AstraZeneca

**Statistical Analysis Plan**

| | |
|---|---|
| Study Code | D1683C00008 |
| Edition Number | 2.0 |
| Date | 29 September 2020 |

# A Multicentre, Randomised, 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 Glycaemic Control on Metformin and Saxagliptin (DS Navigation)

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# LIST OF ABBREVIATIONS

| Abbreviation or special term | Explanation |
|---|---|
| ADA | American Diabetes Association |
| AE | Adverse event |
| AESI | Adverse events of special interest |
| ANCOVA | Analysis of covariance |
| AUC | Area under the curve |
| BMI | Body mass index |
| BP | Blood pressure |
| cm | centimetre |
| CRF | Case report form |
| CV | Conventional Units |
| DPP-4 | Dipeptidyl peptidase-4 |
| eGFR | estimated Glomerular Filtration Rate |
| FDA | Food and Drug Administration |
| FPG | Fasting plasma glucose |
| HbA1c | Haemoglobin A1c/ glycosylated haemoglobin |
| HDL-C | High-density lipoprotein cholesterol |
| HR | Heart rate |
| IP | Investigational product |
| IR | Immediate release |
| ITT | Intent-to-treat |
| kg | kilogram |
| LDL-C | Low density lipoprotein cholesterol |
| LOCF | Last post-baseline observation carried forward |
| MA | Marked abnormality value |
| MDRD | Modification of Diet in Renal Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | Mixed-model repeated-measures |
| MTT | Meal tolerance test |
| PDs | Protocol deviations |
| PE | Physical examination |

| Abbreviation or special term | Explanation |
|---|---|
| PP | Per Protocol |
| PPG | Postprandial plasma glucose |
| PT | Preferred Term |
| SAE | Serious adverse event |
| SAS | Statistical Analysis Software |
| SI | Standard International Units |
| SD | Standard deviation |
| SE | Standard error |
| SOC | System Organ Class |
| T2DM | Type 2 diabetes mellitus |
| TEAE | Treatment emergent adverse event |
| TESAE | Treatment emergent serious adverse event |
| Total-C | Total cholesterol |
| TG | Triglycerides |
| vs. | Versus |
| XR | Extended release |

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## AMENDMENT HISTORY

| Category*: Change refers to | Date | Description of change | In line with the CSP? | Rationale |
|---|---|---|---|---|
| Other: Section 3.5.1 | 29SEP2020 | Updated the definition of TEAE in open label period and double-blind period<br>Added definition of treatment emergent hypoglycaemia in open-label and double-blind treatment | Yes | To help with derivation and interpretation of the results |
| Data presentation: Section 4.2.5.3 | 29SEP2020 | Added rules of how to handle below/above the limit of quantification laboratory parameters | Yes | To clarify the reporting and be consistent with other Dapa studies |
| Other: Section 4.4 | 29SEP2020 | Added a section to address the reduced analysis due to early termination | Yes | To summarize the analysis due to early termination |
| Other: Section 6 | 29SEP2020 | Updated changes of analysis from protocol section | Yes | To address the changes from the protocol due to study early termination |
| Data presentations: Section 8.2 | 29SEP2020 | Removed Albumin and BUN from Marked abnormality criteria tables<br>Updated the units of Total Bilirubin to umol/L | Yes | To accommodate the data collection |

* Pre-specified categories are
Primary or secondary endpoints; Statistical analysis method for the primary or secondary endpoints; Derivation of primary or secondary endpoints; Multiple Testing Procedure; Data presentations; Other

# 1. STUDY DETAILS

## 1.1 Study objectives

### 1.1.1 Primary objective

| Primary Objective: | Outcome Measure: |
|---|---|
| To compare the mean change from baseline in glycosylated haemoglobin (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 |

### 1.1.2 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:<br>1) Fasting plasma glucose (FPG)<br>2) 2-hour postprandial glucose (PPG) from a meal tolerance test (2-hour MTT)<br>3) Total body weight | 1) Mean change from baseline in FPG at Week 24<br>2) Mean change from baseline in 2-hour PPG during an MTT at Week 24<br>3) Mean change from baseline in Total body weight at Week 24 |
| To compare the proportion of subjects achieving a therapeutic glycaemic 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 | Percent of subjects achieving a therapeutic glycaemic response, defined as a HbA1c < 7.0% at Week 24 |

### 1.1.3 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)<br>• AEs of special interest (AESI)<br>• Clinical laboratory tests<br>• Physical examination (PE)<br>• ECG<br>• Vital signs |

### 1.1.4 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 | Percent of subjects who require glycaemic rescue or discontinue study treatment for lack of efficacy up to Week 24 |
| To assess the time to glycaemic 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 double-blind period | Time to glycaemic rescue or discontinuation for lack of efficacy in the double-blind treatment 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 | Mean change from baseline in AUC of glucose obtained during an MTT at Week 24 |

| | |
|---|---|
| To assess the mean percent change from baseline in fasting serum lipids (total cholesterol (Total-C), low density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG)) with dapagliflozin 5 mg or dapagliflozin 10 mg added to saxagliptin 5 mg and metformin vs. placebo added to saxagliptin 5 mg and metformin after 24 weeks of oral administration of double-blind treatment | Mean percent change from baseline in fasting lipids (Total-C, LDL-C, HDL-C, TG) at Week 24 |

## 1.2 Study design

Figure 1 below presents the overall design of the study.

Study D1683C00008 is a 24-week, multicentre, randomised, 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.

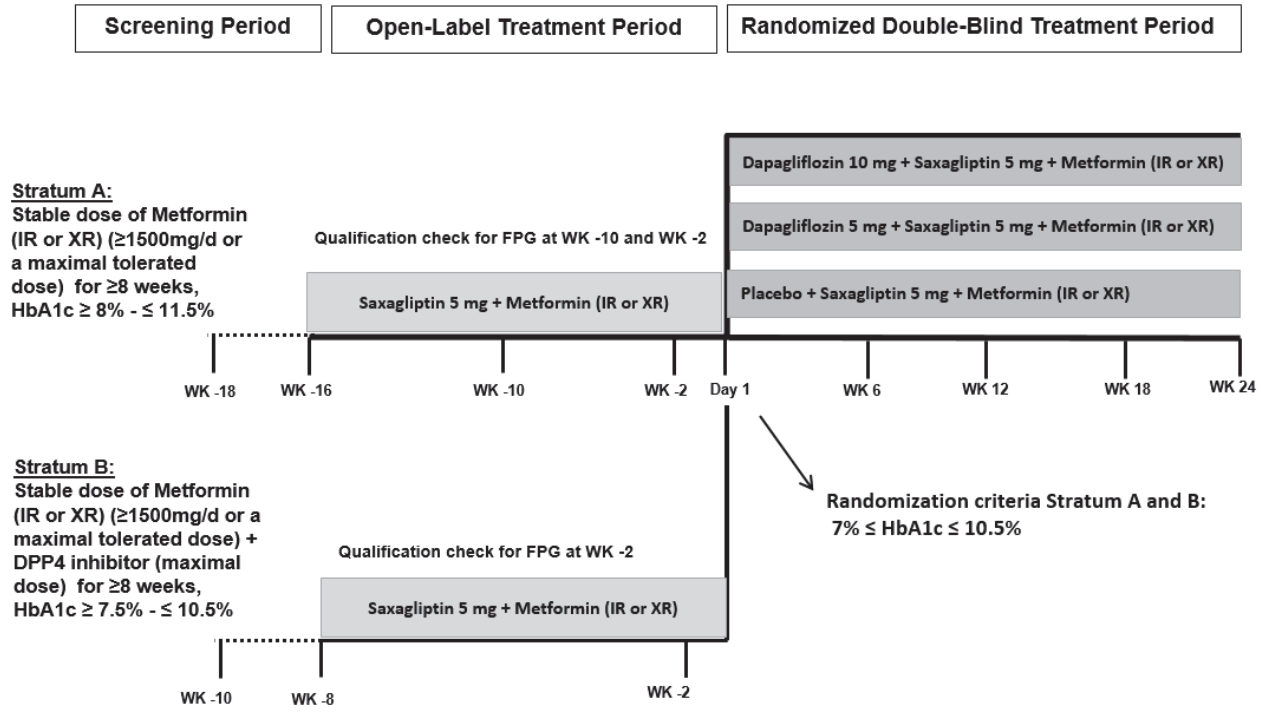
After written informed consents have been obtained at screening visit, subjects will be checked for all applicable inclusion/exclusion criteria, and laboratory samples will be taken and submitted. In Stratum A, subjects should have a stable dose of metformin immediate release (IR)/extended release (XR) (≥ 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 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 of randomisation visit, eligible subjects will be randomised 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 Glucagon-like peptide-1(GLP-1) analogues, other DPP-4 inhibitors and/or sodium glucose cotransporter 2 (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**




## 1.3 Number of subjects

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 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/regions) need to be randomised. 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 randomised. 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 randomised following treatment with saxagliptin 5 mg during an 8-week open-label treatment period.

It is desired to have approximately 33% of the randomised 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 randomised 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.

# 2. ANALYSIS SETS

## 2.1 Definition of analysis sets

The primary efficacy analysis and exploratory analysis will be performed based on Intent-to-treat （ITT）analysis set. Safety analysis for double-blind treatment period will be performed

based on the Safety analysis set. Selected safety analyses for the open-label treatment period will be based on Open-label treated subjects analysis set.

### 2.1.1 Enrolled subjects set

The enrolled subjects set will consist of all subjects who sign informed consent. This data set will be used to summarise the subject disposition data.

### 2.1.2 ITT analysis set

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

### 2.1.3 Per protocol (PP) analysis set

The 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 analysed according to the treatment groups to which they are randomised. The criteria for important protocol deviations are detailed in Section 2.2 below.

### 2.1.4 Safety analysis set

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

### 2.1.5 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.

## 2.2 Violations and deviations

Important protocol deviations (IPD) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or wellbeing.

A list of important protocol deviations and any action to be taken regarding the exclusion of subjects or affected data from the primary efficacy analysis are defined in appendix 1. This list will be finalised before the data has been unblinded. A report will be generated based on both IMPACT and programmatic checking results. IPDs that are determined to have the potential to affect the primary efficacy results are deemed PP Relevant IPDs. Subjects who have any PP relevant IPDs as detailed in appendix 1 will be excluded from the PP analysis set.

# 3. PRIMARY AND SECONDARY VARIABLES

## 3.1 General principles taken for analysis variables

### 3.1.1 Study Day Definition

For the purposes of the data summaries, Study Day 1 is defined as the first dose date of study medication in each treatment period. For visits (or events) that occur on or after first dose date of study medication, study day is defined as:

(date of visit [event] – first dose date of study medication + 1).

For visits (or events) that occur prior to first dose date of study medication, study day is defined as:

(date of visit [event] - first dose date of study medication).

There is no Study Day 0.

For listings (such as for AEs/SAEs that include the derivation of "days since last dose", this is defined as:

(event date – last treatment date of study medication).

Events that occur on the same day as the last dose of study medication will therefore be described as occurring zero days from the last dose of study medication.

### 3.1.2 Duration of Type 2 Diabetes

Duration of T2DM is calculated as the number of years from T2DM diagnosis date to informed consent date:

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

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

If the date T2DM was diagnosed is partially missing, the following rules will take effect:

- Missing day, but month and year are present: the day will be imputed as the 15th day of the month.
- Missing day and month, but year is present: the day and month will be imputed as 30 June of the year (provided that the imputed date is less than the consent date).
- Missing year, but day and month are present: No imputations will occur, and the subject will be excluded from all summaries related to duration of T2DM.
- Missing day, month and year: No imputations will occur, and the subject will be excluded from all summaries related to duration of T2DM.
- If any such imputed date falls after the consent date, then the diagnosis date will be taken as equal to the consent date.

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

### 3.1.3 Definition of Baseline Measurements

Unless otherwise stated, for each subject, double-blind baseline value of a parameter (e.g., efficacy laboratory parameter, safety laboratory test) is defined as the last assessment on or prior to the date of the first dose of the double-blind study medication. Open-label baseline is defined as the last assessment on or prior to the date of the first dose of the open-label medication.

### 3.1.4 Change and Percent Change from Baseline

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

$$C_{Week\ t} = M_{Week\ t} - M_{baseline},$$

where:

- $C_{Week\ t}$ is the change from baseline at Week t,
- $M_{Week\ t}$ is the measurement at Week t,
- $M_{baseline}$ is the measurement at baseline.

Percent change from baseline to any Week *t* is defined as follows:

$$P_{Week\ t} = 100 \times (M_{Week\ t} - M_{baseline}) / M_{baseline}\ .$$

Where $P_{Week\ t}$ is the percent change from baseline at Week *t*, and $M_{Week\ t}$ and $M_{baseline}$ are defined as above.

The "Week t" to which a measurement belongs is determined using the conventions described in section 3.1.5.

### 3.1.5 Visit Windows

For summaries of vital signs and laboratory data, assessments will be assigned to calculated visit windows (using study day) as described in Table 1 for double-blind treatment period and Table 2a and Table 2b for open-label treatment period below.

Inclusion within the visit window should be based on the actual date and not the intended date of the visit. The window for the visits following baseline (including unscheduled visits) will be constructed in such a way that the upper limit of the interval falls half way between the two visits.

For laboratory and non-laboratory parameters, unless otherwise specified, if a subject has more than one measurement included within a window, the assessment closest to the target day will be used. In case of ties between observations located on different sides of the target day, the earlier assessment will be used. In case of ties located on the same side of the target

day (i.e. more than one value for the same day but different time), the value with the earlier entry date/time will be used. If two non-missing values are recorded on the same day and have no assessment time associated with at least one of them, or the same assessment time associated with both of them, the average of the two values will be selected for analysis at that visit.

**Table 1 - Visit Windows for double-blind treatment period**

| Assessment | Visit | Week | Target Day | Day Range |
|---|---|---|---|---|
| **HbA1c, body weight, FPG, laboratory parameters, vital sign parameters** | | | | |
| Screening/Baseline | 0 | | | |
| Week 6 | 1 | 6 | 43 | 2-64* |
| Week 12 | 2 | 12 | 85 | 65-106* |
| Week 18 | 3 | 18 | 127 | 107-148* |
| Week 24 | 4 | 24 | 169 | 149-Last day of double-blind treatment + *x* day** |
| | | | | |
| **MTT, ECG, Lipids, Waist circumference** | | | | |
| Screening/Baseline | 0 | | | |
| Week 24 | 1 | 24 | 169 | 2-Last day of double-blind treatment + *x* day** |

* on or before the last day of double-blind treatment
**In efficacy analysis, *x* = 8 for HbA1c and body weight, *x* =1 for FPG and MTT, and *x* =4 for Lipids; In safety analysis, *x* = 4 for ECG, vital signs, and laboratory data, and *x*=30 for liver function.

**Table 2a- Visit Windows for open-label treatment period, Stratum A**

| Visit | Target Day, Relative to Day 1 of open-label treatment period | Day Range |
|---|---|---|
| HbA1c | | |
| Week -2 | 99 | 72- up to first dose of DB |
| | | |
| FPG | | |
| Week -16 | 2 | 2-21 |
| Week -10 | 43 | 22- 71 |

| | | |
|---|---|---|
| Week -2 | 99 | 72 - up to first dose of DB |

**Table 2b - Visit Windows for open-label treatment period, Stratum B**

| Visit | Target Day, Relative to Day 1 of open-label treatment period | Day Range |
|---|---|---|
| HbA1c | | |
| Week -2 | 43 | 22- up to first dose of DB |
| | | |
| FPG | | |
| Week -8 | 2 | 2-21 |
| Week -2 | 43 | 22- up to first dose of DB |

### 3.1.6 Handling missing data

In general, other than for partial dates, missing data will not be imputed and will be treated as missing, with some exceptions specified for certain efficacy variables.

#### 3.1.6.1 Last post-baseline observation carried forward (LOCF)

In the analysis of change (or percent change) from baseline, as well as response endpoint at Week t LOCF, the Week t measurement will be used. If no Week t measurement is available (subject received rescue medication or discontinued treatment before Week t, or the subject has not discontinued, but the measurement was not taken at Week t), the last post-baseline measurement prior to Week t will be used. Unless specified otherwise, all data prior rescue and/or study treatment discontinuation, will be used for the calculation of LOCF values.

#### 3.1.6.2 Imputation of partial dates

**Concomitant Medication Dates**

Imputation of start dates allows medications for subjects to be classified into the categories of prior, concomitant (or both) for tables. An assessment should be made as to the possibility that the subject's medication could fall into each category given the information available for the dates. If it is possible given the date information that a subject's medication could fall into a given category, then the subjects' medication should be included for tables for that category. If a particular category can be ruled out based on partial or full dates available, then the

subject's medication should be excluded from that category. The following date imputation should accomplish this:

Start Dates

- If year is missing (or the date is completely missing), set equal to the consent date.
- If year is present and month and/or day are missing then impute as the earliest possible date given the partially entered date.
- If the resulting imputed start date is after a non-missing (i.e. not imputed) end date then set the start date equal to the end date.

End Dates

- If year is missing (or the date is completely missing) set equal to the most recent database extraction date.
- If the year is known but month and/or day is missing, then set equal to the latest possible date provided it is not before the concomitant med start date (actual or imputed). If it is before the concomitant med start date then set it equal to this date.

**Adverse Events Dates**

Onset Dates

In case of missing dates, prior to assigning the treatment that the subject received at the onset of an AE or at the time of a laboratory assessment, imputation rules will be applied as follows:

- If the onset date for an AE is missing or incomplete, an imputed date will be derived to slot the event to an appropriate analysis period. This derived date will not be reported in summary tables or listings. Every effort will be made to determine the actual onset date for the event or to obtain a reliable estimate for the onset date from the investigator.
- If an onset date is **missing** (or the year is missing), the **derived onset date** will be calculated as the first non-missing valid date from the following list (in order of precedence):
  - First active study medication date
  - Consent date
  - If a valid non-missing date is not available for any of these dates, the derived onset date will be set to missing.
- If an onset date is **incomplete**, the derived onset date will be calculated using the following algorithm:

- Calculate a **surrogate date** as the first non-missing valid date from the following list (in order of precedence):
  - First active study medication date
  - Consent date
  - Visit date corresponding to the visit at which the event was reported
  - If a valid non-missing date is not available for any of these dates, the surrogate date will be set to missing.

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

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

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

End Dates

A missing or incomplete end date of an AE will be imputed according to the following conventions:
• If an end date is missing, the derived end date will be set to missing
• If an end date is incomplete, set the derived end date to be the latest possible date based on the partial onset date information provided. If only a year is provided, set the derived date to December 31st of that year. If the subject died in the same year, then set the imputed date as the death date. If a year and month is provided, set the derived date to the last day of that month.

## 3.2 Primary efficacy endpoint

The primary efficacy variable is the mean change from baseline in HbA1c at Week 24.

## 3.3 Secondary efficacy endpoints

The following secondary efficacy variables will be analysed:

- 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, only applicable for subjects in China
- 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

## 3.4 Exploratory efficacy endpoints

The following exploratory endpoints will be analysed:

- The proportion of subjects who require glycaemic rescue or discontinue study treatment for lack of efficacy at 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, only applicable for subjects in China
- Mean percent change from baseline in fasting serum lipids (Total-C, LDL-C, HDL-C, TG) during the double-blind treatment period

## 3.5 Safety variables

The following safety data will be collected and analysed: AEs/SAEs, AESI, clinical chemistry/haematology parameters, physical examination, ECG and vital sign measurements.

### 3.5.1 Adverse Events

All AEs and SAEs occurring during the study will be recorded. Details such a start and stop date of AE, causality, action taken with study medication and outcome will be recorded.

Adverse event data will be categorised according to their onset date as follows:

- Pre-treatment AEs: AE onset date < date of first dose of study medication during the open-label period
- Open-label period treatment emergent adverse events (TEAEs): date of first dose of study medication during open-label period ≤ AE onset date ≤ minimum (date of last dose of study medication during open-label treatment period +4 days, date of first dose of study medication during the double-blind treatment period – 1 day) or minimum (date of last dose of study medication during open-label treatment period +30 days, date of first dose of study medication during the double-blind treatment period – 1 day) if SAE
- Open-label period treatment emergent serious adverse events (TESAEs): date of first dose of study medication during open-label treatment period ≤ SAE onset date ≤ minimum (date of last dose of study medication during open-label treatment period

+30 days, date of first dose of study medication during the double-blind treatment period – 1 day)

- Double-blind period TEAEs: date of first dose of study medication during double-blind treatment period ≤ AE onset date ≤ date of last dose of study medication during double-blind treatment period +4 days or date of last dose of study medication during double-blind treatment period +30 days if SAE
- Double-blind period TESAEs: date of first dose of study medication during double-blind treatment period ≤ SAE onset date ≤ date of last dose of study medication during double-blind treatment period +30 days
- Post-treatment AEs: AE onset date > date of last dose of study medication during double-blind treatment period +4, and SAE onset date > date of last dose of study medication during double-blind treatment period +30
- Open-label period treatment emergent hypoglycemia: date of first dose of study medication during open-label period ≤ hypoglycemia onset date ≤ minimum (date of last dose of study medication during open-label treatment period +4 days, date of first dose of study medication during the double-blind treatment period – 1 day) or minimum (date of last dose of study medication during open-label treatment period +30 days, date of first dose of study medication during the double-blind treatment period – 1 day) if SAE
- Double-blind period treatment emergent hypoglycemia: date of first dose of study medication during double-blind treatment period ≤ hypoglycemia onset date ≤ date of last dose of study medication during double-blind treatment period +4 days or date of last dose of study medication during double-blind treatment period +30 days if SAE

### 3.5.2 Laboratory Safety Variables

The following laboratory variables will be summarised:

**Table 3 - Chemistry and haematology assessments**

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

| | |
|---|---|
| | Uric acid<br>Bicarbonate |

**Urinalysis**

Urinalysis assessments will be performed according to Study Plan of protocol and will include the following: blood, protein, albumin, urine ketones, creatinine and calculated urinary albumin: creatinine ratio.

### 3.5.3 Vital sign

Vital sign measurements in this study will include sitting systolic and diastolic BP and heart rate (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.

### 3.5.4 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 of protocol. All clinically significant abnormalities should be recorded as AEs on eCRF as described in Section 5.2.3 of the protocol.

### 3.5.5 Physical examination

Complete and brief physical examinations will be performed at timepoint specified in Study Plan of protocol.

# 4. ANALYSIS METHODS

## 4.1 General principles

Continuous data will be summarised in terms of the number of observations, mean, standard deviation (SD), upper quartile, median, lower quartile, minimum and maximum unless otherwise stated. In addition, 95% confidence interval for the mean (percent) change from baseline will be calculated for continuous efficacy variables. They will be presented by treatment group and time point where applicable. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Descriptive summaries of categorical variables will consist of frequencies and percentages for each treatment group and overall, where applicable.

Descriptive summaries of change from baseline in categorical variables will be provided using shift tables. Frequencies and percentages of subjects within each treatment group will be generated for levels of cross-classifications of baseline and the on-treatment value of the parameter. The on-treatment value can either be the value at a certain time point, or e.g. for laboratory tests, the minimum/maximum value, which has been observed during the treatment period. Treatment group differences will not be assessed in summaries of shifts.

## 4.2 Analysis methods

### 4.2.1 Subject disposition

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion. Summaries of subject disposition will be presented by treatment and overall (column), while summaries in the Enrolled subjects set and Open-label treated subjects analysis set (when applicable) will be presented only stratum and overall (column). The following subject disposition summaries will be provided:

- Number and percentage of subjects in the Enrolled subjects set, Open-label treated subjects analysis set, ITT analysis set, PP analysis set and Safety analysis set will be presented on their own as well as by country and overall (row) (Analysis Population: Enrolled subjects set).

- Number and percentage of screen-failure subjects (i.e., subjects enrolled but not enter the open-label treatment period), further classified by reasons for screen failure (Analysis Population: Enrolled subjects set).

- Number and percentage of subjects who entered open-label treatment period but not randomised, further classified by reasons (Analysis Population: Open-label treated subjects analysis set).

- Number and percentage of subjects who complete the treatment and who withdraw from treatment, further classified by reasons (Analysis Population: ITT analysis set).

- Number and percentage of subjects who complete the study and who withdraw from study, further classified by reasons (Analysis Population: ITT analysis set).

Important PDs will be summarised by treatment for the ITT analysis set. A listing will also be provided.

### 4.2.2 Demographics and other baseline characteristics

Demographic and baseline subject characteristics will be summarised by overall for Open-label treated subjects analysis set, and by treatment group and overall for the ITT analysis set. If the safety analysis set differs significantly (ie., ITT analysis set has 5% subjects less than safety analysis set) from the ITT analysis set, the analysis will be repeated for the safety analysis set. Additionally, the analysis will be repeated for the PP analysis set.

All summaries of continuous variables will be based on non-missing observations. For categorical variables, percentages will be calculated out of the total number of subjects in the data set, overall and by treatment group, where applicable (i.e., each denominator includes the number of subjects with missing/unknown values for the characteristic).

#### 4.2.2.1 Demography data

Standard descriptive statistics will be presented for the continuous variables of:

- Age (years) = integer [(Date of ICF – Date of Birth)/365.25].
- Weight (kg).
- Height (cm).
- Body mass index (BMI) ($kg/m^2$), calculated as: $weight/(height)^2$

The total frequency counts and percentages of subjects will be presented for the categorical variables of:

- Sex (grouped as male, female)
- Age group (years) (grouped as <65, ≥65 and <75，≥75)
- Female/Age (female ≤ 50 years, female > 50 years)
- Body mass index ($kg/m^2$) (grouped as Normal (<25), Overweight (≥25 - <30), Obese (≥30))
- Geographic Region (grouped as China/ Non-China)
- Race (Asian, White, Black of African American, Other)

#### 4.2.2.2 Other baseline characteristics

Standard descriptive statistics will be presented for the continuous variables of:

- Duration of Type 2 Diabetes (years).
- HbA1c
- FPG
- PPG
- Estimate glomerular filtration rate (eGFR, Modification of Diet in Renal Disease (MDRD))

The total frequency counts and percentages of subjects will be presented for the categorical variables of:

- Randomisation stratification factors (Stratum A, Stratum B)
- HbA1c (grouped as: <8.0%, 8.0% to <9.0%, ≥9.0%)
- Duration of Type 2 Diabetes (years) (grouped as < 3, ≥ 3 and ≤ 10, > 10)
- eGFR ($mL/min/1.73m^2$) (grouped as <30, ≥30 and <60, ≥60 and <90, ≥90)
- Metformin dose (mg) (group as: <1500, ≥ 1500 and <1701, ≥1701 and <2500, ≥2500)

#### 4.2.2.3 Medical History

Diabetes related medical history and general medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA). All disease related medical history will be listed and the number and percentage of subjects with any disease related medical history will be summarised for the ITT analysis set by system organ class (SOC) and preferred term (PT).

All general medical history will be listed and summarised similarly.

#### 4.2.2.4 Prior Medications

Prior medications, including any medication (other than study medications) with a start date prior to Day 1 of open-label treatment period, will be summarised by treatment for safety analysis set.

Missing and partial date handling of start and stop dates of prior medications is described in Section 3.1.6.2 above. The WHO Drug Dictionary (WHODD) is used to code the non-study medication.

### 4.2.3 Extent of Exposure and Treatment Compliance

#### 4.2.3.1 Extent of Exposure – Study and Rescue Medication

The extent of exposure to each study medication during the open-label treatment period and double-blind treatment period, respectively, is defined as:

treatment end date of a treatment period – treatment start date of a treatment period +1

The extent of exposure to each study medication will be summarised using the Safety analysis set for the double-blind treatment period and the double-blind treatment period prior to rescue, where the number and percent of subjects with an extent of exposure within specified day ranges (1-7, 8-30, 31-60, 61-90, 91-120, 121-180, > 180 days) will be presented by treatment group.

The mean, standard deviation (SD), median and range of the number of days of exposure to each study medication will also be presented. Summaries will be presented including periods of interruptions (defined by record of 0 tablets of study medications on the CRF).

All rescue medication use during the double-blind treatment period will be summarised and listed by treatment group.

A listing of subjects by batch number of study medication will also be generated.

The extent of exposure to study medication during the open-label treatment period will be summarised by stratum, using the method outlined above for Open-label treated subjects analysis set.

#### 4.2.3.2 Extent of Exposure – Concomitant Medications

Concomitant medications include any medication taken from start of the double-blind treatment period up to the end of the double-blind treatment period.

Concomitant medications will be summarised using the Safety analysis set by drug class and (generic) drug name.

Missing and partial date handling of start and stop dates of concomitant medications is described in Section 3.1.6.2 above.

#### 4.2.3.3 Measurement of Treatment Compliance

Percent treatment compliance is calculated for each study medication during the open-label treatment period, and double-blind treatment period, respectively.

(Number of tablets taken / Planned number of tablets) x 100%

Where the planned number of tablets is calculated as:

(Treatment end date – Treatment start date +1) x prescribed daily number of tablets

The number of tablets taken is calculated as:

total number of tablets dispensed - total number of tablets returned

based on the CRF accountability pages.

A subject is considered compliant if percent compliance is ≥ 80% and ≤ 120%. For each type of medication, the number and percent of subjects compliant will be displayed for open-label treatment period using Open-label treated subjects analysis set and for double-blind treatment period using Safety analysis set.

For metformin, a summary including number and percentage of subjects that ever took metformin therapy at a dose of <1500mg per day, for double-blind treatment period using Safety analysis set and for open-label treatment period using Open-label treated subjects analysis set, will be provided separately in addition to the compliance summary of the IPs.

### 4.2.4 Efficacy analyses

This section addresses separately the analyses to be conducted on the primary efficacy endpoint, on the secondary and other efficacy endpoints. Unless otherwise specified, ITT analysis set will be used.

Summary statistics will be presented for each primary, secondary and exploratory variable as described in Section 4.1, as well as the statistical analyses as described below.

#### 4.2.4.1 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.

#### 4.2.4.2 Primary efficacy outcome variable

The primary endpoint is the change in HbA1c from baseline to Week 24. The primary efficacy analysis will be based on the ITT analysis set including values prior to rescue treatment or discontinuation. Values recorded after rescue treatment or values collected more than 8 days after last dose date of the double-blind study medication are excluded from the analysis.

A mixed-model repeated-measures (MMRM) analysis using 'direct likelihood' will be performed. The SAS procedure PROC MIXED will be used. The preferred model will include the fixed categorical effects of treatment, stratum, time and treatment-by-time interaction as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-time interaction.

The following model will be used:

$$C_{ijkm} = \text{intercept} + ß_1\,[M_{baseline,ijm}] + \tau_i + s_m + \alpha_k + (\alpha\,\tau)_{ik} + (\alpha\,M_{baseline})_{ijkm} + \text{error}_{ijkm}$$

where

- $C_{ijkm}$ is the change from baseline for subject j in treatment group I of stratification group m at time k,
- $ß_1$ is the slope coefficient for the baseline measurement,
- $M_{baseline,ijm}$ is the baseline measurement of subject j in treatment group i of stratification group m,
- $\tau_i$ is the mean effect of treatment group i,
- $s_m$ is the mean effect of randomisation stratification factor group m,
- $\alpha_k$ is the mean effect at time k,
- $(\alpha\,\tau)_{ik}$ is the interaction term between treatment group i and time k.
- $(\alpha\,M_{baseline})_{ijkm}$ is baseline measurement-by-time interaction term for subject j in treatment group i of stratification group m at time k, and
- $\text{error}_{ijkm}$ is the error term for subject j in treatment group i of stratification group m at time k.

An unstructured matrix for the within-subject error variance-covariance will be used. The denominator degrees of freedom will be calculated according to the Kenward-Roger method.

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

- The first backup model is the same as the preferred model but the Kenward-Roger method will be replaced by Satterthwaite approximation.
- The second backup model is the same as the preferred model but the covariance matrices will be assumed in the following order Toeplitz, first-order autoregressive, compound symmetric, variance components.
- The third backup model is the same as the preferred model but without the term for baseline measurement-by-time interaction.

If the back-up model does not converge or has memory issues, the next back-up model will be used in the order.

Point estimates and 95% confidence intervals for the mean change within each treatment group as well as the difference in mean change between each dapagliflozin treatment group and placebo will be calculated. Student t-statistics corresponding to the Type III sums of squares for the differences in the least squares means between each dapagliflozin group and placebo at Week 24 will be calculated.

**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 4.2.4.1. This maintains the familywise type I error rate at 0.05.

**Sensitivity analysis**

To assess the robustness of the primary efficacy analysis for the change in HbA1c from baseline to Week 24, additional sensitivity analyses will be carried out using the following approaches:

1. A MMRM model, similar to the primary analysis, but including data after rescue and/or study treatment discontinuation, will be conducted.

2. Analysis of covariance (ANCOVA) model, with terms for treatment group, stratum, and baseline HbA1c value, including observations prior to rescue and study treatment discontinuation only, where LOCF data will be used for missing value at Week 24. The handling of LOCF is described in Section 3.1.6.1. The analysis will include data prior to the date of the first dose of rescue medication or up to 8 days post the last dose date of the double-blind study medication.

The following ANCOVA model will be used:

$$D_{24,\text{ijk}} = intercept + \beta\,[Y_{0,ijk}\,] + \tau_i + s_k + error_{ijk}$$

where

- $D_{24,\text{ijk}} = Y_{24,\text{ijk}} - Y_{0,\text{ijk}}$ = the Week 24 or Week 24 LOCF change from baseline of subject *j* in treatment group *i* of stratification group k ,
- $Y_{0,\text{ijk}}$ is the baseline measurement of subject *j* in treatment group *i* of stratification group k,
- $Y_{24,\text{ijk}}$ is the Week 24 or Week 24 LOCF measurement of subject *j* in treatment group *i* of stratification group k ,
- $\beta$ is the slope of $D_{24,\text{ijk}}$ regressing on the baseline measurement and,
- $\tau_\text{i}$ is the mean effect of treatment group *i*.
- $s_\text{k}$ is the mean effect of randomisation stratification factor group *k* .
- *Intercept*, $\beta$ and $\tau_\text{i}$, $s_\text{k}$ are unknown parameters to be estimated from the data.
- $error_{ijk}$ is the error term for subject j in treatment group i of stratification group k.

3. A MMRM model, similar to the primary analysis, using subjects in the Per Protocol Analysis Set who have a baseline assessment and any postbaseline assessment.

For each sensitivity analysis, the least squares mean estimates and 2-sided 95% confidence intervals for mean changes from baseline within and (when warranted) differences in mean change from baseline between each dapagliflozin treatment group and placebo will be provided.

**Subgroup analysis of the primary endpoint**

The primary efficacy endpoint of HbA1c will be summarised for the subgroups defined on the basis of the categorised variables listed below:

- 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, ≥ 3 and ≤ 10 years, > 10 years)

Treatment effects will be assessed for above subgroups based on the longitudinal repeated measures analysis model in Section 4.2.4.2 with additional covariates of subgroups, treatment-by-subgroup, time-by-subgroup, and treatment-by-time-by-subgroup. Tests of the treatment by subgroup interaction will be assessed using contrasts of the treatment effect by subgroups at Week 24. The p-value for the test of treatment by baseline HbA1c interaction will use the continuous version of HbA1c. The adjusted mean changes from baseline, SE's, and 95% CIs

for each subgroup and the nominal p-value for subgroup by treatment interaction will be calculated.

If the value of the group variable cannot be determined, the subject will be excluded from the corresponding subgroup analysis. For each subgroup analysis, if, in any treatment group, the number of subjects is less than 10 for a subgroup, then the summary for that subgroup will be displayed but will not be included in tests for subgroup-by-treatment interaction.

#### 4.2.4.3 Secondary efficacy variable

**Mean change from baseline for FPG**

The analysis of the change from baseline for FPG at Week 24 will be performed using the same MMRM model as for the primary efficacy endpoint, as outlined in section 4.2.4.2, including data prior to the date of the first dose of rescue medication or up to 1 days post the last dose date of the double-blind study medication. Point estimates and 2-sided 95% confidence intervals for the mean change within each treatment group, as well as the difference in mean change between each dapagliflozin treatment group and placebo, will be calculated.

A sensitivity analysis using ANCOVA (LOCF) model, outlined in section 4.2.4.2, with terms for treatment group, stratum, and baseline FPG value, including observations prior to rescue and study treatment discontinuation only, will be performed.

**Mean change from baseline in 2-hour PPG during MTT, only applicable for subjects in China**

The mean change from baseline in 2-hour PPG during MTT at Week 24 will be evaluated using ANCOVA, as outlined in section 4.2.4.2, with terms for treatment group, stratum, and baseline 2-hour PPG value, including observations prior to rescue and study treatment discontinuation only, will be performed. Point estimates and 2-sided 95% confidence intervals for the mean change within each treatment group, as well as the difference in mean change between each dapagliflozin treatment group and placebo, will be calculated.

**Mean change from baseline for total body weight**

The analysis of the change from baseline for total body weight at Week 24 will be performed using the same MMRM model as for the primary efficacy endpoint, as outlined in 4.2.4.2, including data prior to the date of the first dose of rescue medication or up to 8 days post the last dose date of the double-blind study medication. Point estimates and 2-sided 95% confidence intervals for the mean change within each treatment group, as well as the difference in mean change between each dapagliflozin treatment group and placebo, will be calculated.

A sensitivity analysis using ANCOVA (LOCF) model, as outlined in section 4.2.4.2, with terms for treatment group, stratum, and baseline total body weight, including observations prior to rescue and study treatment discontinuation only, will be performed.

**Proportion of subjects achieving a therapeutic glycaemic response**

The proportion of subjects achieving a therapeutic glycaemic response (defined as HbA1c <7.0%) at Week 24(LOCF) will be summarised 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 each dapagliflozin treatment group and placebo will be calculated.

#### 4.2.4.4 Exploratory efficacy variables

ITT analysis set will be used for the exploratory analysis.

**Proportion of subjects requiring glycaemic rescue or discontinuing study treatment for lack of efficacy**

The proportion of subjects who require glycaemic rescue or discontinue study for lack of efficacy up to Week 24 will be summarised by treatment group and compared between treatment groups using the logistic regression outlined in section 4.2.4.2. 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 each dapagliflozin treatment group and placebo will be calculated.

**Time to glycaemic rescue or discontinuation for lack of efficacy in the double-blind treatment period**

Time to glycaemic rescue or discontinuation for lack of efficacy in the double-blind treatment period will be presented by treatment group using a Kaplan-Meier curve (Kaplan and Meier 1958). Unless otherwise specified, the plot will be presented only when there are at least 5 events in one treatment group. Additionally, a table will accompany the plot and will display the Kaplan-Meier estimates of the cumulative proportion (with 95% CI calculated based on Greenwood's method when applicable) (Greenwood 1926) of subjects with event at specific time points by treatment group. If the estimated lower bound of 95% CI is below 0 or the estimated upper bound of 95% CI is over 1, then it will be restricted to 0 or 1 respectively.

**Mean change from baseline in AUC glucose obtained during MTT at Week 24, only applicable for subjects in China**

For the mean change from baseline in area under the curve (AUC) of glucose obtained during an MTT, the change in AUC will be estimated based on the Trapezoidal rule using the estimates of change from baseline at Week 24 in postprandial measurements at target times t1, t2, t3, t4 and t5 (0, 30, 60, 120, and 180 minutes respectively after administration of a meal).

To incorporate the correlations among post-prandial measurements at different MTT target time points and an appropriate representation of effect of baseline measurements, the change from baseline at Week 24 in postprandial measurements will be analysed using a longitudinal repeated measures method. The model will include the fixed categorical effects of treatment,

stratum, target time and treatment-by-target time interaction as well as the continuous fixed covariate of baseline measurement at target time 0 of MTT, with an assumption of unstructured matrix for within-subject error variance-covariance if applicable. The SAS® procedure PROC MIXED will be used.

After obtaining the estimates of mean change from baseline at Week 24 in postprandial measurements, the mean change in AUC within a treatment group or difference in mean change in AUC between treatment groups will be estimated within the framework of the mixed model, using the formula based on the Trapezoidal rule:

$$\overline{\Delta AUC} = \sum_{i=1}^{4} (t_{i+1} - t_i) \frac{\hat{\bar{y}}_{t_{i+1}} + \hat{\bar{y}}_{t_i}}{2}$$

where $\hat{\bar{y}}_{t_i}$ is the estimate of mean change from baseline at target time $t_i$ in a treatment group for estimation of mean change in AUC within treatment group, and for estimation of difference in change in AUC between treatment groups, $\hat{\bar{y}}_{t_i}$ is the estimate of mean difference between treatment groups in change from baseline at target time $t_i$. The variability of $\overline{\Delta AUC}$ will also be estimated within the framework of the mixed model in SAS.

Point estimates and 2-sided 95% confidence intervals for the mean change within each treatment group, as well as the difference in mean change between each dapagliflozin treatment group and placebo at each target timepoint, will be calculated.

**Mean percent change from baseline in fasting serum lipids (Total-C, LDL-C, HDL-C, TG)**

The mean percent change from baseline to Week 24 in fasting serum lipids will be analysed separately, using ANCOVA models, as outlined in Section 4.2.4.2.

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. Subsequently, the estimates from the analysis will be back-transformed to original values for reporting in the tables.

Point estimates and 2-sided 95% confidence intervals for the mean change within each treatment group, as well as the difference in mean change between each dapagliflozin treatment group and placebo, will be calculated.

**HbA1c and FPG Analyses in Open-Label**

HbA1c and FPG will be summarised descriptively over time for the open-label treatment period. In addition, the proportion of subjects with HbA1c at Week -2, categorized as [<7%, ≥7% and ≤10.5%, >10.5%], will be summarised using the Open-label Treated Subjects Analysis Set.

### 4.2.5 Safety analyses

Safety analysis, including adverse Events (AEs) and laboratory marked abnormalities (MA), for open-label treatment period will be conducted using open-label treated subjects analysis set.

Safety analyses of the double-blind treatment period will be performed using safety analysis data set, including data after rescue (primary safety analysis). Additional sensitivity analyses for AEs and laboratory MA will be performed excluding data after rescue for the double-blind treatment period. The primary analyses of events of hypoglycaemia will be performed excluding data after rescue.

#### 4.2.5.1 Adverse Events

AEs will be classified by Primary SOC and PT according to the MedDRA. Summaries of AEs will use the version of MedDRA that is current at the time of database lock.

In summaries by SOC and PT, AEs will be sorted by overall decreasing frequency within each SOC and PT. In summaries by PT, AEs will be sorted by decreasing frequency within PT according to the highest of either of the combinational dose group across the study.

Separate pages to capture events of hypoglycaemia are contained within the CRF. Hypoglycaemia or discontinuation due to hypoglycaemia would not be reported on an AE CRF page unless the event fulfilled criteria for an SAE in which case a serious AE (SAE) form would be completed. Hypoglycaemia events that are reported as SAEs will be included in all summaries of AEs or SAEs. Separate summaries will be provided including hypoglycaemia events reported on the special CRF pages.

Analysis of AE will be on treatment-emergent AEs for open-label treatment period and double-blind treatment period, as defined in section 3.5.1.

**All Adverse Events**

An overall summary of adverse events at subject level, including TEAEs, TESAEs, death, hypoglycaemia, severe events, treatment-related events, events leading to the discontinuation of study medication, events leading to death will be presented for open-label treatment period, double-blind treatment period and double-blind treatment period prior to rescue, respectively.

All TEAEs (serious and non-serious, excluding hypoglycaemic events that are not reported as SAEs) will be summarised by SOC and PT for double-blind treatment period. In addition, a subject listing of all reported AEs will be produced, displaying all events including pre-treatment AEs and post-treatment AEs, if any. All TEAEs (serious and non-serious) including all hypoglycaemic events will also be summarised by treatment group, where applicable.

In addition, the following summaries will be provided for the double-blind treatment period (excluding hypoglycaemic events that are not reported as SAEs):

- Most common TEAE by PT and treatment group (i.e., reported by ≥ 2 % of subjects in any treatment group),
- TEAEs by SOC, PT, intensity and treatment group,
- TEAEs related to study medication (by investigator) by SOC, PT and treatment group.
- Proportion of subjects with TEAEs by SOC and PT in subgroups of subjects defined by age category (< 65 and ≥ 65 years), gender and race.

No formal comparisons will be made between treatments. No formal statistical testing will be performed, only summary statistics will be provided.

**Serious Adverse Events**

TESAEs (including hypoglycaemic events) occurring during the double-blind treatment period will be summarised by SOC, PT and treatment group. In addition, the proportion of subjects with related TESAEs will be presented by SOC, PT and treatment group. TESAEs (including hypoglycaemic events) occurring during the open-label treatment period will be summarised by SOC and PT for Open-label treated subjects analysis set.

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

**Adverse Events Leading to Discontinuation of Study Medication**

AEs with an onset during the double-blind treatment period reported with an action taken of discontinuation of study medication will be summarised by SOC, PT and treatment group. This summary will include hypoglycaemia events that reported as SAEs. When summarising AEs leading to discontinuation no upper cutoff day windows are applied.

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

**Adverse Events of Special Interest**

Event categories of adverse events special interest (AESI) for this study 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.

To identify each type of adverse event of special interest, a list of PTs will be selected before database lock and unblinding of the database.

For each category, the number and percentage of subjects with the event is summarised by PT and treatment group in the double-blind treatment period.

## Hypoglycaemic Events

Separate pages to capture events of hypoglycaemia are contained within the CRF. Hypoglycaemic events with an onset from Day 1 of double-blind treatment to and including 4 days after the last dose date of double-blind treatment will be considered as occurring during the double-blind treatment period. The proportion of subjects with hypoglycaemic events will be tabulated by treatment group.

Hypoglycaemia episodes will be categorised according to the American Diabetes Association (ADA) Criteria [ADA 2018] which classifies hypoglycaemia as follows:

**Table 4 - Hypoglycaemia classes**

| | |
|---|---|
| Severe hypoglycaemia: | An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.<br><br>A hypoglycaemia event will be considered as severe hypoglycaemia if it meets all of the following criteria:<br><br>• Require third party assistance<br>• Prompt recovery after carbohydrate or glucagon administration<br>• Include symptoms of neuroglycopenia (such as dizziness, confusion, lethargy, headache, visual disturbances, difficulty concentrating, speech difficulty, somnolence/prolonged sleep etc.)<br>• 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) |
| Hypoglycaemia alert value | Glycaemia level ⩽ 70 mg/dL (3.9 mmol/L) |

Number and percentage of subjects who had any hypoglycaemic event and total number of events by treatment group will be presented for the safety analysis set.

A summary of proportion of subjects having severe hypoglycaemia, clinically significant hypoglycaemia, and hypoglycaemia alert value as categorised by the ADA criteria above will also be presented for the safety analysis set. All incidences of hypoglycaemic events and their ADA categorisation will be listed.

#### 4.2.5.2 Deaths

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

#### 4.2.5.3 Clinical laboratory variables

Unless otherwise specified, laboratory data obtained after the start of open-label study medication dosing up to and including 4 days (30 days for liver function laboratory tests) after the last open-label study medication dosing date (or up to the start of the double-blind treatment period, whichever date comes first) will be considered as obtained during the open-label treatment period. Similarly, laboratory data obtained after the start of study medication dosing up to and including 4 days (30 days for liver function laboratory tests) after the last double-blind dosing date will be considered as obtained during the double-blind treatment period.

All analyses of laboratory data will be performed in both Conventional Units (CV) and Standard International Units (SI).

Listings for lab data include everything in the database.

**Marked Laboratory Abnormalities**

Laboratory abnormalities will be evaluated based on laboratory values meeting pre-defined MAs criteria, as per criteria defined in Appendix 2. The number and percent of subjects with MAs occurring during the double-blind treatment period will be summarised by treatment group and laboratory test. In addition to the primary analysis, a sensitivity analysis of MAs will be performed that excluded data after rescue. To capture all possible drug related liver elevations, liver MA summaries included data up to 30 days after the last dose of double-blind treatment.

An additional summary of laboratory MAs will be presented for the open-label treatment period based on comparison of laboratory values with the baseline value for the open-label treatment period.

**Change from Baseline for Selected Laboratory Parameters Over Time**

Values and changes from baseline at each scheduled time point for clinical laboratory parameters, including serum creatinine, and eGFR by MDRD, will be summarised by treatment group using descriptive statistics for double-blind treatment period.

There will be no imputation for missing values. However, assessment values of the form "<x" (i.e. below the lower limit of quantification) or ">x" (i.e. above the limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "<x" or ">x" in the listings.

#### 4.2.5.4 Vital signs

Values and changes from baseline at each scheduled time point for vital signs, including seated blood pressure and heart rate, will be summarised by treatment group using descriptive statistics for double-blind treatment period.

#### 4.2.5.5 Electrocardiograms

The normality/abnormality of the ECG tracing, as determined by the investigator, will be summarised using shift table to present baseline and Week 24 value. When the data at Week 24 is not available for a discontinued subject, then the last observation before discontinuation of that subject (regardless of rescue) will be used for summary.

## 4.3 China Cohort

Per China Regulatory Authority guidance, in addition to the evaluation of global cohort data for primary, secondary and selected exploratory plus safety objectives, evaluation of consistency in efficacy and safety in China is required to facilitate the benefit-risk assessment for China cohort, defined as subjects in China sites. Therefore, the following data will be presented for the China Cohort using the same analysis methods as outlined in section 4.1 and 4.2.

- subject disposition
- demographics and baseline characteristics
- medical history
- extent of exposure and treatment compliance
- primary, secondary and selected exploratory efficacy endpoints
- safety endpoints including AEs/SAEs, AESI, Clinical laboratory tests, ECG and Vital signs

The same definition of analysis sets outlined in section 2.1 will be applied in China cohort. All efficacy analysis will be considered as exploratory objective for China cohort. A nominal p-value will be provided for the purpose of the completeness of the data analysis. Sensitivity analysis for the primary endpoint might be conducted for China Cohort. For the subgroup analysis in China Cohort, if the value of the grouping variable cannot be determined, the patient will be excluded from the corresponding subgroup analysis. For each subgroup analysis, if, in any treatment group, the number of patients is less than 10 for a subgroup, this subgroup will not be included in the interaction model and descriptive summaries only will be displayed.

## 4.4 Early termination analyses

On Jun 30, 2020 AstraZeneca decided to stop commercialization of QTERNMet/Qtrilmet and to withdraw all active licenses, for business reasons. DS-NAVIGATION will be closed without recruiting subjects in China and patients recruited from Thailand and Vietnam will complete the study.

Therefore, the planned analyses in this study will be conducted over all data available. To support the synopsis format CSR, the following analysis will be performed:

- Summaries of subject disposition, summaries in the Enrolled subjects set and Open-label treated subjects analysis set, as described in Section 4.2.1. Subject disposition will also be listed.
- Summary of analysis set, defined in Section 2.1.
- Demographic and baseline characteristics as described in Section 4.2.2 and Section 4.2.2.1.
- An overall summary of adverse events at subject level, including TEAEs, TESAEs, death, hypoglycaemia, severe events, treatment-related events, events leading to the discontinuation of study medication, events leading to death will be presented for open-label treatment period and double-blind treatment period. TEAEs will also be summarised by SOC and PT in open-label and double-blind treatment. TESAEs will be summarised by SOC and PT in the double-blind period only. AEs and SAEs will also be listed.
- Important protocol deviations, observed HbA1c data, and marked abnormalities by test will be listed.

# 5. INTERIM ANALYSES (NOT APPLICABLE)

# 6. CHANGES OF ANALYSIS FROM PROTOCOL

Due to early termination for business reasons, the analyses planned in this study will not be performed as planned, all but the analyses in Section 4.4.

# 7. REFERENCES

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# 8. APPENDIX

## 8.1 Appendix 1 – IPD MASTER LIST

| IPD code | IPD Category | Explanation | PP Relevant IPD | Exclusion level |
|---|---|---|---|---|
| **1. Inclusion Criteria Deviations: for subject who did not meet any of below criteria (refer to CSP section 3.1)** | | | | |
| 1.1 | Did not fulfil eligibility criteria | Subjects must be willing and able to give signed and dated written informed consent | | |
| 1.2 | Did not fulfil eligibility criteria | 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≥1500mg per day or a maximal tolerated dose for at least 8 weeks prior to screening visit<br>b. For inclusion into open-label treatment period of Stratum B Subjects with T2DM with inadequate glycaemic control, defined as central laboratory HbA1c ≥ 7.0 and ≤ 10.5% obtained at the screening visit (i.e.. Week -10), on stable metformin therapy at a dose≥1500mg 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<br>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<br>d. Body mass index (BMI)≤40.0kg/$m^2$ at the screening visit. | 1. Randomised subjects without Type II diabetes or with central laboratory HbA1c at screening and/or -2 week outside of specified limits such as more than 0.2% outside of specified limits (i.e. violation of inclusion criterion # 2c or screening HbA1c value out of range specified in 2a or 2b)<br><br>2. Randomised subjects who do not receive stable dose of metformin as of the start of open-label (i.e. Violation of inclusion criterion 2a and 2b) | Completely Exclude from PP analysis set |

| IPD code | IPD Category | Explanation | PP Relevant IPD | Exclusion level |
|---|---|---|---|---|
| 1.3 | Did not fulfil eligibility criteria | Age and Reproductive Status<br>a. Men and women, aged ≥ 18 years old at time of screening visit<br>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 | | |
| **2. 3.2)** | **Exclusion Criteria Deviations: for subject who met any of below criteria (refer to CSP section** | | | |
| 2.1 | Did not fulfil eligibility criteria | **Target Disease Exceptions**<br>a. History of diabetes insipidus and type 1 diabetes<br>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<br>c. History of hyperosmolar nonketotic coma<br>d. History of DKA requiring medical intervention (e.g. emergency room visit and/or hospitalization) within 1 month prior to screening<br>e. Subjects age < 40 years with positive GAD antibodies. | | |
| 2.2 | Did not fulfil eligibility criteria | **Medical History and Concurrent Diseases**<br>a. History of bariatric surgery or lap-band procedure within 12 months prior to screening<br>b. Any unstable endocrine, psychiatric or rheumatic disorders as judged by the investigator | | |

| IPD code | IPD Category | Explanation | PP Relevant IPD | Exclusion level |
|---|---|---|---|---|
| | | 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<br>d. Subject is currently abusing alcohol or other drugs or has done so within the last 6 months prior to screening | | |
| 2.3 | Did not fulfil eligibility criteria | **CV disorders**<br>e. Uncontrolled hypertension defined as systolic blood pressure (SBP) ≥ 160 mmHg and/or diastolic blood pressure (DBP) ≥ 100 mmHg<br>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 randomised if their BP remains SBP ≥ 160mmHg or DBP ≥ 100 mmHg measured on Day 1.<br>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. | | |

| IPD code | IPD Category | Explanation | PP Relevant IPD | Exclusion level |
|---|---|---|---|---|
| | | Subjects with stable cardiac disease are not excluded | | |
| 2.4 | Did not fulfil eligibility criteria | **Renal Diseases**<br>g. Subjects with moderate to severe renal impairment [defined as estimate glomerular filtration rate (eGFR) < 60mL/min/1.73 m2 (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)<br>h. Unstable or rapidly progressing renal disease<br>i. Conditions of congenital renal glucosuria | | |
| 2.5 | Did not fulfil eligibility criteria | **Hepatic Diseases**<br>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<br>k. Subjects with severe hepatic impairment (Child-Pugh class C)<br>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 | | |
| 2.6 | Did not fulfil eligibility criteria | **Hematological/Oncological Diseases/Conditions**<br>m. History of hemoglobinopathy, such as sickle cell anemia (SA), thalassemia or chronic or recurrent hemolysis, etc.<br>n. Malignancy within 5 years of the screening visit (with the exception of treated basal cell | 3.Randomised subjects with a history of haemoglobinopathy with the exception of sickle cell trait (SA) or thalassemia; or chronic recurrent haemolysis. (i.e. | Completely Exclude from PP analysis set |

| IPD code | IPD Category | Explanation | PP Relevant IPD | Exclusion level |
|---|---|---|---|---|
| | | or treated squamous cell carcinoma)<br>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)<br>p. Donation of blood or blood products > 400mL or participation in a clinical study requiring withdrawal of > 400mL of blood during within 6 months prior to the screening visit | violation of exclusion criterion #2m) | |
| 2.7 | Did not fulfil eligibility criteria | **Prohibited Treatment and Therapies**<br>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<br>r. Any use of SGLT2 inhibitor within 8 weeks prior to screening<br>s. Prescription and over-the-counter weight loss medications within 3 months prior to screening<br>t. Current treatment with potent cytochrome P450 3A4/5 inhibitors (in countries where dose adjustment would be required by the saxagliptin label)<br>u. Administration of any other investigational drug or participation in any interventional clinical studies within 30 days prior to screening | | |
| 2.8 | Did not fulfil eligibility criteria | **Physical and Laboratory Test Findings**<br>a. Hemoglobin (Hb) ≤ 11.0g/dL (110g/L) for men; Hb ≤ 10.0g/dL (100g/L) for women<br>b. For male subjects with microscopic hematuria urinalysis positive at screening | 4.Randomised Subjects with Abnormal free T4 values at enrolment (i.e. violation of exclusion criterion #3c). | Completely Exclude from PP analysis set |

| IPD code | IPD Category | Explanation | PP Relevant IPD | Exclusion level |
|---|---|---|---|---|
| | | 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.<br>NOTE: Female subjects with hematuria can be randomised, but should be investigated according to local standards and best clinical practices.<br>c. 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 | | |
| 2.9 | Did not fulfil eligibility criteria | **Allergies and Adverse Drug Reaction**<br>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 | | |
| 2.10 | Did not fulfil eligibility criteria | Women who are pregnant or breastfeeding | | |
| 2.11 | Did not fulfil eligibility criteria | a. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g. infections disease) illness<br>b. Subjects on a commercial weight loss program with ongoing weight loss, or on an intensive exercise program<br>c. 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 | | |

| IPD code | IPD Category | Explanation | PP Relevant IPD | Exclusion level |
|---|---|---|---|---|
| 2.12 | Did not fulfil eligibility criteria | • 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 randomised and must be discontinued<br>• 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 randomised and must be discontinued | | |
| **3. Did not discontinue Investigational product (IP) when discontinuation criteria (refer to CSP section 3.9.1) were met** | | | | |
| 3.1 | Subject decision | Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment | | |
| 3.2 | AE/SAE related discontinuation | Subject experiences an AE or SAE that, in the investigator's opinion, necessitates discontinuation from study medication | | |

| IPD code | IPD Category | Explanation | PP Relevant IPD | Exclusion level |
|---|---|---|---|---|
| 3.3 | Pregnancy | Pregnancy confirmed by a positive pregnancy test or otherwise verified | | |
| 3.4 | Serious hypersensitivity | Serious hypersensitivity reaction | | |
| 3.5 | Actue pacratitis | Acute pancreatitis | | |
| 3.6 | Severe non-compliance | Severe non-compliance with the study protocol | | |
| 3.7 | Loss of ability to freely provide consent | 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 | | |
| 3.8 | eGFR | eGFR < 60mL/min/1.73m$^2$ for sustained period of time (12 - 16 weeks)<br>**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.** | | |
| 3.9 | Hepatic function | Initial and repeat laboratory tests meet any of the following criteria:<br>– ALT and/or AST are >3 x ULN and TB >2 x ULN<br>– ALT and/or AST are >5 x ULN for ≥14 consecutive days, at any time after initial confirmatory results<br>– ALT and/or AST are >8 x ULN | | |
| 3.10 | DKA | Consider to temporary interrupt dapagliflozin if DKA is suspected. The subject should be promptly evaluated. If DKA is confirmed, dapagliflozin should be discontinued permanently. | | |
| 3.11 | Hypoglycaemia | Hypoglycaemia events as defined in CSP Section 3.9.2 | | |
| **4. Concomitant & Other Study Medication Deviations** | | | | |
| 4.1 | Prohibited medications during the study | a. Randomised subjects who used anti-hyperglycemic therapy (other than protocol required medications) for ≥14 consecutive days during the | 5.Randomised subjects who used anti-hyperglycemic therapy (other than protocol required | Partially exclude from PP analysis set (if occurs during double blind) |

| IPD code | IPD Category | Explanation | PP Relevant IPD | Exclusion level |
|---|---|---|---|---|
| | | open-label or double-blind period.<br>b. Randomised subjects newly initiating or changing treatment with systemic glucocorticoids for >= 5 days after enrolment<br>c. Randomized subjects receive potent cytochrome P450 3A4/5 inhibitor for ≥14 consecutive days during the open-label or double-blind period, without consultation between investigator and study physician. | medications) for ≥14 consecutive days during the open-label or double-blind period.<br><br>6. Randomised subjects newly initiating or changing treatment with systemic glucocorticoids for >= 5 days after enrolment | Completely exclude from PP analysis set (if occurs during open label)<br>5. Assess relevant deviation for subjects who are randomised. Assess the open-label and double-blind treatment periods together.<br>Exclusion would start from the 14th consecutive day that the medication is taken.<br>6. Assess relevant deviation for subjects who are randomised. Assess the open-label and double-blind treatment periods together. Change includes up or down titration.<br>Exclusion would start from the 5th day that the medication is taken. |
| 4.2 | Adjustment of background medication | Randomised subjects who took metformin < 1500mg per day or adjusted from their maximal tolerated dose for ≥ 2 consecutive weeks after enrolment | 7. Randomised subjects who took metformin < 1500mg per day or adjusted from their maximal tolerated dose for ≥ 2 consecutive weeks after enrolment | Partially exclude from PP analysis set (if occurs during double blind) Completely exclude from PP analysis set (if occurs during open label). Assess relevant deviation for subjects who are randomised. Assess the open-label and double-blind treatment periods together. Exclusion would start from the 14th consecutive day that the medication is < 1500mg per day or adjusted from their maximal tolerated dose |

| IPD code | IPD Category | Explanation | PP Relevant IPD | Exclusion level |
|---|---|---|---|---|
| 4.3 | Saxagliptin treatment non-compliance | Randomized subjects who took no dose of saxagliptin for >= 2 consecutive weeks of the days in the open-label or double-blind period | 8. Randomized subjects who took no dose of saxagliptin for >=2 consecutive weeks of the days in the open-label or double-blind period | Partially exclude from PP analysis set (if occurs during double blind)<br>Completely exclude from PP analysis set (if occurs during open label)<br>Assess relevant deviation for subjects who are randomised. Assess the open-label and double-blind treatment periods together. Exclusion would start from the 14th consecutive day that saxagliptin was stopped. |
| 4.4 | Deviation of rescue treatment procedure | Subjects did not receive open label rescue medications when met rescue criteria | | |
| **5. Investigational Product Deviations** | | | | |
| 5.1 | Drug dispense error | Incorrect investigational drug kit was dispensed. | 9.Randomised subjects who received incorrect study medication or dosing for ≥ 2 consecutive weeks in the double-blind period | Partially exclude from PP analysis set. Assess relevant deviation for subjects who are randomised. Exclusion would start from the 14th consecutive day that the incorrect medication is taken. |
| 5.2 | Take wrong dose | Randomised subjects who received correct drug kit, but took wrong dose for ≥ 2 consecutive weeks in the double-blind period | 10. Randomised subjects who received correct drug kit, but took wrong dose for ≥ 2 consecutive weeks in the double-blind period | Partially exclude from PP analysis set. Assess relevant deviation for subjects who are randomised. Exclusion would start from the 14th consecutive day that the incorrect dose is taken. |
| 5.3 | Incorrect treatment code broken | Treatment code broken incorrectly, i.e. not due to medical emergencies | 11. Treatment code broken incorrectly, i.e. not due to medical emergencies | Partially exclude from PP analysis set. Data after code broken will not be included in analysis. |

| IPD code | IPD Category | Explanation | PP Relevant IPD | Exclusion level |
|---|---|---|---|---|
| 5.4 | IP non-compliance | a. Overall compliance is less than 80% or more than 120% of the IP in the double-blind period.<br>b. Randomised subjects who did not take IP for ≥ 2 consecutive weeks | 12. Overall compliance is less than 80% or more than 120% of the IP in the double-blind period.<br>13.Randomised subjects who do not take IP for ≥ 2 consecutive weeks | 12.Completely exclude from PP analysis set.<br>13.Partially exclude from PP analysis set. Exclusion would start from the 14th consecutive day that the medication is not taken in an interruption. |
| **6. Assessment Deviations** | | | | |
| 6.1 | Deviation of ETD procedure | Subject was discontinued from study treatment early, but Early treatment discontinuation (ETD) visit/End of Treatment visit was not performed | | |
| 6.2 | Deviation of rescue procedure | a. Rescue visit was not performed for rescued subjects<br>b. Subject received rescue therapy before performed rescue visit | | |
| 6.3 | Deviation of central lab repeat test for hepatic function | Repeat central laboratory tests not performed when met any of below criteria:<br>— ALT and/or AST are >3 x ULN and TB >2 x ULN<br>— ALT and/or AST are >5 x ULN for ≥14 consecutive days, at any time after initial confirmatory results<br>— ALT and/or AST are >8 x ULN | | |
| 6.4 | Missing of HbA1c value | HbA1c value was missing during double-blind period | | |
| 6.5 | Deviation of MTT test procedure | Procedure of meal tolerance test (MTT) not followed CSP procedure at day 1 or week 24/rescue visit/ETD visit. | | |
| **7. SAE, Pregnancy and Overdose Reporting Deviations** | | | | |
| 7.1 | SAE reporting | Delay in SAE reporting. | | |
| 7.2 | Pregnancy reporting | Delay in Pregnancy reporting. | | |
| 7.3 | Overdose reporting | Delay in Overdose reporting. | | |

| IPD code | IPD Category | Explanation | PP Relevant IPD | Exclusion level |
|---|---|---|---|---|
| **8. Other Deviations** | | | | |
| 8.1 | Deviation in those with permanently consent withdrawal | Study data collection has not been stopped when subject decided to withdraw his/her consent from the study completely. | 14.Study data collection has not been stopped when subject decided to withdraw his/her consent from the study completely. | Partially exclude from PP analysis set. Data after ICF withdrawal will not be included in the analysis. |
| 8.2 | Incorrect stratification | Subject with wrong stratum allocation after entering open label treatment period | 15.Subject with wrong stratum allocation after entering open label treatment period | Completely exclude from PP analysis set. |
| 8.3 | Others | This option should only be used following discussion with the Global Study Team, in case any IPD not applicable to the predefined categories above needs to be reported | | |

## 8.2 Appendix 2 – MARKED ABNORMALITY CRITERIA

The criteria for marked abnormality for each variable are listed in the following table. Note that a post-baseline lab value will be considered a MA only if it satisfies the specified criteria and is more extreme (farther from the limit) than is the baseline value. If the baseline value is missing, then the observation will be considered an MA if it meets the criteria below.

**Conventional (CV) Units:**

| Clinical Laboratory variables | Units | Marked Abnormality Criteria | |
|---|---|---|---|
| | | Low | High |
| **Hematology** | | | |
| HCT males/females | % | < 20.0% | > 55.0% |
| HCT males/females | % | | > 60.0% |
| Hemoglobin males/females | g/dL | < 6 g/dL | > 18 g/dL |
| Hemoglobin males/females | g/dL | | > 20 g/dL |
| **Blood Chemistry** | | | |
| Total protein | g/dL | | > 10 g/dL |
| ALP | U/L | | > 3X ULN |
| ALT | U/L | | > 3X ULN |
| AST | U/L | | > 3X ULN |
| ALT | U/L | | > 5X ULN |

| Clinical Laboratory variables | Units | Marked Abnormality Criteria | |
|---|---|---|---|
| | | Low | High |
| AST | U/L | | > 5X ULN |
| ALT | U/L | | > 10X ULN |
| AST | U/L | | > 10X ULN |
| ALT | U/L | | > 20X ULN |
| AST | U/L | | > 20X ULN |
| Total Bilirubin | mg/dL | | > 2X ULN if PreRx ≤ ULN;<br>> 3X ULN if PreRx > ULN |
| Glucose, Plasma Unspecified | mg/dL | < 54 mg/dL | > 350 mg/dL |
| Na (Sodium) | mEq/L | < 130 mEq/L | > 150 mEq/L |
| Na (Sodium) | mEq/L | < 120 mEq/L | |
| K (Potassium) | mEq/L | ≤ 2.5 mEq/L | ≥ 6.0 mEq/L |
| HCO3 (Bicarbonate) | mEq/L | ≤ 13 mEq/L | |
| Creatinine | mg/dL | | ≥ 1.5X PreRx CREAT |
| Creatinine | mg/dL | | ≥ 2.5 mg/dL |
| CK (Creatine Kinase)[1] | U/L | | > 5X ULN |
| CK (Creatine Kinase)[1] | U/L | | > 10X ULN |
| Calcium | mg/dL | < 7.5 mg/dL | ≥ 1 mg/dL from ULN **and** ≥ 0.5 mg/dL from PreRx CA |
| Magnesium | mEq/L | < 1 mEq/L | > 4 mEq/L |
| PO4 (Phosphate) | mg/dL | Age 17-65: ≤ 1.8mg/dL<br>Age ≥ 66: ≤ 2.1 mg/dL | Age 17-65: ≥ 5.6 mg/dL<br>Age ≥ 66: ≥ 5.1 mg/dL |
| **Urine** | | | |
| UACR (Urinary Albumin to Creatinine Ratio) | mg/g | | > 1800 mg/g |

[1]For creatine kinase, ULN: Males (<65 years=250 U/L; ≥65 years=203 U/L), Females (<65 years=170 U/L; ≥65 years=160 U/L)

**Standard International Units**

| Clinical Laboratory variables | Units | Marked Abnormality Criteria | |
|---|---|---|---|
| | | Low | High |
| **Hematology** | | | |
| HCT males/females | [ratio] | < 0.20 | > 0.55 |
| HCT males/females | [ratio] | | > 0.60 |

| Clinical Laboratory variables | Units | Marked Abnormality Criteria | |
|---|---|---|---|
| | | Low | High |
| Hemoglobin males/females | g/L | < 60 g/L | > 180 g/L |
| Hemoglobin males/females | g/L | | > 200 g/L |
| **Blood Chemistry** | | | |
| Total protein | g/L | | > 100 g/dL |
| ALP | ukat/L | | > 3X ULN |
| ALT | ukat/L | | > 3X ULN |
| AST | ukat/L | | > 3X ULN |
| ALT | ukat/L | | > 5X ULN |
| AST | ukat/L | | > 5X ULN |
| ALT | ukat/L | | > 10X ULN |
| AST | ukat/L | | > 10X ULN |
| ALT | ukat/L | | > 20X ULN |
| AST | ukat/L | | > 20X ULN |
| Total Bilirubin | umol/L | | > 2X ULN if PreRx ≤ ULN; > 3X ULN if PreRx > ULN |
| Glucose, Plasma Unspecified | mmol/L | < 3 mmol/L | > 19.4 mmol/L |
| Na (Sodium) | mmol/L | < 130 mmol/L | > 150 mmol/L |
| Na (Sodium) | mmol/L | < 120 mmol/L | |
| K (Potassium) | mmol/L | ≤ 2.5 mmol/L | ≥ 6.0 mmol/L |
| HCO3 (Bicarbonate) | mmol/L | ≤ 13 mmol/L | |
| Creatinine | µmol/L | | ≥ 1.5X PreRx CREAT |
| Creatinine | µmol/L | | ≥ 221 µmol/L |
| CK (Creatine Kinase)[1] | ukat/L | | > 5X ULN |
| CK (Creatine Kinase)[1] | ukat/L | | > 10X ULN |
| Calcium | mmol/L | < 1.88 mmol/L | ≥ 0.25 mmol/Lfrom ULN **and** ≥ 0.13 mmol/L from PreRx CA |
| Magnesium | mmol/L | < 0.5 mmol/L | > 2 mmol/L |
| Inorganic phosphorus | mmol/L | Age 17-65: ≤ 0.58 mmol/L Age ≥ 66: ≤ 0.68 mmol/L | Age 17-65: ≥ 1.81 mmol/L Age ≥ 66: ≥ 1.65 mmol/L |

| Clinical Laboratory variables | Units | Marked Abnormality Criteria | |
|---|---|---|---|
| | | Low | High |
| **Urine** | | | |
| UACR (Urinary Albumin to Creatinine Ratio) | mg/mmol | | > 203.62 mg/mmol |

[1]For creatine kinase, ULN: Males (<65 years=4.17 ukat/L; ≥65 years=3.38 ukat/L), Females (<65 years=2.83 ukat/L; ≥65 years=2.67 ukat/L)

**Elevated AT (ALT and/or AST) and Total Bilirubin**

The following three criteria will be summarised in examination of elevated AT (ALT and/or AST) and total bilirubin (the criteria in this section will not be checked against baseline values):

- (AST or ALT > 3XULN) and (Bilirubin > 1.5XULN within 14 days on or after AT elevation)
- (AST or ALT > 3XULN) and (Bilirubin > 2XULN within 14 days on or after AT elevation)
- (AST or ALT > 3XULN) and {(Bilirubin > 2XULN and no ALP >= 2XULN) within 14 days on or after AT elevation)}