screening process. Delete duplicated wordings on HbA1c values blinding details. Remove the urinary glucose values and urinary glucose: creatinine ration from blinded procedure.
3.10.3 Lost to follow-up	Update unblinded FPG process for rescued subjects. Add “Lost to follow-up” section based on new CSP template.
4. Study Plan and Timing of Procedures	Tables and footnotes updated to be consistent with the wordings from section 4.1 to section 4.3. Update hematuria urinalysis procedure. Update ECG and pregnancy test schedule and procedures.
Table 1 Study Design for Stratum A & Stratum B	Delete Spot Urine Glucose Quantification and glucose: creatinine ratio as not needed for well documented products, and delete accordingly over the CSP. Split GFR from clinical chemistry as it is not part of standard chemistry testing. Split TSH from Hepatitis Screening panel and HIV testing. Add Free T4 reflex testing to TSH testing. Add extended period information for subjects with GAD antibodies testing to be consistent with synopsis and section 4.2. Add the collection of unused study medications and empty packaging Review concomitant medications within at least 3 months rather than

	only within 3 months from both ethical and operational perspective.
4.1 Screening visit (Visit 1, Week -18 for Stratum A and Week -10 for Stratum B)	Change urine pregnancy test to serum pregnancy test for Visit 1 to be consistent with table 1 and throughout the CSP. Add ECG testing at screening and be consistent with Table 1. Change the study procedure for hematuria microscopic urinalysis and delete sport urine glucose quantification and glucose: creatinine ratio at screening. Update the requirement for confirmation test in subjects with HCV antibody low positive.
4.2 Open-label treatment period	Delete pregnancy tests from visit 2 to visit 4. Delete hematuria urinalysis during open-label period. Specify a follow-up visit within 3-5 days following receipt of FPG value from central laboratory should be performed for subjects with FPG value > 270 mg/dl to clear potential confusions from readers. And apply this wording throughout the CSP when necessary.
4.3 Double-blind, Double-Dummy Treatment Period	Add details of MTT test requirements. Specify urine pregnancy test will be performed locally at randomization visit.
4.3.1 Randomization (Day 1)	Split GFR from Chemistry and be consistent with Table 1.
4.3.2 Double-blind treatment period (Week 6, 12, 18)	Delete sport urine glucose quantification and glucose: creatinine ratio. Delete haematuria urinalysis in double-blind period.
4.3.3 Week24/Rescue/ Early Treatment Discontinuation visit	Delete pregnancy tests for double-blind treatment period. Specify FPG value assessment for rescue eligibility. Add details of MTT test requirements and delete pregnancy test for Week24/Rescue/Early Treatment Discontinuation. Add the collection of unused study medications and empty packaging Specify that contact IxRS for drug dispensing and remind subjects to fast, bring patient diaries/glucose meter if needed.

5. Study Assessments 5.1 Efficacy assessments	Add total blood volume of each subject over the duration of the study, delete the specific blood volume for each test (previous Table 3 Volume of blood to be withdrawn from each patient) which should be specified in lab manual.
5.2.1.1 Hematology	Delete duplicated wordings on HbA1c values blinding details. Remove the urinary glucose values and urinary glucose: creatinine ration from blinded procedure.
5.2.1.2 Chemistry	Update unblinded FPG process for rescued subjects.
5.2.1.4 Other clinical laboratory evaluations	Detailed tests of hematology and chemistry assessments are deleted here as duplicated with Table 3. Split eGFR from clinical chemistry as it is not part of standard chemistry testing (refer to section 5.2.1.3). Following numbering in this section was updated accordingly. Update the requirement for confirmation test in subjects with HCV antibody low positive. Specify pregnancy testing to be consistent with section 4.
5.2.3 ECG	Clarify the ECG testing at Week 24 and delete duplicated wordings.
5.2.4 Vital Signs	Specify Alcohol/tobacco/nicotine/caffeine restrictions.
5.2.5.3 Hematuria	Update the contents in hematuria.
5.2.5.5 Hepatic events	Delete contents in hepatic events as it is no longer applicable for this study.
5.7 Biomarker	Delete the whole section of “Biomarker” as not applicable to this study.
6.3.2 Follow-up of AEs and SAEs	Add AE/SAE follow-up information based on new CSP template.
6.3.3 Variables	Add saxagliptin into AE causality evaluation.
6.3.7 Hypoglycaemia	Update the hypoglycaemia section. Remove the definition of probable symptomatic hypoglycaemia and relative hypoglycaemia as it's no longer used in ADA 2018. Correct the typo for plasma glucose concentration threshold for clinically significant hypoglycaemia. Clarify overdose definition to include saxagliptin and be consistent

6.5 Overdose 6.7 Medication error	with SOP. Specify the timeline of AstraZeneca response on SAE associated medication error, to be consistent with new CSP template. Specify the medication error report will be applicable for both saxagliptin and dapagliflozin.
7.1 Identify of investigational product(s) 7.7 Concomitant and other treatments Tables 5 Lists prohibited medications and the applicable time frames	Re-evaluate the impact of lactose content in dapagliflozin on lactose-intolerant individuals and update accordingly. Delete the strength (500mg) of Metformin as both IR and XR will be used. Delete table 5 as duplicate with prohibited medication section.
8.2 Sample size estimate	Rephrase the capping information to be consistent with synopsis.
9.3 Study timetable and end of study	Update study timeline to be realistic. Change the order of saxagliptin and dapagliflozin to be consistent with other dapagliflozin studies.
11 List of References	Add the reference of “Levey AS 2007”.
Appendix D Algorithm for Microscopic Hematuria	Delete appendix D as it's no longer applicable in dapagliflozin program.
Appendix E Central Laboratory Assessments	Delete appendix E as not mandatorily required in current CSP template and to avoid discrepancy in lab materials.
Appendix F Actions Required in cases of increases in Liver Biochemistry and evaluation of HY’s Law	Delete appendix F as it's not required in PSSR.
Appendix G Algorithm on Management of Sustained Elevated Liver Safety Abnormalities	Delete appendix G as it's not required in PSSR.

Version 2.0, 16 Jan 2018	
Section	**Summary of change**
Multiple	Correcting typos, cross-references and AstraZeneca House style.
Protocol Synopsis International Co-ordinating Investigator Safety Objectives Statistical methods	Update to reference Double-Dummy Change NPI information Incidence of Adverse event was updated to AEs/SAEs Adverse Events of Special Interest was added Update sample size calculation information and add some language on hierarchical testing on the primary endpoints of the two dapagliflozin + saxagliptin + metformin vs. placebo + saxagliptin + metformin comparisons. Add some language to describe the model fitting and how models will be handled if they don't converge, for the primary analysis of HbA1c.
1 Introduction 1.1 Background and rationale for conducting this study 1.2 Rationale for study design, doses and control groups 1.3 Benefit/risk and ethical assessment	Update dapagliflozin approved countries information to include China Add studies results to demonstrate the efficacy and safety of saxagliptin and dapagliflozin concomitant therapy Update marketing approval and exposure information for dapagliflozin and saxagliptin, also update clinical trials information of saxagliptin and dapagliflozin Include potential risk of DKA and protection against this risk
1 Introduction 1.4 Study Design Figure 1	Add 'dapagliflozin 5 mg + saxagliptin 5 mg + Metformin (IR or XR)' arm and relevant information about dapagliflozin 5 mg Add details regarding Double-Dummy treatment
2 Study Objectives 2.1 Primary objective 2.2 Secondary objectives 2.3 Safety objectives	Add new comparison between dapagliflozin 5 mg + saxagliptin 5 mg + Metformin (IR or XR) and placebo + saxagliptin 5 mg + Metformin (IR or XR) for the primary, secondary, safety and exploratory objectives This section was updated to keep consistent with Protocol Synopsis

2.4 Exploratory objectives	Add details regarding Double-Dummy treatment
3.1 Inclusion criteria: reproductive status	Update text to make it more clear and logical Delete upper limit of age 75 years old to keep consistent with global reference study
3.2 Exclusion criteria	Update safety criteria according to dapagliflozin/saxagliptin PSSR including: exclude type 1 diabetes; further clarify DKA exclusion criteria; update renal and hepatic diseases; clarify allergies and adverse drug reaction criteria
3.3.1 Procedures for randomization	Add new arm 2: dapagliflozin 5 mg, saxagliptin 5 mg, plus metformin IR/XR Add details regarding Double-Dummy treatment
3.5 Methods for assigning treatment groups	Update randomization ratio to 1:1:1 to include new arm information
3.6 Methods for ensuring blinding	Emphasize the blinding of central laboratory assessments in protocol body
4 Study plan and timing of procedures	Correct information for microscopic haematuria to keep consistent with inclusion/exclusion criteria
Table 1 footnote m 4.1.4 Screening visit (Visit 1, Week -18 for stratum A and Week -10 for stratum B)	Add details regarding Double-Dummy treatment
5 Study assessments	Update blood volume according to new request from central laboratory
5.2.1.4 Other clinical laboratory evaluations	Add 'hepatitis screening panel' to keep consistent with the exclusion criteria
6.1.1 Adverse events of special interest	This section was updated to keep the consistent with ongoing dapagliflozin and saxagliptin studies.

6.3.7 Hypoglycaemia	Add section of hypoglycaemia to provide guidance to investigator on how to collect and record hypoglycaemia events
6.7 Medication Error	Add information about Medication Error definition and reporting.
6.8.1.1 Diabetic Ketoacidosis Adjudication Committee	This section was added to meet the requirement for dapagliflozin studies
7. Investigational product and other Treatments 7.1 Identity of investigational product(s) 7.2 Dose and treatment regimens	Update IMP information to include dapagliflozin 5 mg and placebo to match Add details regarding Double-Dummy treatment
8.3 Definitions of analysis sets	Add language to specify that 'Selected safety analyses for the open-label treatment period will be based on open-label safety analysis set'.
8.3.1 Efficacy analysis set	Update the definition of ITT set. Specify that for analysis based on per-protocol set, subjects will be analysed based on randomized treatment.
8.3.3 Open-label safety analysis set	This analysis set is added because selected safety analyses will be performed for the open-label treatment period using the open-label safety analysis set
8.5.1 Analysis of primary analysis set	Add some language to specify the testing of two comparisons based on primary endpoint. Add some language to describe the model fitting and how models will be handled if they don't converge. Make it clear that in the primary analysis, data prior to study treatment discontinuation and rescue will be included. Add details regarding Double-Dummy treatment
8.5.5 Sensitivity analysis	Specify missing data will be imputed by LOCF for analysis of proportion of subjects achieving a therapeutic glycaemic response and 2-hr PPG.

	Make it clear that in the 1st sensitivity analysis for HbA1c based on ITT set, all available data will be included, including data after rescue and/or study treatment discontinuation. In the 2nd sensitivity analysis for HbA1c based on ITT set, data prior to study treatment discontinuation and rescue will be included. Specify that the 3rd sensitivity analyses for HbA1c is to repeat the primary analysis for HbA1c based on per-protocol analysis set.
8.5.7 safety analysis	Update "Open-label treated subjects analysis set" to "Open-label safety analysis set" Remove the definition of frequent events "occurring in at least 5% of subjects" after discussion with study physician and safety physician Make it clear that the main safety analysis will be based on all data, including data after rescue and/or study treatment discontinuation. The additional safety analysis for adverse events, laboratory marked abnormalities and events of hypoglycaemia may be performed excluding data after rescue and study treatment discontinuation.
8.5.8 Methods for multiplicity control	Newly added section based on new CSP template
Version 1.0, 02 Jun 2015	
Initial creation	

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PROTOCOL SYNOPSIS

A Multicenter, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Therapy with Dapagliflozin added to Saxagliptin in Combination with Metformin compared to Therapy with Placebo added to Saxagliptin in Combination with Metformin in Asian Subjects with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin and Saxagliptin

(DS Navigation)

Study site(s) and number of subjects planned

This will be a multicenter study conducted at approximately 45 sites in Asian countries (about 40 sites in China). Approximately 1004 subjects will be screened, and 342 randomized.

Study period		Phase of development
Estimated date of first subject enrolled	Q1 2019	3
Estimated date of last subject completed	Q1 2021	3

Study design

Study D1683C00008 is a 24-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, Phase 3 study designed to investigate if the efficacy and safety of triple combination of dapagliflozin 5 mg or 10 mg added to saxagliptin 5 mg plus metformin is superior to the dual therapy of saxagliptin 5 mg added to metformin in reducing hemoglobin A1c (HbA1c).

After written informed consents have been obtained at screening visit, subjects will be checked for all applicable inclusion/exclusion criteria, and laboratory samples will be taken and submitted. In Stratum A, subjects should have a stable dose of metformin immediate release (IR)/extended release (XR) (≥ 1500 mg/day or a maximal tolerated dose) for at least 8 weeks prior to screening. In Stratum B, subjects should have a stable dose of metformin IR/XR (≥ 1500 mg/day or a maximal tolerated dose) AND a dipeptidyl peptidase-4 (DPP-4) inhibitor (free form combination) at the maximum approved dose for at least 8 weeks prior to screening. Eligible subjects who complete the screening period will enter the lead-in period, which includes open-label saxagliptin 5 mg and metformin IR/XR treatment for 16 weeks in Stratum A or 8 weeks in Stratum B. For subjects in Stratum B, DPP-4 inhibitor will be switched to saxagliptin 5 mg at Week -8. Metformin treatment regimen has to be the same as subjects were using at study entry and keep unchanged throughout the whole study period for both strata. On Day 1 of randomization visit, eligible subjects will be randomized into one of three treatment groups (dapagliflozin 5 mg and dapagliflozin 10 mg placebo to match, dapagliflozin 10 mg and dapagliflozin 5 mg placebo to match or dapagliflozin 5 mg placebo to match and dapagliflozin 10 mg placebo to match). Thereafter subjects will receive oral administration of study treatments once daily for 24 weeks. Scheduled visits will occur at Week 6, 12, 18 and 24 during double-blind treatment period.

Objectives

Primary Objective:	**Outcome Measure:**
To compare the mean change from baseline in glycosylated hemoglobin (HbA1c) achieved with dapagliflozin 5 mg or dapagliflozin 10 mg added to saxagliptin 5 mg plus metformin versus (vs.) placebo added to saxagliptin 5 mg plus metformin after 24 weeks of oral administration of double-blind treatment	Mean change from baseline in HbA1c at Week 24
Secondary Objective:	**Outcome Measure:**
• To compare the mean change from baseline achieved with dapagliflozin 5 mg or dapagliflozin 10 mg added to saxagliptin 5 mg plus metformin vs. placebo added to saxagliptin 5 mg plus metformin after 24 weeks of oral administration of double-blind treatment in the following: 1) Fasting plasma glucose (FPG) 2) 2-hour PPG from a meal tolerance test (2-hour MTT) 3) Total body weight • To compare the proportion of subjects achieving a therapeutic glycemic response, defined as a HbA1c < 7.0%, with dapagliflozin 5 mg or dapagliflozin 10 mg added to saxagliptin 5 mg plus metformin vs. placebo added to saxagliptin 5 mg plus metformin after 24 weeks of oral administration of double-blind treatment	• Mean change from baseline in fasting plasma glucose (FPG) at Week 24 • Mean change from baseline in 2-hour PPG during a meal tolerance test (2-hour MTT) at Week 24 • Mean change from baseline in Total body weight at Week 24 • Percent of subjects achieving a therapeutic glycaemic response, defined as a HbA1c < 7.0% at Week 24

Safety Objective:	**Outcome Measure:**
To evaluate the safety and tolerability of therapy with dapagliflozin 5 mg or dapagliflozin 10 mg added to saxagliptin 5 mg plus metformin vs. placebo added to saxagliptin 5 mg plus metformin after 24 weeks of oral administration of double-blind treatment	• Adverse Events (AEs) /Serious Adverse Events (SAEs) • AEs of special interest (AESI) • Clinical laboratory tests • Physical examination • ECG • Vital signs
Exploratory Objective:	**Outcome Measure:**
• To assess the percent of subjects who require rescue or discontinue study treatment for lack of efficacy with dapagliflozin 5 mg or dapagliflozin 10 mg added to saxagliptin 5 mg plus metformin vs. placebo added to saxagliptin 5 mg plus metformin up to 24 weeks of oral administration of double-blind treatment • To assess the time to glycemic rescue or discontinuation for lack of efficacy with dapagliflozin 5 mg or dapagliflozin 10 mg added to saxagliptin 5 mg plus metformin vs. placebo added to saxagliptin 5 mg plus metformin during the short-term double-blind period • To assess the mean change from baseline in area under the curve (AUC) of glucose obtained during a MTT with dapagliflozin 5 mg or dapagliflozin 10 mg added to saxagliptin 5 mg plus metformin vs. placebo added to saxagliptin 5 mg plus metformin after 24 weeks of oral administration of double-blind treatment • To assess the mean percent change from baseline in fasting serum lipids (Total-C, LDL-C, HDL-C, TG) with dapagliflozin 5 mg or dapagliflozin 10 mg added to saxagliptin 5 mg plus metformin vs. placebo added to saxagliptin 5 mg plus metformin after 24 weeks of oral administration of double-blind treatment	• Percent of subjects who require glycemic rescue or discontinue study treatment for lack of efficacy up to Week 24 • Time to glycemic rescue or discontinuation for lack of efficacy in the double-blind treatment period • Mean change from baseline in AUC of glucose obtained during a MTT at Week 24 • Mean percent change from baseline in fasting lipids (Total-C, LDL-C, HDL-C, TG) at Week 24

Target subject population

Approximately 342 subjects aged ≥18 years who have type 2 diabetes mellitus (T2DM) with inadequate glycemic control (defined as a central laboratory HbA1c ≥ 7.0 and ≤ 10.5% for both strata obtained at the week -2 visit) taking stable metformin IR/XR therapy and open-label saxagliptin 5 mg will be randomized to 1 of 3 treatment groups in a 1:1:1 ratio.

Duration of treatment

Study duration will be at least 42 weeks (Stratum A) or 34 weeks (Stratum B), including a 2-week screening period, a 16-week (Stratum A) or 8-week (Stratum B) lead-in period, and a 24-week double-blind treatment period.

Investigational product, dosage and mode of administration

Dapagliflozin and dapagliflozin placebo to match

Dapagliflozin 5mg tablets, dapagliflozin 10 mg tablets and dapagliflozin 5mg or 10mg placebo to match tablets, administered orally once daily for the 24-week double-blind treatment period.

Other Treatments

Saxagliptin: Saxagliptin 5 mg tablets, administered orally once daily for the lead-in period and the 24-week double-blind treatment period.

Metformin: Throughout the study duration, subjects should continue to adhere to the same metformin treatment regimen as they were using at study entry. Metformin should be administered and stored according to product and country specific labelling.

Rescue therapy: Subjects who require rescue therapy should receive standard of care treatment (insulin or any other antidiabetic agents except Glucagon-like peptide-1 (GLP-1) analogues, other DPP-4 inhibitors and/or SGLT2 inhibitors or metformin).

Statistical methods

The primary endpoint (mean change from baseline in HbA1c at Week 24) will be assessed comparing dapagliflozin 5 mg or dapagliflozin 10 mg added to saxagliptin 5 mg plus metformin vs. placebo added to saxagliptin 5 mg plus metformin. Statistical significance of the primary endpoint will be claimed if the p-values for dapagliflozin 10 mg + saxagliptin 5 mg + metformin vs. placebo + saxagliptin 5 mg + metformin comparison is significant at the 2-sided, 0.05 significance level. As the success of primary endpoint on the dapagliflozin 5 mg + saxagliptin 5 mg + metformin vs. placebo + saxagliptin 5 mg + metformin comparison is important, the sample size is planned to provide at least 90% power for primary endpoint on both comparisons.

With 108 subjects per treatment group with post-baseline assessment, there is 95% power to detect -0.5% difference for dapagliflozin 10 mg + saxagliptin 5 mg + metformin vs. placebo + saxagliptin 5 mg + metformin comparison, assuming a standard deviation (SD) of 1.0% with a 2-sided significance level of 0.05. This sample size will also provide at least 90% power to detect -0.5% difference for both dapagliflozin 10 mg + saxagliptin 5 mg + metformin vs. placebo + saxagliptin 5 mg + metformin and dapagliflozin 5 mg + saxagliptin 5 mg + metformin vs. placebo + saxagliptin 5 mg + metformin comparisons, assuming a SD of 1.0% with a 2-sided significance level of 0.05.

Assuming that 5% of subjects would not have a post-baseline assessment, a total of approximately 342 subjects (114 subjects per treatment arm, with about 91 subjects from China and about 23 subjects from other countries/regions) need to be randomized. In other words, Chinese subjects will constitute about 80% of the total number of subjects. This study includes two strata, based on prior antihyperglycemic treatment. Subjects with HbA1c uncontrolled on a stable dose of metformin (≥ 1500 mg/day or a maximal tolerated dose) are enrolled into a 16-week open-label treatment period (Stratum A), adding saxagliptin 5 mg to metformin. Subjects with HbA1c uncontrolled on a stable dose of metformin (≥ 1500 mg/day or a maximal tolerated dose) AND a maximal dose of a DPP-4 inhibitor are enrolled into an 8-week open-label treatment period (Stratum B), following treatment with saxagliptin 5 mg plus metformin. Subjects from two strata who remain uncontrolled HbA1C are subsequently randomized.

It is desired to have approximately 33% of the randomized subjects coming from Stratum B. In addition, enrolment of subjects with HbA1c ≥ 8.0% and < 9.0% (Stratum A) and subjects with HbA1c ≥ 7.5% and ≤ 8.5% (Stratum B) into the open-label treatment period will be limited to approximately 171 subjects (about 50% of the randomized subjects number in each stratum).

About 40% (Stratum A) and 6.5% (Stratum B) of subjects are expected to be discontinued due to severe lack of glycaemic control (defined as FPG > 270 mg/dL at Week -10 or Week -2 in Stratum A and Week -2 only in Stratum B) during the open-label treatment period. In addition, it is expected that 50% of screened subjects will fail to meet eligible criteria for open-label treatment of each stratum. This leads to a total of 1004 subjects to be screened, with a targeted 380 subjects in Stratum A and 122 subjects in Stratum B to enter the open-label treatment period.

The primary efficacy analysis will compare the change from baseline in HbA1c at Week 24 for dapagliflozin 5 mg or dapagliflozin 10 mg + saxagliptin 5 mg + metformin treatment groups and the placebo + saxagliptin 5 mg + metformin group. Each comparison will be performed at the 0.05 significance level (2-sided) using the hierarchical testing specified in Section8.1. This maintains the familywise type I error rate at 0.05.

The primary efficacy analysis of HbA1c at week 24 will be performed using a mixed-model repeated-measures (MMRM) model with terms for treatment group, stratum, baseline HbA1c value, time, the interaction of treatment and time, and the interaction of baseline HbA1c value and time in the model, including observations prior to rescue and study treatment discontinuation only, without explicitly imputing missing data. 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 issue, the back-up models will be used (e.g. calculate the denominator degrees of freedom using other method like Satterthwaite approximation, use other covariance matrix like Toeplitz, AR (1), use simpler models, and etc.). Details will be documented in statistical analysis plan (SAP). Point estimates and 95% confidence intervals

will be calculated for the adjusted mean changes within each treatment group as well as for the differences in adjusted mean changes between treatment groups.

Intent-to-treat (ITT) analysis set will be used for the primary efficacy analysis.

The same MMRM approach used for HbA1c evaluation will also be used for the analysis of FPG and total body weight. Point estimates and 95% confidence intervals will be calculated for the adjusted mean changes within each treatment group as well as for the differences in adjusted mean changes between treatment groups.

The analysis of covariance (ANCOVA) using last observation carried forward (LOCF) methodology with terms for treatment group, stratum, and baseline 2-hour postprandial plasma glucose (PPG) value will be used to evaluate 2-hour PPG. Point estimates and 95% confidence intervals will be calculated for the adjusted mean changes at Week 24 within each treatment group as well as for the differences in adjusted mean changes between treatment groups.

The proportion of subjects achieving a therapeutic glycaemic response (defined as HbA1c < 7.0%) at Week 24 (LOCF) will be summarized by treatment group and compared between treatment groups using the logistic regression based on methodology of Zhang et al (Zhang 2008) and Tsiatis et al (Tsiatis 2008**)** with adjustment for baseline HbA1c and stratum. Point estimates and 95% confidence intervals will be calculated for the response rate within each treatment group as well as the difference in response rates between treatment groups.

Safety analyses for the double-blind treatment period will be performed using the safety analysis set, including data after rescue. Safety analyses will include, where appropriate, descriptive statistics, counts, and percentages for AEs and other safety measures. No formal statistical tests will be performed for safety endpoints. Selected safety and efficacy analyses will be performed for the open-label treatment period using the open-label treated subjects analysis set.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Clinical Study Protocol (CSP).

Abbreviation or special term	Explanation
ADA	American Diabetes Association
AE	Adverse event
AESI	AEs of special interest
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
AUC	Area under the curve
BMI	Body mass index
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
CAC	Cardiovascular Adjudication Committee
CEC	Clinical Event Committee
CK / CPK	Creatine kinase
CrCl	Creatinine clearance
CRF	Case Report Form (electronic/paper)
CRO	Contract research organization
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CSRAF	Clinical Supplies Return Authorization Form
CV	Cardiovascular
DBP	Diastolic blood pressure
DKA	Diabetic ketoacidosis
DPP-4	Dipeptidyl peptidase-4
ECG	Electrocardiogram
E-code	Enrolment code
ESRD	End-stage renal disease
eCRF	Electronic Case Report Form

Abbreviation or special term	Explanation
eGFR	Estimate glomerular filtration rate
ETD	Early treatment discontinuation
EU	European Union
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GAD	Glutamic acid decarboxylase
GCP	Good Clinical Practice
GLP-1	Glucagon-like peptide-1
GMP	Good manufacturing practice
HAV	Hepatitis A virus
Hb	Hemoglobin
HbA1c	Hemoglobin A1c / glycosylated hemoglobin
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HR	Heart rate
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IP	Investigational Product
IR	Immediate Release
ITT	Intent-to-treat
IxRS	Interactive voice/web response system
Kg	Kilogram
LDL-C	Low density lipoprotein cholesterol
LOCF	Last observation carried forward
MCH	Mean cell hemoglobin
MCHC	Mean cell haemoglobin concentration
MCV	Mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction

Abbreviation or special term	Explanation
MMRM	Mixed-model repeated-measures
MOA	Mechanism of action
MTT	Meal Tolerance Test
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
PP	Per protocol
PPG	Postprandial plasma glucose
PSSR	Project Specific Safety Requirements
RBC	Red blood cell
SA	Sickle cell anemia
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
Scr	Serum creatinine
SD	Standard deviation
SGLT2	Sodium glucose cotransporter 2
SMBG	Self-monitoring of blood glucose
SU	Sulfonylurea
T2DM	Type 2 diabetes mellitus
T4	Thyroxine
TB	Total bilirubin
TG	Triglyceride
TIA	Transient ischemic attack
TSH	Thyroid stimulating hormone
TZD	Thiazolidinedione
ULN	Upper limit of normal
US	United States
UTI	Urinary tract infection
vs.	Versus
WBDC	Web Based Data Capture
WOCBP	Women of childbearing potential
XR	Extended Release

1. INTRODUCTION

1.1 Background and rationale for conducting this study

T2DM is a chronic progressive disease, characterized by hyperglycaemia and an increased risk of microvascular and macrovascular complications. Despite the irrefutable evidence for the importance of maintaining tight glycemic control, achieving and maintaining the glycaemic treatment goal is still challenging. There are approximately 50% of T2DM subjects fail to achieve the American Diabetes Association (ADA) goal for glycemic control of HbA1c < 7.0% (Hoerger et al 2008). In the United States (US) according to NHANES 2004 data, 44.3% of subjects with T2DM have HbA1c levels ≥ 7% (Hoerger et al 2008). This level of poor control appears not to have improved. NHANES 2006 still showed that 40% of subjects have HbA1c > 7% (Nguyen et al 2011). In China, among subjects with diabetes, only 25.8% (95% CI, 24.9%-26.8%) received treatment for diabetes, and only 39.7% of those treated had adequate glycemic control (Xu Y et al 2013). Progressive beta cell failure, weight gain, and hypoglycemia are major obstacles for the achievement of optimal glycemic control (DeFronzo RA et al 2009).

Typically, the treatment paradigm consists of a step wise addition of different classes of antihyperglycemic drugs, as most subjects eventually require 2 or more agents to achieve or maintain glycemic targets. Current sequential add-on second and third line oral therapy mainly includes older classes of oral drugs like sulfonylureas (SUs) and thiazolidinediones (TZDs). Some of their key limitations are weight gain and increased risk of hypoglycaemia (SU only). Hypoglycaemia is a clinically important barrier to optimizing treatment and there is emerging evidence that hypoglycaemia is associated with negative cardiovascular (CV) outcomes. SUs (and insulin) are associated with a high risk of hypoglycaemia and caution is recommended when using combination therapy with agents causing hypoglycaemia if HbA1c is < 8.5% (Rodbard et al 2009). Efforts by subjects to lose weight as part of a therapeutic lifestyle program are undermined by therapies that lead to weight gain. Over 85% of subjects with T2DM are overweight or obese, and additional weight gain is undesirable and often results in reducing treatment compliance by the subjects. TZDs, SUs and insulin, are all associated with a significant weight gain.

Because of the lack of, and delay in, glucose control, the progressive nature of the disease and the limitations of available oral and non-oral therapies, there is a significant medical need for additional oral combination treatment options for T2DM.

Saxagliptin is a DPP-4 inhibitor for the treatment of subjects with T2DM. By increasing and prolonging active incretin concentrations, saxagliptin increases insulin release and decreases glucagon concentrations in the circulation in a glucose-dependent manner. Dapagliflozin is a highly potent, selective, and reversible inhibitor of sodium glucose cotransporter 2 (SGLT2) that improves glycaemic control in subjects with T2DM by reducing renal glucose reabsorption, leading to urinary excretion of excess glucose (glucuresis). Therefore, both saxagliptin and dapagliflozin complement metformin's mechanism of action (MOA). Saxagliptin and dapagliflozin have demonstrated, both individually and in combination with

metformin in general a favourable safety and tolerability profile. They have shown as single agents, as well as in (initial and add-on) combination with metformin, a low propensity for hypoglycaemia consistent with their respective glucose dependent MOA. Both drugs have either demonstrated weight neutrality (saxagliptin) or moderate weight reduction (dapaglifozin). In study MB102-129, which was intended to compare the addition of dapagliflozin vs. placebo as add-on therapy in subjects with T2DM who are inadequately controlled on saxagliptin plus metformin therapy, dapagliflozin showed a significant decrease in HbA1c compared to placebo (-0.82%, -0.10%, respectively). Dapagliflozin also demonstrated significant decrease in FPG (-32.7 mg/dL vs. -5.3 mg/dL, respectively), PPG (-73.5 mg/dL vs. -38.0 mg/dL, respectively), and weight (-1.91 kg vs. -0.41 kg, respectively), and more subjects achieving therapeutic glycaemic response (38.0% vs. 12.4%, respectively). This study also demonstrated a favourable safety and tolerability of dapagliflozin when added on to saxagliptin and metformin.

1.2 Rationale for study design, doses and control groups

This study is a Phase 3 study, performed as part of the clinical development program for both dapagliflozin (a SGLT2 inhibitor) and saxagliptin (a DPP-4 inhibitor) for the treatment of T2DM. The study is intended to compare the addition of dapagliflozin 5 mg or 10 mg vs. placebo as add-on therapy in subjects with T2DM who are inadequately controlled on saxagliptin 5 mg plus metformin therapy.

Metformin is the oral first line gold standard agent. Metformin is a biguanide, its MOA is to decrease hepatic glucose output thus lowering fasting hyperglycaemia. Metformin is recommended as the initial pharmacological therapy because of its glycaemic efficacy, weight neutrality, low risk of hypoglycaemia, good tolerability and relatively low cost (Inzucchi et al 2012). Metformin's dose limiting side effect is gastrointestinal tolerability. However, doses≥ 1500 mg are generally well tolerated.

Saxagliptin is approved in many countries worldwide, including the US, Canada, China and countries in the European Union (EU) as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM. The results from the 8 Phase II and Phase III clinical studies with saxagliptin support the oral dose of 5 mg once daily in a wide range of subjects with T2DM, as either monotherapy, add on combination therapy with metformin, a TZD, a SU, insulin, or initial combination therapy with metformin. Saxagliptin 5 mg resulted in clinically meaningful reductions in HbA1c, as well as FPG, PPG, insulin, C-peptide, and glucagon levels and is the recommended dose according to the approved drug label.

Dapagliflozin is approved in many countries worldwide, including the US, Canada, China and countries in the EU, as an adjunct to diet and exercise to improve glycaemic control in subjects with T2DM. The 5 mg and 10 mg doses are chosen for this study, because in US, Canada, Switzerland and China, the recommended starting dose is 5 mg once daily, and can be increased to 10 mg once daily in subjects tolerating dapagliflozin who require additional glycaemic control. Both strengths of dapagliflozin has demonstrated clinically meaningful reductions in HbA1c individually or as add on therapy with other OADs. Treatment with dapagliflozin, with its unique MOA, induces a persistent loss of excess glucose with associated calories in the urine, resulting in a consistent and maintained reduction of total body weight, in addition to improved glycaemic control. Dapagliflozin also has a mild diuretic effect, which in combination with weight loss, has the potential to reduce blood pressure (BP).

The combination of dapagliflozin 10 mg and saxagliptin 5 mg has been studied initially in 3 Phase III trials. The main study MB102-129, as mentioned above, was intended to compare the addition of dapagliflozin vs. placebo as add-on therapy in subjects with T2DM inadequately controlled on saxagliptin plus metformin therapy. In study CV181-168 (sequential administration) 5 mg saxagliptin or placebo were added to a background of 10 mg dapagliflozin and metformin. In study CV181-169 (dual administration) saxagliptin 5 mg plus dapagliflozin 10 mg or the individual components plus placebo were given to a background of metformin. All of the three studies found the co-administration of dapagliflozin 10 mg and saxagliptin 5 mg to be well tolerated and efficacious.

1.3 Benefit/risk and ethical assessment

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

Prior to approval, dapagliflozin was evaluated in 5 core Phase IIb studies, 16 core Phase III studies, and 3 regional Phase III studies. Dapagliflozin has global market approval and based on global cumulative sale figures up to March 2016 it is estimated that dapagliflozin has been administered for >1,000,000 patient years.

Prior to approval, saxagliptin was evaluated in 6 pivotal Phase III, randomized, double-blind controlled trials at doses of 2.5 mg to 10 mg. When added to standard of care in subjects with T2DM at high CV risk, saxagliptin neither reduced nor increased the risk of the primary composite endpoint of CV death, myocardial infarction (MI), or ischemic stroke (Scirica et al 2013).

Considering the comprehensive previous clinical experience with saxagliptin and dapagliflozin and the combination of dapagliflozin 10 mg and saxagliptin 5 mg has been studied in 3 Phase III trials, the study's design features (including the inclusion, exclusion, and discontinuation criteria), planned safety procedures, and participation in this study presents a minimal and thus acceptable risk to the individual subjects who will be included.

Protection against risks

The present study has been designed with appropriate measures in place to monitor and minimize any of the potential health risks to participating subjects. In order to ensure the safety of all subjects participating in this study, AstraZeneca is conducting a real-time review of all safety information from all ongoing clinical dapagliflozin and saxagliptin studies as they become available. Safety signal detection will include the integration of all available sources of safety information, including clinical study data, AE reports, pre-clinical data, epidemiological studies and literature reports, to identify and characterize unrecognized safety risks or changes in those which are currently expected adverse drug reactions. Any information that may affect the benefit-risk profile of dapagliflozin and saxagliptin will be immediately communicated to relevant Health Authorities and appropriate actions will be taken regarding the clinical program as needed. In addition, all studies which include dapagliflozin are subject to a carefully designed patient risk management plan that includes the temporary and if necessary permanent discontinuation of investigational product (IP) in individual subjects in whom a potential health risk or a laboratory abnormality of clinical concern has been identified. Investigators are also provided guidance on appropriate management of potential risks such as hypoglycaemia, urinary tract infections (UTI) and decreased renal function and also the potential risks of saxagliptin mentioned in the Risk Management Plan.

Ketoacidosis

There have been post marketing reports of ketoacidosis, including diabetic ketoacidosis (DKA), in subjects with type 1 and type 2 diabetes mellitus taking dapagliflozin and other SGLT2 inhibitors. Dapagliflozin is not indicated for the treatment of subjects with type 1 diabetes mellitus.

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

Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (e.g., type 1 diabetes, history of pancreatitis, or pancreatic surgery), insulin dose reduction, reduced caloric intake, or increased insulin requirements due to infections, illness or surgery and alcohol abuse. Dapagliflozin should be used with caution in these subjects.

Potential benefits to subjects

Based on prior clinical trials experience and post-marketing information, both saxagliptin and dapagliflozin have a favourable benefit-risk ratio as monotherapy and add-on combination therapy. Integrated analyses of the safety data from the initial clinical studies demonstrated that the combined use of saxagliptin 5 mg and dapagliflozin 10 mg administered as either a dual or a sequential add-on to metformin was well tolerated in T2DM subjects who were

inadequately controlled on metformin alone. The combined use of saxagliptin 5 mg and dapagliflozin 10 mg was associated with a low risk of hypoglycaemia. Overall, the safety profile of administering the 2 agents together was consistent with prior clinical trials which evaluated the safety of these agents as monotherapy or as add-on therapy. In these 3 Phase III clinical studies, treatment with saxagliptin 5 mg and dapagliflozin 10 mg showed clinically relevant decreases in HbA1c, leading to a large proportion of subjects achieving the therapeutic goal of HbA1c <7%, and modest reduction in body weight in subjects with T2DM. In addition, saxagliptin is expected to be weight neutral and dapagliflozin to reduce weight moderately, while both have shown a low risk for hypoglycaemia in combination with metformin. Subjects are also expected to receive some benefit in the form of increased medical care/attention when participating in study procedures, which includes multiple clinic visits and physical examinations over the duration of the study. Subjects will also receive counselling on dietary and life-style modifications.

Informed consent and alternatives to participation

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

1.4 Study design

Figure 1 presents the overall design of the study.

Study D1683C00008 is a 24-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, Phase 3 study designed to investigate if the efficacy and safety of triple combination of dapagliflozin 5 mg or 10 mg added to saxagliptin 5 mg plus metformin is superior to the dual therapy of saxagliptin 5 mg added to metformin in reducing HbA1c.

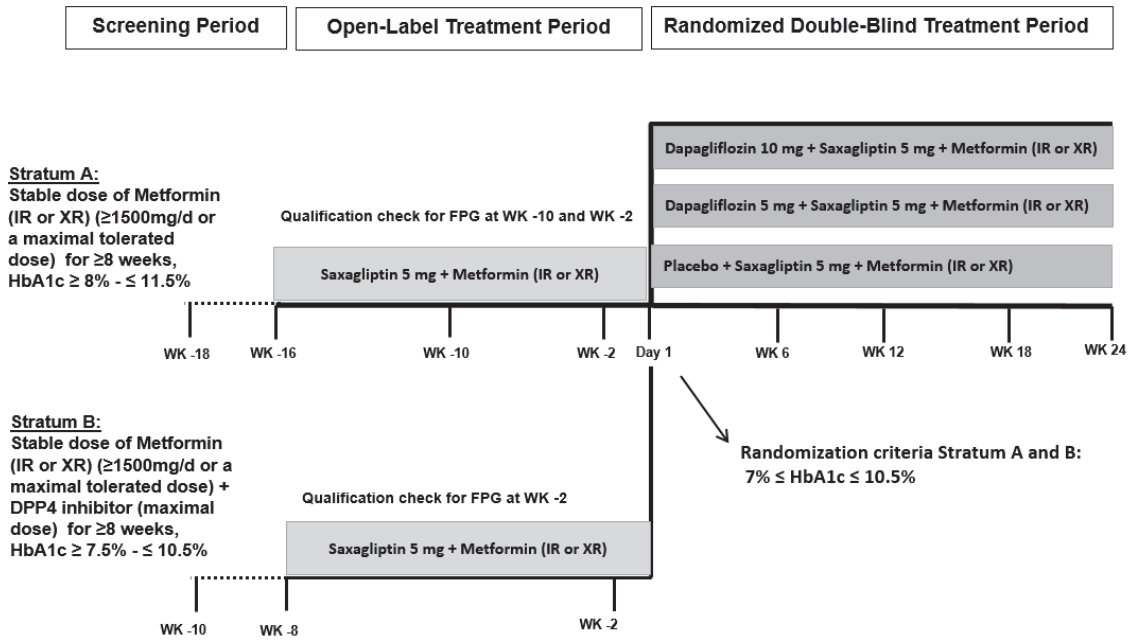
After written informed consents have been obtained at screening visit, subjects will be checked for all applicable inclusion/exclusion criteria, and laboratory samples will be taken and submitted. In Stratum A, subjects should have a stable dose of metformin IR/XR (≥ 1500 mg/day or a maximal tolerated dose) for at least 8 weeks prior to screening. In Stratum B, subjects should have a stable dose of metformin IR/XR (≥ 1500 mg/day or a maximal tolerated dose) AND a DPP-4 inhibitor (free form combination) at the maximum approved dose for at least 8 weeks prior to screening. Eligible subjects who complete the screening period will enter the lead-in period, which include open-label saxagliptin 5 mg and metformin IR/XR treatment for 16 weeks in Stratum A or 8 weeks in Stratum B. For subjects in Stratum B, DPP-4 inhibitor will be switched to saxagliptin 5 mg at Week -8. Metformin treatment regimen has to be the same as they were using at study entry and keep unchanged throughout the whole study period for both strata. On Day 1 (randomization visit), eligible subjects will be randomized into one of three treatment groups (dapagliflozin 5 mg and dapagliflozin 10 mg placebo to match, dapagliflozin 10 mg and dapagliflozin 5 mg placebo to match or dapagliflozin 5 mg placebo to match and dapagliflozin 10 mg placebo to match). Thereafter

subjects will receive oral administration of study treatments once daily for 24 weeks. Clinic visits will be scheduled at Week 6, 12, 18 and 24 during double-blind treatment period.

Subjects with lack of glycaemic control from Week 6 up to but not including Week 24 are eligible to receive open-label rescue medication, in addition to their current double-blind treatment. All rescue decisions are based on central laboratory FPG and repeated confirmatory FPG. It is mandatory for subjects who meet rescue criteria in the double-blind treatment period to first complete the rescue visit procedures before receiving open-label rescue medication in order to ensure important trial endpoint measurements are collected. Following completion of the rescue visit, subjects will be given open-label antidiabetic rescue medication (insulin or other antidiabetic agents except GLP-1 analogues, other DPP-4 inhibitors and/or SGLT2 inhibitors or metformin) which should be initiated at the lowest starting dose and titrated in accordance with the approved product label in the applicable country and by their glycaemic response per the investigator's judgement. Titration visit will be performed either on-site or via telephone at the discretion of the investigator. Rescued subjects then continue in the double-blind treatment period according to their original study visit schedule.

In addition, subjects who prematurely discontinue will be contacted to collect safety data.

Figure 1 Study design



2. STUDY OBJECTIVE

2.1 Primary objective

Primary Objective:	Outcome Measure:
To compare the mean change from baseline in glycosylated hemoglobin (HbA1c) achieved with dapagliflozin 5 mg or dapagliflozin 10 mg added to saxagliptin 5 mg plus metformin versus (vs.) placebo added to saxagliptin 5 mg plus metformin after 24 weeks of oral administration of double-blind treatment	Mean change from baseline in HbA1c at Week 24

2.2 Secondary objectives

Secondary Objective:	Outcome Measure:
• To compare the mean change from baseline achieved with dapagliflozin 5 mg or dapagliflozin 10 mg added to saxagliptin 5 mg plus metformin vs. placebo added to saxagliptin 5 mg plus metformin after 24 weeks of oral administration of double-blind treatment in the following: 1) Fasting plasma glucose (FPG) 2) 2-hour PPG from a meal tolerance test (2-hour MTT) 3) Total body weight • To compare the proportion of subjects achieving a therapeutic glycemic response, defined as a HbA1c < 7.0%, with dapagliflozin 5 mg or dapagliflozin 10 mg added to saxagliptin 5 mg plus metformin vs. placebo added to saxagliptin 5 mg plus metformin after 24 weeks of oral administration of double-blind treatment	• Mean change from baseline in fasting plasma glucose (FPG) at Week 24 • Mean change from baseline in 2-hour PPG during a meal tolerance test (2-hour MTT) at Week 24 • Mean change from baseline in Total body weight at Week 24 • Percent of subjects achieving a therapeutic glycaemic response, defined as a HbA1c < 7.0% at Week 24

2.3 Safety objectives

Safety Objective:	Outcome Measure:
To evaluate the safety and tolerability of therapy with dapagliflozin 5 mg or dapagliflozin 10 mg added to saxagliptin 5 mg plus metformin vs. placebo added to saxagliptin 5 mg plus metformin after 24 weeks of oral administration of double-blind treatment	• Adverse Events (AEs)/Serious Adverse Events (SAEs) • AEs of special interest (AESI) • Clinical laboratory tests • Physical examination • ECG • Vital signs

2.4 Exploratory objectives

Exploratory Objective:	Outcome Measure:
• To assess the percent of subjects who require rescue or discontinue study treatment for lack of efficacy with dapagliflozin 5 mg or dapagliflozin 10 mg added to saxagliptin 5 mg plus metformin vs. placebo added to saxagliptin 5 mg plus metformin up to 24 weeks of oral administration of double-blind treatment • To assess the time to glycemic rescue or discontinuation for lack of efficacy with dapagliflozin 5 mg or dapagliflozin 10 mg added to saxagliptin 5 mg plus metformin vs. placebo added to saxagliptin 5 mg plus metformin during the short-term double-blind period • To assess the mean change from baseline in area under the curve (AUC) of glucose obtained during a MTT with dapagliflozin 5 mg or dapagliflozin 10 mg added to saxagliptin 5 mg plus metformin vs. placebo added to saxagliptin 5 mg plus metformin after 24 weeks of oral administration of double-blind treatment • To assess the mean percent change from baseline in fasting serum lipids (Total-C, LDL-C, HDL-C, TG) with dapagliflozin 5 mg or dapagliflozin 10 mg added to saxagliptin 5 mg plus metformin vs. placebo added to saxagliptin 5 mg plus metformin after 24 weeks of oral administration of double-blind treatment	• Percent of subjects who require glycemic rescue or discontinue study treatment for lack of efficacy up to Week 24 • Time to glycemic rescue or discontinuation for lack of efficacy in the double-blind treatment period • Mean change from baseline in AUC of glucose obtained during a MTT at Week 24 • Mean percent change from baseline in fasting lipids (Total-C, LDL-C, HDL-C, TG) at Week 24

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

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

3.1 Inclusion criteria

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

1. Signed Written Informed Consent

   Subjects must be willing and able to give signed and dated written informed consent

2. Target Population
   a. For inclusion into open-label treatment period of Stratum A

      Subjects with T2DM with inadequate glycaemic control, defined as central laboratory HbA1c ≥ 8.0% and ≤ 11.5% obtained at the screening visit (i.e., Week -18), on stable metformin therapy alone at a dose ≥ 1500 mg per day or a maximal tolerated dose for at least 8 weeks prior to screening visit

   b. For inclusion into open-label treatment period of Stratum B

      Subjects with T2DM with inadequate glycaemic control, defined as central laboratory HbA1c ≥ 7.5% and ≤ 10.5% obtained at the screening visit (i.e., Week -10), on stable metformin therapy at a dose ≥ 1500 mg per day or a maximal tolerated dose AND a DPP-4 inhibitor (free form combination) at the maximum approved dose for at least 8 weeks prior to screening visit

   c. For inclusion into double-blind treatment period of both Stratum A and B

      Subjects with T2DM with inadequate glycaemic control, defined as central laboratory HbA1c ≥ 7.0 and ≤ 10.5% obtained at the Week -2 visit of the open-label treatment period

   d. Body mass index (BMI) ≤ 40.0 kg/m^2 at the screening visit

3. Age and Reproductive Status

   a. Men and women, aged ≥ 18 years old at time of screening visit

   b. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at screening and negative urine pregnancy test within 24 hours prior to the start of IP

      WOCBP must be using an acceptable method of contraception to avoid pregnancy throughout the study and for at least 4 weeks after the last dose of study medication in such a manner that the risk of pregnancy is minimized

      Definitions:

      Acceptable method of birth control: defined as one that results in a failure rate of <1% per year, when used consistently and correctly. The following are considered acceptable methods of contraception: total sexual abstinence; vasectomized sexual partner; male condom with spermicidal gel, tubal occlusion (ligation); intrauterine device; levonorgestrel intrauterine system; etonogestrel implants; normal and low dose combined oral contraceptive pills; norelgestromin/ethinyl estradiol transdermal system; intravaginal device (e.g., ethinyl estradiol and etonogestrel); and desogestrel.

Women NOT of childbearing potential: Women who are permanently or surgically sterilized or postmenopausal. Permanent sterilization includes hysterectomy, and/or bilateral oophorectomy, and/or bilateral salpingectomy.

Postmenopausal women: Women are considered postmenopausal if they have amenorrhea for ≥12 consecutive months after the last menstrual period and marks the end of menstrual cycles.

3.2 Exclusion criteria

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

1. Target Disease Exceptions

   a. History of diabetes insipidus or type 1 diabetes

   b. Symptoms of poorly controlled diabetes that would preclude participation in this trial including but not limited to marked polyuria and polydipsia with greater than 10% weight loss during 3 months prior to screening

   c. History of hyperosmolar nonketotic coma

   d. History of DKA requiring medical intervention (e.g. emergency room visit and/or hospitalization) within 1 month prior to screening

   e. Positive GAD antibodies. Only to be measured and used as exclusion criteria in subjects < 40 years of age

2. Medical History and Concurrent Diseases

   a. History of bariatric surgery or lap-band procedure within 12 months prior to screening

   b. Any unstable endocrine, psychiatric or rheumatic disorders as judged by the investigator

   c. Subject who, in the judgment of the investigator, may be at risk for dehydration or volume depletion that may affect the interpretation of efficacy or safety data

   d. Subject is currently abusing alcohol or other drugs or has done so within the last 6 months prior to screening

   CV disorders

   e. Uncontrolled hypertension defined as systolic blood pressure (SBP) ≥ 160 mmHg and/or diastolic blood pressure (DBP) ≥ 100 mmHg

      Note: Subjects with SBP ≥ 160mmHg and < 180mmHg or a DBP ≥ 100 mmHg and < 110mmHg will be able to enter the open-label treatment period, provided their

hypertension treatment is adjusted as deemed appropriate by the investigator. These subjects cannot be randomized if their BP remains SBP ≥ 160mmHg or DBP ≥ 100 mmHg measured on Day 1.

f. Any of the following CV/Vascular Disease within 3 months of the screening visit, as assessed by the investigator: MI, coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]), unstable angina, Congestive heart failure as New York Association (NYHA) class III-IV (see Appendix C), angioplasty, valvular disease or repair, transient ischemic attack (TIA) or significant cerebrovascular disease, unstable or previously undiagnosed arrhythmia; or are expected to require PCI/CABG or angioplasty during the course of the study. Subjects with stable cardiac disease are not excluded

Renal Diseases

g. Subjects with moderate to severe renal impairment [defined as estimate glomerular filtration rate (eGFR) < 60mL/min/1.73 m^2 (estimated by MDRD) or serum creatinine (Scr) ≥ 1.5 mg/dL in males or ≥ 1.4 mg/dL in females] or end-stage renal disease (ESRD)

h. Unstable or rapidly progressing renal disease

i. Conditions of congenital renal glucosuria

Hepatic Diseases

j. Significant hepatic diseases, including, but not limited to, chronic active hepatitis and/or severe hepatic insufficiency and/or significant abnormal liver function, including subjects with Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) > 3x Upper limit of normal (ULN) and/or Total Bilirubin (TB) > 2x ULN

k. Subjects with severe hepatic impairment (Child-Pugh class C)

l. Positive serologic evidence of current infectious liver disease, including subjects who are known to be positive for hepatitis A viral (HAV) IgM antibody, hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV) antibody

Hematological/Oncological Diseases/Conditions

m. History of hemoglobinopathy, such as sickle cell anemia (SA), thalassemia or chronic or recurrent hemolysis, etc.

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

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

p. Donation of blood or blood products > 400mL or participation in a clinical study requiring withdrawal of > 400mL of blood within 6 months prior to the screening visit

Prohibited Treatment and Therapies

q. Administration of any anti-hyperglycemic therapy (other than metformin, or DPP-4 inhibitors, if applicable) for more than 14 days (consecutive or not) during the 8 weeks prior to screening

r. Any use of SGLT2 inhibitor within 8 weeks prior to screening

s. Prescription and over-the-counter weight loss medications within 3 months prior to screening

t. Current treatment with potent cytochrome P450 3A4/5 inhibitors (in countries where dose adjustment would be required by the saxagliptin label)

u. Administration of any other investigational drug or participation in any interventional clinical studies within 30 days prior to screening

3. Physical and Laboratory Test Findings

a. Hemoglobin (Hb) ≤ 11.0g/dL (110g/L) for men; Hb ≤ 10.0g/dL (100g/L) for women

b. For male subjects with microscopic hematuria urinalysis positive at screening and judged as clinically significant by the investigator will be excluded, but one re-test is allowed after resolution in the opinion of the investigator

NOTE: Female subjects with hematuria can be randomized, but should be investigated according to local standards and best clinical practices

c. Other central laboratory test findings

- Abnormal free thyroxine (T4) values. Abnormal thyroid stimulating hormone (TSH) value at screening will be further evaluated by free T4. Subjects with abnormal free T4 values will be excluded

- Any clinically significant abnormalities in any pre-randomization lab analyses or ECG which in the investigator's opinion would preclude randomization

4. Allergies and Adverse Drug Reaction

History of any serious allergy/hypersensitivity reaction to dapagliflozin, saxagliptin or to any of the excipients, including anaphylaxis or angioedema following exposure to any DPP-4 inhibitor

5. Sex and Reproductive Status

   Women who are pregnant or breastfeeding

6. Other Exclusion Criteria
   a. Prisoners or subjects who are involuntarily incarcerated

   b. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness

   c. Subjects on a commercial weight loss program with ongoing weight loss, or on an intensive exercise program

   d. Employees of AstraZeneca, or their relatives

   e. Subject with any condition which, in the judgment of the investigator, may render the subject unable to complete the study or which may pose a significant risk to the subject

   f. Subject is a participating investigator, study coordinator, employee of an investigator or immediate family member of any of the aforementioned

7. Exclusion Criteria during open-Label Treatment Period

   Note: Enrolment of subjects with HbA1c ≥ 8.0% and < 9.0% (Stratum A) and subjects with HbA1c ≥ 7.5% and ≤ 8.5% (Stratum B) into the open-label treatment period will be limited to approximately 171 subjects (about 50% of the randomized subjects number in each stratum)

   - For subjects in Stratum A

     At Week -10 and Week -2 a FPG qualification check will be performed. Subjects with a central laboratory FPG value > 270 mg/dL will be scheduled for a follow-up visit (within 3 - 5 days following receipt of FPG value from central laboratory) to obtain a second central laboratory FPG value. If the mean of the originally scheduled central laboratory FPG and the repeat central laboratory FPG value is > 270 mg/dL, the subject cannot be randomized and must be discontinued

   - For subjects in Stratum B

     At Week -2 a FPG qualification check will be performed. Subjects with a central laboratory FPG value > 270 mg/dL will be scheduled for a follow-up visit (within 3 - 5 days following receipt of FPG value from central laboratory) to obtain a second central laboratory FPG value. If the mean of the originally scheduled central laboratory FPG

and the repeat central laboratory FPG value is > 270 mg/dL, the subject cannot be randomized and must be discontinued

3.3 Subject enrolment and randomization

Randomization codes will be assigned strictly sequentially as subjects become eligible for randomization via interactive voice/web response system (IxRS).

Investigator(s) should keep a record, the subject screening log, of subjects who entered screening.

The investigator(s) will:

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

2. Assign (using IxRS) potential subject a unique enrolment code (E-code), beginning with 'E + 4-digit site number + 3-digit subject number starting with 001'. For example, the first subject at site 9999 would be assigned the subject number: E9999001. This E-code will be used for identification throughout the study and will not be used for any other participant.

3. Determine subject eligibility. See Section 3.1 and Section 3.2.

At the time of entry into open-label treatment period, the site will contact the IxRS in order that open-label medication saxagliptin 5 mg can be assigned and dispensed.

Subject who does not meet the eligibility criteria is considered as screen failure in the study. These subjects will be terminated from the study and registered as Screen Failure by using IxRS. Re-screening is allowed one single time considering that the subject was not assigned with open-label treatment. The same E-code that the subject received at the first enrolment will be used. All screening assessments and procedures, including re-signing the informed consent form (ICF), should be performed again.

Following completion of the open-label treatment period, subjects who meet all study requirements based on inclusion and exclusion criteria will be randomly assigned by the IxRS at randomization visit (Day 1). Centralized block randomization (not stratified by site) will be used within each stratum.

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

3.3.1 Procedures for randomization

Subjects who meet all study requirements based on inclusion and exclusion criteria will be randomized to 1 of 3 treatment groups in a 1:1:1 ratio:

- **Arm 1:** Dapagliflozin 10 mg, dapagliflozin 5 mg placebo to match, saxagliptin 5 mg, plus metformin IR/XR

- **Arm 2:** Dapagliflozin 5 mg, dapagliflozin 10 mg placebo to match, saxagliptin 5 mg, plus metformin IR/XR

- **Arm 3:** Dapagliflozin 5 mg placebo to match and dapagliflozin 10 mg placebo to match, saxagliptin 5 mg, plus metformin IR/XR

If a subject is discontinued from the study treatment, his/her randomization or enrolment code will not be reused, and the subject will not be allowed to re-enter the study. Randomized subjects who discontinue early from the study will not be replaced.

If a randomization number is allocated incorrectly, no attempt should be made to remedy the error once study material has been dispensed. The subject will continue with the allocated number and study material. AstraZeneca or representative should be notified as soon as the error is discovered. Subsequent subjects will continue using the first unallocated randomization number in the original numbering sequence.

3.4 Procedures for handling incorrectly enrolled or randomized subjects

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

Where a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the subject from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

After written informed consent has been obtained, the subject will be assigned an E-code that is country, centre, and subject specific. The E-code will be used to identify the subject throughout study participation. Subject eligibility will be established before treatment randomization. Subjects who meet all criteria for this study will be randomized to double-blind treatment with a 1:1:1 ratio on Day 1 of randomization visit. Assignment to treatment groups will be determined by a computer-generated random sequence using IxRS.

The number and size of tablets will be identical for the IPs for the 3 treatment arms. Clinical supplies will be identified by randomization kit numbers, where each kit number is specific to a treatment arm. If a subject discontinues from the study, the subject's E-code and

randomization number will not be reused, and the subject will not be allowed to re-enter the study.

The permutation block size will be generated by the study statistician and will be known only by a minimum number of AstraZeneca personnel.

3.6 Methods for ensuring blinding

This is a double-blind study. Subjects, investigators, and all other personnel involved in the conduct of the study are blinded to individual treatment assignments for the duration of the study.

To preserve the blinding of the study, a minimum number of AstraZeneca personnel will see the randomization table and treatment assignments before the study is complete. e.g., AstraZeneca personnel generating the randomization scheme as well as relevant persons at Pharmaceutical Development Supply Chain at AstraZeneca or their designee, where the information is needed to package study drug, the Patient Safety data entry site and the contract research organization (CRO) companies providing the IxRS and carrying out the packaging and labelling of IPs.

At the screening visit, each subject will be assigned a unique sequential subject number by the IxRS. This number will be used for identification throughout the study and will not be used for any other participant.

Subjects who meet the criteria will be randomly assigned by IxRS to one of three double-blind treatment groups in a 1:1:1 ratio using a centralized blocked randomization schedule ratio (not stratified by site) within each stratum.

Randomization schedules for all subject treatment and containers will be generated and kept by AstraZeneca and stored in a secure location with restricted access.

At all study visits when study medication is dispensed, each subject will be assigned a kit number by the IxRS. Kit numbers will be assigned randomly and will correspond to the numbers printed on the packages and kits containing study drug.

During the double-blind treatment period, the HbA1c, FPG and plasma glucose MTT values(China only) will be masked to the investigator and to the Sponsor. These values can be provided to the investigator after the study has been completed through CSR. FPG will be unblinded if the value meets the defined rescue criteria or during following visits after ETD and confirmed with investigator/monitor. In addition, if rescue medication is initiated during double blinded phase, the central laboratory FPG value will be reported to the investigator to ensure proper follow-up of the rescued subject.

Blinding is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject, in which knowledge of the IP is critical to the subject's management, the blind for that subject may be broken by the treating physician.

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized subject, will be available to the investigator(s) or pharmacists from the IxRS. Routines for this will be described in the IxRS user manual that will be provided to each centre.

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

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

3.8 Restrictions

3.8.1 Prohibited and/or restricted treatments

Once enrolled, subjects may not receive any of the following for the duration of the screening, open-label, double-blind treatment periods:

- Antihyperglycemic medication (other than protocol required medication and/or protocol-allowed open-label rescue medication).

- Treatment with any stable replacement or chronic corticosteroid therapy at the time of screening is permitted. During the trial (beginning with screening), newly initiation of treatment with any systemic corticosteroid therapy that will involve ≥ 5 days of therapy is not permitted (inhaled and topical are allowed). The AstraZeneca study physician should be consulted prior to the beginning of therapy for subjects who require systemic corticosteroid treatment.

- In countries where dose adjustment would be required by the local saxagliptin label: if initiation of treatment with any potent cytochrome P450 3A4/5 inhibitor during the trial is required, the AstraZeneca study physician should be consulted prior to beginning therapy with any potent cytochrome P450 3A4/5 inhibitor.

3.8.2 Other restrictions

Once screened and qualified for entry, subjects will be instructed as follows:

- Fast overnight for at least 8 hours prior to each study site visit, i.e., no food or beverage except water. Allowed medications can be taken with water only.

- Continue metformin therapy at current dosage and at approximately the same time each day, except that any morning dose of metformin should be delayed on the morning of study site visits.

- Delay administering the IPs, saxagliptin and metformin on the morning of the clinic visit and bring study medications to each study site visit.

- Refrain from alcohol intake and intense exercise 24 hours prior to each visit and recommend not using tobacco/nicotine within 12 hours prior to each visit.

- Do not donate blood for the duration of the study and for 3 months following the last study visit.

- Comply with prescribed dosing regimen to preserve study integrity and ensure patient safety.

- Discuss any new prescriptions and over-the-counter or herbal/nutritional therapies with the investigator, as concomitant use could result in alterations to their glycaemic control and may place them at risk for significant hypoglycaemic episodes.

- Make every attempt to adhere to the diet and exercise counselling and to the protocol visit schedule.

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

If a subject comes to a visit without following above instructions, the subject should be re-scheduled for the required visit (if possible within the allowed time-window). The Sponsor or designee should be contacted if the investigator is informed of any restriction violations.

3.9 Discontinuation of investigational product

3.9.1 Procedures for discontinuation of a subject from investigational product

Subjects MUST discontinue IP for any of the following reasons:

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment

- Subject experiences an AE or SAE that, in the investigator’s opinion, necessitates discontinuation from study medication

- Pregnancy confirmed by a positive pregnancy test or otherwise verified

- Serious hypersensitivity reaction

- Acute pancreatitis

- Severe non-compliance with the study protocol

- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness

- eGFR < 60mL/min/1.73m^2 for sustained period of time (16 weeks)

  Note: Dapagliflozin based on its MOA has been shown to reduce eGFR by up to 10% with initiation of therapy; however, this has in general been reversible and not resulted in renal failure and eGFR values returned to baseline within 12 - 24 weeks of continued therapy.

- Initial and repeat laboratory tests meet any of the following criteria:

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

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

  - ALT and/or AST are >8 x ULN

- Consider to temporary interrupt dapagliflozin if DKA is suspected. The subject should be promptly evaluated. If DKA is confirmed, dapagliflozin should be discontinued permanently.

- Hypoglycaemia events as defined in Section 3.9.2.

Note: Discontinuation of non-IP at the discretion of the investigator should be reported to Sponsor and recorded in eCRF.

3.9.2 Discontinuation guideline due to hypoglycaemic events

Subjects will be recommended to continue on the study and not discontinue from treatment based on single episodes of hypoglycaemia or symptoms of hypoglycaemia unless clinically indicated. The assessment of a single finger stick or central laboratory glucose value should not be the sole assessment used to determine subject discontinuation due to hypoglycaemia.

Clinical indications for discontinuation due to hypoglycaemia may include the following:

Multiple occasions of episodes outlined below that, in the opinion of the investigator, indicate that continued treatment with study therapy is not in the best interest of the subject. This includes, but is not limited to:

- Multiple symptomatic episodes of hypoglycaemia (e.g., sweating, shakiness, increased heart rate (HR), confusion, dizziness, light-headedness, or hunger) in the absence of

environmental factors known to contribute to hypoglycaemia (i.e., excess physical activity, concurrent illness, or missed or delayed meal)

OR

- More than 1 episode of severe hypoglycaemia as defined by the ADA. (See Section 6.3.7 for ADA definition of severe hypoglycaemia.)

Down titration of blinded IP and/or background antihyperglycemic agent will not be allowed at any time during the study.

If finger stick glucose values are discordant from glycaemia control assessed by the central laboratory or with clinical symptoms, the subject's glucose meter should be tested and the procedure for using it reviewed with the subject.

Section 5.2.5.1 provides additional guidance on management and reporting of hypoglycaemia.

3.9.3 Procedures for discontinuation of a subject from investigational product

At any time, subjects are free to discontinue IP or withdraw from the study (i.e., IP and assessments – see Section 3.10), without prejudice to further treatment. A subject that decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator(s). AEs will be followed up (See Section 6.3.2); diary cards and all study medications should be returned by the subject.

Subjects who discontinue the IP and/or study early will have Early treatment discontinuation (ETD) procedures performed as shown in the Study Schedule (refer to Section 4).

Subjects that discontinue IP should continue in the study returning on their next regularly scheduled visits. At their next regularly scheduled visits all protocol specified visits and procedures should be performed with the exception of IP management. Medication for the management of subject's diabetes would be under care and direction of the investigator. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

3.10 Criteria for withdrawal

Every effort should be made to conduct all protocol-required procedures to complete the study. Subjects may be removed from the study for the following reasons.

- Screen failures: see Section 3.10.1.
- Withdrawal by subject: see Section 3.10.2.

- AE: Subject experiences an AE that, in the investigator's opinion, necessitates withdrawal from the study.

- Investigator Decision: investigator feels it is in the subject's best interest to terminate participation for reasons other than an AE.

- Protocol Violation: Subject is noncompliant with protocol procedures, becomes pregnant, violates study entry criteria, or starts an exclusionary concomitant medication.

- Lost to Follow-Up: Subject fails to return for study visits and cannot be reached with reasonable, repeated attempts.

- Study Terminated by Sponsor: The Sponsor discontinues the study protocol.

- Administrative Reasons: Regulatory authority discontinues the study protocol or the clinical study site discontinues participation.

Any withdrawal must be fully documented in the subject's source records and recorded in the electronic Case Report Form (eCRF). The documentation must include the reason for the withdrawal and details of any sequelae (followed until symptoms resolve or improve, as appropriate).

If a subject is withdrawn from the study during double-blind treatment period, they must complete the procedures outlined in Section 4 and Sponsor should be contacted.

3.10.1 Screen failures

Screening failures are subjects who do not fulfil the eligibility criteria for the study, and therefore must not be randomized. These subjects should have the reason for study withdrawal recorded as 'Screen failure' (i.e., subject does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomized subjects).

3.10.2 Withdrawal of the informed consent

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

A subject who withdraws consent will always be asked about the reason(s) and the presence of any AE. The investigator will follow up AEs outside of the clinical study.

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

3.10.3 Lost to follow-up

A subject will be considered potentially lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule.

- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject or next of kin by e.g. repeat telephone calls, certified letter to the subject´s last known mailing address or local equivalent methods. These contact attempts should be documented in the subject's medical record.

- Efforts to reach the subject should continue until the end of the study. Should the subject be unreachable at the end of the study the subject should be considered to be lost to follow up with unknown vital status at end of study.

3.11 Discontinuation of the study

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

- meet individual stopping criteria or are otherwise considered significant

- are assessed as causally related to study drug

- are not considered to be consistent with continuation of the study

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

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

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Study design for Stratum A & Stratum B

Procedural Outline - Stratum A										
Procedure	**Screening Period**	**Open-Label Treatment Period (visit windows ± 2 days)** [c]			**Double-Blind, Double Dummy Treatment Period (visit windows ± 5 days)** [c]					
	WK (-18)	**WK (-16)**	**WK (-10)**	**WK (-2)**	**Day 1**	**WK 6**	**WK 12**	**WK 18**	**WK 24**	**Rescue/ ETD**
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**/**
Obtain informed consent [a]	X									
Demography	X									
Review medical history	X									
Review eligibility criteria	X	X [b]			X [d]					
Brief physical examination				X	X	X	X	X		
Complete physical examination	X								X	X
Body weight	X	X	X	X	X	X	X	X	X	X
Vital signs (BP and HR)	X	X	X	X	X	X	X	X	X	X
Height	X									
BMI	X									
Waist circumference		X			X				X	X
12-Lead ECG	X				X				X	X
Provide diet and exercise counselling		X	X	X	X	X	X	X	X	X

Procedural Outline - Stratum A										
Procedure	**Screening Period**	**Open-Label Treatment Period (visit windows ± 2 days)** [c]			**Double-Blind, Double Dummy Treatment Period (visit windows ± 5 days)** [e]					
	WK (-18)	**WK (-16)**	**WK (-10)**	**WK (-2)**	**Day 1**	**WK 6**	**WK 12**	**WK 18**	**WK 24**	**Rescue/ ETD**
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**/**
Provide glucose meter/ Supplies/Instructions/Patient diaries		X	X	X	X	X	X	X		X [v]
Review patient diaries			X	X	X	X	X	X	X	X
Review concomitant medications/Procedures	X	X	X	X	X	X	X	X	X	X
Assess adverse events, Hypoglycaemia events [f]	X	X	X	X	X	X	X	X	X	X
Pregnancy test (WOCBP only) [g]	X (Serum)				X (Urine)					
Clinical chemistry [h], hematology	X	X	X	X	X	X	X	X	X	X
eGFR [i]	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X
Hematuria microscopic urinalysis [j]	X									
HbA1c	X			X	X	X	X	X	X	X
FPG	X	X	X [k]	X [k]	X [l]	X	X	X	X [l]	X [l]

Procedural Outline - Stratum A										
Procedure	**Screening Period**	**Open-Label Treatment Period (visit windows ± 2 days)** [c]			**Double-Blind, Double Dummy Treatment Period (visit windows ± 5 days)** [e]					
	WK (-18)	**WK (-16)**	**WK (-10)**	**WK (-2)**	**Day 1**	**WK 6**	**WK 12**	**WK 18**	**WK 24**	**Rescue/ ETD**
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**/**
Assess FPG for rescue [m]						X	X	X		X
MTT (glucose) [n]					X				X	X
GAD antibodies [o]	X									
Hepatitis screening panel [p], HIV test	X									
TSH, free T4 [q]	X									
Fasting serum lipids (Total-C, LDL-C, HDL-C, TG) [r]					X				X	X
Contact IxRS	X	X	X	X	X	X	X	X	X [s]	X [t]
Dispense open-label study medication [u]		X	X	X	X	X	X	X		X [v]
Dispense blinded study medication					X	X	X	X		X [v]
Collect unused study medication and empty packaging			X	X	X	X	X	X	X	X [v]
Review study medication compliance			X	X	X	X	X	X	X	X

Abbreviations: BP = Blood pressure, HR = Heart rate, BMI = Body Mass index, ETD = Early treatment discontinuation, WOCBP = Women of childbearing potential

Note for Stratum A

a. Informed consent must be completed before any study related procedures performed.
b. Visit 2 (WK -16) cannot be performed until all laboratory results from the screening period have been received and reviewed to confirm eligibility. The lead-in period should start within 2 weeks (± 2 days) after completion of the screening visit, and may start as late as 6 weeks after completion of screening visit for subjects who need to test GAD antibodies to make sure all laboratory results have been received.
c. Visit 3 (WK -10) and Visit 4 (WK -2) can be performed 6 weeks and 14 weeks after administration of open-label treatment (Visit 2) separately, with ± 2 days visit windows.
d. Visit 5 (Day 1) can be performed after the completion of open-label treatment, with ± 5 days visit window. All applicable inclusion/exclusion/ randomization criteria must be verified by investigator before dosing on Day 1.
e. After the randomization visit (Day 1), subjects will be scheduled for study visits at 6-week intervals, with ± 5 days visit window.
Subjects who discontinue IP should perform ETD visit first, and then continue in the study original visits and procedures with the exception of blinded IP management, and medication after ETD will be under care and direction of the investigator (see Section 3.9.3).
Rescued subjects must first complete the Rescue visit procedures before receiving rescue medication, and then continue in the double-blind treatment period according to their original visit schedule (see Section 4.3).
f. Assess and record adverse event (SAE will be recorded from the time of signing informed consent, AE will be recorded from the time of first administration of open-label study medication throughout the open-label and double-blind treatment period and including the last visit). Signs and symptoms of hypoglycaemia, hypoglycaemia episode or discontinuation due to hypoglycaemia should not be reported on the AE eCRF page, unless the event fulfils protocol criteria for a SAE (see Section 6.3).
g. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test (performed in central laboratory) at screening and negative urine pregnancy test (performed locally) within 24 hours prior to the first administration of double-blind treatments.
h. Refer to Table 3 for detailed tests. If CK>400 IU/L, Troponin I test is required.
i. Glomerular Filtration Rate will be calculated by the central laboratory using the re-expressed abbreviated (four-variable) Modification in Diet and Renal Disease (MDRD) formula and results will be reported to the sites and the Sponsor (see Section 5.2.1.3).
j. For male subjects with microscopic hematuria urinalysis positive at screening and judged as clinically significant by the investigator will be excluded, but one re-test is allowed after resolution in the opinion of the investigator (see Section 5.2.1.4).
k. FPG must be ≤ 270 mg/dL to be eligible (see Section 3.2 for more details)
l. Blood collection for FPG will not be required at Visit 5 (Day 1), WK 24/ETD or rescue if MTT was performed at the same visit since the sampling of FPG would be covered in MTT. For subjects in Vietnam and Thailand, and those without MTT performed, blood samples should be collected for FPG.
m. During blinded-treatment period of WK 6 up to but not including WK 24, subjects may be eligible for the addition of open-label rescue medication (insulin or any other antidiabetic agents except GLP-1 analogues, other DPP-4 and/or SGLT2 inhibitors or metformin) to their blinded treatment regimen in order to treat ongoing hyperglycaemia, based upon central laboratory FPG values and repeated confirmatory FPG criteria. Rescued subjects will then continue in the double-blind treatment period according to their original visit schedule (see Section 4.3).
n. For subjects in China, maximum of 2 MTTs will be performed per subject: one at Day 1 and the other one at either WK 24 or Rescue/ETD visit, whichever occurs first. Subject must be fasted for at least 8 hours prior to the MTT and consume at least 150 grams of carbohydrate per day for the three

days prior to MTT. In addition, subjects must abstain from tobacco, alcohol and caffeine for at least 24 hours prior to the MTT. There are 5 samples collected per MTT visit at Day 1 (draw at time 0 pre-meal, 30, 60 120, 180 mins post meal), and 6 samples collected per MTT visit at Week 24/Rescue/ETD visit (draw at time -60 mins pre-meal, 0 pre-meal, 30, 60, 120, 180 mins post meal), refer to Section 5.1.

o. GAD antibodies will only to be measured and used as an exclusion criterion in subjects < 40 years of age. Results must be reviewed by investigator prior to the entry into the open-label period.

p. After reviewed all applicable inclusion and exclusion criteria, potential eligible subjects, in the opinion of the investigator, with HCV antibody low positive results should have unscheduled visit as soon as possible to collect additional blood sample for HCV confirmation test in central laboratory during screening period (see Section 5.2.1.5).

q. Abnormal thyroid stimulating hormone (TSH) value at screening will be further evaluated by free T4. Subjects with abnormal free T4 values will be excluded (see Section 5.2.1.5).

r. Reflex testing will occur for Direct LDL-C if TG > 400 mg/dL (4.52mmol/L), refer to Section 5.1.3.2.

s. Contact IxRS to register study completion at WK 24.

t. Contact IxRS if drug dispensing required

u. Dispensing of open-label study medication: Saxagliptin 5 mg is dispensed by IxRS. Metformin will be prescribed by site investigator. Subjects should continue to receive the same metformin treatment regimen as they were using at study entry and keep unchanged throughout the whole study period.

v. Open-label study medication and/or glucose meter/supplies/Instructions/patient diaries could be dispensed at rescue/ETD visit if needed. Blinded study medication could be dispensed at rescue visit if needed. Collect unused study medication and empty packaging if needed.

Procedural Outline - Stratum B									
Procedure	**Screening Period**	**Open-Label Treatment Period (visit windows ± 2 days)** [3]		**Double-Blind, Double Dummy Treatment Period (visit windows ± 5 days)** [5]					
	WK (-10)	**WK (-8)**	**WK (-2)**	**Day 1**	**WK 6**	**WK 12**	**WK 18**	**WK 24**	**Rescue/ ETD**
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**/**
Obtain informed consent [1]	X								
Demography	X								
Review medical history	X								
Review eligibility criteria	X	X [2]		X [4]					
Brief physical examination			X	X	X	X	X		
Complete physical examination	X							X	X
Body weight	X	X	X	X	X	X	X	X	X
Vital signs (BP and HR)	X	X	X	X	X	X	X	X	X
Height	X								
BMI	X								
Waist circumference		X		X				X	X
12-Lead ECG	X			X				X	X
Provide diet and exercise counselling		X	X	X	X	X	X	X	X

Procedural Outline - Stratum B									
Procedure	**Screening Period**	**Open-Label Treatment Period (visit windows ± 2 days)** [3]		**Double-Blind, Double Dummy Treatment Period (visit windows ± 5 days)** [5]					
	WK (-10)	**WK (-8)**	**WK (-2)**	**Day 1**	**WK 6**	**WK 12**	**WK 18**	**WK 24**	**Rescue/ ETD**
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**/**
Provide glucose meter/ Supplies/Instructions/Patient diaries		X	X	X	X	X	X		X [22]
Review patient diaries			X	X	X	X	X	X	X
Review concomitant medications/procedures	X	X	X	X	X	X	X	X	X
Assess adverse events, [6] Hypoglycaemia events	X	X	X	X	X	X	X	X	X
Pregnancy test (WOCBP only) [7]	X (Serum)			X (Urine)					
Clinical chemistry [8], hematology	X	X	X	X	X	X	X	X	X
eGFR [9]	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X
Hematuria microscopic urinalysis [10]	X								
HbA1c	X		X	X	X	X	X	X	X
FPG	X	X	X [11]	X [12]	X	X	X	X [12]	X [12]

Procedural Outline - Stratum B									
Procedure	**Screening Period**	**Open-Label Treatment Period (visit windows ± 2 days)** [3]		**Double-Blind, Double Dummy Treatment Period (visit windows ± 5 days)** [5]					
	WK (-10)	**WK (-8)**	**WK (-2)**	**Day 1**	**WK 6**	**WK 12**	**WK 18**	**WK 24**	**Rescue/ ETD**
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**/**
Assess FPG for rescue [13]					X	X	X		X
MTT (glucose) [14]				X				X	X
GAD antibodies [15]	X								
Hepatitis screening panel [16], HIV test	X								
TSH, free T4 [17]	X								
Fasting serum lipids (Total-C, LDL-C, HDL-C, TG) [18]				X				X	X
Contact IxRS	X	X	X	X	X	X	X	X [19]	X [20]
Dispense open-label study medication [21]		X	X	X	X	X	X		X [22]
Dispense blinded study medication				X	X	X	X		X [22]
Collect unused study medications and empty packaging			X	X	X	X	X	X	X [22]
Review study medication compliance			X	X	X	X	X	X	X

Abbreviations: BP = Blood pressure, HR = Heart rate, BMI = Body Mass index, ETD = Early treatment discontinuation, WOCBP = Women of childbearing potential

Note for Stratum B

1 Informed consent must be completed before any study related procedures performed.

2 Visit 2 (WK -8) cannot be performed until all laboratory results from the screening period have been received and reviewed to confirm eligibility. The lead-in period should start within 2 weeks (± 2 days) after completion of the screening visit, and may start as late as 6 weeks after completion of screening visit for subjects who need to test GAD antibodies to make sure all laboratory results have been received.

3 Visit 3 (WK -2) can be performed 6 weeks after administration of open-label treatment (Visit 2), with ± 2 days visit windows.

4 Visit 4 (Day 1) can be performed after the completion of open-label treatment, with ± 5 days visit window. All applicable inclusion/exclusion/ randomization criteria must be verified by investigator before dosing on Day 1.

5 After the randomization visit (Day 1), subjects will be scheduled for study visits at 6-week intervals, with ± 5 days visit window.
Subjects who discontinue IP should perform ETD visit first, and then continue in the study original visits and procedures with the exception of blinded IP management, and medication after ETD will be under care and direction of the investigator (see Section 3.9.3).
Rescued subjects must first complete the Rescue visit procedures before receiving rescue medication, and then continue in the double-blind treatment period according to their original visit schedule (see Section 4.3).

6 Assess and record adverse event (SAE will be recorded from the time of signing informed consent, AE will be recorded from the time of first administration of open-label study medication throughout the open-label and double-blind treatment period and including the last visit). Signs and symptoms of hypoglycaemia, hypoglycaemia episode or discontinuation due to hypoglycaemia should not be reported on the AE eCRF page, unless the event fulfils protocol criteria for a SAE (see Section 6.3).

7 Women of childbearing potential (WOCBP) must have a negative serum pregnancy test (performed in central laboratory) at screening and negative urine pregnancy test (performed locally) within 24 hours prior to the first administration of double-blind treatments.

8 Refer to Table 3 for detailed tests. If CK>400 IU/L, Troponin I test is required.

9 Glomerular Filtration Rate will be calculated by the central laboratory using the re-expressed abbreviated (four-variable) Modification in Diet and Renal Disease (MDRD) formula and results will be reported to the sites and the Sponsor (see Section 5.2.1.3).

10 For male subjects with microscopic hematuria urinalysis positive at screening and judged as clinically significant by the investigator will be excluded, but one re-test is allowed after resolution in the opinion of the investigator (see Section 5.2.1.4).

11 FPG must be ≤ 270 mg/dL to be eligible (see Section 3.2 for more details).

12 Blood collection for FPG will not be required at Visit 5 (Day 1), WK 24/ETD or rescue if MTT was performed at the same visit since the sampling of FPG would be covered by MTT. For subjects in Vietnam and Thailand, and those without MTT performed, blood samples should be collected for FPG.

13 During blinded-treatment period of WK 6 up to but not including WK 24, subjects may be eligible for the addition of open-label rescue medication (insulin or any other antidiabetic agents except GLP-1 analogues, other DPP-4 and/or SGLT2 inhibitors or metformin) to their blinded treatment regimen in order to treat ongoing hyperglycaemia, based upon central laboratory FPG values and repeated confirmatory FPG criteria. Rescued subjects will then continue in the double-blind treatment period according to their original visit schedule (see Section 4.3).

14 For subjects in China, maximum of 2 MTTs will be performed per subject, one at Day 1 and the other one at either WK 24 or Rescue/ETD visit, whichever occurs first. Subject must be fasted for at least 8 hours prior to the MTT and consume at least 150 grams of carbohydrate per day for the three

days prior to MTT. In addition, subjects must abstain from tobacco, alcohol and caffeine for at least 24 hours prior to the MTT. There are 5 samples collected per MTT visit at Day 1 (draw at time 0 pre-meal, 30, 60 120, 180 mins post meal), and 6 samples collected per MTT visit at Week 24/Rescue/ETD visit (draw at time -60 mins pre-meal, 0 pre-meal, 30, 60, 120, 180 mins post meal), refer to Section 5.1.

15 GAD antibodies will only to be measured and used as an exclusion criterion in subjects < 40 years of age. Results must be reviewed by investigator prior to the entry into the open-label period.

16 After reviewed all applicable inclusion and exclusion criteria, potential eligible subjects, in the opinion of the investigator, with HCV antibody low positive results should have unscheduled visit as soon as possible to collect additional blood sample for HCV confirmation test in central laboratory during screening period (see Section 5.2.1.5).

17 Abnormal thyroid stimulating hormone (TSH) value at screening will be further evaluated by free T4. Subjects with abnormal free T4 values will be excluded (see Section 5.2.1.5).

18 Reflex testing will occur for Direct LDL-C if TG > 400 mg/dL (4.52mmol/L), refer to Section 5.1.3.2.

19 Contact IxRS to register study completion at WK 24.

20 Contact IxRS if drug dispensing required

21 Dispensing of open-label study medication: Saxagliptin 5 mg is dispensed by IxRS. Metformin will be prescribed by site investigator. Subjects should continue to receive the same metformin treatment regimen as they were using at study entry and keep unchanged throughout the whole study period.

22 Open-label study medication and/or glucose meter/supplies/Instructions/patient diaries could be dispensed at rescue/ETD visit if needed. Blinded study medication could be diepensed at rescue visite if needed. Collect unused study medication and empty packaging if needed.

4.1 Enrolment/screening period

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

Informed consent for protocol D1683C00008 will be obtained in written form prior to performing any protocol-required procedures. In order to assess eligibility during screening visit, subjects are required to fast overnight for at least 8 hours (no food or beverage, except water), to refrain from alcohol intake and intense exercise for 24 hours, and are recommended not using tobacco/nicotine/caffeine within 12 hours prior to the screening visit. Subjects should delay administering their morning dose of anti-diabetes drugs on the morning of screening visit as well (see Section 3.8.2).

4.1.1 Screening Visit (Visit 1, Week -18 for Stratum A and Week -10 for Stratum B)

Subjects will be assessed to ensure that they meet eligibility criteria. Subjects who do not meet these criteria must not be enrolled into the study.

The following will be performed during this visit:

- The subject's demography, completed medical and surgical history will be recorded
- Inclusion and exclusion criteria will be verified
- A complete physical examination will be conducted
- Body weight and height will be measured
- BMI will be calculated
- Vital signs (sitting systolic and diastolic BP and HR) will be measured.

  Note: Subjects with SBP ≥ 160mmHg and < 180mmHg or a DBP ≥ 100 mmHg and < 110mmHg will be able to enter the open-label treatment period, provided their hypertension treatment is adjusted as deemed appropriate by the investigator. These subjects cannot be randomized if their BP remains SBP ≥ 160mmHg or DBP ≥ 100 mmHg measured on Day 1.

- All prior medications within at least 3 months and concomitant medications (including prescription medications over the counter and herbal / nutritional supplements) will be reviewed
- Contact IxRS to obtain unique subject enrolment number
- 12-lead ECG will be performed
- Blood samples will be collected for the following assessments:
  - Chemistry and Hematology

- eGFR (calculated according to the Glomerular Filtration Rate, MDRD formula)
- HbA1c
- FPG
- Hepatitis screening panel, refer to Section 5.2.1.5.
- HIV
- TSH, and free T4 will be evaluated if TSH is abnormal, refer to Section 5.2.1.5.
- GAD antibodies. Only to be measured and used as exclusion criteria in subjects < 40 years age (GAD antibodies results must be reviewed by investigator prior to entry into open-label treatment period)
- Perform serum pregnancy test for WOCBP in central laboratory

- Urine samples will be collected for the following assessments:
  - Urinalysis
  - Hematuria microscopic urinalysis
- Review and record SAE if necessary (SAE will be recorded from the time of signing informed consent, see Section 6.3)
- Schedule the entry into open-label treatment visit to occur in the morning and remind subjects to be fasting for next visit

Note: For male subjects with microscopic hematuria urinalysis positive at screening and judged as clinically significant by the investigator will be excluded, but one re-test is allowed after resolution in the opinion of the investigator. Female subjects with hematuria can be randomized, but should be investigated according to local standards and best clinical practices (see Section 5.2.1.4).

4.2 Open-label treatment period

Eligible subjects who complete the screening period will enter the open-label treatment period, which included open-label saxagliptin 5 mg and metformin IR/XR treatment for 16 weeks in Stratum A or 8 weeks in Stratum B. The DPP-4 inhibitor will be switched to saxagliptin 5 mg at Week -8 in Stratum B. Subjects will continue to receive the same metformin treatment regimen as they were using at study entry and keep unchanged throughout the whole study period for both strata. Metformin will be prescribed by site investigators. Subjects will be instructed on using of a diary to record self-monitored glucose, study medication and hypoglycaemia.

Prior to each visit, subjects are required to fast overnight (at least 8 hours), to refrain from alcohol intake and intense exercise for 24 hours, and are recommended not using tobacco/nicotine/caffeine within 12 hours prior to each visit. Subjects should delay administering their morning dose of anti-diabetes drugs on the morning of the study site visit. Refer to Section 3.8.2 for other restrictions.

4.2.1 Visit 2 (Week -16 for Stratum A and Week -8 for Stratum B)

The below procedures will be performed during the visit for the eligible subjects:

- Review concomitant medications, AEs and hypoglycaemia episodes
- Inclusion and exclusion criteria will be further verified
- Body weight and waist circumference will be measured
- Vital signs (sitting systolic and diastolic BP and HR) will be measured
- Provide diet and exercise counselling
- Blood samples will be collected for the following assessments:
  - Chemistry and Hematology
  - eGFR (calculated according to the Glomerular Filtration Rate, MDRD formula)
  - FPG
- Urine sample will be collected for the following assessment:
  - Urinalysis
- Dispense glucose meter and supplies, provide instruction on their use, and instruct the subjects to self-monitor their blood glucose at least one time per day (see Section 5.2.5.1)
- Dispense patient diaries and provide instruction on recording hypoglycaemia episodes, and study medication intake
- Contact IxRS to dispense open-label study medication saxagliptin 5 mg and instruct subjects to take saxagliptin and metformin at site
- Remind subjects to be fasted, to withhold study medication and bring study medication, patient diaries and glucose meter to the next scheduled visit.

4.2.2 Visit 3 (Week -10 for Stratum A)

The following will be performed during this visit:

- Review concomitant of medications, AEs and hypoglycaemia episodes
- Body weight will be measured
- Vital signs (sitting systolic and diastolic BP and HR) will be measured
- Provide diet and exercise counselling
- Blood samples will be collected for the following assessments:
  - Chemistry and Hematology
  - eGFR (calculated according to the Glomerular Filtration Rate, MDRD formula)
  - FPG. Subjects with a central laboratory FPG value > 270 mg/dL will be scheduled for a follow-up visit (within 3 - 5 days following receipt of FPG value from central laboratory) to obtain a second central laboratory FPG value. If the mean of the originally scheduled central laboratory FPG and the repeat central laboratory FPG value is > 270 mg/dL, the subject cannot be randomized and must be discontinued
- Urine sample will be collected for the following assessment:
  - Urinalysis
- Collect unused study medications and empty packaging
- Review patient diaries from previous visit to assess study medication compliance and dispense patient diaries as needed
- Re-dispense glucose meter, supplies and provide instructions as needed
- Contact IxRS to dispense open-label study medication saxagliptin 5 mg and instruct subjects to take saxagliptin and metformin at site
- Remind subjects to be fasting, withhold study medication and to bring study medication, patient diaries and glucose meter to the next scheduled visit

4.2.3 Visit 3 (Week -2 for Stratum B)

The following will be performed during this visit:

- Review concomitant medications, AEs and hypoglycaemia episodes
- Brief physical examination will be performed
- Body weight will be measured

- Vital signs (sitting systolic and diastolic BP and HR) will be measured
- Provide diet and exercise counselling
- Blood samples will be collected for the following assessments:
  - Chemistry and Hematology
  - eGFR (calculated according to the Glomerular Filtration Rate, MDRD formula)
  - HbA1c. This will be used to evaluate subjects' eligibility at randomization (see Section 3.1)
  - FPG. Subjects with a central laboratory FPG value > 270 mg/dL will be scheduled for a follow-up visit (within 3 - 5 days following receipt of FPG value from central laboratory) to obtain a second central laboratory FPG value. If the mean of the originally scheduled central laboratory FPG and the repeat central laboratory FPG value is > 270 mg/dL, the subject cannot be randomized and must be discontinued
- Urine sample will be collected for the following assessment:
  - Urinalysis
- Collect unused study medications and empty packaging
- Review patient diaries from previous visit to assess study medication compliance and dispense patient diaries as needed
- Contact IxRS to dispense open-label study medication saxagliptin 5 mg and instruct subjects to take saxagliptin and metformin at site
- Re-dispense glucose meter, supplies and provide instructions as needed
- Remind subjects to be fasting, withhold study medication and to bring study medication, patient diaries and glucose meter to the next scheduled visit

4.2.4 Visit 4 (Week -2 for Stratum A)

Perform the same procedures as detailed in Visit 3 of Stratum B (Section 4.2.3).

4.3 Double-blind, double-dummy treatment period

After the randomization visit (Day 1), subjects will complete study visits at 6-week intervals according to Study Plan (Table 1) until the end of the randomized treatment period (Week 24). During Week 6 to 24 of the double-blind treatment period of the trial, subjects may be eligible for the addition of open-label rescue medication (insulin or any other antidiabetic agents except GLP-1 analogues, other DPP-4 and/or SGLT2 inhibitors or metformin) to their blinded

treatment regimen in order to treat ongoing hyperglycaemia, based upon central laboratory FPG values and repeated confirmatory FPG criteria (see Table 2).

Table 2 Lack of glycaemic control criteria for initiation of rescue medication

Visit Label	Central Laboratory FPG
Week 6	FPG > 270 mg/dL (15.0 mmol/L)
After Week 6 up to but not including Week 12	FPG > 240 mg/dL (13.3 mmol/L)
From Week 12 up to but not including Week 24	FPG > 200 mg/dL (11.1 mmol/L)

Subjects with a central laboratory FPG value meeting the lack of glycaemic control criterion at a pre-specified visit will be scheduled for a follow-up visit (within 3 - 5 days following receipt of FPG value from central laboratory) to obtain a second central laboratory FPG value and review the subject's glucose meter readings. If the repeat central laboratory FPG value still meets the criterion, the subject must be rescued. Subjects should continue receiving study medication while receiving rescue therapy. Subjects who meet rescue criteria in the double-blind treatment period must first complete the Rescue Visit procedures before receiving open-label rescue medication to ensure that important trial endpoint measurements are collected (See Section 4.3.3). Following completion of the Rescue Visit, rescued subjects will be given open-label rescue medication to be initiated at the lowest starting dose and titrated in accordance with the approved product label in the applicable country at the discretion of the investigator, in addition to their double-blinded study medication. Rescued subjects will then continue in the double-blind treatment period according to their original visit schedule. Following initiation of open-label rescue antidiabetic medication, rescued subjects should be scheduled for titration visits (either on site visits or telephone visits are determined by investigators) to increase their antidiabetic medication dose, as tolerated and in accordance with the approved product label for that country and by their glycaemic response and as per the investigator's judgment. Adjustment of study medication (includes metformin) will not be allowed at any time during the study.

Note: Rescue medication will not be provided by Sponsor in this study.

All of the procedures of treatment period listed below are for both Stratum A and B. Prior to each visit (except MTT related visits), subjects are required to fast overnight (at least 8 hours), refrain from alcohol intake and intense exercise for 24 hours, and are recommended not using tobacco/nicotine/caffeine within 12 hours prior to each visit. Subjects should delay administering their morning dose of anti-diabetes drugs on the morning of the study site visit. Please see Section 5.1 for restrictions on MTT related visit.

4.3.1 Randomization (Day 1)

Only for subjects in China, prior to visit assessment on Day 1, investigator should confirm that subjects' dietary intake for the three days prior to MTT included at least 150 grams of carbohydrate per day, subject fasted for at least 8 hours prior to the visit except water

(including abstaining from tobacco, alcohol and caffeine for 24 hours, and subject did not take their morning dose of IPs, saxagliptin, and metformin. Otherwise the visit should be rescheduled within 3 days (see refer to Section 5.1 for detailed MTT related procedures and requirements).

The following will be performed during this visit:

- Inclusion/exclusion and randomization criteria will be verified
- Body weight will be measured
- Vital signs (sitting systolic and diastolic BP and HR) will be assessed
- Waist circumference will be measured
- 12-lead electrocardiogram (ECG) will be performed
- Review concomitant medications, AEs and hypoglycaemia episodes
- Perform brief physical examination
- Blood samples will be collected prior to administration of study medications for the following assessments:
  - Chemistry and Hematology
  - eGFR (calculated according to the Glomerular Filtration Rate, MDRD formula)
  - HbA1c
  - FPG. Blood collection for FPG will not be required if MTT was performed at the same visit
  - For subjects in China, perform MTT and obtain blood samples as described in Section 5.1. The study medications (including IPs, saxagliptin and metformin) should be given within 2 hours AFTER MTT is completed (refer to Section 5.1)
  - Fasting serum lipid concentrations (total cholesterol, low density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG))
- Urine samples will be collected for the following assessments:
  - Urinalysis
  - Perform urine pregnancy test for WOCBP locally

- Collect unused study medications and empty packaging
- Review patient diaries from previous visit to assess study medication compliance and dispense patient diaries as needed
- Contact IxRS to randomize subject and obtain study medication dispensing kit and bottle assignment number
- Dispense open-label saxagliptin 5 mg and double-blind, double dummy study medication and instruct subjects to take open-label and double-blind study medications at site
- Provide diet and exercise counselling (see Section 5.3.1)
- Re-dispense glucose meter, supplies and provide instructions as needed
- Remind subjects to be fasting, withhold study medications and to bring study medications, patient diaries and glucose meter to the next scheduled visit

4.3.2 Double-blind treatment period (Week 6, 12, 18)

The following will be performed during this visit:

- Review concomitant medications, AEs and hypoglycaemia episodes
- Body weight will be measured
- Vital signs (sitting systolic and diastolic BP and HR) will be assessed
- Perform brief physical examination
- Blood samples will be collected prior to administration of study medications for the following assessments:
  - Chemistry and Hematology
  - eGFR (calculated according to the Glomerular Filtration Rate, MDRD formula)
  - HbA1c
  - FPG
- Urine sample will be collected for the following assessment:
  - Urinalysis
- During blinded-treatment period of WK 6 up to but not including WK 24, once the FPG value is available from the central laboratory, check whether the FPG is over

rescue limits. If so, bring subject back within 3-5 days following receipt of FPG value from central laboratory for an unscheduled confirmatory visit to confirm the high FPG and assess eligibility for rescue during the double-blind treatment period as listed in Section 4.3.

- Collect unused study medications and empty packaging as needed
- Review patient diaries from previous visit to assess study medication compliance and dispense patient diaries as needed
- Contact IxRS to dispense open-label saxagliptin 5 mg and double-blind, double dummy study medications
- Provide diet and exercise counselling (see Section 5.3.1)
- Re-dispense glucose meter, supplies and provide instructions as needed
- Remind subjects to be fasting, withhold study medications and to bring study medications, patient diaries and glucose meter to the next scheduled visit

4.3.3 Week24/Rescue/Early Treatment Discontinuation visit

Only for subjects in China, prior to the visit assessment if MTT to be performed, investigator should confirm that subjects' dietary intake for the three days prior to MTT included at least 150 grams of carbohydrate per day, subject fasted for at least 8 hours except water (including abstaining from tobacco, alcohol and caffeine for 24 hours, and subject did not take their morning dose of IPs, saxagliptin, and metformin. Otherwise, the visit should be rescheduled within 3 days (refer to Section 5.1 for detailed MTT related procedures and requirements).

Randomized subjects completing the 24 weeks double-blind treatment period, ETD or requiring rescue should have the following procedures completed:

- Review concomitant medications, AEs and hypoglycaemia episodes
- Body weight will be measured
- Vital signs (sitting systolic and diastolic BP and HR) will be assessed
- Waist circumference will be measured
- 12-lead ECG will be performed
- Perform complete physical examination
- Blood samples will be collected prior to administration of study medications for the following assessments:

- Chemistry and Hematology
- eGFR (calculated according to the Glomerular Filtration Rate, MDRD formula)
- HbA1c
- FPG. Blood collection for FPG will not be required if MTT was performed at the same visit.
- For subjects in China, perform MTT and obtain blood samples as described in Section 5.1. The study medication should be given 1 hour BEFORE administration of the meal supplement. MTT will not be conducted at Week 24 if subject has been rescued or discontinued from treatment prior to Week 24. In the event an MTT is performed during the course of a rescue visit, first dose of rescue medication should be taken after completion of the MTT.
- Fasting serum lipid concentrations (total cholesterol, LDL-C, HDL-C, and TG)

- Urine sample will be collected for the following assessment:
  - Urinalysis
- Once the FPG value is available from the central laboratory at ETD visit after WK 6 of double-blind treatment, check whether the FPG is over rescue limits. If so, bring subject back within 3-5 days following receipt of FPG value from central laboratory for an unscheduled confirmatory visit to confirm the high FPG and assess eligibility for rescue during the double-blind treatment period as listed in Section 4.3.
- Collect unused study medications and empty packaging as needed
- Review patient diaries from previous visit to assess study medication compliance and dispense patient diaries as needed
- Provide diet and exercise counselling (see Section 5.3.1)
- Re-dispense glucose meter, supplies and provide instructions if needed (only for rescue visit or ETD visit)
- Contact IxRS to register study completion at Week 24
- Dispense open-label saxagliptin 5 mg and/or double-blind, double dummy study medications if needed
- Remind subjects to be fasting, bring patient diaries and glucose meter to the next scheduled visit if needed.

Subjects who discontinue IP should perform ETD visit first, and then continue in the study original visits and procedures with exception of blinded IP management, and medication after ETD will be under care and direction of the investigator (see Section 3.9.3).

Rescued subjects must first complete the Rescue visit procedures before receiving rescue medication, and then continue in the double-blind treatment period according to their original visit schedule (see Section 4.3).

5. STUDY ASSESSMENTS

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

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

Volume of blood

The total volume of blood that will be drawn for each subject over the duration of the study will be approximately 88 mL in Stratum A and 81.5 mL in Stratum B. For subjects who are eligible for rescue or perform additional ETD visit in any of stratum, there will be additional blood sample with approximately 6.5 mL required. The collection of additional samples performed locally or for unscheduled visit is at the discretion of the investigator and should be recorded appropriately, thus requiring additional sample volumes. Detailed instruction for blood sample collection will be described in central laboratory manual.

5.1 Efficacy assessments

Blood and urine samples will be obtained at specified time points for laboratory evaluations. The central laboratory or designated reference laboratory for this study will perform the analysis of all scheduled laboratory tests (except urine pregnancy test which will be performed locally at randomization visit), and will provide reference ranges for these tests. All samples for clinical laboratory testing must be collected in the morning after the subject has fasted for at least 8 hours prior to collection. The detailed methods for specimen collection, handling, processing, shipping, and storage will be supplied in the Investigator's Laboratory Manual provided by the central laboratory.

During the double-blind treatment period, the HbA1c, FPG and plasma glucose MTT values (China only) will be blinded to the investigator and to the Sponsor. These values can be provided to the investigator after the study has been completed through CSR. FPG will be unblinded if the value meets the defined rescue criteria or during following visits after ETD and confirmed with investigator/monitor. In addition, if rescue medication is initiated during

double blinded phase, the central laboratory FPG value will be reported to the investigator to ensure proper follow-up of the rescued subject.

All glycaemic efficacy objectives will be based on values measured by central laboratory. Any self-monitored plasma glucose measured by the subject and FPG measured by the site using glucometer will be used only for safety purposes.

Meal Tolerance Test (MTT), only for subjects in China

A maximum of 2 MTTs will be performed per subject: one at Day 1 and the other one at either Week 24 or Rescue/ETD visit, whichever occurs first.

If the administration of study drug is contraindicated (e.g., discontinuation due to AE, pregnancy, or decreased creatinine clearance (CrCl)), the MTT should NOT be performed. The MTT visit should be rescheduled within 3 days if the subject did not comply with all of the following:

- Confirm that the subjects' dietary intake for the three days prior to MTT included at least 150 grams of carbohydrate per day
- Confirm that the subject fasted for at least 8 hours prior to the visit except water (including abstaining from tobacco, alcohol and caffeine for 24 hours prior to the MTT)
- Confirm that the subject did not take their morning dose of study medications, saxagliptin, dapagliflozin and metformin prior to the visit

Note: In the event more than 2-time points are missing from randomization visit (Day 1) MTT, the investigator should contact study physician prior to proceeding with the Week 24 or Rescue/ETD visit, as there might be situations where the analysis cannot be performed in the absence of key time point expected to be obtained at randomization visit (Day 1). In these situations, conducting a MTT at Week 24 or Rescue/ETD visit may not be required.

MTT procedures for Day 1:

- Insert saline lock, if appropriate
- Draw Time 0 blood sample for glucose
- Start timer immediately AFTER drawing Time 0 blood sample
- Administer the meal supplement for about 10 minutes, start immediately after Time 0 blood sample is drawn
- Draw specimen for post-meal glucose at 30, 60, 120, 180 minutes
- Give study medications within 2 hours AFTER MTT is completed

At Week 24 or Rescue/ETD,

- Insert saline lock, if appropriate
- Draw Time -60 minutes blood sample BEFORE taking study medications for glucose
- Give study medications 1 hour BEFORE administration of the meal supplement
- Draw Time 0 blood sample for glucose
- Administer the meal supplement for about 10 minutes, start immediately after Time 0 blood sample is drawn
- Draw specimen for post-meal glucose at 30, 60, 120, 180 minutes
- Remove saline lock

In the event an MTT is performed during the course of a rescue visit, first dose of rescue medication should be taken after completion of the MTT.

5.1.1 Primary efficacy variable

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

5.1.2 Secondary efficacy variable

5.1.2.1 Postprandial glucose (PPG) at 120 minutes(China only)

The change from baseline to Week 24 in the 120-minute postprandial glucose value during an MTT. PPG will be analysed by a central laboratory according to the procedures described in the Laboratory Manual which will be distributed to each study site during site initiation.

5.1.2.2 Fasting plasma glucose (FPG)

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

5.1.2.3 Glycaemic response (HbA1c<7.0%)

The proportion of subjects achieving a therapeutic glycaemic response at Week 24, defined as HbA1c <7.0%, will be assessed using information gathered from the eCRF and the central laboratory.

5.1.2.4 Body weight

The subject's body weight will be recorded in kilogram (kg) to one decimal place, with light clothing and no shoes. All readings should be recorded as accurately as possible and the same scale should be used for all assessments for a given subject. The same scale should be used throughout the study, and calibrated on a regular basis as recommended by the manufacturer.

5.1.3 Exploratory efficacy variables

5.1.3.1 Postprandial glucose AUC

The change from baseline to Week 24 in the postprandial glucose AUC from 0 to 180 minutes in response to an MTT. PPG will be analysed by a central laboratory according to the procedures described in the Laboratory Manual which will be distributed to each study site during site initiation.

5.1.3.2 Fasting serum lipids

Fasting serum lipids (TC, LDL-C, HDL-C and TG) will be analysed by a central laboratory in accordance with procedures mentioned in the Laboratory Manual [Reflex testing will occur for Direct LDL-C if TG > 400 mg/dL (4.52mmol/L)].

5.1.3.3 Rescue/Discontinuation

The proportion of subjects require glycaemic rescue or discontinue study treatment for lack of efficacy and time to glycaemic rescue or discontinuation for lack of efficacy will be assessed using information gathered from the eCRF and the central laboratory.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Laboratory safety assessments will be performed as presented in the Study Plan (Table 1). Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection, and results (including values, units, and reference ranges) will be recorded on the appropriate eCRF.

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

5.2.1.1 Hematology

Hematology assessments refer to Table 3.

5.2.1.2 Chemistry

Chemistry assessments refer to Table 3. If CK>400 IU/L, Troponin I test is required.

5.2.1.3 eGFR

eGFR is calculated according to the 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 mg/dL].

Table 3 Laboratory safety variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
Haemoglobin (Hb)	Aspartate transaminase (AST)
Hematocrit	Alanine transaminase (ALT)
Red blood cell (RBC)	ALK-P
Mean cell volume (MCV)	Creatine kinase (CK/CPK). If CK>400 IU/L, test Troponin I.
Mean cell hemoglobin (MCH)	Total bilirubin
Mean cell haemoglobin concentration (MCHC)	Creatinine
White blood cell count and differential	Sodium
Platelet count	Potassium
	Chloride
	Calcium
	Magnesium
	Phosphorus
	Total Protein
	Uric acid
	Bicarbonate

5.2.1.4 Urinalysis

- Urinalysis assessments will be performed according to Study Plan (Table 1) and will include the following: blood, protein, albumin, urine ketones, creatinine, and calculated urinary albumin: creatinine ratio.

- At screening visit, microscopic urinalyses will be tested at Central Laboratory as detailed in the laboratory manual, and hematuria result must be evaluated. One re-test of microscopy for hematuria urinalysis after resolution is allowed in subjects with positive result of hematuria at screening period in the opinion of investigators.

  Interpretable microscopic hematuria is defined as ≥ 3 RBC/HPF without the presence of epithelial cells. Urine samples that are positive for hematuria WITH the presence of epithelial cells are not interpretable and must be repeated. For this study, the presence

of epithelial cells is defined as ≥ 1+ as reported by the central laboratory. It is the responsibility of investigators to estimate based on the result whether the sample is interpretable or not.

5.2.1.5 Other clinical laboratory evaluations

Thyroid Hormones

Blood samples will be collected for the measurement of TSH at Visit 1 (Screening), as presented in the Study Plan (Table 1). Abnormal TSH value at screening will be further evaluated by free T4. Subjects with abnormal free T4 values will be excluded.

Hepatitis Screening Panel

- HAV IgM antibody
- HBsAg
- HCV antibody

Note: After reviewed all applicable inclusion and exclusion criteria, potential eligible subjects, in the opinion of the investigator, with HCV antibody low positive results should have unscheduled visit as soon as possible to collect additional blood sample for HCV confirmation test in central laboratory during screening period.

Pregnancy Testing

All WOCBP will provide samples for pregnancy tests (serum test in central laboratory during screening and urine test locally on Day 1) according to the schedule presented in the Study Plan (Table 1). Subjects must be not enrolled or randomized or must be discontinued if confirmed pregnancy (see Section 3.9.1).

5.2.2 Physical examination

A brief physical examination should include CV, lungs, abdomen and extremities, and any organ systems pertinent to the subject's signs, symptoms or AEs.

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

5.2.3 ECG

A 12-lead ECG will be performed at Screening, Day 1, Week 24/ETD and/or rescue, according to the schedule presented in the Study Plan (Table 1).

Standard 12-lead ECGs will be performed after approximately 5 minutes of quiet rest with the subject in a supine position. If the ECG must be performed with the subject in another position

(sitting, standing, etc.), the investigator should record the alternate position. The investigator should date and sign the ECG tracing and record the clinical significance of any abnormal result on the tracing. ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the clinical study site and entered as 'Normal' or 'Abnormal' in the eCRF. If the ECG is evaluated as "Abnormal", the investigator should document the specific abnormality. All clinically significant abnormalities should be recorded as AEs on eCRF.

5.2.4 Vital signs

Vital sign measurements in this study will include sitting systolic and diastolic BP and HR. Vital signs should be measured at every visit after the subject rests for approximately 5 minutes and with the subject in a sitting position.

BP measurement with a properly calibrated and validated instrument should be used. Subjects should be seated quietly for at least 5 minutes in a chair rather than on an examination table, with feet on the floor and arm supported at heart level. An appropriate sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure accuracy. At least 2 measurements should be made at least 30 seconds apart. The average of 2 readings is to be entered in the eCRF. This will be documented in the source documents at the investigative site. The same arm should be used for all BP measurements during the study.

Refrain from alcohol intake and intense exercise 24 hours prior to each visit and recommend not using tobacco/nicotine/caffeine within 12 hours prior to each visit.

It is critical that the BP and HR measurements be obtained prior to the administration of blinded study medication.

5.2.5 Other safety assessments

5.2.5.1 Self-monitoring of blood glucose (SMBG) and Hypoglycaemia events

Glucose meters will be supplied to each study site. At the entry into Open-Label Treatment Period (Week -16 visit for subjects in Stratum A and Week -8 for subjects in Stratum B), subjects will receive a glucose meter, supplies and instruction on their use. Supplies will be provided to allow for approximately 60 blood glucose assessments per month for duration of the study. The investigator may require more frequent readings based on local clinical practice. Subjects should bring their glucose meter with them to each study visit to ensure that it is functioning properly. The glucose meters should be calibrated according to instructions given in the package leaflet. Subjects may keep the glucose meters at the end of the study.

The Sponsor recommends instructing the subjects to self-monitor their blood glucose at least one time per day, and in the occurrence of hypoglycaemic symptoms, and to contact the investigator in the event of an unusually high or low blood glucose value. In addition, subjects should comply with site's instructions with regard to SMBG and should promptly report to the site blood glucose values and/or signs and symptoms suggestive of a hypoglycaemia episode.

The memory of the glucose meter should be reviewed to compare with the patient diary, as applicable. The glucose values should be reviewed by the site to identify any unusual high or

low values, and to confirm that the values were obtained for the subject. If finger stick glucose values are discordant from glycaemic control assessed by central laboratory or with clinical symptoms, the subject's glucose meter should be tested and procedure for using it reviewed with the subject.

Hypoglycaemia Events

Hypoglycaemia may be an expected event in subjects who are treated for diabetes. Subjects and their family members must be aware of the possibility that hypoglycaemia may occur and the dangers associated with low blood sugar.

Study subjects must be properly instructed on the recognition and management of hypoglycaemia. Subjects should record in their diaries any hypoglycaemic symptoms. They should be encouraged to measure, when possible, their blood glucose values when they have symptoms of hypoglycaemia. Subjects should carry with them easily ingestible forms of carbohydrate at all times in order to treat an event of hypoglycaemia should it occur.

During clinical trials, subjects frequently report symptoms of hypoglycaemia when asked, even when treated with placebo or medications not otherwise associated with hypoglycaemia. As hypoglycaemia is an important event associated with diabetes therapy, all episodes which could be consistent with the clinical definition of hypoglycaemia **as assessed by the investigator** should be documented and reported on the appropriate eCRF page.

Hypoglycaemia eCRF pages will be used to document all reported episodes of hypoglycaemia. **The investigator is responsible for questioning the subject about all symptoms reported on the hypoglycaemia log and for determining if they meet the clinical definition of hypoglycaemia. Only symptoms and/or blood glucose values deemed by the investigator to meet the definition of hypoglycaemia should be reported on the hypoglycaemia eCRF pages.** Signs and symptoms of hypoglycaemia, hypoglycaemia episode or discontinuation due to hypoglycaemia should not be reported on the AE eCRF page, unless the event fulfils protocol criteria for a SAE (see Section 6.2), in which case an SAE form must be completed in addition to the hypoglycaemia eCRF pages for hypoglycaemia.

The diary will be returned by the subject and reviewed by site personnel at every subsequent visit. Completed diary pages will be added to the subject's source record, and data from the diary will be entered in the appropriate eCRF. A new diary for the next period will be handed over to the subject if needed.

5.2.5.2 Urinary infections

The following is presented to assist in the classification and management of UTI. It is not intended to supplant investigators' clinical judgement:

IP should be withheld in subjects with clinical evidence of upper tract UTIs (e.g. pyelonephritis) or presumed urosepsis until the course of treatment of the infection has been completed and clinical recovery has occurred.

It is recommended that a follow-up urine culture should be obtained within 7 days of clinical recovery from all UTIs. Whether or not additional therapy is prescribed because of culture results should be determined by investigator judgement, after consultation with AstraZeneca study physician.

It is the investigator's responsibility to report, as applicable based on investigator's judgement and subject's medical history, related AEs as defined in Section 6. Additional information, including but not limited to completion of supplemental eCRFs may be requested for certain AEs and/or laboratory abnormalities which are reported/identified during the course of the study.

5.2.5.3 Cardiovascular events (Cardiovascular Adjudication Committee, CAC)

An independent Adjudication Committee, blinded to the treatment of the subjects, will adjudicate *cardiac failure* events **requiring hospitalization** reported in the study. CAC adjudication manual/charter of operations further defines and describes the procedure for the handling, reporting and classification of these events.

5.2.5.4 Potential events of Diabetic Ketoacidosis (DKA Adjudication Committee)

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

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

5.3 Other assessments

5.3.1 Diet and exercise counselling

Starting at the lead-in period, subjects will be instructed on a diet and exercise program in accordance with the ADA or similar local guidelines to be followed for the study duration.

A registered dietitian, registered nurse, physician, certified diabetes educator, nutritionist, or other qualified member of the study team who has appropriate documented training will provide this counselling.

In addition, as part of the diet and exercise program, the investigator or designee should ensure that each subject receives an adequate daily intake of minerals and vitamins, in accordance with the National Academy of Sciences or similar local guidelines.

5.3.2 Height and body mass index (BMI)

Measurement of height should be performed with the subject's shoes removed. The subject's knee should be straightened, head held erect, and eyes forward.

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

5.3.3 Waist circumference

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

5.4 Pharmacokinetics-Not Applicable

5.5 Pharmacodynamics-Not Applicable

5.6 Genetics-Not Applicable

5.7 Biomarker-Not Applicable

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

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

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

6.1.1 Adverse events of special interest

The following AEs are classified as AEs that should be given special attention. They include: hypoglycaemia, volume depletion, cardiac failure (including confirmed adjudicated hospitalization due to cardiac failure events), hypersensitivity reactions, pancreatitis, severe cutaneous adverse reactions, malignancies (including pancreatic cancer, breast cancer and bladder cancer), genital infections, UTIs, liver injury, renal impairment/renal failure, DKA, AEs leading to amputation and potential risk factor AEs for amputations affecting lower limbs (“preceding events”) and fracture.

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

To ensure that data on amputations is systematically collected, amputations and underlying conditions relevant to amputation will be recorded on a specific eCRF page. The AE leading to amputation should be recorded in the eCRF as AE/SAE.

In addition to amputation, non-serious and serious events potentially placing the subject at risk for a lower limb amputation ("preceding events") should also be recorded in the eCRF as AE/SAE, whether or not an amputation has taken place. The lower limb "preceding events" of interest include diabetic foot related conditions, vascular, wounds/injury/trauma, infection and neuropathy. If any of these or other potentially relevant event have occurred, relevant information must be provided (this will be collected on a dedicated eCRF page - for details see eCRF instruction).

6.2 Definitions of serious adverse event

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

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

For further guidance on the definition of a SAE, see Appendix A to the CSP.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

AEs will be collected from the time of first administration of open-label study medication saxagliptin 5 mg throughout the Open-label and Double-blind, double dummy treatment period and including the last visit.

SAEs will be recorded from the time of signing informed consent throughout the Open-label and Double-blind, double dummy treatment period and including the last visit.

All AEs will be recorded on source documents and the eCRF.

6.3.2 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAE/non-serious AEs, will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.

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

6.3.3 Variables

The following variables will be collect for each AE;

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

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

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

- Causality assessment in relation to study procedure(s)
- Description of AE.

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

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

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

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

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

6.3.5 Adverse events based on signs and symptoms

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

6.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report (CSR). Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and other safety variables should therefore only be reported as

AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

For instructions how to handle AE based on ECG see section 5.2.3 and safety analyses for ECG recording see section 8.5.7.

6.3.7 Hypoglycaemia

Subjects will be asked to test their blood glucose if they experience symptoms suggestive of hypoglycaemia and to record specific symptoms and glucose values in the subject diary.

Study site personnel must obtain accurate information for the subject's file and for the hypoglycaemia page of the eCRF.

Hypoglycemia episodes will be classified in the CSR according to 2018 ADA Criteria as follows (ADA 2018).

Severe hypoglycaemia:

An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Glycaemia level may not be available during such an event, but neurological recovery attributable to the restoration of blood glucose to normal is considered sufficient evidence that the event was induced by a low blood glucose concentration.

In summary, hypoglycaemia event will be considered as severe hypoglycaemia if it meets all of the following criteria:

- Require third party assistance
- Prompt recovery after carbohydrate or glucagon administration
- Include symptoms of neuroglycopenia (such as dizziness, confusion, lethargy, headache, visual disturbances, difficulty concentrating, speech difficulty, somnolence/prolonged sleep etc.)

- Glycaemia level, if available, of less than or equal to 70 mg/dL (3.9 mmol/L)

Clinically significant hypoglycaemia: Glycaemia level < 54 mg/dL (3.0 mmol/L).

Hypoglycemia alert value: Glycaemia level ≤ 70 mg/dL (3.9 mmol/L)

Since the glycaemic threshold for activation of glucagon and epinephrine secretion as glucose levels decline is normally 65 to 70mg/dL (3.6 to 3.9mmol/L) and since antecedent blood glucose concentrations of less than or equal to 70mg/dL (3.9mmol/L) reduce sympathoadrenal responses to subsequent hypoglycaemia, this hypoglycaemia alert value of ≤ 70 mg/dL (3.9 mmol/L) can be important for therapeutic dose adjustment of glucose-lowering drugs.

If any episodes of probable symptomatic hypoglycaemia (episodes for which symptoms of hypoglycaemia are not accompanied by a blood glucose determination, but which were presumably caused by a blood glucose concentration less than or equal to 70 mg/dL [3.9 mmol/L]) are reported by subjects, the investigator should evaluate and properly record as such in the subject's source records and follow them according to clinical practice. But this category of hypoglycaemia is not considered as clinically significant and will be not recorded in eCRF or reported in CSR.

6.3.8 Hy's Law-Not Applicable

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the eCRF.

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

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

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

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

If the WBDC system is not available, then the investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

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

6.5 Overdose

Overdose is defined as the accidental or intentional ingestion of any dose of study medication provided by Sponsor that is considered both excessive and medically important. For the purpose of this study, an overdose is defined as a dose of dapagliflozin or saxagliptin in excess of that specified in the CSP (i.e., take more than 1 tablet per day for any of dapagliflozin or its placebo to match or saxagliptin).

For other non-IP (metformin or rescue therapy), overdose will not be collected unless overdose in those medications associated with SAE.

If an overdose is suspected, monitoring of vital functions as well as treatment as appropriate should be performed:

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

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

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

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

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the subject's clinical status. Saxagliptin and its active metabolite are removed by hemodialysis (23% of dose over 4 hours). The removal of dapagliflozin by hemodialysis has not been studied.

6.6 Pregnancy

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

6.6.1 Maternal exposure

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

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

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

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

The same timelines apply when outcome information is available.

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

6.6.2 Paternal exposure

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

6.7 Medication error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for saxagliptin or dapagliflozin that either causes harm to the subject or has the potential to cause harm to the subject.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or subject.

Medication error includes situations where an error

- Occurred
- Was identified and intercepted before the subject received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the subject

- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature
- Wrong subject received the medication (excluding IxRS errors)
- Wrong drug administered to subject (excluding IxRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IxRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Subject accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Subject failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 6.4) and within 30 days for all other medication errors.

6.8 Management of IP related toxicities <<Dose Reductions>>

Dose reductions are not permitted in this study.

6.9 Study governance and oversight

6.9.1 Clinical Event Committee (CEC)

6.9.1.1 Diabetic Ketoacidosis Adjudication Committee

All potential events of DKA will be submitted to an independent DKA Adjudication Committee. The committee will be kept blinded to the treatment codes. A separate DKA Adjudication Manual will define and describe the procedures for the collection of DKA information, handling, adjudication criteria and reporting of these events. Please also refer to Section 5.2.5.4.

6.9.1.2 Cardiovascular Adjudication Committee

An independent CAC blinded to the treatment of the subjects, will adjudicate heart failure events requiring hospitalization reported in the study. A separate Adjudication Manual will define and describe the procedure for the handling, reporting and classification of these events. Please also refer to Section 5.2.5.3.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

IP will be packaged in bottles. The tablets contain lactose, in quantities not likely to cause discomfort in lactose-intolerant individuals. Primary packaging of the IP will be carried out by AstraZeneca or their designee in accordance with Good Manufacturing Practice (GMP).

Investigational product	Dosage, route, form and strength	Manufacturer
Dapagliflozin 10 mg	10 mg, orally, Green, plain, diamond-shaped, film-coated tablet	AstraZeneca
Dapagliflozin 5 mg	5 mg, orally, Green, plain, diamond-shaped, film-coated tablet	AstraZeneca
Dapagliflozin 10 mg placebo to match	Does not contain active ingredient, orally, Green, plain, diamond-shaped, film-coated tablet	AstraZeneca
Dapagliflozin 5 mg placebo to match	Does not contain active ingredient, orally, Green, plain, diamond-shaped, film-coated tablet	AstraZeneca

Non-IP:

Saxagliptin (Onglyza®): 5 mg tablets. Sourced by Sponsor. *

Metformin: Not sourced by Sponsor. To be prescribed by Investigator.

* Onglyza® to be used in China. Saxagliptin to be used in all countries outside China.

7.2 Dose and treatment regimens

The study medications include investigational drugs (dapagliflozin 5 mg, dapagliflozin 10 mg and dapagliflozin placebo to match) and non-IPs (saxagliptin 5 mg, metformin and rescue therapy). Study medication should be taken in the morning and should be taken at approximately the same time of the day during the study period. Subjects should be instructed to abstain from all food for 8 hours prior to each clinical visit; however, drinking water is allowed. For all visits, the subjects should visit the study centre in the morning without taking the IPs, saxagliptin 5 mg, metformin. In the morning prior to each visit, acceptable concomitant medications can be taken with water only.

- Open-label saxagliptin 5 mg tablets will be administered orally once daily for the open-label treatment period and the 24-week double-blind treatment period

- Open-label metformin IR/XR will be administered orally with food at doses ≥ 1500 mg/day or a maximal tolerated dose and keep unchanged for the open-label treatment period and the 24-week double-blind treatment period

- Subjects randomized to the 5 mg treatment arm will receive one tablet of dapagliflozin 5 mg and one tablet of dapagliflozin 10 mg placebo to match, to be administered orally once daily for the 24-week double-blind treatment period

  Subjects randomized to the 10 mg treatment arm will receive one tablet of dapagliflozin 10 mg and one tablet of dapagliflozin 5mg placebo to match, to be administered orally once daily for the 24-week double-blind treatment period

  Subjects randomized to the placebo arm, will receive one tablet of dapagliflozin 5 mg placebo to match and one tablet of dapagliflozin 10 mg placebo to match, to be administered orally once daily for the 24-week double blind treatment period

If any dose is missed, it should be taken as soon as noticed, unless it is almost time for the next dose, in which case subjects should skip the missed dose and take the medicine at the next regularly scheduled time. Advise subjects not to take 2 doses of dapagliflozin at the same time.

7.3 Labelling

Single panel labels or booklet labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

The label will include at least the following information:

- Name of sponsor

- IP/study drug dosage form, route of administration, and quantity of dosage units

- Storage conditions
- Study code
- Enrolment code (to be added on the label when IP is dispensed)
- Directions for use
- The name of Principal Investigator, where applicable (to be added on the label when IP is dispensed)
- The period of use e.g., expiry date
- "For clinical study use only"
- "Keep out of reach of children"

7.4 Storage

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

7.5 Compliance

The administration of dapagliflozin and saxagliptin should be recorded in the appropriate sections of the eCRF.

Each time for the dispensing of saxagliptin and/or dapagliflozin, compliance will be reinforced. When saxagliptin and/or dapagliflozin is returned, compliance will be assessed based on returned tablet counts. Compliance should be between ≥80% and ≤120%. The investigator (or designee) will record the amounts of study medication dispensed and returned at each site, as well as document reasons for non-compliance, in the source document. The dates of all study medication dosing, including interruptions, missed doses or overdose, must be recorded on the eCRF. If the subject is not compliant with recording study drug doses during the study period, non-compliance should be noted as a protocol deviation and the Sponsor should be notified. The subject may continue in the study, but should be counselled on the importance of taking their study medication and applicable ancillary medications as prescribed.

Metformin should be administered according to product and country specific labelling and monitored by investigator.

7.6 Accountability

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

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

Study site personnel will account for all study medications received at the site, unused study medications and for appropriate destruction. Certificates of delivery, destruction, and return should be signed.

A drug disposition form will be provided to record all study medication dispensed to or returned from each subject. Upon completion of the study, all unused study medication, and copies of completed drug disposition forms should be returned to the Sponsor (or designee). Used study medication kits may be disposed at study sites after accountability has been verified by the Sponsor (or designee) and may not be returned to the Sponsor (or designee).

For unused study medication, a clinical supplies return authorization form (CSRAF) will be completed by the clinical research associate at the closeout visit. The completed CSRAF should be enclosed with each return drug shipment to the Sponsor (or designee). The study site personnel must maintain documentation of any missing, damaged, or unreturned study medication.

7.7 Concomitant and other treatments

Subjects must follow the medication restrictions outlined in the inclusion and exclusion criteria (Sections 3.1and 3.2, respectively) during the study. Dosages for certain concomitant medications should be maintained constant during the study, unless instructed otherwise by the investigator or a treating physician. Any change in regimen for any concomitant medication, including restricted concomitant medications, must be reported to the Sponsor. Concomitant herbal or nutritional therapies must also be entered into the eCRF.

7.7.1 Saxagliptin

Saxagliptin 5 mg tablets, administered orally once daily for the open-label period and the 24-week double-blind treatment period, and will be provided by the Sponsor.

7.7.2 Metformin

Up to Week 24, subjects should continue to administer the same type and dose of metformin therapy they were using at study entry. Metformin should be administered and stored according to product and country-specific labelling.

Metformin will not be provided by the Sponsor.

7.7.3 Rescue therapy

Subjects must first complete rescue procedures before receiving open-label rescue therapy. Subjects who require rescue therapy (i.e., FPG rescue criteria met) should receive standard of care treatment. Subjects should continue receiving study medication while receiving rescue therapy.

If rescue therapy fails, further therapy will be given at the discretion of the investigator.

7.7.4 Other concomitant medication

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

7.8 Post Study Access to Study Treatment

At the end of the study, the Sponsor will not continue to supply study drug to subjects/investigators unless the Sponsor chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care therapy.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical hypotheses

The primary hypothesis in this study is that the mean change from baseline in HbA1c at Week 24 achieved with dapagliflozin 10 mg added to saxagliptin 5 mg plus metformin is superior to that achieved with placebo added to saxagliptin 5 mg plus metformin.

The secondary hypotheses will be tested only if dapagliflozin 10 mg added to saxagliptin 5 mg plus metformin is found to be superior to placebo added to saxagliptin 5 mg plus metformin in mean change from baseline in HbA1c at Week 24.

The secondary hypothesis in this study is that the mean change from baseline in HbA1c at Week 24 achieved with dapagliflozin 5 mg added to saxagliptin 5 mg plus metformin is superior to that achieved with placebo added to saxagliptin 5 mg plus metformin.

8.2 Sample size estimate

The primary endpoint (mean change from baseline in HbA1c at Week 24) will be assessed comparing dapagliflozin 5 mg or dapagliflozin 10 mg added to saxagliptin 5 mg plus metformin versus (vs.) placebo added to saxagliptin 5 mg plus metformin. Statistical significance of the primary endpoint will be claimed if the p-values for dapagliflozin 10 mg + saxagliptin 5 mg + metformin vs. placebo + saxagliptin 5 mg + metformin comparison is significant at the 2-sided, 0.05 significance level. As the success of primary endpoint on the dapagliflozin 5mg + saxagliptin 5 mg + metformin vs. placebo + saxagliptin 5 mg + metformin comparison is important, the sample size is planned to provide at least 90% power for primary endpoint on both comparisons.

With 108 subjects per treatment group with post-baseline assessment, there is 95% power to detect -0.5% difference for dapagliflozin 10mg + saxagliptin 5 mg + metformin vs. placebo + saxagliptin 5 mg + metformin comparison, assuming a standard deviation (SD) of 1.0% with a 2-sided significance level of 0.05. This sample size will also provide at least 90% power to detect -0.5% difference for both dapagliflozin 10mg + saxagliptin 5 mg + metformin vs. placebo + saxagliptin 5 mg + metformin and dapagliflozin 5mg + saxagliptin 5 mg +

metformin vs. placebo + saxagliptin 5 mg + metformin comparisons, assuming a standard deviation (SD) of 1.0% with a 2-sided significance level of 0.05.

Assuming that 5% of subjects would not have a post-baseline assessment, a total of approximately 342 subjects (114 subjects per treatment arm, with about 91 subjects from China and about 23 subjects from other countries/region) need to be randomized. In other words, subjects in China will constitute about 80% of the total number of subjects. This study includes two strata, based on prior antihyperglycemic treatment. Stratum A includes subjects whose HbA1c is uncontrolled on a stable dose of metformin and are enrolled into a 16-week open-label treatment period, adding saxagliptin 5 mg to metformin. Subjects in stratum A who remain uncontrolled are subsequently randomized. Stratum B includes subjects whose HbA1c is uncontrolled on a stable dose of metformin and a maximal dose of a DPP-4 inhibitor who are randomized following treatment with saxagliptin 5 mg during an 8-week open-label treatment period.

It is desired to have approximately 33% of the randomized subjects coming from Stratum B. In addition, Enrolment of subjects with HbA1c $\geq$ 8.0% and < 9.0% (Stratum A) and subjects with HbA1c $\geq$ 7.5% and $\leq$ 8.5% (Stratum B) into the open-label treatment period will be limited to approximately 171 subjects (about 50% of the randomized subjects number in each stratum).

About 40% (Stratum A) and 6.5% (Stratum B) of subjects are expected to be discontinued due to severe lack of glycaemic control (defined as FPG > 270 mg/dL at Week -10 or Week -2 in Stratum A and Week -2 only in Stratum B) during the open-label treatment period. In addition, it is expected that 50% of screened subjects will fail to meet eligible criteria for each stratum. This leads to a total of 1004 subjects to be screened, with a targeted 380 subjects in Stratum A and 122 subjects in Stratum B to enter the open-label treatment period.

8.3 Definitions of analysis sets

The primary efficacy analysis will be performed based on ITT analysis set. Safety analysis for double-blind treatment period will be performed based on the safety analysis set. Selected safety and efficacy analyses for the open-label treatment period will be based on open-label treated subjects analysis set.

8.3.1 Efficacy analysis sets

The ITT analysis set will include all randomized subjects who received at least one dose of double-blind study medication during the double-blind treatment period. Subjects will be analyzed according to the treatment groups to which they are randomized.

The per protocol (PP) analysis set is a subset of the ITT set that includes subjects without important protocol deviations that could potentially affect the primary efficacy interpretability of the study results. Subjects will be analyzed according to the treatment groups to which they are randomized. The criteria for PP relevant important protocol deviations will be established after protocol deviation reviews, before the data has been unblinded.

8.3.2 Safety analysis set

The safety analysis set will include all randomized subjects who have received at least 1 dose of double-blind study medication during the double-blind treatment period. Subjects will be analyzed according to treatment actually received. Subject receiving different treatment as assigned by randomization during the entire course of study, will be analyzed based on the first treatment the subject actually received.

8.3.3 Open-label treated subjects analysis set

The open-label treated subjects analysis set will consist of all subjects who receive at least one dose of open-label study medication during the open-label treatment period.

8.3.4 PK analysis set-Not Applicable

8.3.5 PRO analysis set-Not Applicable

8.4 Outcome measures for analyses

8.4.1 Primary efficacy variable

Mean change from baseline in HbA1c at Week 24 will used as primary efficacy variable

8.4.2 Secondary efficacy variables

- Mean change from baseline in FPG at Week 24
- Mean change from baseline in 2-hour PPG during a 2-hour MTT at Week 24
- Mean change from baseline in total body weight at Week 24
- Proportion of subject achieving a therapeutic glycaemic response, defined as a HbA1c < 7.0% at Week 24

8.4.3 Exploratory variables

- The proportion of subjects who require glycaemic rescue or discontinue study treatment for lack of efficacy up to Week 24
- Time to glycaemic rescue or discontinuation for lack of efficacy in the double-blind treatment period
- Mean change from baseline in AUC glucose obtained during MTT at Week 24
- Mean percent change from baseline in fasting serum lipids (Total-C, LDL-C, HDL-C, TG) during the double-blind treatment period

8.5 Methods for statistical analyses

All personnel involved with the analysis of the study will remain blinded until database lock. Analyses will be performed by AstraZeneca or its representatives. The SAP will be finalized prior to unblinding of data.

8.5.1 Analysis of the primary variable (s)

The primary efficacy analysis compared the change from baseline in HbA1c at Week 24 for each of dapagliflozin 5 mg or dapagliflozin 10 mg + saxagliptin 5 mg + metformin treatment groups and the placebo + saxagliptin 5 mg + metformin group. Each comparison was performed at the 0.05 significance level (2-sided) using the hierarchical testing specified in Section 8.1. This maintains the familywise type I error rate at 0.05.

The primary efficacy analysis of HbA1c at Week 24 will be performed using a mixed-model repeated-measures (MMRM) model with terms for treatment group, stratum, baseline HbA1c value, time, the interaction of treatment and time, and the interaction of baseline HbA1c value and time in the model, including observations prior to rescue and study treatment discontinuation only, without explicitly imputing missing data. Point estimates and 95% confidence intervals will be calculated for the adjusted mean changes within each treatment group as well as for the differences in adjusted mean changes between treatment groups.

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 issue, the back-up models will be used [e.g. calculate the denominator degrees of freedom using other method like Satterthwaite approximation, use other covariance matrix like Toeplitz, AR (1), use simpler models, and etc.]. Details will be documented in SAP.

ITT analysis set will be used for the primary efficacy analysis.

8.5.2 Analysis of the secondary variable(s)

The same MMRM approach used for HbA1c evaluation will be also used for the analysis of FPG and total body weight. Point estimates and 95% confidence intervals will be calculated for the adjusted mean changes within each treatment group as well as for the differences in adjusted mean changes between treatment groups.

For subjects in China, the ANCOVA using last observation carried forward (LOCF) methodology with terms for treatment group, stratum, and baseline 2-hour PPG value will be used to evaluate 2-hour PPG. Point estimates and 95% confidence intervals will be calculated for the adjusted mean changes at Week 24 within each treatment group as well as for the differences in adjusted mean changes between treatment groups.

The proportion of subjects achieving a therapeutic glycaemic response (defined as HbA1c < 7.0%) at Week 24 (LOCF) will be summarized by treatment group and compared between treatment groups using the logistic regression based on methodology of Zhang et al (Zhang

2008) and Tsiatis et al (Tsiatis 2008**)** with adjustment for baseline HbA1c and stratum. Point estimates and 95% confidence intervals will be calculated for the response rate within each treatment group as well as the difference in response rates between treatment groups will be calculated.

8.5.3 Subgroup Analysis

Specifically, the treatment effect on the adjusted mean change from baseline in HbA1c will be examined in the following subgroups:

- Baseline HbA1c (< 8.0%, 8.0% to <9.0%, ≥ 9.0%)
- Gender (male, female)
- Age (<65, ≥ 65 years)
- Female/Age (female ≤ 50 years, female > 50 years)
- Duration of T2DM (< 3 years,3-10 years, > 10 years)

8.5.4 Interim analysis-Not Applicable

8.5.5 Sensitivity analysis

Two separate sensitivity analyses for HbA1c will be performed based on ITT analysis set:

1. The MMRM approach with terms for treatment group, stratum, baseline HbA1c value, time, the interaction of treatment and time, and the interaction of baseline HbA1c value and time in the model, including data after rescue and/or study treatment discontinuation.

2. ANCOVA (LOCF) model, with terms for treatment group, stratum, and baseline HbA1c value, including observations prior to rescue and study treatment discontinuation only, where last post-baseline observation carried forward (LOCF) will be used for missing value at Week 24.

The third sensitivity analyses for HbA1c is to repeat the primary analysis for HbA1c based on per protocol analysis set.

Sensitivity analyses for FPG and total body weight will consist of ANCOVA analyses using LOCF methodology based on ITT analysis set.

8.5.6 Exploratory Analysis (if applicable)

The percent of subjects who require glycaemic rescue or discontinue study for lack of efficacy up to Week 24 will be assessed by summarizing the difference in percentages between treatment groups and analyze the variable of time to glycaemic rescue or discontinuation for lack of efficacy in the double-blind treatment period using the Kaplan-Meier methodology.

Analyses of the mean change from baseline for continuous endpoints will be performed using an MMRM or ANCOVA method depending upon the availability of repeated measurements for the endpoint. Among them, AUC of glucose during MTT will only be analyzed based on data of subjects in China.

For lipids (Total-C, LDL-C, HDL-C, TG), the natural logarithms of the post- to pre-treatment ratios, and the natural logarithm (Ln) of the baseline lipid measurement, will be used in the model.

ITT analysis set will be used for the exploratory analysis.

8.5.7 Safety analysis

Safety analyses for the double-blind treatment period will be performed using the Safety analysis set, including data after rescue. Safety analyses will include, where appropriate, descriptive statistics, counts and percentages for AEs and other safety measures. No formal statistical tests will be performed.

The number and percent of subjects with at least one AE will be summarized for each treatment group, including summaries of AEs, SAEs, AEs leading to discontinuation, and AEs of special interest. Summaries will include the number of subjects with events by specified system organ classes and preferred terms.

Additionally, the incidence of AEs and frequency of recurring AEs will be summarized for each treatment group for both frequent events and for selected AEs of special interest.

Values and changes from baseline at each scheduled time point for clinical laboratory parameters and vital signs, including seated BP and HR, will be summarized by treatment group using descriptive statistics. The normality/abnormality of ECG tracings, as determined by the investigator, will be summarized by shift tables overall and by ECG tracing at baseline. The number and percent of subjects with laboratory values meeting marked abnormality criteria will be summarized for each treatment group. Other safety assessments including Scr and eGFR by MDRD, will be summarized by treatment group using descriptive statistics of values and changes from baseline at each scheduled time point.

Additional analyses for AEs and laboratory marked abnormalities may be performed excluding data after rescue and study treatment discontinuation. The primary analyses of events of hypoglycaemia will be performed excluding data after rescue and study treatment discontinuation.

Selected safety analyses will be performed for the open-label treatment period using the Open-label treated subjects analysis set.

8.5.8 Methods for multiplicity control

The primary efficacy analysis compared the change from baseline in HbA1c at Week 24 for each of dapagliflozin 5 mg or dapagliflozin 10 mg + saxagliptin 5 mg + metformin treatment

groups and the placebo + saxagliptin 5 mg + metformin group. Each comparison was performed at the 0.05 significance level (2-sided) using the hierarchical testing specified in Section 8.1. This maintains the familywise type I error rate at 0.05.

8.6 China cohort

Per China Regulatory Authority guidance, in addition to the evaluation of global cohort data for primary, secondary and selected exploratory objectives plus safety objectives, evaluation of consistency in efficacy and safety in China is required to facilitate the benefit-risk assessment for subjects in China sites (China cohort). Hence, the efficacy and safety data in China cohort will be analysed separately where the same endpoint definitions and the same analysis methods (as detailed in Section 8.5) are applied.

Definition of analysis sets in section 8.3 will be applied in China cohort.

Details of China cohort analysis will be specified in SAP, which is to be finalized before data lock.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

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

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

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

9.2 Monitoring of the study

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

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in

accordance with the Laboratory Manual and that study drug accountability checks are being performed

- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts)

- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject

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

9.2.1 Source data

Refer to the CSA location of source data.

9.2.2 Study agreements

The investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

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

The study is expected to start in Q4 2018 and continues to Q4 2020.

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

9.4 Data management by AstraZeneca or delegate

Data management will be performed by AstraZeneca Data Management Centre staff according to the Data Management Plan.

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

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

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

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

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

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

SAE Reconciliation

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

Data associated with human biological samples

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

Management of external data

Data Management determines the format of the data to be received from external vendors and coordinates the flow of data to the clinical database. Data Management will assure that the data collection tool for IxRS are tested and validated. External data reconciliation will be done with the clinical database as defined in the Data Management Plan.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

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

10.2 Subject data protection

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

10.3 Ethics and regulatory review

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

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

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

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

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

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

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

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

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

10.4 Informed consent

The Principal Investigator(s) at each centre will:

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

- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the investigator's Study File
- Ensure a copy of the signed ICF is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the ICF that is approved by an Ethics Committee.

10.5 Changes to the protocol and informed consent form

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

If there are any substantial changes to the study protocol, then these changes will be documented in a new version of the study protocol.

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

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 10.3.

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

10.6 Audits and inspections

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

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12. APPENDIX A ADDITIONAL SAFETY INFORMATION

12.1 Further guidance on the definition of a serious adverse event (SAE)

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious. Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

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

12.2 A guide to interpreting the causality question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

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

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

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

13.1 Labelling and shipment of biohazard samples

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample

containment standards are encouraged wherever possible when road or rail transport is used.

14. APPENDIX C NEW YORK HEART ASSOCIATION FUNCTIONAL CLASS

I. Subjects without limitation of physical activity. Ordinary activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

II. Subjects with slight limitation of physical activity who are comfortable at rest. Ordinary activity results in palpitation, dyspnea, or fatigue.

III. Subjects with marked limitation of physical activity. Although subjects are comfortable at rest, less than ordinary activity will lead to symptoms.

IV. Subjects with inability to carry on any physical activity without discomfort. Symptoms may be present at rest.