Protocol Number: D1680C00019

Official Title: A 26 Week, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel Group, Phase 3 Trial with a 26 Week Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 5 and 10 mg, and Saxagliptin 2.5 and 5 mg in Pediatric Patients with Type 2 Diabetes Mellitus who are between 10 and below 18 years of age

NCT Number: NCT03199053

Document Date: 07 December 2022

AstraZeneca

Statistical Analysis Plan

Study Code	CV181375/D1680C00019
Edition Number	5.0
Date	07 DEC 2022

A 26 Week, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel Group, Phase 3 Trial with a 26 Week Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 5 and 10 mg, and Saxagliptin 2.5 and 5 mg in Pediatric Patients with Type 2 Diabetes Mellitus who are between 10 and below 18 years of age

A 26 Week, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel Group, Phase 3 Trial with a 26 Week Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 5 and 10 mg, and Saxagliptin 2.5 and 5 mg in Pediatric Patients with Type 2 Diabetes Mellitus who are between 10 and below 18 years of age

Study Statistician [redacted]

A 26 Week, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel Group, Phase 3 Trial with a 26 Week Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 5 and 10 mg, and Saxagliptin 2.5 and 5 mg in Pediatric Patients with Type 2 Diabetes Mellitus who are between 10 and below 18 years of age

Global Product Statistician [redacted]

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Term	Definition
5-OH-saxagliptin	5-hydroxy-saxagliptin
ADA	American Diabetes Association
AE	Adverse event
AEOSI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Antinuclear Antibody
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AT	Aminotransferases
ATC	Anatomical therapeutic chemical (classification)
AZ	AstraZeneca
BMI	Body mass index
BP	Blood pressure
BUN	Blood Urea Nitrogen
CDC	Centers for Disease Control and Prevention
CDT	Carbohydrate deficient transferrin
CI	Confidence interval
CMV	Cytomegalovirus
CK	Creatine Kinase
CRF	Case report form
CSR	Clinical study report
CTX-1	Carboxyterminal cross-linked telopeptide of Type 1 collagen
CV	Coefficient of Variation
DILI	Drug-induced liver injury
DKA	Diabetic ketoacidosis
DMC	Data monitoring committee
DPP-4	Dipeptidyl-peptidase-4
EBV	Epstein-Barr virus

Term	Definition
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ETD	Early treatment discontinuation
FSH	Follicle stimulating hormone
FPG	Fasting plasma glucose
GAD	Glutamic acid decarboxylase
GGT	Gamma-glutamyl-transpeptidase
HAV	Hepatitis A virus
HbA1c	Glycosylated haemoglobin
HBsAg	Hepatitis B surface antigen
HCG	Beta-human chorionic gonadotropin
HCO3	Bicarbonate
HCV	Hepatitis C virus
HDL	High density lipoprotein
HSV	Herpes Simplex Virus
IGF-1	Insulin-like growth factor-1
IGFBP3	Insulin-like growth factor binding protein-3
IP	Investigational product
IR	Immediate release
ISPAD	International Society of Paediatric and Adolescent Diabetes
ITT	Intent-to-treat
IU	International unit
IWRS	Interactive web/voice recognition system
K	Potassium
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LH	Luteinizing hormone
LKM	Liver/Kidney Microsomal Antibody
LLN	Lower limit of normal

Term	Definition
LLOQ	Lower Limit of quantification
LS Means	Least squares means
LT	Long-term
MA	Marked abnormality
MAR	Missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical dictionary for regulatory affairs
MI	Multiple imputation
MI-RD	Multiple imputation retrieved drop-outs
MI-WO	Multiple imputation wash-out
MNAR	Missing not at random
Na	Sodium
OR	Odds ratio
PK	Pharmacokinetic
PO4	Phosphate
PreTx	Pre-treatment
PT	Preferred term
PTH	Parathyroid hormone
PT/INR	Prothrombin time
RBC	Red blood cell
RPD	Relevant protocol deviation
SAE	Serious adverse event
SAP	Statistical analysis plan
SCSM	Supply Chain Study Management
SD	Standard deviation
SE	Standard error
SI	Standard International (unit)
SMA	Anti-Smooth Muscle Antibody
SMBG	Self-monitoring blood glucose
SOC	System organ class
ST	Short-term

Term	Definition
ST+LT	Short-term + long-term
TB	Total bilirubin
T2DM	Type 2 diabetes mellitus
TIBC	Total iron binding capacity
TSH	Thyroid stimulating hormone
UACR	Urinary albumin to creatinine ratio
ULN	Upper limit of normal
US/USA	United States of America
WBC	White blood cell
WOCBP	Women of childbearing potential
WHO DD	World health organisation drug dictionary
XR	Extended release

AMENDMENT HISTORY

Version/Date	Brief description of change
V1.0 26 June 2018	Initial SAP approved
V2.0 01 November 2019	Addition of randomised withdrawal period and exploratory analyses for subjects who are randomised to withdraw background metformin Addition of weighted analyses during the combined short-term and long-term period to account for subjects who undergo the third randomisation Addition of exploratory time to event endpoints during the short-term and the combined short term and long-term period relative to time to rescue medication initiation or discontinuation from study medication due to lack of efficacy Removal of analyses based on mixed model for repeated measures Addition of amputation analysis
V2.1 12 February 2021	Updates to incorporate protocol amendment #5 Addition of Week 104 analyses presented by original treatment Addition of XIGDUO™ (dapagliflozin/metformin) subgroup analyses Addition of global/country situation analyses Update to compliance derivation to handle kits not returned Addition of exposure and compliance sensitivity analyses accounting for interruptions Update to sensitivity analyses using the Evaluable Subjects Data Set to exclude records collected after rescue medication initiation or early treatment discontinuation Addition of tipping point analysis for the primary efficacy endpoint HbA1c Addition of derivation for selecting the FPG record at each visit for use in the secondary efficacy analysis Additional analyses added for incidence rate of markedly abnormal laboratory results Additional analyses added for growth and maturation markers and bone biomarkers in SI units Addition of derivation for height velocity imputation Addition of treatment presentation for tables and figures appendix Format updates to align with Dapagliflozin conventions guide

Version/Date	Brief description of change
V2.2 29 March 2021	Removal of accounting for interruption compliance and exposure analyses Additional information on how to choose between the MI-RD or MI-WO methods and specified that the method will be consistent for each endpoint but can differ between treatments Change of seed used for multiple imputation and number of imputations reduced from 1,000 to 200 Addition of derivation to cut off the LT period and Post term follow-up period when the Week 56 visit was missed Change of split of AE summaries and listings for the ST+LT and Week 104 follow-up periods Addition of Rescue Insulin partial start and end date imputation
V3.0 25 June 2021	Addition of derivation to cut off the assessments and events that occurred on or before the Week 32 visit when the Week 32 visit was missed for the sensitivity analyses that use data up to Week 32 to exclude data from the randomised withdrawal analyses Change to Week 32 and Week 40 visit window for the LT period to use the third randomisation treatment start date as the cutoff (if applicable)
V3.1 27 January 2022	Updates to incorporate protocol amendment #6 Primary efficacy endpoint updated to use overall treatment and the secondary efficacy endpoints were updated to follow the order/hierarchy of overall, followed by low dose/high-dose regimen testing, followed by low-dose regimen testing Sample size section was updated Alpha was updated to be 0.05 and 97.5% confidence intervals removed from efficacy analyses Exposure by actual dose and treatment taken summaries added Addition of derivation of subgroup by treatment interaction p-value for imputed data Update to order of sensitivity analyses for primary endpoint Update to metformin subgroup analyses Alignment between model used for cox proportional-hazards and Kaplan-Meier log rank to include stratification factors
V4.0 09 February 2022	Protocol amendment #6 date included Up versioned for signatures

Version/Date	Brief description of change
V4.1 21 November 2022	Change of treatment presentation for PK analysis to use the highest dose received in the ST period Addition of ST period analyses for subject disposition related to the global/country situation analysis and IPDs Update to reasons for exclusions for the randomised withdrawal subjects data set to account for subjects who were unable to go through the 3rd randomisation due to the protocol amendment not being approved Additional concomitant medication analysis between Week 56 and Week 104 Update to compliance wording where compliance cannot be calculated Additional retrieved drop-out analysis for HbA1c and FPG for the ST period Additional FPG missing data summary Update to common PT AE ST+LT period table presentation to include incidence rate and addition of metformin subgroup analysis Addition of listings of preferred terms used in the selection of AEOSIs and COVID-19 related AEs Update to DKA events section to clarify that these are suspected DKA events Addition of listings for additional data collected during the Week 104 follow-up period
V5.0 07 December 2022	Changes of analysis from protocol section completed Up versioned for signatures

1. STUDY DETAILS

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under AstraZeneca (AZ) Protocol CV181375 (D1680C00019). This SAP should be read in conjunction with the study protocol and case report form (CRF). The version of this SAP has been developed using Revised Protocol Number 06 dated 07 February 2022, and version 4.0 of the CRF dated 24 February 2021. Any further changes to the protocol or CRF may necessitate updates to the SAP.

1.1 Study objectives

1.1.1 Primary objective

To determine if there will be a greater mean reduction from baseline in glycosylated haemoglobin (HbA1c) achieved after 26 weeks of oral double-blind add-on therapy of dapagliflozin (5 mg or 10 mg [all doses and regimens combined]) or saxagliptin (2.5 mg or 5 mg [all doses and regimens combined]) compared to placebo in paediatric Type 2 diabetes mellitus (T2DM) subjects with HbA1c levels of 6.5 to 10.5% on diet and exercise and metformin (immediate release [IR] or extended release [XR]), insulin, or metformin (IR or XR) plus insulin.

1.1.2 Secondary objectives

(a) To determine if there will be a greater mean reduction from baseline HbA1c achieved after 26 weeks of oral double-blind add-on therapy of dapagliflozin 5 mg or saxagliptin 2.5 mg (with titration to the high-dose for those who do not achieve the glycaemic target of HbA1c < 7% at 12 weeks) compared to placebo in paediatric T2DM subjects with HbA1c levels of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.

(b) To determine if there will be a greater mean reduction from baseline HbA1c achieved after 26 weeks of oral double-blind add-on therapy of dapagliflozin 5 mg or saxagliptin 2.5 mg compared to placebo in paediatric T2DM subjects with HbA1c levels of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.

(c) To compare mean reduction from baseline of HbA1c at Week 26 achieved while remaining on the low-dose drug (dapagliflozin 5 mg or saxagliptin 2.5 mg) versus up-titration to the high-dose (dapagliflozin 10 mg or saxagliptin 5 mg) amongst paediatric T2DM subjects on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin who do not achieve an HbA1c < 7% at Week 12.

(d) To determine if there will be a greater mean reduction from baseline in Fasting Plasma Glucose (FPG) achieved after 26 weeks of oral double-blind add on therapy of dapagliflozin (5 mg or 10 mg [all doses and regimens combined]) or saxagliptin (2.5 mg or 5 mg [all doses and regimens combined]) compared to placebo in paediatric T2DM subjects with HbA1c of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.

(e) To determine if there will be a greater mean reduction from baseline FPG achieved after 26 weeks of oral double-blind add-on therapy of dapagliflozin 5 mg or saxagliptin 2.5 mg (with titration to the high-dose for those who do not achieve the glycaemic target of HbA1c < 7% at 12 weeks) compared to placebo in paediatric T2DM subjects with HbA1c levels of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.

(f) To determine if there will be a greater mean reduction from baseline FPG achieved after 26 weeks of oral double-blind add-on therapy of dapagliflozin 5 mg or saxagliptin 2.5 mg compared to placebo in paediatric T2DM subjects with HbA1c levels of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.

(g) To compare mean reduction from baseline of FPG at Week 26 achieved while remaining on the low-dose drug (dapagliflozin 5 mg or saxagliptin 2.5 mg) versus up-titration to the high-dose (dapagliflozin 10 mg or saxagliptin 5 mg) amongst paediatric T2DM subjects on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin who do not achieve an HbA1c < 7% at Week 12.

(h) To compare the percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% after 26 weeks of oral double-blind add-on therapy of dapagliflozin (5 mg or 10 mg [all doses and regimens combined]) or saxagliptin (2.5 mg or 5 mg [all doses and regimens combined]) versus placebo in paediatric T2DM subjects with HbA1c of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.

(i) To compare the percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% after 26 weeks of oral double-blind add-on therapy of dapagliflozin 5 mg or saxagliptin 2.5 mg (with titration to the high-dose for those who do not achieve the glycaemic target of HbA1c < 7% at 12 weeks) versus placebo in paediatric T2DM subjects with HbA1c levels of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.

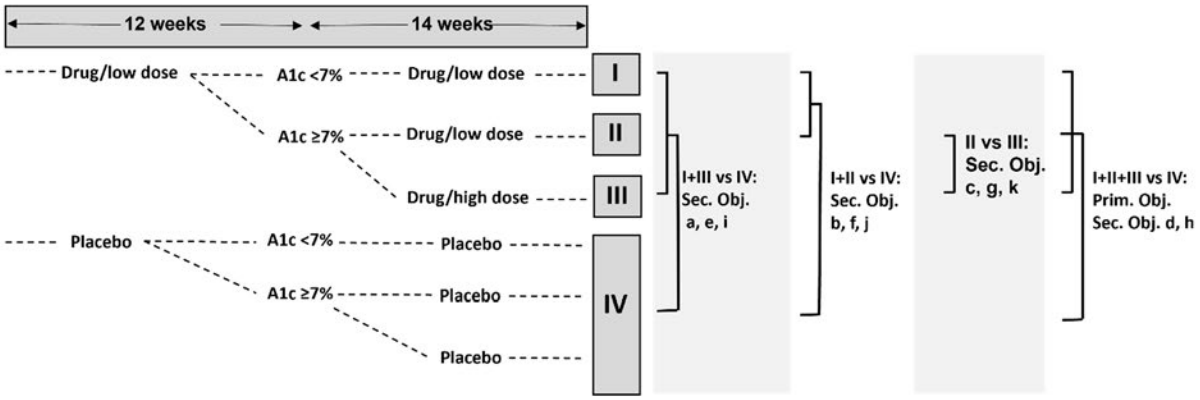
(j) To compare the percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% after 26 weeks of oral double-blind add-on therapy of dapagliflozin 5 mg or saxagliptin 2.5 mg compared to placebo in paediatric T2DM subjects with HbA1c levels of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.

(k) To compare the percentage of paediatric T2DM subjects on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% at Week 26 while remaining on the low-dose drug (dapagliflozin 5 mg or saxagliptin 2.5 mg) versus up-titration to the high-dose (dapagliflozin 10 mg or saxagliptin 5 mg) amongst subjects who do not achieve an HbA1c < 7% at Week 12.

Of note secondary objectives will be presented in hierarchical testing order and labelled numerically in Section 4.5.1.

At the end of 26 weeks of investigational product (IP) administration, study participants will belong to one of four subgroups (I-IV); the primary objective and secondary objectives a to k will encompass comparisons of results from multiple combinations of these subgroups, as schematised below.

Figure 1 Schematic of group comparisons in study primary and secondary objectives



1.1.3 Safety objectives

- To assess the safety and tolerability, including the incidence of adverse events (AEs) and events of hypoglycaemia, of dapagliflozin and saxagliptin as add-on to diet and exercise and metformin (IR or XR), or insulin, or metformin (IR or XR) plus insulin in paediatric T2DM subjects when administered for up to 26 weeks of short-term (ST) double-blind treatment, and, separately, up to 52 weeks of total treatment.
- To assess the incidence of diabetic ketoacidosis (DKA) with dapagliflozin and saxagliptin as add-on to diet and exercise and metformin (IR or XR), or insulin, or metformin (IR or XR) plus insulin in paediatric T2DM subjects when administered for up to 26 weeks of ST double-blind treatment, and, separately, up to 52 weeks of total treatment.
- To assess measures of growth and maturity and Tanner staging and markers of bone health in paediatric T2DM subjects when administered dapagliflozin or saxagliptin as add-on to diet and exercise and metformin (IR or XR), or insulin, or metformin (IR or XR) plus insulin for up to 26 weeks of ST double-blind treatment, and, separately, for up to 52 weeks of total treatment; and for an additional 52 weeks after the study has been completed and study-related treatment has been discontinued.
- To assess the safety and tolerability of dapagliflozin (or saxagliptin) monotherapy in paediatric subjects who are randomised to withdraw background metformin.

1.1.4 Exploratory objectives

- To compare the percentage of subjects requiring glycaemic rescue medication or discontinuing study medication due to lack of efficacy with dapagliflozin or saxagliptin

against the percentage with placebo during 26 weeks of oral double-blind add-on treatment in paediatric T2DM subjects with HbA1c of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.

- To assess time to initiation of glycaemic rescue medication or discontinuation of study medication due to lack of efficacy with dapagliflozin, saxagliptin or placebo during the 26-week ST treatment period and during the 52-week ST+LT treatment period in paediatric T2DM subjects with HbA1c of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.
- To assess the mean change from baseline in HbA1c achieved with dapagliflozin therapy versus placebo, and separately, achieved with saxagliptin therapy versus placebo after 52-weeks of oral blinded add-on treatment in paediatric T2DM subjects with HbA1c of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.
- To assess the mean change from baseline in FPG achieved with dapagliflozin therapy versus placebo, and separately, achieved with saxagliptin therapy versus placebo after 52-weeks of oral blinded add-on treatment in paediatric T2DM subjects with HbA1c of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.
- To assess the percentage of subjects with baseline HbA1c $\geq$ 7% who achieve an HbA1c level < 7% after 52 weeks of oral blinded add-on therapy with dapagliflozin versus placebo, or saxagliptin versus placebo in paediatric T2DM subjects with HbA1c of 6.5 to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin.
- To assess the effect of monotherapy of dapagliflozin therapy (and separately saxagliptin therapy) for subjects randomised to withdraw background metformin relative to dapagliflozin + metformin (and separately saxagliptin + metformin) and relative to placebo + metformin during the randomised withdrawal period using change in HbA1c, change in FPG, achievement of therapeutic glycaemic response (HbA1c < 7%) and time to rescue or discontinuation due to lack of glycaemic control.

1.1.5 Pharmacokinetic / Pharmacodynamic objective

- To explore the pharmacokinetic (PK) and exposure-response relationship of dapagliflozin and, separately, saxagliptin and its metabolite 5-hydroxy-saxagliptin (5-OH-saxagliptin) in subjects aged 10 to below 18 years with T2DM based on the collection of population PK samples.

1.2 Study design

The proposed study is a 26-week Phase 3b, multicentre, randomised, placebo-controlled, double-blind, parallel-group study with a 26-week safety extension period to evaluate the safety and efficacy of dapagliflozin (5 mg and 10 mg), and, separately, saxagliptin (2.5 mg and 5 mg) in paediatric subjects with T2DM, and an additional post-study visit at Week 104 for assessment of measures of growth and maturity.

This study will consist of 4 study periods:

(i) **Screening period.** This period starts with enrolment and ends at the start of the lead-in period.

(ii) **Lead-in period**. During this 2-week period, subjects will be instructed on a diet and exercise program (in accordance with the American Diabetes Association [ADA] or similar local guidelines) to be followed for the study duration. Subjects will maintain their baseline types and/or doses of antidiabetic therapy throughout the study. No placebo or study medication will be provided during the lead-in period.

(iii) **26-week double-blind short-term (ST) treatment period**. On the Day 1 visit, subjects who meet all protocol-specific enrolment and randomisation criteria will be randomised.

(iv) **26-week double-blind long-term (LT) treatment period**. After completing the ST treatment period, all subjects will enter the 26-week LT treatment period.

The 52-week treatment period will be referenced as the ST+LT treatment period.

The **Randomised withdrawal period** is defined, for those subjects eligible for the 3rd randomisation, as the time from 3rd randomisation (Week 32 or Week 40) until end of LT period (Week 52).

Subjects who discontinue IP treatment before the end of the study treatment period will enter a non-treatment, follow-up phase in which subjects will follow their visit schedules with modified assessments until study completion.

In addition, there will be 2 post-study visits:

(i) **Week 56** (phone visit), to assess AEs and serious adverse events (SAEs).

(ii) **Week 104** (office visit), to assess measures of growth and maturity, height, weight, AEs and SAEs.

Approximately 243 paediatric subjects aged 10 to below 18 years of age will be randomised in a 1:1:1 ratio to receive dapagliflozin 5 mg, saxagliptin 2.5 mg, or placebo. Approximately 81 subjects will be randomised to each treatment arm.

Randomised schedules will be generated and kept by the Sponsor or designee. Randomisation will be stratified based on baseline anti-diabetes treatment regimen (stable baseline dose of metformin [IR or XR], a stable baseline dose of insulin, or a stable combination of metformin [IR or XR] and insulin), sex, and age (≥10 to <15 years, ≥15 to <18 years). Each subject will be assigned a unique sequential subject number by the Interactive Web / Voice Response System (IWRS). This subject identifier will be used for identification throughout the study and will not be used for any other participant.

After randomisation, it is expected that at least 50% of subjects will be on a stable baseline dose of metformin, with or without concurrent insulin therapy. At least 30% of total randomised

subjects will be between the ages of 10 and 14 years and at least one third, but no more than two thirds, female subjects.

After the lead-in period, eligible subjects with HbA1c of 6.5% to 10.5% at screening will be randomised (Day 1). A blinded HbA1c assessment will be performed at Week 12. At Week 14, subjects will be up-titration randomised to new treatment assignments, based on the Week 12 HbA1c assessment.

The new treatment assignments from Week 14 will be determined as follows.

- All subjects with Week 12 HbA1c values < 7% will remain on previously assigned low-dose randomised treatment (blinded dapagliflozin 5 mg, or blinded saxagliptin 2.5 mg, or blinded placebo) after the Week 12 assessment.

- Subjects assigned to the blinded dapagliflozin treatment arm at Day 1 randomisation with Week 12 HbA1c values ≥ 7% (irrespective of whether they were rescued or not prior to Week 12) will be Up-titration Randomised in a 1:1 ratio to continue on the low-dose treatment (blinded dapagliflozin 5 mg) or up-titrate to the high-dose treatment (blinded dapagliflozin 10 mg) after the Week 12 assessment.

- Subjects assigned to the blinded saxagliptin treatment arm at Day 1 randomisation with Week 12 HbA1c values ≥ 7% (irrespective of whether they were rescued or not prior to Week 12) will be Up-titration Randomised in a 1:1 ratio to continue on the low-dose treatment (blinded saxagliptin 2.5 mg) or up-titrate to the high-dose treatment (blinded saxagliptin 5 mg) after the Week 12 assessment.

- To maintain the blinding of treatments as well as HbA1c results, all placebo subjects and all subjects taking saxagliptin or dapagliflozin with an HbA1c < 7% at Week 12 will go through a dummy 2nd randomisation process that will be indistinguishable (for the subjects and site personnel) from the actual 2nd randomisation.

After a 26-week, double-blind, ST treatment period, the primary efficacy endpoint will be assessed. Dapagliflozin and, separately, saxagliptin, will be compared against the single shared placebo comparator.

After completion of the ST treatment period, all subjects will enter the LT treatment period. Subjects who are receiving background medication with insulin only or insulin + metformin (and who are therefore not eligible for the third randomisation) will continue with their randomised study medication assigned after the Week 12 assessment in the double-blind LT treatment period until Week 52 or early discontinuation of IP.

Subjects who are receiving background medication with metformin only will undergo a third randomisation (randomised withdrawal of background medication) at either Week 32 or Week 40. Eligibility for randomised withdrawal from background medication will be restricted to subjects who are receiving background medication with metformin only, and who have HbA1c < 7.5% at Week 26 or Week 32 provided they have not initiated rescue glycaemic control

therapy or been withdrawn from study drug. Subjects who are receiving background medication with metformin only, who do not qualify for the third randomisation at Week 32 due to an HbA1c $\geq$ 7.5% at Week 26, may qualify for the third randomisation at Week 40 if HbA1c $<$ 7.5% at Week 32. Subjects who have passed Week 40 will not be included in the randomised withdrawal of background medication. Rescued subjects and subjects who discontinue IP will not be eligible for randomised withdrawal of background medication at Week 32 or Week 40.

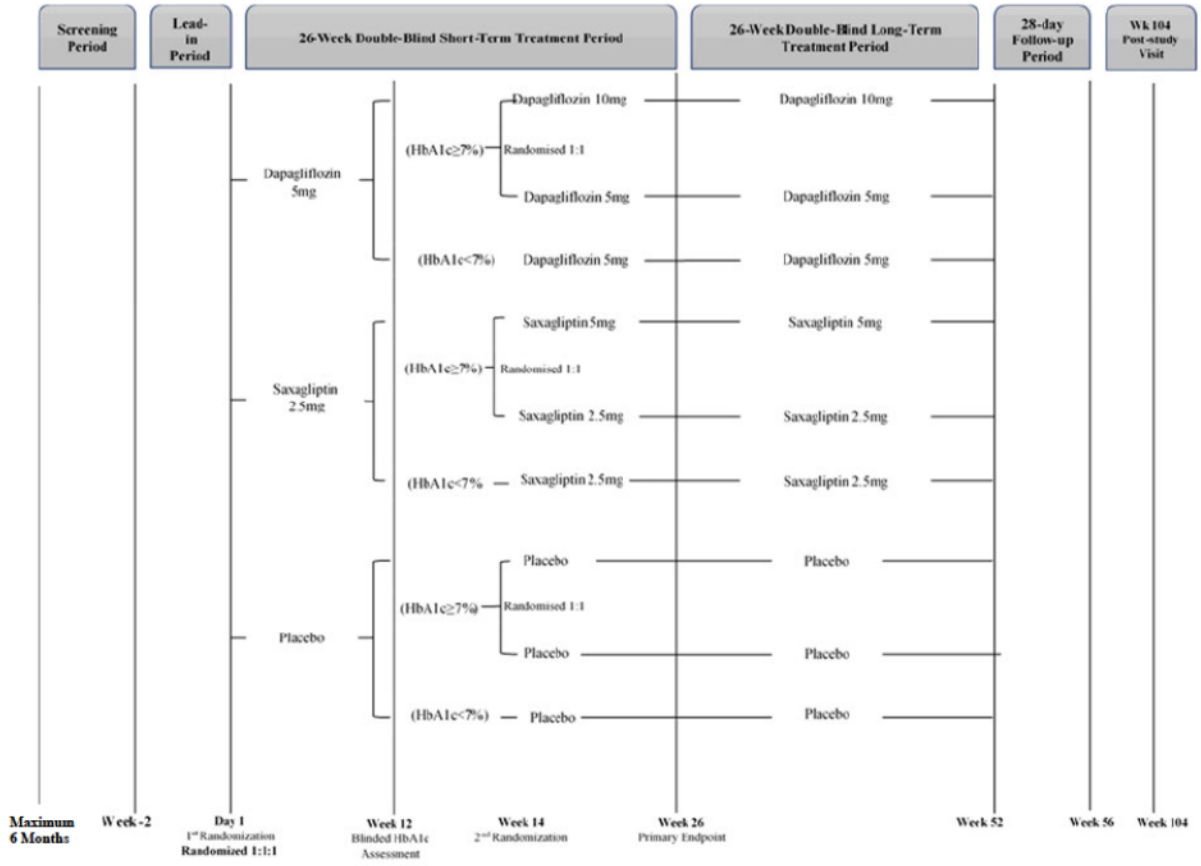
During the third randomisation:

- Eligible subjects who are receiving active treatment will be grouped into two separate strata for dapagliflozin and saxagliptin, and then randomised 1:1 within each strata to either discontinue background medication with metformin or to continue background medication with metformin. For subjects on active treatment who are randomised to withdraw background medication with metformin, those who are currently receiving high doses of saxagliptin (5 mg) or dapagliflozin (10 mg) will continue to receive the high doses, whereas subjects who are currently receiving low doses of saxagliptin (2.5 mg) or dapagliflozin (5 mg) will have their doses up-titrated to the high doses (saxagliptin 5 mg or dapagliflozin 10 mg). Subjects in the active treatment arms who are randomised to continue background medication with metformin will continue with their current dose of either saxagliptin or dapagliflozin.

- Eligible subjects who are receiving placebo will be randomised 1:1:1 to either withdraw background medication with metformin and switch to active treatment with either saxagliptin 5 mg or dapagliflozin 10 mg or to remain on background medication with metformin and continue with placebo.

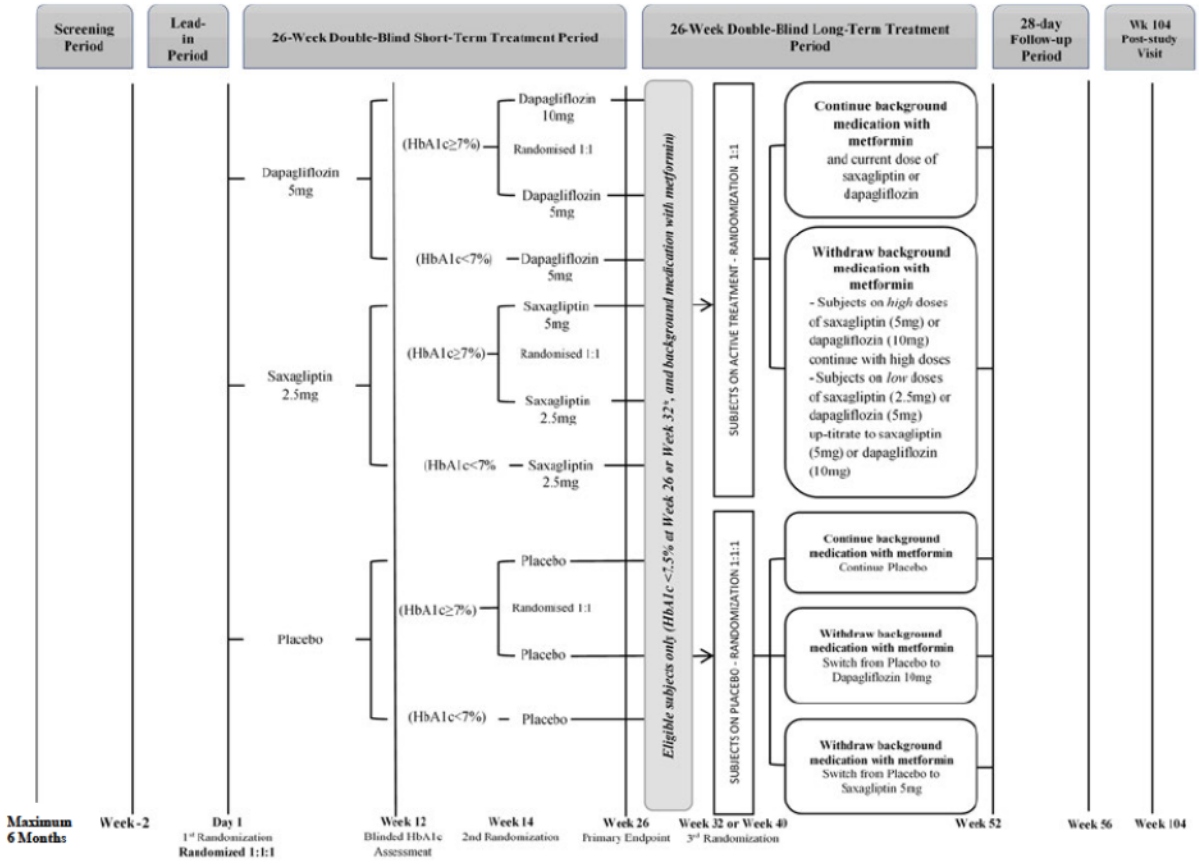
The study design schematic for subjects not undergoing randomised withdrawal of background medication at Week 32 or Week 40 is presented in Figure 2.

Figure 2 Study design schematic for subjects not undergoing randomised withdrawal of background medication at Week 32 or Week 40



The study design schematic for subjects undergoing randomised withdrawal of background medication at Week 32 or Week 40 is presented in Figure 3.

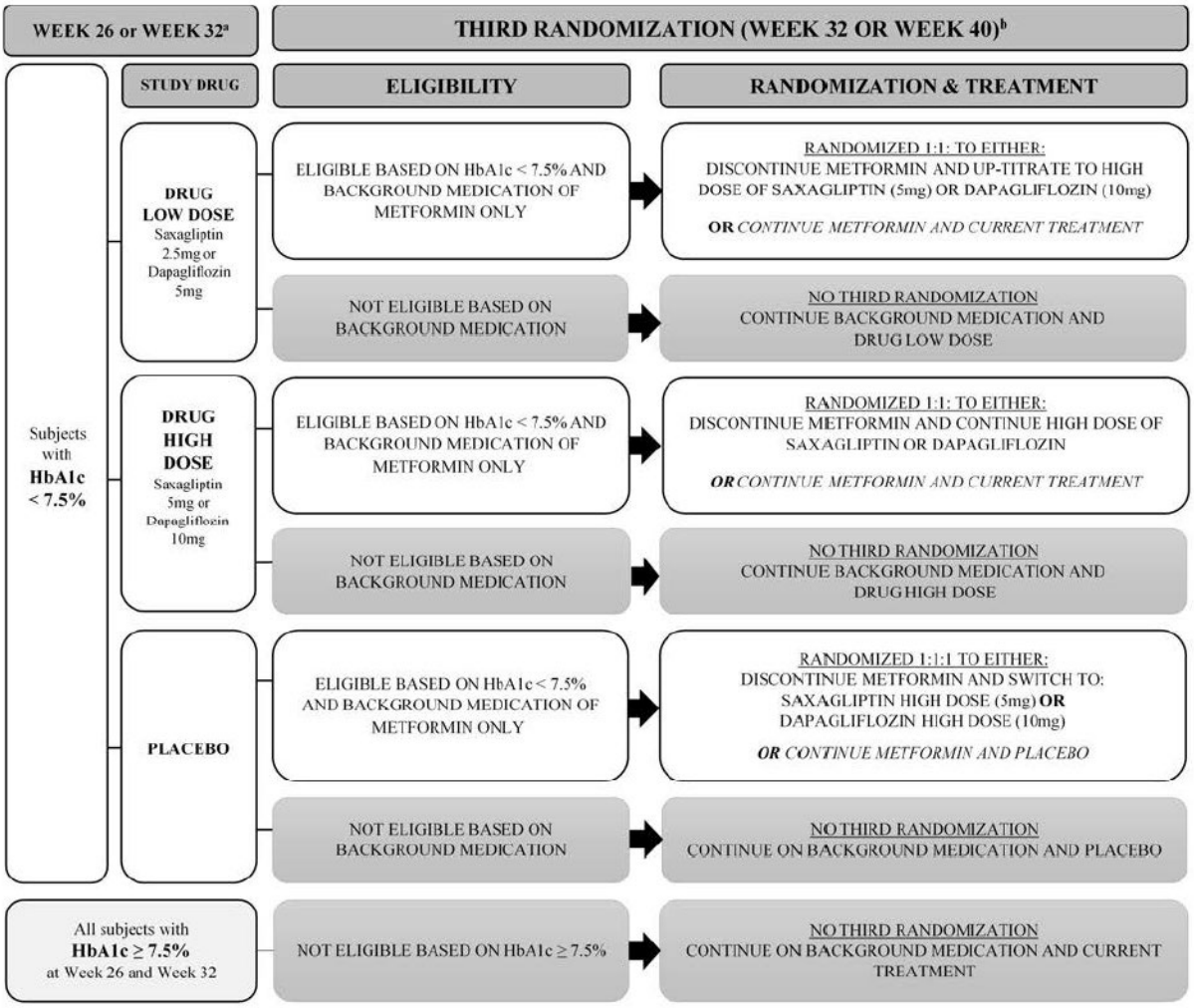
Figure 3 Study design schematic for subjects undergoing randomised withdrawal of background medication at Week 32 or Week 40



*Subjects who fail to qualify at Week 26 due to HbA1c ≥ 7.5% at Week 26 may qualify at Week 32 if HbA1c < 7.5% at Week 32.

The subgroups following the third randomisation at Week 32 or Week 40 are presented in Figure 4.

Figure 4 Subgroups following the third randomisation at Week 32 or Week 40



[a] Subjects who fail to qualify for the third randomisation due to HbA1c ≥ 7.5% at Week 26 may qualify at Week 32 if HbA1c < 7.5% at Week 32.

[b] Subjects who meet the eligibility criteria at Week 26 will undergo the third randomisation at Week 32, and subjects who meet the eligibility criteria at Week 32 will undergo the third randomisation at Week 40. Subjects who have passed Week 40 of the study will not be eligible for the third randomisation.

Subjects who discontinue IP prior to the Week 52 visit should have all early treatment discontinuation (ETD) procedures performed (ETD visit). Subjects will then continue in the study according to the Early Discontinued follow-up visit schedule, until study completion. Discontinued subjects will not be replaced.

Subjects who are rescued prior to the Week 52 visit should have all rescue procedures performed prior to their first intake of rescue (Rescue visit). Subjects who are rescued prior to Week 12 and have not discontinued IP will go through the second randomisation, as described above. Rescued subjects will continue in the study according to their original visit schedule.

Schedules of study assessments and procedures by study period are provided in the Appendix (Section 8.1).

1.3 Number of subjects

The sample size for this study was selected to be consistent with the research hypotheses.

Dapagliflozin and saxagliptin will be compared with placebo separately. Within each group of hypotheses, multiplicity adjustment with respect to the comparisons will be made using a hierarchical approach. No comparisons between dapagliflozin and saxagliptin will be performed.

The sample size for this study is based on the ability to detect a 0.75% improvement over placebo for dapagliflozin or saxagliptin in change from baseline in HbA1c at Week 26 (ST) with approximately 80% power for each comparison at a two-sided alpha level of 0.05. If 243 paediatric subjects are randomised and analysed, and each treatment compared to placebo at a 2 sided alpha=0.05 level, this will provide approximately 80% power for each comparison to detect a 0.75% reduction in HbA1c change from baseline versus placebo assuming a standard deviation of 1.7%.

Day 1 Randomisation will be stratified based on the baseline anti-diabetic treatment regimen (stable baseline dose of metformin [IR or XR], a stable baseline dose of insulin, or a stable combination of metformin [IR or XR] and insulin), sex, and age (≥10 to <15 years, ≥15 to <18 years).

The standard deviation estimate of 1.7% is based on a blinded review of the ongoing study data.

1.4 Blinding and unblinding

The investigator, AZ personnel, CRO personnel, and subjects will remain blinded to treatment allocation throughout the ST+LT treatment period. The database used for the analysis of the ST+LT data will be locked after all subjects have completed the ST+LT treatment period of the study. The locked database will be unblinded to the Sponsor and the CRO study team for reporting purposes.

After Day 1, and for the duration of the study, the HbA1c and the urinary glucose values, including the urinary glucose: creatinine ratio, will be masked to the Sponsor and will not be available to the investigator. In the event of an HbA1c result >8.0% during the LT treatment period (when these values require subject rescue), the investigator will be informed via an HbA1c alert from the central laboratory but will remain blinded to the HbA1c result.

For subjects who are randomised to withdraw background metformin, the investigator and the sponsor may be partially unblinded to the subject's treatment assignment. Given that discontinuation of background metformin will occur in an unblinded manner, all subjects who are randomised to withdraw background metformin will either maintain or start high-dose dapagliflozin or saxagliptin as monotherapy.

Blinding is critical to the integrity of this clinical trial. However, in the event of a medical emergency or pregnancy, during which knowledge of the identity of the investigational product is critical to the subject's management, procedures are in place to have the blind broken for an individual subject. A listing of all subjects whose treatment is unblinded during the study will be included in the Clinical Study Report (CSR).

The exception is for those personnel analysing the PK data, those analysing dipeptidyl-peptidase-4 (DPP-4) data, the AZ Supply Chain Study Management (SCSM) team and the responsible personnel carrying out the packaging and labelling of IPs. The Day 1 Randomisation code will be provided to ensure appropriate treatment allocation and that only PK samples from subjects who were on the relevant active study treatment are analysed. Similarly, the Day 1 Randomisation code will be provided to ensure appropriate treatment allocation and that only DPP-4 samples from subjects who were on active study treatment are analysed.

1.5 Protocol amendments

This amended SAP is based on (Revised Protocol Number 06 dated 07 February 2022).

Table 1 Protocol History

Document	Date of issue	Summary of change
Original Protocol	02-Mar-2016	Not applicable
Revised Protocol 01	11-Oct-2016	Subsequent to recent Health Authority feedback, the original study design has been entirely revised in accordance with the United States Food and Drug Administration (FDA) specified preferred study objectives and design.
Revised Protocol 02	04-Apr-2017	The protocol has been revised to reflect the cessation of Bristol-Myers Squibb's role in the study and the specified preferred objectives and procedures following European Medicines Agency (EMA) and FDA review. A post-study visit has also been added at Week 104.
Revised Protocol 03	04-Oct-2018	Based on recommendations provided by the FDA, the protocol has been revised to reflect modifications in the study design, i.e., the addition of a randomised withdrawal of background medication in a subset of eligible subjects from the active treatment arms, and randomised withdrawal of background medication/switch to active treatment in a subset of eligible subjects in the placebo arm. Collection of vital status has been removed.
Revised Protocol 04	27-Jun-2019	The protocol has been revised to reflect modifications to the study design, i.e., the extension of the screening period and change of the screening/retesting design, the update of safety concerns and monitoring of adverse events of interest, the revision of fasting blood glucose, growth, bone and maturity markers measurements, as well as Tanner staging schedules in subjects who discontinued the investigational product early, and the clarification of initiation or up-titration of insulin at the Rescue Visit and adverse events/serious adverse events collection until study completion. In addition, the correction of the investigational product dispensation schedule is incorporated, and some common language is added/revised in several sections for harmonisation across all AZ clinical study protocols.

Document	Date of issue	Summary of change
Revised Protocol 05	24-Sep-2020	The protocol was revised to specify that visits should be delayed to maintain an interval of at least 12 weeks between the Week 14 and Week 26 visits and between the third randomisation visit (for subjects undergoing third randomisation) and the Week 52 visit in case the Week 14 or third randomisation visit is delayed. This change was instituted because HbA1c is derived from the average of the blood glucose fluctuation in the preceding 3 months and therefore, approximately 12 weeks of exposure to a new dose is needed to demonstrate efficacy. Short- and long-term period study visits can be delayed by a maximum of 11 months in total. If the duration of investigational product administration is longer than 52 (+1) weeks, the safety follow-up period should be shortened such that the complete study duration does not exceed 104 weeks. The Week 104 visit should not be delayed. If more than 12 weeks elapse between the HbA1c collection at Week 26 and the third randomisation at Week 32, or the HbA1c collection at Week 32 and the third randomisation at Week 40, the subject should not go through this randomisation as the HbA1c value would no longer be reliable to ascertain eligibility for the third randomisation. Other updates include guidance on changes needed to the clinical conduct due to the coronavirus disease 2019 (COVID-19) pandemic (e.g., sending the investigational product directly to subjects' homes, home visits by study site personnel/vendor, allowing off-site monitoring visits); updates to the text for consistency with the latest AstraZeneca template; and minor clarifications.

Revised Protocol 06	07-Feb-2022	The following revisions were made to the protocol: To allow for flexibility in scheduling, the window period for Week 104 post-dose visit was modified from "± 7 days" to "-28 days to + 7 days" from the original scheduled date. Based on discussions with FDA, the primary objective was modified to assess the effect of all doses and regimens combined for each drug versus placebo. In line with this, the primary and secondary objectives were reordered and updated. The reordering was done to make overall analysis (all doses for each treatment) as the primary objective. The primary objective was updated as follows: To determine if there will be a greater mean reduction from baseline in HbA1c achieved after 26 weeks of oral double blind add-on therapy of dapagliflozin (5 mg or 10 mg [all doses and regimens combined]) or saxagliptin (2.5 mg or 5 mg [all doses and regimens combined]) compared with placebo. The secondary objectives were updated to follow the order/hierarchy of overall, followed by low-dose/high-dose regimen testing, followed by low-dose regimen testing. Corresponding to the change in primary objective, the primary analysis was updated as: The primary efficacy analysis will be performed using an analysis of covariance (ANCOVA). Other key changes include: Based on discussions with the FDA, the analyses were updated to use a full alpha of 0.05 to test each drug versus placebo rather than current split into 0.025. Updated text: "For each drug, the comparison vs placebo will be tested at a 2 sided alpha level of 0.05." For power analysis, the assumption of an effect size of 0.75% rather than 0.5% was used. Accordingly sample size section was updated to include the following changes: Text deleted: The Bonferroni method to control the type 1 error rate across two comparisons with respect to the two groups of research

Document	Date of issue	Summary of change
		hypotheses (dapagliflozin vs placebo and saxagliptin vs placebo) will be used. Assuming a standard deviation of 0.9% for change from baseline HbA1c at Week 26, and 50% of subjects will undergo the second randomization, a total of 237 pediatric subjects will be randomized in a 1:1:1 ratio to receive dapagliflozin 5 mg (79 subjects), saxagliptin 2.5 mg (79 subjects), or placebo (79 subjects) respectively. Assuming that 2% of subjects do not have a primary endpoint, a total of approximately 243 subjects will be randomized. Revised text included: "If 243 pediatric subjects are randomized and analyzed, and each treatment compared to placebo at a 2-sided alpha=0.05 level, this will provide approximately 80% power for each comparison to detect a 0.75% reduction in HbA1c change from baseline assuming a standard deviation of 1.7%." Text deleted: The anticipated difference of 0.5% between each study drug (saxagliptin and dapagliflozin) and placebo used in sample size estimation is consistent with estimates that were obtained in adult clinical trials with saxagliptin or dapagliflozin as add-on to anti-diabetic medication where the primary endpoint was improvement in HbA1c after 24 weeks treatment. The standard deviation estimate of 0.9% is consistent with estimates obtained in these adult studies as well as with published estimates from pediatric trials of other anti-diabetic medications. Revised text included: "The standard deviation estimate of 1.7% is based on a blinded review of the ongoing study data." Other updates to the text for consistency and minor clarifications.

No protocol amendments or administrative letters that may affect the SAP have been processed beyond Protocol version 06 on which this SAP is based on.

1.6 Timing of analyses and reporting

There will be 2 database lock points.

1. Analysis of data from the ST treatment period, the combined ST+LT treatment period (a total of 52 weeks) and including the non-treatment follow-up visit at Week 56 will be performed after all subjects have completed or have been discontinued from the study (including completion of non-treatment follow-up after the last dose, where applicable).
2. Analysis of data from the additional 48-week follow-up period to assess measures of growth over time will be performed after all subjects have completed or have been discontinued from this period (a total of 104 weeks).

1.7 Data monitoring committees

An independent Data Monitoring Committee (DMC) comprised of Paediatric and Endocrine therapeutic area specialists and statisticians will be formed and will convene on a regular basis to review trial data. The DMC will be responsible for safeguarding the interests of the subjects in the trial by assessing the safety and efficacy of the interventions during the trial, and for reviewing the overall conduct of the clinical trial. The DMC will provide recommendations about stopping or continuing the trial and will be governed by a separate DMC Charter.

1.8 Adjudication committees

1.8.1 Cardiovascular adjudication committee

An independent Cardiovascular Adjudication Committee, blinded to the treatment of the subjects, will adjudicate all potential events of congestive heart failure requiring hospitalisation (see study protocol for more details).

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

1.8.2 Hepatic adjudication committee

An independent Hepatic Adjudication Committee, blinded to the treatment of the subjects, will determine the probability that drug-induced liver injury (DILI) is the cause of liver-related abnormalities, including but not limited to, hepatic disorders leading to death, and liver laboratory abnormalities such as elevated Aspartate aminotransferase (AST) and/or Alanine aminotransferase (ALT) with or without total bilirubin (TB) elevations (see study protocol for more details).

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

1.8.3 Diabetic Ketoacidosis (DKA) adjudication committee

An independent DKA Adjudication Committee, blinded to the treatment of the subjects, will adjudicate all potential events of DKA.

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

2. ANALYSIS SETS

2.1 Treatment groups

The "as randomised" treatment group is defined as the treatment group to which a subject was randomised at the start of the double-blind treatment period (even if the treatment they received was different).

The "as treated" treatment group is the same as the "as randomised" treatment group, except in cases where information was available which indicated that a subject received a different treatment for the entire course of their participation in the study (or period). In this case, the "as treated" treatment group is set to the treatment the subject actually received. In case a subject never received the treatment as assigned by randomisation, then the "as treated" treatment group is the first treatment received.

2.2 Definition of analysis sets

2.2.1 Enrolled Subjects Data Set

The Enrolled Subjects Data Set will consist of all subjects who sign informed consent.

2.2.2 Randomised Subjects Data Set

The Randomised Subjects Data Set is the primary efficacy dataset and will consist of all randomised subjects who receive at least one dose of study medication during the treatment period. This is also known as the Intent-to-Treat (ITT) population. In analyses of the Randomised Subjects Data Set, subjects will generally be presented in the treatment group to which they were randomised at the start of the ST treatment period (even if the treatment they received is different).

2.2.3 Up-titration Randomised Subjects Data Set

The Up-titration Randomised Subjects Data Set will consist of the subset of randomised subjects who are Up-titration Randomised because their HbA1c is greater than or equal to 7% at Week 12 (regardless of rescue medication initiation). This data set will be used for efficacy analysis comparing low-dose and high-dose treatment regimens in subjects who do not achieve glycaemic control (HbA1c $< 7\%$) at Week 12. In analyses of the Up-titration Randomised Subjects Data Set, subjects will be presented in the treatment group to which they were randomised at the second randomisation.

2.2.4 Evaluable Subjects Data Set

The Evaluable Subjects Data Set will be a subset of the Randomised Subjects Data Set. All data points after a relevant protocol deviation will be excluded from this dataset. Relevant protocol deviations (RPDs) are defined as deviations that could potentially affect the interpretability of the study results (as described in Table 2 and Table 3). All decisions to exclude subjects from the Randomised Subjects Data Set to form the Evaluable Subjects Data Set will be made prior to the unblinding of the study. The set of subjects within this dataset is also known as the Per-Protocol population. This dataset will be used for sensitivity analysis of the primary efficacy endpoint if greater than 10% of subjects in any treatment group included in the primary analysis (overall dapagliflozin or overall saxagliptin, and all placebo subjects) have RPDs. In analyses of the Evaluable Subjects Data Set, subjects will be presented in the treatment group to which they were randomised at the start of the ST treatment period.

2.2.5 Treated Subjects Data Set

The Treated Subjects Data Set (also known as Safety Analysis Data Set) is the primary safety dataset and will consist of all subjects who receive at least one dose of study medication. In analyses of the Treated Subjects Data Set, subjects will generally be presented by randomised treatment group, except if information indicates that a subject received a different treatment for the entire course of their participation in the study (or period). In this case, the safety data for such a subject will be presented by the first treatment actually received. Exceptions to this will be made for some analyses of the effects of monotherapy or randomised withdrawal of metformin.

2.2.6 Randomised Withdrawal Subjects Data Set

The Randomised Withdrawal Subjects Data Set will be a subset of the Randomised Subject Data Set and will consist of all subjects belonging to the metformin randomisation strata of background medication who will be re-randomised at Week 32 or Week 40 (as described in Section 1.2). This data set will be used to analyse efficacy and safety during the randomised withdrawal period using the treatment assignment from the third randomisation.

2.2.7 Pharmacokinetic (PK) Analysis Data Set

The PK Analysis Data Set will be used for all PK analyses and will consist of all subjects who receive at least one dose of study medication (dapagliflozin or saxagliptin) and have at least 1 PK sample collected. The PK data will be presented using the highest treatment actually received during the ST period (as described in Section 2.1).

2.3 Violations and deviations

Subjects who deviate from protocol conditions (e.g., important inclusion/exclusion criteria) will be reported as having important protocol deviations. A list of Important protocol deviations is provided in Table 4.

Important protocol deviations are identified in the site deviation logs and are categorised using the Protocol deviation guidance document.

Important protocol deviations that are determined to affect the primary efficacy results are deemed RPDs. The RPDs for this study are listed in Table 2 and Table 3.

A sensitivity analysis of the primary efficacy endpoint will be conducted if greater than 10% of subjects included in the primary analysis (overall dapagliflozin or overall saxagliptin, and all placebo subjects) have RPDs during the ST period. This applies for dapagliflozin or saxagliptin separately. This sensitivity analysis will exclude data from subjects with RPDs during the ST period. There will be no data exclusions for important protocol deviations not deemed RPDs.

Subjects having RPDs will be summarised by treatment group and overall for the ST and ST+LT period, and a listing by subject will be provided for the ST+LT period. Subjects with other important (excluding relevant) protocol deviations will be summarised for the ST and ST+LT period and listed for the ST+LT period separately. Any subject with both relevant and other important (excluding relevant) protocol deviations will appear in both listings. Any protocol deviations with a start date prior to Day 1 will be presented for the ST period.

Disallowed concomitant medications are specified in the protocol and will be confirmed by the study physician. The current ATC codes corresponding to these medications will be provided by a medically qualified expert prior to unblinding and database lock/freeze.

Table 2 List of relevant protocol deviations during the ST period

Number	RPD criteria	Exclusion Level
1	Randomised Subjects without T2DM or with central laboratory HbA1c obtained at enrolment not within ± 0.2% of the protocol-specific HbA1c range	Complete exclusion
2	Randomised Subjects not satisfying the target population baseline antihyperglycemic therapy requirement (metformin [IR or XR], or insulin, or metformin [IR or XR] plus insulin)	Complete exclusion
3	Randomised Subjects with randomisation strata error – age, sex, background medication	Complete exclusion
4	Randomised Subjects who used antihyperglycemic medication (other than protocol allowed medication) for 7 or more consecutive days during the ST period	Partial exclusion (All efficacy data starting with the 7th day of administration non-protocol required antihyperglycemic medication will be excluded)

Number	RPD criteria	Exclusion Level
5	Randomised Subjects who were treated with any systemic corticosteroid therapy for ≥ 5 consecutive days initiated or changed during ST period, or within 5 days prior to randomisation	Partial exclusion (All efficacy data starting with the 5th day of systemic corticosteroid therapy will be excluded)
6	Randomised subjects whose background Metformin dose was not stable and/or background Insulin dose increases or decreases 20% or more above baseline dose and/or there is a gap of greater than 14 days of background Metformin or Insulin during the ST treatment period	Partial exclusion (All efficacy data starting with the date background Metformin dose changed or background Insulin dose increased/decreased ≥20% or 15th day of gap in background medication)
7	Randomised subjects with treatment compliance < 80% or > 120% during the ST treatment period	Complete exclusion
8	Randomised Subjects who receive no double-blind medication for 14 or more consecutive days during the ST treatment period	Partial exclusion (All efficacy data starting with the 14th day of interruption will be excluded)
9	Randomised subjects who received incorrect study medication for 14 or more consecutive days during the ST treatment period	Partial exclusion (All efficacy data starting with the 14th day of incorrect study medication will be excluded)
10	Abnormal free thyroxine values at enrolment	Complete exclusion
11	History of hemoglobinopathy, with the exception of sickle cell trait or thalassemia minor; or chronic or recurrent haemolysis	Complete exclusion

Table 3 List of relevant protocol deviations during the ST+LT period

Number	RPD criteria	Exclusion Level
12	Randomised Subjects who used antihyperglycemic medication (other than protocol allowed medication) for 7 or more consecutive days during the ST+LT treatment period	Partial exclusion (All efficacy data starting with the 7th day of administration non-protocol required antihyperglycemic medication will be excluded)
13	Randomised Subjects who were treated with any systemic corticosteroid therapy for ≥ 5 consecutive days initiated or changed during ST+LT treatment period, or within 5 days prior to randomisation	Partial exclusion (All efficacy data starting with the 5th day of systemic corticosteroid therapy will be excluded)
14	Randomised subjects whose background Metformin dose was not stable and/or background Insulin dose increases or decreases 20% or more above baseline dose and/or there is a gap of greater than 14 days of background Metformin or Insulin during the ST+LT treatment period	Partial exclusion (All efficacy data starting with the date background Metformin dose changed or background Insulin dose increased/decreased ≥20% or 15th day of gap in background medication)
15	Randomised subjects with treatment compliance < 80% or > 120% during the ST+LT treatment period	Complete exclusion
16	Randomised Subjects who receive no double-blind medication for 14 or more consecutive days during the ST+LT treatment period	Partial exclusion (All efficacy data starting with the 14th day of interruption will be excluded)
17	Randomised subjects who received incorrect study medication for 14 or more consecutive days during the ST+LT treatment period	Partial exclusion (All efficacy data starting with the 14th day of incorrect study medication will be excluded)

Table 4 List of Important Protocol Deviations

Number	Important protocol deviation criteria
01	Inclusion Criteria
02	Exclusion Criteria

Number	Important protocol deviation criteria
03	Study Drug
04	Assessment Safety
05	Lab/Endpoint Data
06	Visit Window
07	Informed Consent
08	Prohibited Co-Medication
09	Overdose/Misuse
10	Other (diary completion, site staff qualifications, safety reports etc.)

3. ENDPOINTS

3.1 Primary efficacy endpoints

The primary efficacy endpoint for analysis is the change from baseline in HbA1c at Week 26 of the ST period. Analysis of HbA1c will be performed only in conventional (US) units (%).

HbA1c will be assessed at the time points shown in the Appendix (Section 8.1), and at non-treatment / unscheduled visits (if applicable), based on a single central laboratory test at each time point. For the primary analysis, missing HbA1c at Week 26 will be imputed based on multiple imputation (as described in Section 4.1.12).

3.2 Secondary efficacy endpoints

The secondary efficacy endpoints are:

- Change from baseline in FPG at Week 26.

  Central laboratory measurements of FPG will be used for the analysis and will be restricted to measurements obtained in the fasting state. Fasting plasma glucose will be assessed at the time points shown in Appendix (Section 8.1) and at non-treatment / unscheduled visits (if applicable), based on a single central laboratory test at each time point. For secondary analyses, multiple imputation will be used to impute missing FPG values for Week 26 (as described in Section 4.1.12).

- Percentage of subjects with baseline HbA1c $\geq$ 7% who achieve a HbA1c level < 7% at Week 26.

3.3 Exploratory efficacy endpoints

The following exploratory efficacy endpoints are defined for the study:

3.3.1 Exploratory efficacy endpoints for short term assessment of dapagliflozin and saxagliptin

- Percentage of subjects who require glycaemic rescue medication or discontinue the study medication due to lack of efficacy during the 26-week treatment period.
- Time to initiation of glycaemic rescue medication or discontinuation of study medication due to lack of efficacy during the 26-week treatment period.

3.3.2 Exploratory efficacy endpoints for short term plus long-term assessment of dapagliflozin and saxagliptin

- Change from baseline in HbA1c at Week 52.
- Change from baseline in FPG at Week 52.
- Percentage of subjects with baseline HbA1c $\geq$ 7% who achieve a HbA1c level $<$ 7% at Week 52.
- Time to initiation of glycaemic rescue medication or discontinuation of study medication due to lack of efficacy during the 52-week treatment period.

3.3.3 Exploratory efficacy endpoints for monotherapy assessment of dapagliflozin and saxagliptin

- Change from withdrawal baseline in HbA1c during the randomised withdrawal period.
- Change from withdrawal baseline in FPG during the randomised withdrawal period.
- Percentage of subjects who achieve or maintain an HbA1c level $<$ 7% at the end of the randomised withdrawal period.
- Time to initiation of glycaemic rescue medication or discontinuation of study medication due to lack of efficacy using the start time of randomised withdrawal period as the reference point.

3.4 Safety endpoints

The assessment of safety will be based on the analyses of the incidence of AEs, SAEs, adverse events of special interest (AEOSI), hypoglycaemic events, discontinuations due to AEs, marked abnormalities in clinical laboratory tests, vital signs, Tanner staging, measures of growth and maturation, DKA events, and safety laboratory tests.

3.4.1 Adverse events

AEs (serious and non-serious, excluding hypoglycaemic or DKA events that are not reported as SAEs) will be collected throughout the study up to Week 56, and will also be collected quarterly between Week 56 and Week 104 via phone assessment. Adverse events will be classified by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA), based on the MedDRA version current at the time of database lock. Each subject will be counted once within a SOC or PT in AE frequency tables, under the maximum intensity within each category. For summaries of AEs by relationship to study drug, as assessed by the investigator (related, not related), subjects will be counted under the most

related instance within each SOC or PT. For the summary of AEs that occurred in ≥ 5% of the subjects within a treatment group (based on PTs) the number of AEs will also be presented.

Events will be considered treatment-emergent if:

- The event started on or after the first dose of IP (Day 1) and up to and including 4 days for AEs and 30 days for SAEs after the last dose date.
- The event started before Day 1 but increased in intensity or relatedness to study medication on or after Day 1.
- The event onset date is missing or partial (unless the stop date of the event indicates that the event cannot be treatment emergent).
- Events will be considered treatment emergent unless they can be proven not to be so from the data.

Details for handling of missing and partial event dates for determining treatment emergence are provided in the Appendix (Section 8.2).

Listings will include the AE duration, calculated as AE stop date - AE start date + 1. AE duration will be calculated only when complete dates (at least day, month, year) for the start and stop date are provided. Each AE will be graded for intensity (mild, moderate, severe). If intensity is missing, the event will be regarded as severe. Each AE will also be assessed for relationship to the study drug (related, not related). Adverse events with missing relationship to study drug will be considered treatment-related for the purpose of summarising AEs related to study drug. Adverse events with missing flag indicating serious will be considered serious for AE summaries.

Any treatment for AEs will be reported under prior and concomitant medications (excluding rescue medication which will be reported separately). The AE number will be recorded to the corresponding medication for cross-linking purposes.

Adverse events of special interest

Adverse events of special interest will be selected by MedDRA PT and include, but are not limited to: amputations/peripheral revascularisations; changes in growth; drug-induced liver injury/marked hepatic laboratory abnormalities (including liver function test abnormalities accompanied by jaundice or hyperbilirubinemia); hypersensitivity reactions (including anaphylaxis, angioedema, exfoliative skin conditions); severe cutaneous adverse reactions (including bullous pemphigoid); genital mycotic infections; necrotising fasciitis of the perineum (Fournier's gangrene); urinary tract infections (including urosepsis/pyelonephritis); opportunistic infections; decreased lymphocyte and/or thrombocyte counts; oral soft tissue conditions (e.g., stomatitis); pancreatitis; cardiac failure (including hospitalisation for heart failure); acute kidney injury, renal impairment and/or renal failure; volume depletion; bone fractures; hyperlipidaemia; hypoglycaemic events; hyperglycaemic events; ketoacidosis; malignancies (including bladder cancer); and arthralgia.

Adverse events of special interest will be programmatically identified based on a predefined list of PTs.

Amputations and underlying conditions relevant to amputation will be recorded on a specific CRF page. The AE leading to amputation should be recorded in the eCRF as an AE/SAE. Events potentially placing the subject at risk for a lower limb amputation ("preceding events") should also be recorded in the eCRF as an AE/SAE whether or not an amputation has taken place.

A final review will take place prior to database lock to ensure new terms not already included in the older MedDRA version are captured within the categories for the new higher MedDRA version. The list will be provided by AZ prior to Week 56 database lock.

Hepatic adverse events

A list of PTs will be selected before Week 56 database lock of the study to facilitate identification of events of hepatic disorders.

Incidence rate (exposure-adjusted)

Where specified, event summaries may include the exposure adjusted incidence rate. The incidence rate will be expressed per 100 patient-years. This is calculated as:

$$Incidence\ rate\ = 100 * \frac{n\ subjects\ with\ \geq 1\ event\ of\ interest}{\text{sum}[\min(exposure\ time, time\ to\ event)]}$$

The sum of min(exposure time, time to event) will be computed by summing up the minimum of exposure time or time to event per subject across all subjects for each treatment and dose as treated (defined in Section 2.1).

For analyses using first treatment as treated (total dapagliflozin, total saxagliptin, placebo), exposure time and time to event are defined as:

> Exposure time (years) per subject is computed as (last date of exposure for that subject - date of first dose in the study + 1)/365.25. Time to event (years) for subjects having the event is computed as (date of onset of event – date of first dose in the study +1)/365.25.

For analyses using dose at onset of AE to account for the change in treatment and dose at the 2nd and 3rd randomisations, exposure time and time to event are defined as:

> Exposure time (years) per subject for each treatment and dose as treated is computed as (last date of exposure to treatment and dose for that subject - date of first exposure to treatment and dose + 1)/365.25. Time to event (years) for subjects having the event whilst on the current treatment and dose is computed as (date of onset of event – date of first exposure to treatment and dose +1)/365.25.

For incidence rate analyses for events prior to rescue, if no event occurred prior to rescue medication initiation then the date of rescue medication initiation is used instead of last date of exposure.

3.4.2 Deaths

Deaths in the study include all deaths recorded on the disposition page of the CRF (i.e., reason for discontinuation is death), the AE page (events with fatal outcome), or the SAE page (SAEs that result in death).

3.4.3 Other safety events

3.4.3.1 Diabetic ketoacidosis

A DKA event will not be reported on an AE CRF page unless the event fulfilled SAE criteria, in which case it should also be reported in the SAE form. Separate pages to capture details of DKA events are contained within the CRF. Details include signs and symptoms, contributing factors, whether local labs were performed, and whether the event is classified as an SAE. Adjudication findings (definite DKA, probable DKA, possible DKA, not DKA) will also be provided for DKA events sent to the Adjudication committee.

3.4.3.2 Hypoglycaemia

Hypoglycaemia event will not be reported on an AE CRF page unless the event fulfilled SAE criteria, in which case it should also be reported in the SAE form. Hypoglycaemic events that meet SAE criteria will be recorded as SAEs by the Investigator in the AE CRF pages. Separate pages to capture details of hypoglycaemia events are contained within the CRF. Details include symptoms, contributing factors, blood glucose measurements during the episode, date and time of last meal, third party intervention, any treatment(s) received, and whether the episode is classified as an SAE. Any self-monitored blood glucose (SMBG) measurements taken by the subjects on the days that they experience hypoglycaemia symptoms will be recorded in the CRF.

Hypoglycaemia episodes will be classified using ADA[1] and International Society of Paediatric and Adolescent Diabetes (ISPAD)[2] categories. Derivation details based on the information collected in the separate CRF pages for hypoglycaemia are provided in the Appendix (Section 8.9).

3.4.4 Safety Laboratory tests

Blood and urine samples will be obtained at specified time points for laboratory evaluations (see Appendix Section 8.1) and will be performed by central and local laboratories. The central laboratory for this study will perform the analysis of all scheduled laboratory tests and will provide reference ranges for these tests. The following selected laboratory parameters will be summarised:

Haematology:

- Haematocrit,

- Haemoglobin,
- Platelet count,
- White blood cell (WBC) count,

Blood chemistry:

- Bilirubin, total,
- Alanine aminotransferase (ALT),
- Alkaline phosphatase (ALP),
- Aspartate aminotransferase (AST),
- Urate,
- Estimated GFR (eGFR) using Schwartz equation (derived by the central laboratory): eGFR (mL/min/1.73m^2) = 0.413 x (height [cm])/serum creatinine [mg/dl],
- Creatinine, serum,
- Electrolytes - sodium, potassium, phosphate, chloride, magnesium and calcium,
- Protein, total,

Urine Analysis:

- Albumin,
- Albumin to creatinine ratio,
- Glucose: creatinine ratio,
- Spot urine for glucose.

Additionally, eGFR will also be described by age group using the randomisation strata: ≥ 10 and < 15 years; ≥ 15 and < 18 years.

Fasting serum lipid panel:

- Cholesterol, total,
- Triglycerides,
- High density lipoproteins (HDL) cholesterol,
- Calculated low density lipoproteins (LDL) cholesterol.

3.4.4.1 Pregnancy testing

Pregnancy will be reported as an SAE. For women of child-bearing potential (WOCBP), pregnancy will be recorded in the subject's daily e-diary based on urine HCG pregnancy testing performed at site or at home. If a urine HCG test is positive, serum pregnancy testing will be performed by the central laboratory for confirmation. The study drug will be discontinued in subjects discovered to be pregnant at any time during the study.

3.4.5 Vital signs

Vital signs include blood pressure (BP) (mmHg) and heart rate (beats per minute). These measurements will be obtained at the time points indicated in the Appendix (Section 8.1).

3.4.6 Electrocardiograms

Electrocardiograms (ECGs) will be assessed during the lead-in visit, Week 26, Week 52, and, if applicable, during the ETD and Rescue visits. Overall evaluation of ECG is collected by visit as normal or abnormal, and the relevance of the abnormality is termed as "clinically significant" or "not clinically significant". Any ECG finding that is judged by the investigator as a potentially clinically significant change (worsening) compared with the baseline value will be recorded as an AE.

3.4.7 Physical examinations

Complete and targeted physical examinations will be performed at the time points indicated in the Appendix (Section 8.1).

Abnormal findings prior to signing the informed consent will be recorded in the CRF in the medical history or AE pages depending on their onset date. Any physical examination finding that is judged by the investigator as a potentially clinically significant change (worsening) compared with a baseline value should be reported as AEs. No physical examination summaries will be presented.

3.4.8 Body weight, height and body mass index

Body weight and height will be measured at the time points indicated in the Appendix (Section 8.1). Body mass index (BMI) at each time point is derived from the actual weight (kg) divided by the actual height (m) squared measured at that time point. If either weight or height is missing at a given visit, no imputation of BMI will be performed.

In addition, the z-score adjusted for age and sex using Centres for Disease Control and Prevention (CDC) for normalised body weight, height and BMI will be derived at each time point.

Method of BMI calculation:

- Convert pounds (lb.) to kilograms (kg = lb. / 2.2),
- Convert inches (in) to centimetres (cm = in X 2.54),
- BMI = (weight in kg) / (height in cm/100)^2,

Round to one decimal place (if 0.05 or greater, round up).

Normalised height, weight and BMI will also be summarised adjusted for age and sex and will be derived as z-score using CDC growth charts. Z-scores are calculated as:

$$Z = \frac{\left[\left(\left(\frac{value}{M}\right) ** L\right) - 1\right]}{S * L}$$

where:

- value = the child's height, weight or BMI;
- M, L and S correspond to values in the growth chart[3] and vary according to the child's sex and age (months) or sex and height.

Details regarding age derivation are given in the Appendix (Section 8.6.1). For subjects ≥20 years old the normalised value will be based on the age of 239.5 months.

In addition, normalised BMI will also be presented using the following categories of percentiles: ≥ 95th (refers to Obese), ≥ 85th and < 95th (refers to Overweight), ≥ 5th and < 85th (refers to Healthy Weight), and < 5th (refers to Underweight).

3.4.9 Measures of growth and maturity

Measures of growth and maturity include Tanner staging and central laboratory evaluations of growth and maturation markers and bone biomarkers. These will be assessed during the lead-in visit (Tanner staging only) or Day 1 prior to first dose (growth, bone and maturation markers only), and at Week 26, Week 52, Week 104, and (if applicable) at the ETD, Rescue and non-treatment follow-up visits.

Tanner staging is a measure of pubertal development rated on a scale of stage 1 to stage 5 (for details see Appendix Section 8.10.1). Tanner staging will be determined based on investigator assessment and the subjects' self-reports.

Growth and maturation markers

- Thyroid-stimulating hormone (TSH),
- Free thyroxine (assessed at Screening if TSH is abnormal),
- Luteinising hormone (LH) (females only),
- Follicle-stimulating hormone (FSH) (females only),
- Oestradiol (females only),
- Total testosterone (males only),
- Insulin-like growth factor-1 (IGF-1),
- Insulin-like growth factor binding protein-3 (IGFBP-3),
- Calcitonin,
- 25-hydroxy vitamin D.

Bone biomarkers

- Bone alkaline phosphatase,
- Osteocalcin,
- Parathyroid hormone (PTH),

- Carboxyterminal cross-linked telopeptide of Type 1 collagen (CTX-1).

3.5 Other variables

Other variables include demographics, diabetes-related and other baseline characteristics, randomisation stratification factors, exposure to rescue medication (insulin), and exposure and compliance to study medication.

3.5.1 Demographic and baseline characteristic variables

Demographics data are collected on or prior to first randomisation. For subjects that are rescreened, demographics data collected at re-screening will be used in the analysis.

Demographic and baseline characteristics are listed in Table 5. Diabetes-related baseline characteristics are listed in Table 6. Renal function baseline characteristics are listed in Table 7.

Table 5 Demographic and Baseline Characteristics

Characteristic	Summarised as	Categories
Sex	Categorical	Male Female
Age	Categorical and Continuous	≥ 10 and < 15 years ≥ 15 and < 18 years
Race	Categorical	White Black or African American Asian Native Hawaiian or Other Pacific Islander American Indian or Alaska Native Other
Ethnicity	Categorical	Hispanic/Latino Non-Hispanic/Latino
Baseline Height (cm) and Normalised Height	Continuous	-
Baseline Body Weight (kg) and Normalised Weight	Continuous	-
Normalised BMI	Categorical and Continuous	Percentiles as defined by CDC* ≥ 95th ≥ 85th and < 95th ≥ 5th and < 85th < 5th
Geographic region	Categorical	Regions as defined in Appendix Table 22 Asia/Pacific Europe Latin America North America

** ≥ 95th refers to Obese; ≥ 85th and < 95th refers to Overweight; ≥ 5th and < 85th refers to Healthy Weight; < 5th refers to Underweight.*

Table 6 Diabetes-Related Baseline Characteristics

Characteristic	Summarised as	Categories
Duration of Type 2 Diabetes Mellitus (see below for calculation)	Categorical and Continuous	< 2 years ≥ 2 and ≤ 5 years > 5 years
HbA1c	Categorical and Continuous	< 6.5% ≥ 6.5 and < 8% ≥ 8 and ≤ 10.5% > 10.5%
FPG	Continuous	
Background anti-diabetic medication	Categorical	Metformin only Insulin only Metformin + Insulin
Background anti-diabetic medication total daily dose	Continuous	Metformin dose Insulin dose
Combinations of randomisation stratification factors	Categorical	Male - ≥ 10 and < 15 years - Metformin only Male - ≥ 10 and < 15 years - Insulin only Male - ≥ 10 and < 15 years - Metformin + Insulin Male - ≥ 15 and < 18 years - Metformin only Male - ≥ 15 and < 18 years - Insulin only Male - ≥ 15 and < 18 years - Metformin + Insulin Female - ≥ 10 and < 15 years - Metformin only Female - ≥ 10 and < 15 years - Insulin only Female - ≥ 10 and < 15 years - Metformin + Insulin Female - ≥ 15 and < 18 years - Metformin only Female - ≥ 15 and < 18 years - Insulin only Female - ≥ 15 and < 18 years - Metformin + Insulin

Table 7 Baseline Renal Function Characteristics

Characteristic	Summarised as	Categories
eGFR	Categorical and Continuous	< 60 mL/min/1.73 m^2 ≥ 60 and < 90 mL/min/1.73 m^2 ≥ 90 and < 120 mL/min/1.73 m^2 ≥ 120 mL/min/1.73 m^2

Total Daily Dose of Metformin or Insulin

If several medications are ongoing on Day 1, the doses will be summed.

Duration of diabetes

Duration of diabetes will be calculated as the number of years from T2DM diagnosis date to informed consent date:

(Date of informed consent - date of T2DM diagnosis + 1) / 365.25.

Rules for handling missing or partial T2DM diagnosis dates are provided in the Appendix (Section 8.4). Duration of diabetes, even if partially imputed, will be included in the relevant listing. Only observed dates will be presented in the listings.

3.5.2 Medical history

Medical history includes medical conditions with onset prior to the informed consent signature, that stopped prior to screening or were ongoing at screening. Medical conditions will be coded using the current version of MedDRA at the time of database lock to map each verbatim term to a SOC and PT.

3.5.3 Prior and concomitant medications

Information on all prior and concomitant medications and therapies will be reviewed throughout the study and at Week 56. Treatment details for subjects receiving background insulin and/or metformin will be recorded separately to other non-study medications. All medications will be coded using the current version (at the time of database lock) of World Health Organisation Drug Dictionary (WHO DD), and the Anatomical Therapeutic Chemical (ATC) classification system.

Medications will be classified as prior or concomitant. A prior medication is defined as any medication that started and stopped prior to the first randomised dose. Concomitant medications are those with either

- A recorded medication start date falling within the analysis period (ST or ST+LT treatment period), or
- A recorded medication start date prior to the first day of double-blind study medication without any recorded medication stop date prior to the start of the ST treatment period, or
- A recorded medication start date prior to the first day of ST study medication with a recorded medication stop date after the start of the ST treatment period.

Rules for classifying medications as prior or concomitant in case of partial, missing or invalid start and stop dates are described in the Appendix (Section 8.3). Only observed dates will be presented in the listings.

Antidiabetic concomitant medications will be selected using WHO-DD ATC coding:

- All insulin antidiabetic medication (A10A)
- All non-insulin antidiabetic medication (A10 but not A10A)

3.5.4 Exposure to study treatment

Study medication is dispensed at randomisation and at the time points indicated in the Appendix (Section 8.1). From Day 1 to Week 14 subjects are instructed to take two tablets daily. From Week 14 to Week 52 subjects are instructed to take three tablets daily.

For the ST and ST+LT period, subjects' exposure will be presented under the first treatment received (i.e. total dapagliflozin, total saxagliptin, and placebo). Additional summaries will be presented by actual dose and treatment to account for subjects on active study medication switching to high-dose at Week 14 and subjects changing treatment or up-titrating after the third randomisation.

For the randomised withdrawal period, subjects' exposure will be presented under the treatment received after the third randomisation (i.e. accounting for subjects switching from placebo to dapagliflozin or saxagliptin).

Exposure prior to rescue medication initiation includes exposure up to and on the day of rescue medication initiation.

Treatment duration (days) will be calculated as:

- ST period: date of last dose during the ST period - date of first dose + 1,
- ST+LT period: date of last dose - date of first dose + 1,
- Randomised Withdrawal period: date of last dose - date of first dose in the Randomised Withdrawal period + 1.

Treatment duration (days) by dose (low, high) for dapagliflozin and saxagliptin will be calculated as:

For subjects who were randomised to up-titrate at Week 14:

- Low-dose: date of last dose up to Week 14 visit – date of first dose + 1,
- High-dose:
    - For the ST period: date of last dose during the ST period – date of first dose after the Week 14 visit + 1,
    - For the ST+LT period: date of last dose – date of first dose after the Week 14 visit + 1,

For subjects who were randomised to not up-titrate or were responders at Week 14 (low-dose only):

- ST period: date of last dose during the ST period - date of first dose + 1,
- ST+LT period: date of last dose - date of first dose + 1.

3.5.5 Exposure to rescue medication

If a subject has rescue insulin records with overlapping start and end dates, then maximum total daily dose of rescue insulin will be calculated as:

- If the rescue insulin records have different preferred names then the total daily dose for each record will be summed,
- If the rescue insulin records have the same preferred name then from the start of overlap the maximum total daily dose will be the total daily dose from the rescue insulin record with the larger dose.

Partial rescue insulin start and end dates are imputed as defined in Appendix 8.4.

3.5.6 Treatment compliance

Treatment compliance (%) for the study medication during the treatment period is defined for each subject as 100 X the number of tablets taken over the period divided by the number of tablets that should have been taken in that treatment period (the sum of the number of the tablets that should have been taken in each exposure record within that period). Compliance will be derived based only on complete dispensed and returned information (i.e. no imputation will be done on fully missing returned kits, missing returned date, or unknown number of returned tablets) and corresponding exposure records. If one or more kits (including unscheduled kits) for a visit were not returned, then the kits and exposure record for that visit are not used in the compliance calculation.

Compliance for the ST period will sum visits from Day 0 up to and including Week 26, compliance for the ST+LT period will sum all visits, and compliance for the randomised withdrawal period will sum visits after the third randomisation (Week 32 or Week 40 as applicable).

- The number of tablets taken in a period is: n dispensed (70 tablets x the number of kits dispensed) - n returned during that period.
- The number of tablets that should have been taken for each exposure record is calculated as follows:

  For exposure records up to and including Week 14 visit (or early treatment discontinuation for subjects who discontinue treatment prior to Week 14):

- (Date of last dose in the visit – date of first dose in the visit +1) X 2 tablets/day

For exposure records after Week 14 visit:

- (Date of last dose in the visit – date of first dose in the visit +1) X 3 tablets/day

If the subject underwent the third randomisation to withdrawal from metformin, then the number of tablets that should have been taken in the randomised withdrawal period is:

- (Date of last dose - date of first dose + 1) X 3 tablets/day, for visits after the third randomisation (Week 32 or Week 40 as applicable)

A subject is considered compliant if overall treatment compliance is between ≥ 80% and ≤ 120% of that prescribed. If compliance cannot be calculated for a subject, then their compliance will be presented as Unknown in the summary tables.

3.6 Pharmacokinetic/ pharmacodynamic assessments

Blood samples for determination of plasma levels of dapagliflozin, saxagliptin and its metabolite 5-OH-saxagliptin will be taken at the times presented in the Appendix Section 8.1 (Table 17). In addition, FPG will be collected at pre-dose and 2 hours post dose, and DPP-4 activity will be taken at the times presented in the Appendix Section 8.1 (Table 17) for the pharmacodynamic assessments. Plasma concentration data will be summarised as part of this SAP and included in the CSR.

Pharmacokinetics and exposure-response relationship analysis will be summarised and reported in a separate report as needed. If such a report is produced, full details of the analytical methods used will be described.

4. ANALYSIS METHODS

4.1 General principles

SAS version 9.4, or higher, will be used to produce all tables, listings, and figures. All table, listing, and figure specifications are provided as separate documents; these must be read in conjunction with the corresponding SAP version.

The confirmatory analyses of the primary and secondary endpoints within each drug (dapagliflozin vs. placebo and saxagliptin vs. placebo) will be performed using a hierarchical testing approach within each drug at the two-sided 0.05 level (with corresponding 95% CIs). No comparisons will be performed between dapagliflozin and saxagliptin.

When fitting models which involve the stratification variables, in case of non-convergence the stratification level may be combined with other levels or one or more stratification variables may be removed from the model.

For each imputation and statistical model described below adjusted on randomisation strata, in case of non-convergence (i.e.: because of sparse data), the following back-up models will be used in the presented order:

1) Remove randomisation strata of sex,
2) Remove randomisation strata of sex and age,
3) Remove randomisation strata of sex and age and collapse randomisation strata of background medication in two modalities to present (metformin only and insulin only grouped with metformin + insulin),
4) Remove randomisation strata of sex, age and background medication.

4.1.1 Definitions

Baseline

Unless stated otherwise, for each subject, baseline value of a parameter (e.g., efficacy laboratory parameter, safety laboratory test, ECG or physical measurement endpoint) is defined as the last assessment on or prior to the date of the first dose of the double-blind study medication in the ST treatment period (Day 1).

If there are multiple assessments with the same date and time, the average value will be used as baseline.

For subjects belonging to the Randomised Withdrawal Subjects Data Set, the withdrawal baseline value for a given parameter is defined as the closest available value on or before the day of first dose in the Randomised Withdrawal period.

Change from baseline

Change from baseline to any Week *t* in the analysis period (i.e., ST treatment period and ST+LT treatment period) is defined as follows:

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

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

The "Week t" to which a measurement belongs is determined using the conventions described in Table 8 (Section 4.1.6).

Last observation carried forward (LOCF)

A post-baseline missing value will be imputed by the last available non-missing post-baseline or post-withdrawal baseline (as applicable) value. If the first scheduled post-baseline or post-withdrawal baseline value is missing, no imputation will be done.

Day 1 is the date of first dose of study drug in the ST period.

Study day is defined relative to the date of first dose (Day 1) received in ST treatment period, and is calculated as:

- If assessment date is before the date of first dose: assessment date - date of first dose in the ST period (Day 1).
- If assessment date is on or after the date of first dose: assessment date - date of first dose in the ST period (Day 1) + 1.

Treatment response to HbA1c

A treatment responder at Week *t* is a subject with HbA1c < 7% at Week *t* (irrespective of baseline value). HbA1c response at Week t will be derived by dichotomising HbA1c values at Week t (binary variable, set to 1 if HbA1c < 7% at Week t and 0 if HbA1c ≥ 7% at Week t). Where specified, missing HbA1c responses at Week t will be derived from imputed continuous values of HbA1c for Week t.

Rescue medication initiation

Rescue medication initiation is defined as the first date/time of rescue insulin recorded on the Rescue Insulin eCRF. Partial rescue insulin start dates are imputed as defined in Appendix 8.4.

Prior to rescue medication initiation

An assessment or event is defined as prior to rescue if the date/time of the assessment or event occurred prior to the date/time of first rescue medication. If the assessment or event only has date collected, then prior to rescue includes assessments or events that occurred on the day of first rescue medication.

Subjects may have been rescued (i.e. had a rescue visit per the protocol guidance), but have not had their insulin dose increased if they were on background insulin or started insulin if they were on background metformin only, if their high HbA1c or FPG results meeting the rescue criterion were managed by diet and exercise. These subjects who did not start or increase total daily insulin dose after the rescue visit and is thus not recorded on the Rescue Insulin eCRF will be included in the sensitivity analyses.

4.1.2 Descriptive summaries of continuous variables

Descriptive summary statistics for continuous variables will include: number of non-missing records n, mean, standard deviation (SD), median, minimum and maximum. If appropriate, 1st and 3rd quartiles will also be presented. For PK plasma concentrations, summary statistics will additionally include geometric mean, geometric SD (following back transformation of a log transformed geometric mean) and the coefficient of variation (CV%).

Data reporting details (such as number of decimals) are provided in the Appendix (Section 8.12).

4.1.3 Descriptive summaries of categorical variables

Categorical data will be summarised for each treatment group or regimen as the number and percentage of subjects in each category. Percentages will be calculated out of the total number of subjects in the analysis set (and treatment group as appropriate) for the variable summarised.

Weighted proportions will be calculated as the weighted count of subjects with the event out of the total number of weighted subjects in the analysis set (and treatment group as appropriate).

4.1.4 Summaries of shift in categorical variables

Descriptive summaries of change from baseline in selected categorical variables will be provided using shift tables. Only subjects with baseline and post-treatment or post-study/follow-up (as applicable) assessments will be included in the shift table summaries. Frequencies and percentages of subjects within each treatment group or regimen will be generated for levels of cross-classifications of baseline, the on-treatment value and the post-study/follow-up value (if applicable) of the parameter. The on-treatment value can either be the value at a certain time point, or (for example, laboratory tests) the minimum/maximum value in the direction of toxicity which has been observed during the analysis period. Summaries of shifts will only include the frequency and percentage of subjects by shift category and treatment group. No differences in these percentages between treatment groups or regimens will be assessed.

4.1.5 Treatment regimens

The following treatment regimens are considered for analysis:

- Low-dose/high-dose: Initial treatment of the low-dose (5 mg of dapagliflozin or 2.5 mg of saxagliptin) followed by up-titrating to the high-dose (10 mg of dapagliflozin or 5 mg of saxagliptin) for those who do not achieve the glycaemic target of HbA1c < 7% at Week 12 (not responding and re-randomised to high-dose) and continuing treatment with the low-dose for those achieving the glycaemic target of HbA1c < 7% at Week 12 (responding and not re-randomised; Groups I & III in Figure 1).
- Low-dose: Initial treatment of the low-dose (5 mg of dapagliflozin or 2.5 mg of saxagliptin) followed by continuing treatment on the low-dose drug for those who do not achieve the glycaemic target of HbA1c < 7% at Week 12 (not responding and re-randomised to low-dose) and those achieving glycaemic target of HbA1c < 7% at Week 12 (responding and not re-randomised; Groups I & II in Figure 1).
- Placebo, all subjects randomised to placebo.

Subjects who are receiving background medication with insulin only, or metformin + insulin (and who are therefore not eligible for the third randomisation) will continue with their randomised study medication assigned after the Week 12 assessment in the double-blind LT treatment period. After completion of assessments at Week 26, a subset of eligible subjects who are receiving background medication with metformin only will undergo a third randomisation (randomised withdrawal of background medication) at either Week 32 or Week 40. The following treatment comparisons are considered for this analysis:

- For subjects initially randomised to dapagliflozin (or saxagliptin): Initial treatment of the overall (combined low-dose and high-dose) dapagliflozin (or saxagliptin) with metformin compared to high-dose dapagliflozin (or saxagliptin) without metformin.
- For subjects initially randomised to placebo: Initial treatment of the placebo with metformin compared to high-dose dapagliflozin (or saxagliptin) without metformin.
- For all subjects, regardless of initial randomisation, based on third randomisation (for AE and marked abnormality [MA] laboratory analysis only).

For Week 104 analyses, subjects will be summarised based on both the first and last treatment received and also repeated for the subset of Week 104 completers (subjects who had the Week 104 visit).

Refer to Appendix 8.13 for full details on the presentation of the treatment labels for the analysis.

4.1.6 Treatment and dose assignments

For dose at onset analyses, subjects will be presented under the treatment and dose received.

For assessments taken on the day of the planned dose change (Week 14, Week 32/40 [if subject underwent the third randomisation]), subjects will be assigned to the previous dose. For events (adverse events) that occurred on the day of the planned dose change, subjects will be assigned to the new dose.

For PK analyses, subjects will be presented under the treatment and dose received on the day of the assessment.

4.1.7 Data summaries and listings

Dapagliflozin and saxagliptin will be summarised separately. For demographics and efficacy analyses, analyses will be presented by treatment regimen (low-dose, low-dose/high-dose). In addition, for demographics, and (where specified) efficacy analyses, analyses will also be provided for overall drug (combining all doses of each drug). For safety analyses, analyses will be presented by overall drug. The common placebo group will be included in each summary.

Demographics and efficacy analyses will be based on the Randomised Subjects Data Set and the randomised treatment assignment. Selected demographics and efficacy summaries and analyses will also be provided for the Up-titration Randomised and Randomised Withdrawal Subjects Data Sets. In addition to the analyses based on the Randomised Subjects Data Set, a sensitivity analysis of the primary efficacy endpoint will be performed using the Evaluable Subjects Data Set if greater than 10% of subjects of any treatment or placebo have RPDs. Safety analyses will be based on the Treated Subjects Data Set and the actual treatment assignment.

In addition, within the analyses of dapagliflozin and saxagliptin separately, the overall (combined low-dose and high-dose) efficacy and safety analyses will be repeated for the subgroup of subjects on a stable baseline dose of metformin IR or XR (with or without insulin). For these analyses, the dapagliflozin or saxagliptin treatment groups will be combined and compared to the (common) placebo group.

Data summaries and specific analyses by study period will be restricted to the cut-off dates defined in Table 8. Comparisons are based on onset dates for events and the date of assessment for other parameters (laboratory tests, vital signs etc.). The ST and ST+LT periods start from Baseline (day of first dose in the ST period) and the Randomised Withdrawal period starts from Randomised Withdrawal Baseline (day of first dose in the Randomised Withdrawal period).

The time is included in the comparisons only if both dates being compared have the time provided.

For those data which will be listed, each subject will appear in the listings with their subject identifier, age, sex, race and background medication. Only subjects with data available will be presented in the listings. If a visit took place but no data is entered for the type of assessment being listed (other than 'Not Done'), the entry will not be listed. Subject data listings will be sorted by subject identifier, treatment group, dose (low, low/high) as per first randomisation, up-titration, and third randomisation, and if applicable, parameter group, parameter name, nominal visit name, analysis visit name (Baseline, Week 2, etc.), visit date and date/time of assessment (with corresponding day relative to first dose), unless specified otherwise. Events that occurred after first rescue medication use will be flagged in the efficacy listings.

Table 8 Cut-off dates for analyses by analysis type and study period

Data	Analysis type*	ST period[a]	ST+LT period[a]	Randomised withdrawal period[a,e]
Safety analyses				
AE, non-serious DKA	Prim	• Start of LT period (if applicable) • Date of last dose during the ST period + 4 days[b]	• Week 52/ETD date + 4 days[b]	• Week 52/ETD date + 4 days[b]
	Sens	• Start of LT period (if applicable) • Date of last dose during the ST period + 4 days[b] • First rescue intake[d]	• Week 52/ETD date + 4 days[b] • First rescue intake[d] • Week 32[f] /ETD date + 4 days[b] • Week 32[f] /ETD date + 4 days[b] • First rescue intake[d]	• Week 52/ETD date + 4 days[b] • First rescue intake[d]
SAE (including serious DKA, serious Hypoglycaemia)	Prim	• Start of LT period (if applicable) • Date of last dose during the ST period + 30 days[b]	• Week 52/ETD date + 30 days[b]	• Week 52/ETD date + 30 days[b]
	Sens	• Start of LT period (if applicable) • Date of last dose during the ST period + 30 days[b] • First rescue intake[d]	• Week 52/ETD date + 30 days[b] • First rescue intake[d] • Week 32[f] /ETD date + 30 days[b] • Week 32[f]/ETD date + 30 days[b] • First rescue intake[d]	• Week 52/ETD date + 30 days[b] • First rescue intake[d]
Non-serious Hypoglycaemia	Prim	• Start of LT period (if applicable) • Date of last dose during the ST period + 4 days[b] • First rescue intake[d]	• Week 52/ETD date + 4 days • First rescue intake[d]	• Week 52/ETD date + 4 days • First rescue intake[d]
	Sens	• Start of LT period (if applicable) • Date of last dose during the ST period + 4 days[b]	• Week 52/ETD date + 4 days • Week 32[f]	• Week 52/ETD date + 4 days
Safety laboratory tests (excl. liver function)	Prim	• Start of LT period (if applicable) • Date of last dose during the ST period + 4 days	• Week 52/ETD date + 4 days	• Week 52/ETD date + 4 days
	Sens[c]	• Start of LT period (if applicable) • Date of last dose during the ST period + 4 days • First rescue intake[d]	• Week 52/ETD date + 4 days • First rescue intake[d] • Week 32[f] /ETD date + 4 days • Week 32[f] /ETD date + 4 days • First rescue intake[d]	• Week 52/ETD date + 4 days • First rescue intake[d]
Liver function tests	Prim	• Start of LT period (if applicable) • Date of last dose during the ST period + 30 days	• Week 52/ETD date + 30 days	• Week 52/ETD date + 30 days

Data	Analysis type*	ST period[a]	ST+LT period[a]	Randomised withdrawal period[a,e]
Safety analyses				
Vital signs, ECG, Growth markers	Prim	• Start of LT period (if applicable) • Date of last dose during the ST period + 4 days	• Week 52/ETD date + 4 Days	• Week 52/ETD date + 4 days
Body weight, Height, BMI, Tanner staging	Prim	• Start of LT period (if applicable) • Date of last dose during the ST period + 8 days	• Week 52/ETD date + 8 days	• Week 52/ETD date + 8 days
UACR, Urinary glucose	Prim	• Start of LT period (if applicable) • Date of last dose during the ST period + 1 day	• Week 52/ETD date + 1 day	• Week 52/ETD date + 1 day
Efficacy analyses				
HbA1c	Prim	• Start of LT period (if applicable)	• Week 56/EOS date	• Week 56/EOS date
	Sens	• Start of LT period (if applicable) • Date of last dose during the ST period + 8 days • First rescue intake[d]	• Week 52/ETD date + 8 days • First rescue intake[d] •	• Week 52/ETD date + 8 days • First rescue intake[d]
FPG	Prim	• Start of LT period (if applicable)	• Week 56/EOS date	• Week 56/EOS date
	Sens	• Start of LT period (if applicable) • Date of last dose during the ST period + 1 day • First rescue intake[d]	• Week 52/ETD date + 1 day • First rescue intake[d]	• Week 52/ETD date + 1 day • First rescue intake[d]

*Prim = Primary. Sens = Sensitivity. ETD = early treatment discontinuation.

[a] The earliest date should be used if multiple dates are listed.

[b] When summarising AEs leading to discontinuation, no upper cut-off day windows (i.e., 4 days and 30 days from last dosing date for AEs and SAEs respectively) are applied.

[c] For safety laboratory tests sensitivity analysis is used for marked laboratory abnormality summaries only.

[d] Only for analyses that exclude data after rescue.

[e] The randomised withdrawal period starts from either Week 32 or Week 40 depending on the visit the third randomisation occurred at.

[f] These sensitivity analyses use data up to Week 32 to exclude data from the randomised withdrawal analyses.

For analyses using data up to Week 32, in cases where Week 32 visit date is missing an imputed Week 32 date will be derived using the earliest possible date of the following:

- Week 26 date (target day 183) extrapolated to estimate the Week 32 date (target day 225)
- Third randomisation date
- Next visit date after Week 32

For analyses presenting the post-study visit, non-treatment follow-up visits or Week 104, no cut-off dates apply. Unscheduled Week 104 visits will be summarised as Week 104.

4.1.7.1 Visit windows

As subjects do not always adhere to the terms and conditions defined in the study protocol, visit windows will be used to assign each clinical assessment to a scheduled visit (for data that will be summarised by visit, as shown in Table 9, Table 10, and Table 11).

To apply the visit windows, note the following rules for defining the start and end of each study period:

- The ST period starts from Day 1 (start date of IP) and ends on the start date of the Week 26 visit or early discontinuation from the study, whichever is earlier. For subjects who did not enter the LT period, there is no cut-off date.
- For subjects entering the LT period, the LT period starts from the day after the end of the ST period and ends on the date of Week 56 visit or early discontinuation from the study, whichever is earlier.
- The Randomised Withdrawal period starts from the date of first intake of third randomisation treatment (i.e., IP issued on the Week 32 or Week 40 visit) and ends on the date of Week 56 visit or early discontinuation from the study, whichever is earlier.
- The post-study period starts from the day after the end of the LT period and ends on the date of Week 104 visit or date of lost to follow-up, whichever is earlier.

For subjects who entered the LT period but skipped the Week 26 visit, then the event date from the Continuation Long Term Follow up CRF will be used (if available). For subjects who entered the post-study period but skipped the Week 56 visit, then the latest visit date during the ST+LT period will be used to extrapolate the estimated Week 56 date (target day 395).

Prior to slotting the data must be restricted to the cut-offs defined for each variable and period as per Table 8. Slotting must be repeated for each type of analysis applicable to a variable (primary and each sensitivity analysis).

Visit windows for post-baseline (after Day 1) assessments that will be slotted for the ST period are shown in Table 9. Visit windows for assessments that will be slotted for the LT and randomised withdrawal period and the post-study (Week 104) visit are shown in Table 10 and Table 11.

Table 9 Visit windows for ST period assessments

Visit	Target Day	Day Range by Type of Assessment		
		Vital Signs	**Safety laboratory panel, FPG, HbA1c, PK/PD[a], Urinary glucose, Height, Weight**	**Growth and maturation markers, Tanner staging, ECG, Fasting lipid panel**
Week 6	43	2 to 64	2 to 64	
Week 12	85	65 to 92	65 to 113	
Week 14	99	93 to 120		
Week 20	141	121 to 162	114 to 162	
Week 26	183	163 to Week 26/ED (whichever is earlier)	163 to Week 26/ED (whichever is earlier)	2 to Week 26/ED (whichever is earlier)

ED = Early discontinuation from the study.

[a] PK/PD assessments include plasma samples for analysis of dapagliflozin, saxagliptin, 5-OH-saxagliptin, FPG and DPP-4 activity.

Table 10 Visit windows for LT period and post-study (Week 104) assessments

Visit	Target Day (LT Day[a])	Day Range by Type of Assessment	
		Vital signs, Safety laboratory panel, FPG, HbA1c, Height, Weight	**Growth and maturation markers, Tanner staging, ECG, Fasting lipid panel**
Week 32	225 (43)	LTSTDT to 252 / RWSTDT [only applicable for subjects going through the third randomisation] (whichever is earlier)	
Week 40	281 (99)	253 / RWSTDT +1 [only applicable for subjects going through the third randomisation] (whichever is earlier) to 322	
Week 52	365 (183)	323 to Week 56/ED (whichever is earlier)	LTSTDT to Week 56/ED (whichever is earlier)
		Growth and maturation markers, Tanner staging, Height, Weight, BMI	
Week 104	728	Week 56 + 1 day to Week 104 / date of last contact (if earlier than Week 104)	

ED = Early discontinuation from the study. LTSTDT = LT start date (i.e., day following the last day of the ST period). RWSTDT = randomised withdrawal period start date (i.e., date of first IP dose received in randomised withdrawal period).

[a] LT day is the target day counting from the start of the LT period (LTSTDT). Target day is based on counting from Day 1 (date of first IP dose in the study).

Table 11 Visit windows for randomised withdrawal period assessments

Visit	Target Day	Date Range by Type of Assessment	
		Vital signs, Safety laboratory panel, FPG, HbA1c, Height, Weight	**Growth and maturation markers, Tanner staging, ECG, Fasting lipid panel**
Withdrawal Baseline		The closest available value on or before RWSTDT	
Week 40	281	RWSTDT +1 day to 322 (for subjects who were third randomised at Week 32 only)	
Week 52	365	RWSTDT + 1 day (for subjects who were third randomised at Week 40) or 323 (for subjects who were third randomised at Week 32) to Week 56 visit/ED (whichever is earlier)	RWSTDT to Week 56 visit/ED (whichever is earlier)

ED = Early study discontinuation. RWSTDT = randomised withdrawal period start date (i.e., date of first IP dose received in randomised withdrawal period).

For laboratory and non-laboratory parameters, 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. For observations with the same date and time, including missing times and including potential baseline values, an average will be taken if the two or more values with the same date and time.

In addition, for the efficacy FPG analyses as there are multiple time points collected at each visit, then the record with the earliest time on the day selected using the above definition will be used for each visit in the analysis. If there are multiple values collected with the same time, then an average will be taken. If there are multiple values collected on the same day where one of the records only has the date available, then the records with the date/time present are selected over the records with only date present. Only FPG assessments documented with the subject in a fasting state will be summarised and listed.

For the shift tables for nominal ECG parameter of normal/abnormal the following rules apply. If more than one ECG measurement is performed within a specified time window, an abnormal ECG value will be chosen over a normal ECG value. If two or more abnormal or two or more normal ECG values are within the same time window, the one closest to the target date will be used.

Data collected during unscheduled visits will also be slotted.

4.1.7.2 Handling of rescreened subjects

A rescreened subject is defined as a subject who fails the initial screening attempt and is then screened failed and rescreened under a new subject identifier. Successful rescreen subjects will not be counted as a screen failure. In case of rescreening, all the data (including that from the initial screening and rescreening) will be presented under the latest rescreened subject ID and will be used in summary tables, figures and listings. The exception is for demographic and baseline characteristics analyses, where the data collected under the latest rescreened subject ID will be used (e.g. age, date of diabetes mellitus diagnosis). For rescreened subjects, the original subject identifier(s) will also be presented in the demography listing for cross-linking purposes. Records from the initial screening attempt(s) will be flagged in AE, prior and concomitant medication, medical history, laboratory, and vital sign listings.

4.1.7.3 Handling of implausible glucose results

It was identified prior to Week 56 database lock during ongoing data review that there was an implausible FPG value recorded for one subject at their Day 1 visit. This was investigated and confirmed by the central laboratory and it was decided that the results will be used in the primary analysis.

A sensitivity analysis of the secondary efficacy endpoints for FPG excluding this result and any other outliers may be conducted post-Week 56 database lock, if deemed necessary.

4.1.8 Missing data

If not stated otherwise, no imputation of missing data will be done. Efforts will be made to follow the subjects and collect the data even after the subjects discontinue the treatment.

For the primary and secondary efficacy analysis based on laboratory data (i.e. HbA1c, FPG) missing data will be handled using multiple imputation, as described in Section 4.1.12. Approaches that will be used to handle missing data for other efficacy analyses will be described in the respective analysis sections.

Information regarding handling of missing or partial event or medication dates is provided in the Appendix (Sections 8.2 and 8.3).

4.1.9 Weighted analysis of covariance (ANCOVA)

In summaries of primary and secondary efficacy endpoints examining the change from baseline at Week t, an ANCOVA model of the differences between Week t and baseline measurements will be used, controlling for baseline value as a covariate, and treatment group (regimen) and randomisation strata as fixed effects. Only main effects of the randomisation strata will be included in the model. The model will have the following form:

$$D_{t,ijm} = intercept + \beta\,[Y_{0,ijm}] + \tau_j + \omega_m + error_{ijm}$$

where:

- $D_{t,ijm} = Y_{t,ijm} - Y_{0,ijm}$ = the Week t change from baseline of subject i in treatment group j and stratum m.
- $Y_{0,ijm}$ is the baseline measurement of subject i in treatment group j and in strata m,
- $Y_{t,ijm}$ is the Week t measurement of subject i in treatment group j and in strata m,
- β is the slope of $D_{t,ijm}$ regressing on the baseline measurement,
- τ_j is the mean effect of treatment group j,
- ω_m is the mean effect of randomisation stratum m,
- *Intercept*, β and τ_j are unknown parameters to be estimated from the data.

Weights will be used in the ANCOVA model to test the treatment regimens compared to placebo, $\mathbf{H_{01}}: \tau_{TR1} - \tau_{Pla} = 0$ and $\mathbf{H_{02}}: \tau_{TR2} - \tau_{Pla} = 0$.

The weight matrices to test hypotheses $\mathbf{H_{01}}$ and $\mathbf{H_{02}}$ are denoted by $\boldsymbol{W_1}$ and $\boldsymbol{W_2}$ respectively, defined as follows:

$$\boldsymbol{W_1} = Diag\begin{bmatrix} \mathbf{1}_{1\times n} \\ \mathbf{1}_{1\times rn} \\ \mathbf{2}_{1\times(1-r)n/2} \\ \mathbf{0}_{1\times\frac{(1-r)n}{2}} \end{bmatrix} \quad \boldsymbol{W_2} = Diag\begin{bmatrix} \mathbf{1}_{1\times n} \\ \mathbf{1}_{1\times rn} \\ \mathbf{0}_{1\times\frac{(1-r)n}{2}} \\ \mathbf{2}_{1\times(1-r)n/2} \end{bmatrix}$$

where r is the proportion of response (HbA1c < 7%), n is the number of subjects within an arm, and based on a 1:1:1 randomisation.

$\boldsymbol{W_1}$: For the comparison of the low-dose/high-dose treatment regimen versus placebo (used for secondary endpoints), all dapagliflozin and saxagliptin subjects who had HbA1c < 7% at Week 12 and remained on the low-dose will be assigned a weight of 1. The dapagliflozin and saxagliptin subjects who had HbA1c ≥ 7% at Week 12 and continued on the low-dose will be assigned a weight of 0. The dapagliflozin and saxagliptin subjects who had HbA1c ≥ 7% at Week 12 and received the high-dose will be assigned a weight of 2. All subjects who do not undergo the second randomisation and all placebo subjects will be assigned a weight of 1.

$\boldsymbol{W_2}$: For the comparison of the low-dose treatment regimen versus placebo (used for secondary endpoints), all dapagliflozin and saxagliptin subjects who had HbA1c < 7% at Week 12 and remained on the low-dose will be assigned a weight of 1. The dapagliflozin and saxagliptin subjects who had HbA1c ≥ 7% at Week 12 and continued on the low-dose will be assigned a weight of 2. The dapagliflozin and saxagliptin subjects who had HbA1c ≥ 7% at Week 12 and received the high-dose will be assigned a weight of 0. All subjects who do not undergo the second randomisation and all placebo subjects will be assigned a weight of 1.

For the comparison of overall drug treatment versus placebo (used for the primary endpoint analysis and some secondary endpoints) no weighting will be used (i.e. all treatment groups will be assigned a weight of 1).

It follows that parameters can be estimated with appropriate design and weight matrix by

$$\widehat{\boldsymbol{\beta}} = (\boldsymbol{X'WX})^{-1}\boldsymbol{X'WY} \sim \boldsymbol{N}(\boldsymbol{\beta}, \boldsymbol{\Sigma})$$

such that $\widehat{\boldsymbol{\beta}} = [\hat{\beta}_{Intcpt} \quad \hat{\beta}_{Tr} \quad \hat{\beta}_{Base} \quad \hat{\beta}_{Strata}]^{\boldsymbol{T}}$

and the design matrix for *i*-th subject $\boldsymbol{x_i} = [1 \quad Trt \quad x_{baseline} \quad \gamma_{Strata}]$.

The model will provide least squares mean (LS mean) estimates and 2-sided 95% confidence intervals for mean changes from baseline within each treatment group (regimen) and differences in mean change from baseline between a treatment group (regimen) and placebo. Note that CIs will not be obtained directly from the model, but will be derived by combining the results obtained from running the ANCOVA model in each imputed data set, as described in Section 4.1.12.4. If there is no missing data for all treatment groups in the analysis at a visit, then the ANCOVA model will be run on the non-imputed data and no combining of results from each imputed data set is necessary.

Standardised model residuals will be used to examine model assumptions and to detect outliers and potentially influential observations. The "Influence Diagnostics" output produced by PROC MIXED and box plots of standardised residuals will be used to facilitate this diagnostic analysis. If influential outliers are present additional sensitivity analyses will be performed with the outliers excluded, in order to assess their impact on treatment (regimen) comparisons.

4.1.10 Proportion of subjects with a pre-defined characteristic (responders) at Week t

The proportion of subjects with a *pre-defined characteristic (responders)* at Week t will be analysed using a weighted or unweighted logistic regression when there are at least 5 responders by treatment group. For proportion of responders (e.g., meeting HbA1c criteria), estimates, confidence intervals, and tests will be obtained using a weighted or unweighted logistic regression. Odds ratios (and corresponding standard errors [SE]) representing the responder odds in the dapagliflozin/saxagliptin treatment group (or regimen) versus placebo group will be generated adjusted for baseline variable (e.g., adjustment for baseline HbA1c) and each randomisation stratification factor using the SAS LOGISTIC procedure.

The frequencies of response/non-response and the associated crude response rates (as percentages) will be presented by treatment group (or regimen). In addition, weighted or non-weighted adjusted percentages, standard errors, and 95% CIs for each treatment group (or regimen) will also be displayed. Adjusted odd ratio and corresponding 95% Log likelihood confidence interval, and p-values (uncorrected) will also be presented.

For the HbA1c responder endpoints, if there is no missing data for all treatment groups in the analysis at Week t, then the logistic regression model or Fisher's exact test will be run on the non-imputed data and no combining of results from each imputed data set is necessary.

In case of non-convergence because of sparse data subsequent backup models will be used in removing randomisation strata in sequential order and/or collapsing the randomisation strata of background medication as defined in Section 4.1. A subsequent back-up model in the order presented Section 4.1 will only be provided if the preceding back-up model does not converge.

When there are less than 5 responders in any treatment group, the unadjusted (and difference) proportions, weighted or non-weighted exact 95% confidence interval, and p-values from the weighted or unweighted Fisher's exact test (when applicable) will be provided.

4.1.11 Estimates for time-to-event analyses

Cox proportional hazards models with stratification factors (including sex, age group [≥ 10 and < 15 years, ≥ 15 and < 18 years] and background antidiabetic medication [metformin only, insulin only, metformin + insulin]) as covariates will be displayed by treatment group. Time to event (in days) will be calculated as: date of event - date of first dose + 1. Subjects that permanently discontinue treatment but remain in the study will be included in the analysis. Subjects who do not have the event will be censored at the Week t visit date or the last visit date for those withdrawing from the study before Week t visit. Subjects lost to follow-up during the applicable period will be censored at their latest assessment date whereas subjects having skipped Week t visit will be censored at their next visit date or the latest Week t assessment date amongst all subjects (whichever is earlier).

Kaplan-Meier plots of time to event variables will be displayed by treatment group. Unless otherwise specified, the plot will be presented only when there are at least 5 "events" in each treatment group. Additionally, a table will accompany the plot and will display the Kaplan-Meier estimates of the cumulative event probabilities (with 95% CI calculated based on Greenwood's method when applicable) 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. The p-value from a pairwise Log-Rank test (stratified by sex, age, and background medication) of the null hypothesis of no difference between treatment arms in the probability of an event will be presented.

4.1.12 Multiple imputation

Missing quantitative Week t data at study endpoint will be imputed from one of the 2 missing not at random (MNAR) imputation models for missing Week t data.

The preferred model will be to use a "retrieved drop-out" multiple imputation (MI-RD) model to represent the MNAR process. This will be used if there is sufficient data from 'retrieved drop-outs', defined as subjects who discontinued the treatment (but not the study) and had a Week t HbA1c value. If any of the required imputation models needed for any of the regimens (low, low/high, overall) within dapagliflozin or saxagliptin have less than 5 retrieved drop-out

observations available to fit the model, then MI-WO "wash-out" method will be used for analyses of all regimens for that endpoint. This is a "copy to reference method". Both MI-RD or MI-WO will be implemented using a baseline to predict Week t values in the MNAR model.

The randomisation strata will be coded using indicator variables as follows and used in the multiple imputation steps:

- randomisation strata of background medication will be coded as
  - met (1) and ins (0) if metformin only,
  - met (0) and ins (1) if insulin only,
  - met (0) and ins (0) if metformin + insulin;
- randomisation strata of background medication if randomisation strata of insulin only and insulin with metformin are grouped will be coded as
  - metins (1) if metformin only,
  - metins (0) if insulin only or insulin with metformin;
- randomisation strata of age group will be coded as
  - age (1) if age $\geq$ 10 and < 15 years,
  - age (0) if age $\geq$ 15 and < 18 years;
- randomisation strata of sex will be coded as
  - sex (1) if male,
  - sex (0) if female.

Each imputation model will use a common seed value of 2717.

In case of non-convergence because of sparse data, subsequent backup imputation models will be used in removing randomisation strata in sequential order and/or collapsing the randomisation strata of background medication as defined in Section 4.1. A subsequent back-up model in the order presented Section 4.1 will only be provided if the preceding back-up model does not converge.

4.1.12.1 Monotone Data Pattern

Prior to imputation, intermittent missing HbA1c/FPG values (i.e., missing values both preceded and followed by at least one non-missing value) will be imputed under a "missing at random" (MAR) model for missing data using a Markov chain Monte Carlo (MCMC) method of imputation.

Since in general the missing pattern will not be monotone, the first step for any of the methods presented below will be to use the Markov Chain Monte Carlo (MCMC) method in conjunction

with the MONOTONE statement of the SAS MI procedure to partially impute quantitative parameters, separately for each treatment regimen (i.e. low-dose, low-dose/high-dose and placebo) and by weight, to create imputed datasets with just enough missing quantitative values to generate two hundred (200) imputed data sets with a monotone missing data pattern (for each treatment regimen), assuming a MAR missing data pattern. Subjects withdrawing from IP before the up-titration will be assigned a weight of 1 and will be included in each imputation model (low-dose and low-dose/high-dose regimen). Indicators of randomisation strata (as described in Section 4.1.12) and visit (i.e., baseline HbA1c/FPG along with all visits per protocol up to Week t) will be the parameters included in MCMC models.

The random seed number for the MCMC stage will be 2717.

4.1.12.2 Retrieved Drop-Outs Multiple Imputation Method

Missing HbA1c/FPG data will be imputed separately by treatment regimen of each drug (i.e., low-dose, low-dose/high-dose, and placebo) and weight (as applicable). Subjects not going through up-titration randomisation due to discontinuation of study medication will be assigned a weight of 1 and imputed in the both the low-dose and low-dose/high-dose regimens.

Using monotone datasets generated as described in Section 4.1.12.1, the remaining missing HbA1c/FPG data will be imputed separately for each treatment group and weight (as applicable) using a REGRESSION method in conjunction with the MONOTONE statement and the MNAR statement of the SAS MI procedure.

- Step 1: The imputation model used to create monotone data pattern (see Section 4.1.12.1) will include factors and covariates in the following order: indicators representing randomisation strata of sex, age group and background medication, baseline HbA1c/FPG as well as HbA1c/FPG from all visits per protocol up to Week t.
- Step 2: Using an imputation model with terms for indicators representing randomisation strata of sex, age group and background medication, baseline HbA1c/FPG followed by Week t HbA1c/FPG, for each treatment regimen and weight, subjects that discontinue treatment prior to Week t with baseline and an (off-treatment) Week t assessment available will be used to impute within each missing Week t values (for that treatment regimen) after baseline. Separate models will be performed for each treatment regimen and weight (as applicable) to impute Week t missing data in the multiply imputed monotone datasets generated by Step 1. For this step, one imputation will be performed for each of the 200 imputed datasets from Step 1 to form "complete datasets".
- Step 3: Imputed values from each of the 200 imputation datasets selected from Step 2 and the non-missing data will be used to calculate change from baseline. The HbA1c/FPG change from baseline values at Week t will be analysed by an ANCOVA with terms for baseline HbA1c/FPG, randomisation strata, and treatment group as described in Section 4.1.9. In case of non-convergence, the imputation and ANCOVA model will be simplified by removing/collapsing the randomisation strata indicator variables in a stepwise manner as described in Section 4.1.

- Step 4: Results from each ANCOVA model will be combined as described in Section 4.1.12.4.

If convergence in all treatment regimens (including placebo) is still not achieved the alternative imputation method (MI-washout) will be used.

4.1.12.3 Wash-out multiple imputation method

Using the monotone datasets generated as described in Section 4.1.12.1, the remaining missing data will be imputed separately for each treatment group using a REGRESSION method in conjunction with the MONOTONE statement and either MNAR statement (for dapagliflozin/saxagliptin treatment groups) or MAR (for placebo treatment group) of the SAS MI procedure. Weight will not be included in the imputation model.

- Step 1: The imputation model used to create monotone data pattern (see Section 4.1.12.1) will include factors and covariate in the following order: indicators representing randomisation strata of sex, age group and background medication, baseline HbA1c/FPG as well as HbA1c/FPG from all visits per protocol up to Week t.
- Step 2: For subjects from dapagliflozin/saxagliptin treatment group, Week t data from the placebo group subjects with non-missing baseline will be used in modelling the MNAR process. The imputation model will include, in the following order, indicators representing randomisation strata of sex, age group and background medication as well as, baseline HbA1c/FPG and Week t HbA1c/FPG.

  While for subjects from placebo treatment group, missing data will be imputed sequentially at each assessment using a MAR imputation based on all non-missing data from that visit and data from all prior visits (after imputation). The indicators representing randomisation strata will be included in modelling the MAR processes in the same order as described in Step 1. Therefore, the model will include, in the following order, indicators representing randomisation strata of sex, age group and background medication as well as, baseline HbA1c/FPG, and HbA1c/FPG from all visits per protocol prior to and including Week t.

- Step 3: Imputed values from each of the 200 imputation datasets selected from Step 2 and the non-missing data will be analysed by ANCOVA applied at Week t, with terms for baseline HbA1c/FPG, randomisation strata and treatment group as described in Section 4.1.9. In case of non-convergence, the imputation and ANCOVA model will be simplified by removing/collapsing the randomisation strata indicator variables in a stepwise manner as described in Section 4.1.
- Step 4: Results from each ANCOVA model will be combined as described in Section 4.1.12.4.

4.1.12.4 Combining multiple imputation results

Continuous endpoints

The analysis model will be evaluated in each of the imputed datasets, and the point estimates and SEs will be combined using Rubin's rules to produce valid global estimates with corresponding CIs and p-values. SAS MIANALYZE procedure will be used for this purpose.

Categorical endpoints

HbA1c will be categorised as < 7% (responders) or ≥ 7% (non-responders) and will be derived from dichotomising the imputed continuous values of HbA1c.

A logistic regression (the SAS LOGISTIC procedure) will be used when there are at least 5 responders by treatment regimen. If there are less than 5 subjects in any treatment regimen, the Fisher's exact test will be used.

- If the logistic model is used, prior to applying Rubin's rules (as described in Section 4.1.12.4) the odds ratio and its SE will be log-transformed (as detailed below).

If Fisher's exact test is used, the final estimates for the proportion of responders, difference in proportion of responders and p-value will correspond to the median of these estimates across all imputed data sets.

Log-transformation of odds ratio estimates

Rubin's combination rules assume that the multiple imputation estimates are asymptotically normally distributed. However, the estimates of odds ratios follow a log-normal distribution. A log transformation can be used to normalise these estimates in order to be able to apply Rubin's combination rules, as follows:

- Obtain log-transformed odds ratio (OR) and SE from each imputed dataset
  log_OR=log(OR)
  log_OR_SE=log(upper_CI) - log(lower_CI)/(2*1.96)

- Combine transformed estimates using MIANALYZE

- Back-transform combined estimates (ESTIMATE and STDERR are the results from PROC MIANALYZE):
  Pooled_OR=EXP(ESTIMATE)
  Pooled_lower_CI=pooled_OR*EXP(-1.96*STDERR)
  Pooled_upper_CI=pooled_OR*EXP(+1.96*STDERR)

The above code assumes that 95% CIs are used. If different width is required, the 1.96 multiple will need to be adjusted accordingly.

Further information and the SAS code can be found in Reference 4.

4.1.12.5 Multiple imputation under MAR hypothesis

Using the monotone datasets generated as described in Section 4.1.12.1, the remaining missing HbA1c or FPG data will be imputed separately for each treatment regimen and weight (as applicable) using a REGRESSION method in conjunction with the MONOTONE statement of the SAS MI procedure and MAR assumption.

- Step 1: Prior to imputation, the MCMC method will be used in the MI procedure to impute just enough missing values under a "missing at random" (MAR) model to generate 200 imputed data sets with a monotone missing data pattern. The imputation model with include factors and covariates in the following order: indicators of randomisation strata and baseline HbA1c/FPG as well as HbA1c/FPG at all visits per protocol prior to Week t.

- Step 2: Missing data will be imputed sequentially at each assessment using a MAR imputation based on all non-missing data from that visit and data from all prior visits (after imputation). The indicators representing randomisation strata will be included in the same order as described in Step 1. Therefore, the model will include, in the following order, indicators representing randomisation strata of sex, age group, and background medication as well as, baseline HbA1c/FPG, treatment regimen, and all previous HbA1c/FPG values (all visits per protocol prior to Week t).

- Step 3: Imputed values from each of the 200 imputation datasets selected from Step 2 and the non-missing data will be analysed by ANCOVA applied at Week t, with terms for baseline HbA1c, randomisation strata, and treatment regimen as described in Section 4.1.9. In case of non-convergence, the imputation model will be simplified removing/collapsing the randomisation strata indicator variables in a stepwise manner as described in Section 4.1.

- Step 4: Results from each ANCOVA model will be combined as described in Section 4.1.12.4.

4.1.12.6 Tipping point analysis

A series of analyses will be performed with increasing values of δ (where δ represents HbA1c [%]) until the analysis conclusion of a statistically significant treatment effect no longer holds. The value of δ that overturns the primary results will represent a tipping point. An interpretation of clinical plausibility of the assumption underlying the tipping point will be provided. Values of δ will be examined until a p-value >0.05000 is obtained for the difference between groups in LS Means.

Using the monotone datasets generated as described in Section 4.1.12.1 and Step 1 of either MI-RD (as described in Section 4.1.12.2) or MI-WO (as described in Section 4.1.12.3) dependent on if there is sufficient data to perform the MI-RD model (as specified in Section 4.1.12) the remaining steps will be performed:

- Step 2: The MI procedure will be used with a MONOTONE statement to impute the remaining monotone missing data in the multiple imputed data sets generated in the first step. The imputed data for Week 26 will first be estimated under the MAR assumption ($\delta=0$). In subsequent models, a common set of δ values will then be added to the MNAR imputed values for Week 26 for the active treatment regimens (only), while imputed values for the placebo treatment group remain with no δ addition.

  For the first imputation model ($\delta=0$), 200 imputation datasets will be generated using the 200 monotone datasets generated in Step 1. For the subsequent imputation models ($\delta > 0$), the same monotone datasets as those used for the first imputation model will be used.

- Step 3: For each value of delta, imputed values from each of the 200 imputation datasets selected from Step 2 and the non-missing data will be analysed by ANCOVA applied at Week t, with terms for baseline HbA1c, randomisation strata and treatment group as described in Section 4.1.9. In case of non-convergence, the imputation and ANCOVA model will be simplified by removing/collapsing the randomisation strata indicator variables in a stepwise manner as described in Section 4.1.

- Step 4: For each value of delta, results from each ANCOVA model will be combined as described in Section 4.1.12.4.

4.2 Study population

Study population data for the treatment period will be presented. A table presenting the number and percentage of subjects in the Randomised Subjects Data Set, Up-titration Randomised Subjects Data Set, Evaluable Subjects Data Set, Treated Subjects Data Set, Randomised Withdrawal Subjects Data Set and Pharmacokinetic Analysis Data Set will be provided. Subjects excluded from each analysis set and reason(s) for exclusion will be listed.

For the Randomised Withdrawal Subjects Data Set, subjects who passed Week 32/Week 40 prior to protocol amendment 4 being approved in their country were not eligible to qualify for this potential randomisation and will be presented under the reason for exclusion "Other" in the summary table.

4.2.1 Subject disposition

The subject disposition for the screening period, ST+LT period, randomised withdrawal period and post-study visit Week 104 will be summarised:

- Disposition for the screening period will be based on the Enrolled Subjects Data Set (who signed informed consent), and will include the number of subjects enrolled, passed the screening period, discontinued from the screening period and a summary of the corresponding reasons for discontinuation. The number of rescreens and total number of times rescreened will also be presented for subjects who were rescreened.

- Disposition for the combined ST+LT treatment period will be based on the Randomised Subjects Data Set and will be presented by randomised treatment group and overall using overall treatment regimen and placebo. This summary will include subjects that entered the ST treatment period, completed the ST treatment period, discontinued from the study during the ST treatment period and reasons for study discontinuation, discontinued treatment during the ST treatment period and reasons for treatment discontinuation, subjects up-titration status, subjects that entered the LT treatment period, completed the LT treatment period, discontinued from the study during the LT treatment period and reasons for study discontinuation, discontinued treatment during the LT treatment period and reasons for treatment discontinuation, and subjects who completed the 56-week visit.
  In addition, for Week 104 follow-up CSR the summary will also include the number of subjects who continued into the post-term extension, completed the Week 104 visit, discontinued during the post-term extension.

- Disposition for the randomised withdrawal period will be based on the Randomised Withdrawal Subjects Data Set. This will be presented by randomised treatment group for the 1st and 3rd randomisations and overall. This summary will include the number of subjects who went through the 3rd randomisation, were randomised to withdrawal from Metformin, completed the randomised withdrawal period, discontinued from the randomised withdrawal period and a summary of the corresponding reasons for discontinuation, completed IP during the randomised withdrawal period, discontinued IP during the randomised withdrawal period and a summary of the corresponding reasons for IP discontinuation, and subjects who completed the 56-week visit.
- The number of subjects completing the study and who discontinued the study related to the global/country situation will be tabulated by discontinuation reason separately for the ST period, ST+LT period, and Week 104 follow-up period.

In addition, subjects from Randomised Subjects Data Set will be summarised by country and study site.

Subject disposition will also be listed by subject.

4.2.2 Global/country situation impact

An overall summary of the number and percentage of subjects in the study during the global/country situation will be provided using the Randomised Subjects Data Set, including:

- Subjects randomised prior to the start of the global/country situation (prior to 11 March 2020),
- Subjects who are no longer in the study at the start of the global/country situation (discontinued study or completed Week 104 visit),
- Subjects ongoing in the study at the start of the global/country situation,
  - Subjects in the ST+LT period (up to Week 56),
  - Subjects in the Week 104 follow-up period,

- Subjects randomised after the start of the global/country situation.

Furthermore, the number and percentage of subjects impacted by the global/country situation will be presented overall and by impact category (visit impacted, study drug impacted, drug accountability impacted, concomitant medication not started, withdrawal from study due to global/country situation).

Important protocol deviations that are related to the global/country situation will be summarised within the important protocol deviation table by deviation category. These will be identified using protocol deviations starting with the word "COVID".

In addition, to capture supplementary information on the global/country situation impact, details on visits impacted, concomitant medications not started, dispensation or returning of study medication kits, and exposure start dates that were impacted will be collected. Details on the global/country situation data will be listed by-subject using the Enrolled Subjects Data Set. This will be presented for the Week 56 CSR using all data up to Week 56 database lock and also for the Week 104 CSR addendum using all data up to Week 104 database lock.

4.2.3 Demographic and other baseline characteristics

Frequency distributions and summary statistics for demographics and baseline characteristics (age, sex, race, ethnicity, baseline body weight, normalised baseline body weight, baseline height, normalised baseline height, baseline BMI, normalised baseline BMI, and region), including diabetes-related characteristics (duration of type 2 diabetes, baseline HbA1c, baseline FPG, background antidiabetic medication, total daily dose of metformin and insulin, and baseline renal function [eGFR]) will be summarised by treatment group based on first randomisation and overall using the Randomised Subjects Data Set, the Up-titration Randomised Subjects Data Set, the Randomised Withdrawal Subjects Data Set and, if deemed necessary, the Evaluable Subjects Data Set. No statistical test will be carried out for comparison of demographics or baseline characteristics among the treatment groups.

Randomisation stratification factors (including age group, sex, and background antidiabetic medication) will be summarised by treatment group based on first randomisation and overall using the Randomised Subjects Data Set. A listing of differences between the stratification factors recorded on the IWRS and collected on the CRF will be presented. For age, only subjects with a complete date of birth collected will be compared.

4.2.4 Specific and general medical history

The number and percentage of subjects with general medical history findings and current medical conditions will be summarised by SOC and PT (sorted by decreasing frequency by SOC and PT based on the total group) by treatment group and overall using the Randomised Subjects Data Set. All medical history details will be listed.

4.2.5 Prior and concomitant medications

The number and percentage of subjects taking concomitant medications will be summarised for the ST and ST+LT periods by WHO DD ATC classification, generic term and treatment group

based on the Treated Subjects Data Set. Concomitant medications will be listed for the combined ST+LT period and in addition during the study. Prior medications will not be included in the summaries but will be included and identified in the medications listing.

Concomitant anti-diabetes medications will be recorded over the course of the study and will be included in concomitant medication summaries. These will also be summarised separately by insulin anti-diabetes concomitant medications and non-insulin anti-diabetes concomitant medications (as described in Section 3.5.3). A separate table will be presented for insulin anti-diabetes concomitant medications used as rescue medication.

In addition, a summary of disallowed medications (as defined in the protocol) will be provided for each period. Disallowed medications used concomitantly during the study will be flagged in the listings.

A summary of all concomitant medications started between Week 56 and Week 104 (regardless of protocol defined disallowed medications) will be provided.

Separate listings for the ST+LT period will be provided for background metformin and background insulin and a further listing will be provided for insulin as rescue medication.

4.3 Extent of exposure to study treatment

4.3.1 Extent of exposure to IP treatment

Extent of exposure to IP will be summarised (regardless of rescue medication initiation) using the Treated Subjects Data Set for the ST and ST+LT treatment periods, and the Randomised Withdrawal Subjects Data Set for the randomised withdrawal period. These summaries will be repeated for exposure prior to rescue medication initiation.

Extent of exposure is defined as last dose date - first dose date + 1, with the last dose date being the last dose of the concerned period. Extent of exposure (days) will be summarised by treatment group as a continuous variable as well as for pre-specified day ranges (ST period: 1-7, 8-14, 15-28, 29-42, 43-56, 57-70, 71-84, 85-98, 99-140, 141-182, > 182 days; ST+LT period: 1-90, 91-180, 181-270, 271-365, and > 365 days; randomised withdrawal period: 1-7, 8-14, 15-28, 29-42, 43-56, 57-70, 71-112, 113-154, > 154). In addition, the exposure in terms of total patient-years will be summarised by treatment group using the sum of the exposure to IP of all subjects (in years) in a treatment group.

Individual subject dosing and exposure to IP by study period will be listed.

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

4.3.2 Exposure to rescue medication

The maximal total daily dose (insulin units) will be summarised using the Treated Subjects Data Set for the for the ST, ST+LT periods, and the Randomised Withdrawal Subjects Data Set for the randomised withdrawal period. For the ST period, the summary will include all rescue medication used up to the start of the LT period. For the ST+LT period the summary will include

all rescue medication used up to the last day in the ST+LT period (irrespective of whether the subject had early discontinued IP treatment). For the randomised withdrawal period the summary will include all rescue medication used from the randomised withdrawal baseline up to the last day in the randomised withdrawal period (irrespective of whether the subject had early discontinued IP treatment). Rescue treatment details will be listed as described in Section 4.2.5.

In addition, the number and percentage of subjects initiating rescue medication prior to Week 12 by categorical HbA1c (< 7%, ≥ 7%) result at Week 12 will be summarised.

4.3.3 Compliance to IP treatment

Compliance to IP treatment will be summarised for the ST and ST+LT periods based on the Treated Subjects Data Set and for the randomised withdrawal period based on the Randomised Withdrawal Subjects Data Set, as the number and percentage of subjects with < 80%, ≥ 80% and ≤ 120%, and > 120% compliance. Study treatment compliance by subject and study period will be included in the corresponding listings for exposure to IP treatment.

4.4 Primary efficacy endpoint analysis

4.4.1 Primary analysis of the primary endpoint

The primary efficacy analysis will compare the mean reduction in HbA1c from baseline at Week 26 between overall drug treatment (low-dose and high-dose) and placebo. The ITT estimand (which will be estimated using data regardless of premature treatment discontinuation, regardless of rescue medication initiation and with multiple imputation) will be evaluated as the primary estimand.

Listings of HbA1c and FPG results used for the efficacy analysis will be presented with flags to identify data collected prior to rescue medication initiation or treatment discontinuation.

The primary efficacy analysis will be performed using an ANCOVA model, as described in Section 4.1.9. Separate models will be used for dapagliflozin and saxagliptin analyses, and each analysis will include the (common) placebo control. Each model will have terms for baseline HbA1c value, treatment group, and randomisation strata variables (age group, sex and background medication). Missing values for Week 26 will be imputed using multiple imputation method assuming the data are not missing at random. No weights will be used in the multiple imputation or ANCOVA for this analysis.

An overview of the analysis steps are as follows:

i) Impute missing Week 26 HbA1c data using multiple imputation (as described in Section 4.1.12).
ii) Analyse data by applying the ANCOVA model (described in Section 4.1.9) in each of the imputed data sets to calculate the LS means and corresponding SEs for the adjusted mean changes within each treatment group as well as for the differences in adjusted mean changes

between treatment groups. If any stratification variables in the imputation model are collapsed, then the ANCOVA model will be collapsed correspondingly.

iii) Combine point estimates and SEs using Rubin's rules (as per Section 4.1.12.4) to produce valid global estimates with corresponding p-values and CIs.

Combined LS means and 95% confidence intervals for the mean change in HbA1c for each treatment group as well as the difference in the estimated mean change between the dapagliflozin/saxagliptin treatment group and placebo will be calculated. The p-value of the difference in Week 26 estimates between dapagliflozin/saxagliptin and placebo will be presented.

Both the MI-RD and wash-out imputation methods will be presented for the primary endpoint. If all of the imputation models have at least 5 observations, then MI-RD will be the primary analysis and wash-out will be the sensitivity analysis. Conversely, if any of the imputation models have less than 5 observations, then wash-out will be the primary analysis and MI-RD will be the sensitivity analysis. A summary of the number and percentage of subjects who were retrieved drop-outs will be presented by visit for the ST period for both HbA1c and FPG.

4.4.2 Sensitivity analysis for primary endpoint

4.4.2.1 Analysis excluding data following rescue medication initiation/early treatment discontinuation

To assess the robustness of the primary efficacy analysis for the primary endpoint of the change in HbA1c from baseline to Week 26, an additional sensitivity analysis will be performed excluding data following rescue medication initiation or early discontinuation of treatment (i.e., those data will be considered missing and will be imputed together with other missing Week 26 data). This analysis will be performed as for the primary analysis of the primary endpoint but changing the method of imputation as described below.

Multiple imputation for this sensitivity analysis will assume MAR within each treatment regimen. This means that the distribution of missing data in subjects who discontinued treatment early or who used rescue medication prior to Week 26 will be imputed based on data from other subjects in the same treatment regimen who completed the ST treatment and did not use rescue during the ST period.

The following two steps will be used:

- Step 1: Prior to imputation, the MCMC method will be used as described in Section 4.1.12.1. The imputation model with include factors and covariates in the following order: indicators of randomisation strata and baseline HbA1c as well as Week 6, Week 12, Week 20 and Week 26 HbA1c.
- Step 2: Using the monotone datasets generated as described above, impute missing Week 26 HbA1c data using multiple imputation under MAR hypothesis (as described in Section 4.1.12.5).

Dummy coding of categorical variables will be implemented prior to imputation as described in Section 4.1.12.

Downstream steps (analysis of each imputed data set using the ANCOVA model described in Section 4.1.9, and combining results as described in Section 4.1.12.4) will be performed as for the primary analysis.

4.4.2.2 Analysis based on Evaluable Subjects Data Set

To assess the robustness of the primary efficacy analysis for the primary endpoint of the change in HbA1c from baseline to Week 26, an additional sensitivity analysis using the same approach as the sensitivity efficacy analysis in Section 4.4.2.1 may be performed using the Evaluable Subjects Data Set if greater than 10% of the subjects for any treatment group or placebo in the Randomised Subjects Data Set have relevant protocol deviations. For this analysis all HbA1c collected after relevant protocol deviations onset or after rescue medication initiation/early discontinuation of treatment will be set to missing prior to multiple imputation process. An ANCOVA model will be used for this analysis.

4.4.2.3 Missing data patterns

The pattern of missing data for the primary endpoint will be provided (as produced by PROC MI in SAS). This summary arranges the response data (in this case HbA1c) into "patterns" (for example, the number and percentage of subjects with no missing data at any visit, or with missing data only for the last visit, or with missing data for the last two visits, and so on) regardless of/excluding values after rescue medication initiation or premature end of study medication, by treatment group. This also provides mean HbA1c by missing data pattern.

In addition, descriptions of missing HbA1c as well as HbA1c data collected following rescue medication initiation or discontinuation study medication will include a description per visit by treatment group during the short-term period of:

- the cumulative number of subjects who discontinued study medication,
- the cumulative number of subjects who discontinued study medication but still on study,
- the cumulative number of subjects rescued,
- the cumulative number of subjects rescued but still on study,
- the cumulative number of subjects rescued or who discontinued study medication,
- the cumulative number of subjects rescued or who discontinued study medication but still on study,
    - the number of subjects rescued or who discontinued study medication but still having a Week t HbA1c value,
    - the number of subjects rescued or who discontinued study medication and missing Week t HbA1c value,

- the cumulative number of subjects withdrawn from study,
- the number of subjects still on treatment, still on study, not rescued but who missed a given visit,
- the number of subjects missing Week t HbA1c value,
- a graphical summary presenting the monotone missing data pattern from baseline to Week 26 presenting HbA1c values regardless of rescue medication initiation as well as presenting HbA1c values collected prior to rescue medication initiation or discontinuation of study medication by treatment group, along with a corresponding summary table.

4.4.2.4 Tipping point analysis

To assess the robustness of the primary efficacy analysis for the primary endpoint of the change in HbA1c from baseline to Week 26, an additional sensitivity analysis using a tipping point will be performed at Week 26 as described in Section 4.1.12.6 for the same ANCOVA model used for the primary analysis (Section 4.4.1).

4.4.3 Subgroup analyses for primary endpoint

4.4.3.1 Analysis of change from baseline in HbA1c at Week 26 within subgroups

The subgroup-by-treatment interaction will be assessed for the primary efficacy endpoint using the MI-WO imputation method and the ANCOVA model used for the primary analysis of the change from baseline in HbA1c at Week 26 with subgroup, and subgroup-by-treatment interaction as additional effects. Separate imputation models for each subgroup will be used. This will be repeated for subgroups based on race, ethnicity, sex, age group (using randomisation strata), region, baseline antidiabetic treatment, baseline HbA1c, and baseline BMI, using the categories defined in the Appendix (Table 19). The adjusted mean changes from baseline, SEs, 95% CIs, and p-value for each subgroup and the nominal p-value for subgroup by treatment interaction will be calculated.

The subgroup by treatment interaction p-value will be calculated as the median p-value from the set of all imputations.

Models for subgroup analyses which evaluate baseline HbA1c level will include terms for the categorised baseline HbA1c level and not (continuous) baseline values.

Statistical significance of a Week 26 treatment regimen*subgroup interaction will be assessed at an unadjusted 0.10 level.

In addition, a forest plot of adjusted mean difference from placebo ± 95% confidence interval (CI), p-values for each subgroup category and p-value for interaction by subgroup will be displayed.

Subjects with missing data for the grouping variable will be excluded from the corresponding subgroup analysis. For each subgroup, if, in any treatment group, the number of subjects is less than 10 for a subgroup category, adjusted estimates and their differences and corresponding

statistics will not be displayed for that subgroup, and only descriptive statistics will be presented for that category and included in the analysis results. Interaction p-value will not be provided either.

For baseline antidiabetic treatment subgroup, if the number of subjects within 'insulin only' or 'metformin + insulin' category is less than 10, then these two categories will be grouped into 'insulin +/- metformin'. In case of non-convergence because of sparse data, subsequent backup imputation models will be used collapsing the randomisation strata of background medication as defined in Section 4.1 and collapsing the region into 'North America + Europe' and 'Rest of the World'.

4.4.3.2 Metformin subgroup analysis for primary analysis of change from baseline in HbA1c at Week 26

The ANCOVA model used for the primary analysis (Section 4.4.1) of the change from baseline in HbA1c at Week 26 will also be repeated for the subgroup of subjects on a stable baseline dose of metformin IR or XR (with or without insulin). The same multiple imputation method used for the primary analysis of the endpoint will be used for this subgroup analysis. The indicator for background medication used in the multiple imputation step for insulin only and insulin with metformin will be grouped as defined in Section 4.1.12.

4.4.4 Other analyses for primary endpoint

4.4.4.1 Analysis of change from baseline in HbA1c at Week 6, Week 12, and Week 20

Additional analyses for change from baseline in HbA1c will be performed at Week 6, Week 12 and Week 20. Data will be multiply imputed based on the same approach as described for the primary analysis in Section 4.4.1, and will include all data regardless of rescue medication initiation or adherence. Analysis will be based on the same multiply imputed data sets produced for the primary analysis of the primary endpoint. Analysis will be performed by fitting the ANCOVA model described for the primary endpoint in Section 4.1.9. The analysis model will be evaluated in each imputed data set and the results will be combined using Rubin's rules as described in Section 4.1.12.4 for each visit.

In addition, a line plot of LS mean ± 95% confidence interval (CI) by visit up to Week 26 will be displayed.

4.5 Secondary efficacy endpoint analysis

4.5.1 Hierarchical Testing

Secondary efficacy endpoint analyses will also be performed separately for each drug (dapagliflozin and saxagliptin). For each drug, the following sequential testing order will be employed to control multiplicity of testing for the secondary objectives at a family-wise Type I error rate of 0.05 (2-sided). For each grouping of endpoints, for example for all reduction in HbA1c/FPG from baseline endpoints for the Randomised Subjects Data Set, for each treatment (dapagliflozin and saxagliptin) the same multiple imputation method will be used.

1. Comparison of mean reduction in HbA1c from baseline at Week 26 between the low-dose/high-dose treatment regimen and placebo

2. Comparison of mean reduction in HbA1c from baseline at Week 26 between the low-dose treatment regimen and placebo

3. Comparison of mean reduction in FPG from baseline at Week 26 between overall drug treatment and placebo

4. Comparison of mean reduction in FPG from baseline at Week 26 between the low-dose/high-dose treatment regimen and placebo

5. Comparison of mean reduction in FPG from baseline at Week 26 between the low-dose treatment regimen and placebo

6. Comparison of the percentage of subjects with baseline HbA1c $\geq$ 7% who achieve an HbA1c level < 7% at Week 26 between overall drug treatment and placebo

7. Comparison of the percentage of subjects with baseline HbA1c $\geq$ 7% who achieve an HbA1c level < 7% at Week 26 between the low-dose/high-dose treatment regimen and placebo

8. Comparison of the percentage of subjects with baseline HbA1c $\geq$ 7% who achieve an HbA1c level < 7% at Week 26 between the low-dose treatment regimen and placebo

9. Comparison of mean reduction in HbA1c from baseline at Week 26 between the high-dose and the low-dose in subjects who do not achieve an HbA1c < 7% at Week 12

10. Comparison of mean reduction in FPG from baseline at Week 26 between the high-dose and the low-dose in subjects who do not achieve an HbA1c < 7% at Week 12

11. Comparison of the percentage of subjects with baseline HbA1c $\geq$ 7% who achieve an HbA1c level < 7% at Week 26 between the high-dose and the low-dose in subjects who do not achieve an HbA1c < 7% at Week 12

For each drug (dapagliflozin or saxagliptin) if the primary endpoint is significant, the statistical tests will be formally evaluated, starting from the first secondary efficacy endpoint and continuing in the order above. Each secondary endpoint for a given drug will be tested if the previous secondary endpoint is significant at the two-sided 0.05 level. The testing procedure will stop at the first secondary endpoint that does not reach statistical significance. From then onwards, p-values and CIs will continue to be reported, but no claim will be based these p-values. A clear distinction will be made between p-values whereby claims can and cannot be made.

Hierarchical testing of the primary and secondary efficacy endpoints will be presented for either the Randomised Subjects Data Set or Up-titration Randomised Subjects Data Set (as applicable per endpoint). Point estimates, 95% CIs and p-values will be summarised.

4.5.2 Comparison of mean reduction in HbA1c from baseline at Week 26 between the low-dose/high-dose treatment regimen and placebo

Data will be multiply imputed based on the same approach as described for the primary analysis of the primary endpoint in Section 4.4.1 at all scheduled time points up to and including Week 26, and will include all data regardless of rescue medication initiation or adherence. Analysis will be performed by fitting the weighted ANCOVA model described in Section 4.1.9. The analysis model will be evaluated in each imputed data set and the results will be combined using Rubin's rules as described in Section 4.1.12.4.

The weight matrix W1 described in Section 4.1.9 for the comparison of the low-dose/high-dose treatment regimen versus placebo will be used for this analysis.

In addition, a line plot of LS mean ± 95% confidence interval (CI) by visit up to Week 26 will be displayed.

4.5.2.1 Sensitivity analysis for secondary endpoint of change from baseline in HbA1c at Week 26 between the low-dose/high-dose treatment regimen and placebo excluding data following rescue medication initiation/early treatment discontinuation

The above primary analysis (Section 4.5.2) for the comparison of mean reduction in HbA1c from baseline at Week 26 between the low-dose/high-dose treatment regimen and placebo will be repeated excluding data following rescue medication initiation or early treatment discontinuation but missing data will be imputed assuming MAR as described in Section 4.1.12.5. A weighted ANCOVA model will be used for this analysis.

4.5.2.2 Subgroup analysis for secondary endpoint of change from baseline in HbA1c at Week 26 between the low-dose/high-dose treatment regimen and placebo

The above primary analysis (Section 4.5.2) for the comparison of mean reduction in HbA1c from baseline at Week 26 between the low-dose/high-dose treatment regimen and placebo will be repeated for subgroups based on race, ethnicity, sex, age group (using randomisation strata), region, baseline antidiabetic treatment, baseline HbA1c and baseline BMI, using the categories defined in the Appendix (Table 19) and will follow the same approach as the one described in Section 4.4.3.1 using a weighted ANCOVA model.

4.5.2.3 Metformin subgroup analysis for primary analysis of secondary endpoint of change from baseline in HbA1c at Week 26 between the low-dose/high-dose treatment regimen and placebo

The weighted ANCOVA model used for the primary analysis (Section 4.5.2) of the change from baseline in HbA1c at Week 26 will also be repeated for the subgroup of subjects on a stable baseline dose of metformin IR or XR (with or without insulin). The same multiple imputation method used for the primary analysis of the endpoint will be used for this subgroup analysis. The indicator for background medication used in the multiple imputation step for insulin only and insulin with metformin will be grouped as defined in Section 4.1.12.

4.5.3 Comparison of mean reduction in HbA1c from baseline at Week 26 between the low-dose treatment regimen and placebo

Data will be multiply imputed based on the same approach as described for the primary analysis of the primary endpoint in Section 4.4.1 at all scheduled time points up to and including Week 26, and will include all data regardless of rescue medication initiation or adherence. Analysis will be performed by fitting the weighted ANCOVA model described in Section 4.1.9 in each of the imputed data sets and combining the results using Rubin's rules, as described in Section 4.1.12.4. The weight matrix W2 described in Section 4.1.9 for the comparison of the low-dose treatment regimen versus placebo will be used for this analysis.

4.5.3.1 Sensitivity analysis for secondary endpoint of mean reduction in HbA1c from baseline at Week 26 between the low-dose treatment regimen and placebo excluding data following rescue medication initiation/early treatment discontinuation

The above primary analysis (Section 4.5.3) for the comparison of mean reduction in HbA1c from baseline at Week 26 between the low-dose treatment regimen and placebo will be repeated excluding data following rescue medication initiation or early treatment discontinuation but missing data will be imputed assuming MAR as described in Section 4.1.12.5.

4.5.3.2 Metformin subgroup analysis for secondary endpoint of change from baseline in HbA1c at Week 26 between the low-dose treatment regimen and placebo

The weighted ANCOVA model used for the primary analysis (Section 4.5.3) for the change from baseline in HbA1c at Week 26 will also be repeated for the subgroup of subjects on a stable baseline dose of metformin IR or XR (with or without insulin). The same multiple imputation method used for the primary analysis of the endpoint will be used for this subgroup analysis. The indicator for background medication used in the multiple imputation step for insulin only and insulin with metformin will be grouped as defined in Section 4.1.12.

4.5.4 Comparison of mean reduction in FPG from baseline at Week 26 between overall drug treatment and placebo

Data will be multiply imputed based on the same approach as described for the primary analysis of the primary endpoint in Section 4.4.1 at all scheduled time points up to and including Week 26, replacing HbA1c with FPG, and will include all data regardless of rescue medication initiation or adherence. Only FPG assessments documented with the subject in a fasting state will be summarised and listed. Analysis will be performed by fitting the ANCOVA model described for the primary analysis of the primary endpoint in Section 4.4.1 (replacing HbA1c with FPG). The analysis model will be evaluated in each imputed data set and the results will be combined using Rubin's rules as described in Section 4.1.12.4. No weights will be used in the multiple imputation or ANCOVA for this analysis.

In addition, a line plot of LS mean ± 95% confidence interval (CI) by visit up to Week 26 will be displayed.

4.5.4.1 Sensitivity analysis for secondary endpoint of mean reduction in FPG from baseline at Week 26 between overall drug treatment and placebo excluding data following rescue medication initiation/early treatment discontinuation

The above primary analysis (Section 4.5.4) for the comparison of mean reduction in FPG from baseline at Week 26 between overall drug treatment (low-dose and high-dose) and placebo will be repeated excluding data following rescue medication initiation or early treatment discontinuation but missing data will be imputed assuming MAR as described in Section 4.1.12.5.

4.5.4.2 Metformin subgroup analysis for comparison of mean reduction in FPG from baseline at Week 26 between overall drug treatment and placebo

The ANCOVA model used for the primary FPG analysis (Section 4.5.4) of the change from baseline in FPG at Week 26 between overall drug treatment and placebo will also be repeated for the subgroup of subjects on a stable baseline dose of metformin IR or XR (with or without insulin). The same multiple imputation method used for the primary analysis of the endpoint will be used for this subgroup analysis. The indicator for background medication used in the multiple imputation step for insulin only and insulin with metformin will be grouped as defined in Section 4.1.12. No weights will be used in the multiple imputation or ANCOVA for this analysis.

4.5.4.3 Missing data patterns

A summary of missing FPG as well as FPG data collected following rescue medication initiation or discontinuation study medication will be presented for the short-term period, as described in Section 4.4.2.3.

4.5.5 Comparison of mean reduction in FPG from baseline at Week 26 between the low-dose/high-dose treatment regimen and placebo

Data will be multiply imputed based on the same approach as described for the primary analysis in Section 4.4.1 at all scheduled time points up to and including Week 26, replacing HbA1c with FPG, and will include all data regardless of rescue medication initiation or adherence. Analysis will be performed by fitting the weighted ANCOVA model described in Section 4.1.9(replacing HbA1c with FPG). The analysis model will be evaluated in each imputed data set and the results will be combined using Rubin's rules as described in Section 4.1.12.4. The weight matrix W1 described in Section 4.1.9 for the comparison of the low-dose/high-dose treatment regimen versus placebo will be used for this analysis.

In addition, a line plot of LS mean ± 95% confidence interval (CI) by visit up to Week 26 will be displayed.

4.5.5.1 Sensitivity analysis for secondary endpoint of mean reduction in FPG from baseline at Week 26 between the low-dose/high-dose treatment regimen and

placebo excluding data following rescue medication initiation/early treatment discontinuation

The above primary analysis (Section 4.5.5) for the comparison of mean reduction in FPG from baseline at Week 26 between the low-dose/high-dose treatment regimen and placebo will be repeated excluding data following rescue medication initiation or early treatment discontinuation but missing data will be imputed assuming MAR as described in Section 4.1.12.5. A weighted ANCOVA model will be used for this analysis.

4.5.6 Comparison of mean reduction in FPG from baseline at Week 26 between the low-dose treatment regimen and placebo

Data will be multiply imputed based on the same approach as described for the primary analysis of the primary endpoint in Section 4.4.1 at all scheduled time points up to and including Week 26, between the low-dose treatment regimen and placebo, replacing HbA1c with FPG, and will include all data regardless of rescue medication initiation or adherence. Analysis will be performed by fitting the weighted ANCOVA model described in Section 4.1.9 (replacing HbA1c with FPG). The weight matrix W2 described in Section 4.1.9 for the comparison of the low-dose treatment regimen versus placebo will be used for this analysis. The analysis model will be evaluated in each imputed data set and the results will be combined using Rubin's rules as described in Section 4.1.12.4.

4.5.6.1 Sensitivity analysis for secondary endpoint of mean reduction in FPG from baseline at Week 26 between the low-dose treatment regimen and placebo excluding data following rescue medication initiation/early treatment discontinuation

The above primary FPG analysis (Section 4.5.6) for the comparison of mean reduction in FPG from baseline at Week 26 between the low-dose treatment regimen and placebo will be repeated excluding data following rescue medication initiation or early treatment discontinuation, but missing data will be imputed assuming MAR as described in Section 4.1.12.5.

4.5.7 Comparison of the percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% at Week 26 between overall drug treatment and placebo

Data will be multiply imputed based on the same approach as described for the primary analysis of the primary endpoint in Section 4.4.1, and will include all data regardless of rescue medication initiation or adherence. HbA1c response (< 7%) will be derived from dichotomising the imputed continuous values of HbA1c.

The proportion of responders (subjects achieving an HbA1c < 7% at Week 26) will be analysed using logistic regression and summarised as described in Section 4.1.10. No weights will be used in the multiple imputation or logistic regression for this analysis.

4.5.7.1 Sensitivity analysis for secondary endpoint of percentage of subjects who achieve an HbA1c level < 7% at Week 26 between overall drug treatment and placebo

The above primary analysis (Section 4.5.7) of the percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% at Week 26 between overall drug treatment (low-dose and high-dose) and placebo will be repeated with the difference that subjects with any baseline HbA1c value will be used. A logistic regression model will be used for this analysis.

4.5.7.2 Metformin subgroup analysis for comparison of percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% at Week 26 between overall drug treatment and placebo

The logistic regression model used for the primary analysis (Section 4.5.7) of the percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% at Week 26 between overall drug treatment (low-dose and high-dose) and placebo will also be repeated for the subgroup of subjects on a stable baseline dose of metformin IR or XR (with or without insulin). The same multiple imputation method used for the primary analysis of the endpoint will be used for this subgroup analysis. The indicator for background medication used in the multiple imputation step for insulin only and insulin with metformin will be grouped as defined in Section 4.1.12.

4.5.8 Comparison of the percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% at Week 26 between the low-dose/high-dose treatment regimen and placebo

Data will be multiply imputed based on the same approach as described for the primary analysis of the primary endpoint in Section 4.4.1, and will include all data regardless of rescue medication initiation or adherence. HbA1c response (< 7%) will be derived from dichotomising the imputed continuous values of HbA1c and Rubin's rules will be used to combine analyses across the multiple imputations. Estimates will be derived from a weighted logistic regression or Fisher's exact test (as appropriate) and combined as described in Section 4.1.12.4. The weight matrix W1 (described in Section 4.1.9) for the comparison of the low-dose/high-dose treatment regimen versus placebo will be used for this analysis.

4.5.8.1 Sensitivity analysis for secondary endpoint of percentage of subjects who achieve an HbA1c level < 7% at Week 26 between the low-dose/high-dose treatment regimen and placebo

The above primary analysis (Section 4.5.8) of percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% at Week 26 between the low-dose/high-dose treatment regimen and placebo will be repeated with no restriction on baseline HbA1c values. A weighted logistic model will be used for this analysis.

4.5.8.2 Metformin subgroup analysis for comparison of percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% at Week 26 between the low-dose/high-dose treatment regimen and placebo

The weighted logistic regression model used for the primary analysis (Section 4.5.8) of the percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% at Week 26 between the low-dose/high-dose treatment regimen and placebo will also be repeated for the subgroup of subjects on a stable baseline dose of metformin IR or XR (with or without insulin). The same multiple imputation method used for the primary analysis of the endpoint will be used for this subgroup analysis. The indicator for background medication used in the multiple imputation step for insulin only and insulin with metformin will be grouped as defined in Section 4.1.12.

4.5.9 Comparison of the percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% at Week 26 between the low-dose treatment regimen and placebo

Data will be multiply imputed based on the same approach as described for the primary analysis of the primary endpoint in Section 4.4.1, between the low-dose treatment regimen and placebo, and will include all data regardless of rescue medication initiation or adherence. HbA1c response (< 7%) will be derived from dichotomising the imputed continuous values of HbA1c and Rubin's rules will be used to combine analyses across the multiple imputations. Estimates will be derived from logistic regression or Fisher's exact test (as appropriate) and combined as described in Section 4.1.12.4. The weight matrix W2 described in Section 4.1.9 for the comparison of the low-dose treatment regimen versus placebo will be used for this analysis.

4.5.9.1 Sensitivity analysis for secondary endpoint of percentage of subjects who achieve an HbA1c level < 7% at Week 26 between the low-dose treatment regimen and placebo

The above analysis (Section 4.5.9) of percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% at Week 26 between the low-dose treatment regimen and placebo will be repeated with no restriction on baseline HbA1c values.

4.5.9.2 Metformin subgroup analysis for comparison of percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% at Week 26 between the low-dose treatment regimen and placebo

The weighted logistic regression model used for the primary analysis (Section 4.5.9) of the percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% at Week 26 between the low-dose treatment regimen and placebo will also be repeated for the subgroup of subjects on a stable baseline dose of metformin IR or XR (with or without insulin). The same multiple imputation method used for the primary analysis of the endpoint will be used for this subgroup analysis. The indicator for background medication used in the multiple imputation step for insulin only and insulin with metformin will be grouped as defined in Section 4.1.12.

4.5.10 Comparison of mean reduction in HbA1c from baseline at Week 26 between the high-dose and the low-dose in subjects who do not achieve an HbA1c < 7% at Week 12

Analysis will be based on the Up-titration Randomised Subjects Data Set and further restricted to subjects on dapagliflozin (or saxagliptin) who had HbA1c ≥ 7% at Week 12 and will include all data regardless of rescue medication initiation or adherence. Missing data in values of HbA1c at Week 26 will be imputed using the multiple imputation approach described in Section 4.1.12. If the MI-WO method is used, Placebo subjects from the Randomised subjects data set will be used in the imputation models to impute missing values for active treatment subjects in the Up-titration randomised subjects data set.

Change from baseline HbA1c at all scheduled time points up to and including Week 26will be compared between the subjects who are Up-titration Randomised to remain on the low-dose and the subjects who are up-titration randomised to the high-dose using the ANCOVA model described in Section 4.1.9, without weights. The analysis will be evaluated in each imputed data set and the results will be combined using Rubin's rules as described in Section 4.1.12.4. The indicator for background medication used in the multiple imputation step for insulin only and insulin with metformin will be grouped as defined in Section 4.1.12. No weights will be used in the multiple imputation or ANCOVA for this analysis.

4.5.10.1 Sensitivity analysis for secondary endpoint of mean reduction in HbA1c from baseline at Week 26 between the high-dose and the low-dose in subjects who do not achieve an HbA1c < 7% at Week 12 excluding data following rescue medication initiation/early treatment discontinuation

The above analysis (Section 4.5.10) for the comparison of mean reduction in HbA1c from baseline at Week 26 between the high-dose and the low-dose in subjects who do not achieve an HbA1c < 7% at Week 12 will be repeated excluding data following rescue medication initiation or early treatment discontinuation but missing data will be imputed assuming MAR as described in Section 4.1.12.5. No weights will be used in the multiple imputation or ANCOVA for this analysis.

4.5.10.2 Metformin subgroup analysis for comparison of mean reduction in HbA1c from baseline at Week 26 between the high-dose and the low-dose in subjects who do not achieve an HbA1c < 7% at Week 12

The ANCOVA model used for the primary analysis (Section 4.5.10) of the mean reduction in HbA1c from baseline at Week 26 between the high-dose and the low-dose in subjects who do not achieve an HbA1c < 7% at Week 12 will also be repeated for the subgroup of subjects on a stable baseline dose of metformin IR or XR (with or without insulin). The same multiple imputation method used for the primary analysis of the endpoint will be used for this subgroup analysis. The indicator for background medication used in the multiple imputation step for insulin only and insulin with metformin will be grouped as defined in Section 4.1.12. No weights will be used in the multiple imputation or ANCOVA for this analysis.

4.5.11 Comparison of mean reduction in FPG from baseline at Week 26 between the high-dose and the low-dose in subjects who do not achieve an HbA1c < 7% at Week 12

Analysis will be based on the Up-titration Randomised Subjects Data Set and further restricted to subjects on dapagliflozin (or saxagliptin) who had HbA1c ≥ 7% at Week 12 and will include all data regardless of rescue medication initiation or adherence. Missing data in values of FPG at Week 26 will be imputed using the multiple imputation approach described in Section 4.1.12. If the MI-WO method is used, Placebo subjects from the Randomised subjects data set will be used in the imputation models to impute missing values for active treatment subjects in the Up-titration randomised subjects data set.

Change from baseline FPG at all scheduled time points up to and including Week 26will be compared between the subjects who are Up-titration Randomised to remain on the low-dose and the subjects who are Up-titration Randomised to the high-dose using the ANCOVA model described in Section 4.1.9, without weights. The analysis will be evaluated in each imputed data set and the results will be combined using Rubin's rules as described in Section 4.1.12.4. No weights will be used in the multiple imputation or ANCOVA for this analysis.

4.5.11.1 Sensitivity analysis for secondary endpoint of mean reduction in FPG from baseline at Week 26 between the high-dose and the low-dose in subjects who do not achieve an HbA1c < 7% at Week 12 excluding data following rescue medication initiation/early treatment discontinuation

The above primary analysis (Section 4.5.11) for the comparison of mean reduction in FPG from baseline at Week 26 between the high-dose and the low-dose in subjects who do not achieve an HbA1c < 7% at Week 12 will be repeated excluding data following rescue medication initiation or early treatment discontinuation but missing data will be imputed assuming MAR as described in Section 4.1.12.5. The indicator for background medication used in the multiple imputation step for insulin only and insulin with metformin will be grouped as defined in Section 4.1.12. No weights will be used in the multiple imputation or ANCOVA for this analysis.

4.5.11.2 Metformin subgroup analysis for comparison of mean reduction in FPG from baseline at Week 26 between the high-dose and the low-dose in subjects who do not achieve an HbA1c < 7% at Week 12

The ANCOVA model used for the primary analysis (Section 4.5.11) of the mean reduction in FPG from baseline at Week 26 between the high-dose and the low-dose in subjects who do not achieve an HbA1c < 7% at Week 12 will also be repeated for the subgroup of subjects on a stable baseline dose of metformin IR or XR (with or without insulin). The same multiple imputation method used for the primary analysis of the endpoint will be used for this subgroup analysis. The indicator for background medication used in the multiple imputation step for insulin only and insulin with metformin will be grouped as defined in Section 4.1.12. No weights will be used in the multiple imputation or ANCOVA for this analysis.

4.5.12 Comparison of the percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% at Week 26 between the high-dose and the low-dose in subjects who do not achieve an HbA1c < 7% at Week 12

Analysis will be based on the Up-titration Randomised Subjects Data Set, further restricted to subjects on dapagliflozin (or saxagliptin) who had HbA1c ≥ 7% at Week 12 and will include all data regardless of rescue medication initiation or adherence. Missing data in values of HbA1c at Week 26 will be imputed using the multiple imputation approach described in Section 4.1.12. If the MI-WO method is used, Placebo subjects from the Randomised subjects data set will be used in the imputation models to impute missing values for active treatment subjects in the Up-titration randomised subjects data set.

HbA1c response (< 7%) will be derived from dichotomising the imputed continuous values of HbA1c. Estimates will be derived from logistic regression or Fisher's exact test (as appropriate) and combined as described in Section 4.1.12.4. No weights will be used in the multiple imputation or logistic regression for this analysis.

4.5.12.1 Metformin subgroup analysis for comparison of the percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% at Week 26 between the high-dose and the low-dose in subjects who do not achieve an HbA1c < 7% at Week 12

The logistic regression model used for the primary analysis (Section 4.5.12) of the percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% at Week 26 between the high-dose and the low-dose in subjects who do not achieve an HbA1c < 7% at Week 12 will also be repeated for the subgroup of subjects on a stable baseline dose of metformin IR or XR (with or without insulin). The same multiple imputation method used for the primary analysis of the endpoint will be used for this subgroup analysis. The indicator for background medication used in the multiple imputation step for insulin only and insulin with metformin will be grouped as defined in Section 4.1.12. No weights will be used in the multiple imputation or logistic regression for this analysis.

4.6 Exploratory efficacy analyses

Exploratory endpoints will not be statistically tested. As with the primary and secondary efficacy analyses, separate models will be used for dapagliflozin and saxagliptin analyses, and each analysis will include the (common) placebo group. Exploratory analyses will be performed for overall dapagliflozin and overall saxagliptin separately, by combining all treatment groups (low-dose and high-dose).

Details are provided below.

4.6.1 Exploratory efficacy endpoints for short-term period

These analyses will be conducted on the Randomised Subjects Data Set and the comparisons will be between overall dapagliflozin (or saxagliptin) and placebo.

4.6.1.1 Analysis of subjects requiring glycaemic rescue medication or discontinuing study medication due to lack of efficacy

The proportion of subjects requiring glycaemic rescue medication or discontinuing study medication due to lack of efficacy at or prior to Week 26 will be analysed between overall drug treatment (low-dose and high-dose) and placebo using a logistic regression.

This will be analysed using a logistic regression and summarised as described in Section 4.1.10. No weights will be used in the logistic regression for this analysis.

In addition, this analysis will be repeated for the subgroup of subjects on a stable baseline dose of metformin IR or XR (with or without insulin).

4.6.1.2 Time to glycaemic rescue medication or discontinuation of study medication due to lack of efficacy

A time-to-event analysis (where event is first use of rescue medication or discontinuation of study medication due to lack of efficacy, whichever is earlier) during the 26-week treatment period will be analysed using a Cox proportional hazards model as described in Section 4.1.11. Estimates of the hazard ratio and 95% CI will be provided.

In addition, an analysis based on Kaplan-Meier estimates will be calculated and 95% CIs and nominal p-value from a pairwise log rank test will be presented.

Rules for censoring are described in Section 4.1.11.

In addition, both analyses will be repeated for the subgroup of subjects on a stable baseline dose of metformin IR or XR (with or without insulin). No Kaplan-Meier plot will be presented for the subgroup analysis.

4.6.1.3 Percentage of subjects who initiate glycaemic rescue medication

The number and percentage of subjects who require glycaemic rescue medication during the 26-week treatment period will be provided.

In addition, this analysis will be repeated for the subgroup of subjects on a stable baseline dose of metformin IR or XR (with or without insulin).

4.6.2 Exploratory efficacy endpoints for short-term and long-term period

These analyses will be conducted on the Randomised Subjects Data Set and the comparisons will be between overall dapagliflozin (or saxagliptin) and placebo.

These analyses will first be presented without considering the third randomisation, i.e. including all subject's data up to Week 52 or last visit (if earlier than Week 52). Then, to account for the randomised withdrawal of background metformin at Week 32 or Week 40, additional analyses will be performed:

- Additional weighted analyses of change in HbA1c, FPG, and the percentage of subjects with HbA1c < 7% will be performed excluding subjects randomised to withdraw from

metformin (Sections 4.6.2.1 and 4.6.2.2). For the weighted analyses, dapagliflozin (or saxagliptin) subjects who went through the third randomisation and withdrew metformin will be assigned a weight of 0, and those randomised to stay on metformin will be assigned a weight of 2. All other dapagliflozin (or saxagliptin) subjects will be assigned a weight of 1. Placebo subjects randomised to withdraw metformin and switch to active treatment will be assigned a weight of 0. Placebo subjects randomised to stay on metformin will be assigned a weight of 3. All other placebo subjects will be assigned a weight of 1. For this analysis, subjects with a weight of 0 will be excluded from the summary statistics, multiple imputation steps, and ANCOVA/logistic regression model.

4.6.2.1 Analysis of change from baseline at Week 52 in HbA1c and FPG

Change from baseline at Week 52 in HbA1c and, separately, FPG will be analysed using the ANCOVA model described in Section 4.1.9. This analysis includes all data regardless of rescue medication initiation or adherence. The analysis will be evaluated in each imputed data set and the results will be combined using Rubin's rules as described in Section 4.1.12.4. Missing data in values of HbA1c at Week 52 will be imputed using the multiple imputation approach described in Section 4.1.12. Point estimates and 2-sided 95% CIs for the mean change within each treatment group, as well as the difference in mean change between each drug and placebo will be calculated. Nominal p-values will be presented. No weights will be used in the multiple imputation or ANCOVA for this analysis.

Additional analyses for change from baseline in HbA1c and FPG will be performed at Week 6, Week 12, Week 20, Week 26, Week 32 and Week 40. Data will be multiply imputed based on the same approach as described for the in Section 4.5.4, and will include all data regardless of rescue medication initiation or adherence. Analyses will be based on the same multiply imputed data sets produced for Week 52 assessments. Analysis will be performed by fitting the same ANCOVA model as the one described above and in Section 4.1.9. The analysis model will be evaluated in each imputed data set and the results will be combined using Rubin's rules as described in Section 4.1.12.4 for each visit.

In addition, a line plot of LS means ± 95% confidence interval (CI) by visit up to Week 52 will be displayed for both HbA1c and FPG.

4.6.2.2 Analysis of the percentage of subjects with baseline HbA1c ≥ 7% who achieve a HbA1c level < 7% at Week 52

Data will be multiply imputed based using the same approach as described for the primary analysis in Section 4.4.1, and will include all data regardless of rescue medication initiation or adherence. HbA1c response (< 7%) will be derived from dichotomising the imputed continuous values of HbA1c and Rubin's rules will be used to combine analyses across the multiple imputations. The proportion of responders (subjects achieving an HbA1c < 7% at Week 52) will be analysed using logistic regression and summarised as described in Section 4.1.10. No weights will be used in the multiple imputation or logistic regression for this analysis.

4.6.2.3 Analysis of subjects requiring glycaemic rescue medication or discontinuing study medication due to lack of efficacy

The proportion of subjects requiring glycaemic rescue medication or discontinuing study medication due to lack of efficacy at or prior to Week 52 will be analysed between overall drug treatment (low-dose and high-dose) and placebo using a logistic regression.

This will be analysed using a logistic regression and summarised as described in Section 4.1.10. No weights will be used in the logistic regression for this analysis.

4.6.2.4 Time to glycaemic rescue medication or discontinuation of study medication due to lack of efficacy

A time-to-event analysis (where event is first use of rescue medication or discontinuation of study medication due to lack of efficacy, whichever is earlier) during the 52-week treatment period will be analysed using a Cox proportional hazards model as described in Section 4.1.11. Estimates of the hazard ratio and 95% CI will be provided.

In addition, an analysis based on Kaplan-Meier estimates will be calculated and 95% CIs and nominal p-value from a pairwise log rank test will be presented.

Rules for censoring are described in Section 4.1.11.

4.6.2.5 Percentage of subjects who initiate glycaemic rescue medication

The number and percentage of subjects who require glycaemic rescue medication during the 52-week treatment period will be provided.

In addition, this analysis will be repeated for the subgroup of subjects on a stable baseline dose of metformin IR or XR (with or without insulin).

4.6.3 Exploratory efficacy analyses for monotherapy assessment during the randomised withdrawal period

These analyses will be conducted during the randomised withdrawal period using the Randomised Withdrawal Subjects Data Set.

The endpoints will be summarised within each treatment group (as defined in Section 2.1) from the original randomisation as follows:

- For subjects initially randomised the dapagliflozin (or saxagliptin) group, the subjects re-randomised to withdraw metformin will be compared to the subjects re-randomised to stay on metformin. Separate analyses will be performed for subjects respectively randomised to either dapagliflozin or saxagliptin group.
- For subjects initially randomised to the placebo group, the subjects who were re-randomised to switch to dapagliflozin (or saxagliptin) monotherapy will be compared to the subjects who were re-randomised to stay on placebo with background metformin. Separate analyses will be performed respectively for subjects re-randomised to

dapagliflozin and for those re-randomised to saxagliptin, using the those re-randomised to placebo as comparator.

4.6.3.1 Observed and change from withdrawal baseline in HbA1c and FPG

Descriptive summaries of observed and change from withdrawal baseline in HbA1c and, separately, FPG for withdrawal baseline and post-withdrawal baseline visits will be provided. This analysis will include all data regardless of rescue medication initiation or adherence. No imputation will be performed.

4.6.3.2 Percentage of subjects who achieve or maintain a HbA1c level < 7% at the end of the withdrawal period

The number and percentage of subjects who achieve or maintain a HbA1c level < 7% at the end of the withdrawal period will be provided. This analysis will include all data regardless of rescue medication initiation or adherence. No imputation will be performed.

4.6.3.3 Time to glycaemic rescue medication or discontinuation of study medication due to lack of efficacy

A time-to-event analysis (where event is first use of rescue medication or discontinuation of study medication due to lack of efficacy, whichever is earlier) during the 52-week treatment period will be analysed. Date of first dose will be date of first dose in the randomised withdrawal period. Kaplan-Meier estimates will be calculated, and 95% CIs will be presented. No Kaplan-Meier plot will be presented for this analysis.

Rules for censoring are described in Section 4.1.11.

4.6.3.4 Percentage of subjects who initiate glycaemic rescue medication

The number and percentage of subjects who require glycaemic rescue medication during the randomised withdrawal treatment period will be provided. Date of first dose will be date of first dose in the randomised withdrawal period.

4.7 Safety

Safety analyses will be conducted for the ST, ST+LT, and randomised withdrawal (as applicable) periods. An additional safety analysis will be provided for the post-study visit at Week 104, to summarise assessments of measures of growth and maturity by treatment group. Summaries will be based on the Treated Subjects Data Set unless otherwise stated.

The primary analyses of safety will include data regardless of rescue medication initiation, unless otherwise specified. Additional sensitivity analyses on data collected prior to rescue will be performed for AEs and laboratory marked abnormalities.

Dapagliflozin and saxagliptin will be summarised separately. Both low-dose and high-dose dapagliflozin/saxagliptin groups will be combined for dapagliflozin/saxagliptin to provide the

safety summary for overall dapagliflozin/saxagliptin compared to placebo. A common placebo group will be included in each summary.

Additional analyses will be performed during the ST+LT period to account for the randomised withdrawal design:

- Safety analyses conducted during the ST+LT period will also be conducted during the treatment period up to Week 32.
- Safety analyses conducted during the ST+LT period will also be conducted based on the treatment received at the time of the assessment to account for changes in treatment during the randomised withdrawal period (dapagliflozin/saxagliptin/placebo).
- Weighted analysis will be conducted for select safety parameters including adverse events, marked abnormal labs and ECGs using the original randomised groups to assess the effects of dapagliflozin (or saxagliptin) versus placebo on safety endpoints for subjects on background medication (i.e., excluding subjects re-randomised to withdraw from metformin).

  The weight matrix denoted by $\boldsymbol{W_3}$ is defined as follows:

$$\boldsymbol{W_3} = Diag\begin{bmatrix} \mathbf{0}_{1\times\frac{rn}{2}} \\ \mathbf{2}_{1\times\frac{rn}{2}} \\ \mathbf{1}_{1\times(1-r)n} \\ \mathbf{0}_{1\times\frac{2rn}{3}} \\ \mathbf{3}_{1\times\frac{rn}{3}} \\ \mathbf{1}_{1\times(1-r)n} \end{bmatrix}$$

  where r is the proportion of subjects eligible for the third randomisation and n is the number of subjects within an arm.

  $\boldsymbol{W_3}$: For the weighted analyses, dapagliflozin (or saxagliptin) subjects who went through the third randomisation and withdrew metformin will be assigned a weight of zero, and those randomised to stay on metformin will be assigned a weight of 2. All other dapagliflozin (or saxagliptin) subjects will be assigned a weight of 1. Placebo subjects randomised to withdraw metformin and switch to active treatment will be assigned a weight of 0. Placebo subjects randomised to stay on metformin will be assigned a weight of 3. All other placebo subjects will be assigned a weight of 1.

- Safety analyses will be conducted during the randomised withdrawal period using the Randomised Withdrawal Subjects Data Set.

  For subjects initially randomised to the dapagliflozin (or saxagliptin) group, the subjects re-randomised to withdraw metformin will be compared to the subjects re-randomised to stay on metformin. Separate analyses will be performed for subjects respectively randomised to either dapagliflozin or saxagliptin group.

For subjects initially randomised to the placebo group, the subjects who were re-randomised to switch to dapagliflozin (or saxagliptin) monotherapy will be compared to the subjects who were re-randomised to stay on placebo with background metformin. Separate analyses will be performed respectively for subjects re-randomised to dapagliflozin and for those re-randomised to saxagliptin, using the those re-randomised to placebo as comparator.

Additional analyses (for AEs, hypoglycaemic events, and MA labs only) will also be performed to compare all subjects taking dapagliflozin (or saxagliptin) monotherapy versus those taking placebo with background metformin during the randomised withdrawal period (adding placebo subjects randomised to withdraw metformin and switched to dapagliflozin [or saxagliptin]) monotherapy to dapagliflozin (or saxagliptin) subjects randomised to withdraw metformin).

4.7.1 Adverse events

4.7.1.1 All adverse events

Adverse events will be summarised as number and percentage of subjects by treatment group experiencing at least one AE within a category. Where specified, the number of events and incidence rate will also be provided. No statistical test will be performed to compare AE rates between treatment groups.

Only treatment emergent AEs with onset up to the cut-off dates defined in Table 8 will be included in AE summaries. All AEs (including pre-treatment events) will be listed. Where relevant, AE listings will also include the most recent treatment dose received on or prior to AE onset.

The primary analyses of AEs will include data regardless of rescue medication initiation. Additional sensitivity analyses for AEs will be restricted to data collected prior rescue medication initiation.

An overall AE summary will be provided for the ST, ST+LT and randomised withdrawal periods, presenting the number and percentage of subjects by treatment group reporting at least 1 AE (excluding hypoglycaemic and DKA events that are not reported as SAEs) for the categories presented below. Incidence rates (as described in Section 3.4.1) adjusted for exposure time for ST+LT period might also be reported (as appropriate). The summary will be provided for both primary and sensitivity analyses for all treated subjects:

- At least one AE,
- At least one hypoglycaemia event,
- At least one AE or hypoglycaemia event,
- At least one SAE,
- At least one hypoglycaemia SAE,

- At least one adjudicated DKA SAE,
- At least one AE leading to discontinuation of study medication,
- At least one SAE leading to discontinuation of study medication,
- At least one hypoglycaemia SAE leading to discontinuation of study medication,
- At least one adjudicated DKA SAE leading to discontinuation of study medication,
- Deaths,
- At least one related AE,
- At least one related SAE,
- At least one AEOSI.

This analysis will be repeated for the combined ST+LT period up to Week 32 and also by treatment group received at the time of AE onset.

A weighted analysis for the overall AE summary will also be provided based on the ST+LT period, to account for the randomised withdrawal design (see Section 4.7 for details), and will include all data regardless of rescue medication initiation.

In addition, the overall AE summary will be repeated for subgroups based on race, ethnicity, sex, age group (using randomisation strata), region, baseline antidiabetic treatment, baseline HbA1c and baseline BMI, using the categories defined in the Appendix (Table 19). This will be provided based on the ST+LT period and will include all data regardless of rescue medication initiation and prior to rescue medication initiation. The overall AE summary will also be presented for the subgroup of subjects on a stable baseline dose of metformin IR or XR (with or without insulin).

The number and percentage of subjects with at least one AE will be summarised by SOC, PT and treatment group. AEs will be sorted by decreasing frequency within each SOC and PT according to the overall active treatment group, and, where applicable, by high dose active treatment or active treatment with background medication. As appropriate the number of events will also be displayed.

All adverse events will be summarised by SOC and PT (including incidence rate presented for PTs for the ST+LT period), regardless of rescue medication initiation unless otherwise specified, for:

- The ST period and the combined ST+LT period (including incidence rate).
- The ST period and the combined ST+LT period (including incidence rate), prior to rescue medication initiation.
- The combined ST+LT period, up to Week 32.

- The combined ST+LT period, excluding subjects randomised to withdrawal from metformin. A weighted analysis will be conducted on the Treated Subjects Data Set using the original randomised group and presenting weighted proportions.
- The combined ST+LT period. AEs will be summarised by treatment group received at the time of AE onset. For placebo subjects re-randomised to switch to dapagliflozin (or saxagliptin), AEs will be analysed in the placebo group to the beginning of the randomised withdrawal period and in the dapagliflozin (or saxagliptin) group if the event onset occurs during the randomised withdrawal period. AEs will be presented as incidence rate adjusted for exposure, as described in Section 3.4.1.
- The randomised withdrawal period. AEs with a date of onset occurring after the withdrawal baseline will be summarised using the Randomised Withdrawal Subjects Data Set separately for the three treatment comparisons described in Section 4.1.5.

The following descriptive summaries will also be provided for the ST, ST+LT and randomised withdrawal period, regardless of rescue medication initiation, for:

- Any AE by SOC, PT and maximum intensity (mild, moderate, severe).
- Any AE related to study drug (not related, related [including AEs with missing relationship to study drug]) by SOC and PT.
- Any AE by SOC and PT for common PTs (defined as PTs reported by ≥ 5% of the subjects in any treatment group within the period). Number of events (and incidence rate for the ST+LT period) will also be presented.
- Any non-serious AE by SOC and PT

Summaries of AEs by SOC and PT will be provided by treatment group for the ST, ST+LT and randomised withdrawal period, regardless of rescue medication initiation, for the following subgroups:

- Age group using the randomisation strata (≥ 10 and < 15 years, ≥ 15 and < 18 years)
- Sex (male, female)
- Race (white, non-white)
- Baseline antidiabetic treatment (metformin only, insulin only, combination of metformin and insulin)

with age, sex and baseline antidiabetic treatment category being defined based on randomisation strata.

The ST+LT period presentations for Any AE by SOC and PT and Any AE by SOC and PT for common PTs will also be presented for the subgroup of subjects on a stable baseline dose of metformin IR or XR (with or without insulin).

In addition, AEs not included in the ST+LT analysis period per Table 8 and those AEs reported quarterly between Week 56 and Week 104 will also be summarised for the post-study visit at Week 104.

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

A listing of all reported AEs falling into the ST+LT period will be produced. A separate listing will be provided for all AEs during the study.

Adverse events of special interest

MedDRA preferred terms and their groupings will be used to identify AEOSIs (as specified in Section 3.4.1) and will be listed and documented in the Study Master File. The number and percentage of subjects experiencing any of the specified AEOSIs and the individual terms that constitute each AEOSI grouping will be presented by preferred term for the ST, ST+LT and randomised withdrawal periods. Incidence rates of AEOSIs will also be presented for PTs for the ST+LT period. A glossary of the preferred terms used to identify AEOSIs will be provided by AEOSI category, along with a flag identifying any preferred term searched for but not present in the study.

COVID-19 related adverse events

A glossary of preferred terms related to COVID-19 will be provided, along with a flag identifying any preferred term searched for but not present in the study.

4.7.1.2 Deaths

Deaths will be identified from the status page, AE page, or the SAE page (with a death date, cause of death, outcome or SAE categorisation present) of the CRF. A listing of all deaths that occur will be produced for the ST+LT and Week 104 periods separately, and will present the period of occurrence. Any deaths that occur during the study will be described in depth as narratives in the CSR.

4.7.1.3 Serious adverse events

All SAEs (including hypoglycaemic and type 2 DKA events classified as SAEs) will be described in narratives, regardless of investigator assessment of causality. SAEs with an onset from Day 1 of the ST period up to and including 30 days after the last dose date in period (or up to and not including the start date of the LT period (if applicable), whichever comes first, for the ST period) will be considered as occurring during ST period. For subjects treated during the LT period, SAEs with an onset from Day 1 of the ST period up to and including 30 days after the last dose date will be considered as occurring during the combined ST+LT period. For the randomised withdrawal period, this listing will include all deaths on and after the date of withdrawal baseline until the date of Week 52 or date of last visit + 30 days (if earlier than Week 52). Number of events and incidence rates adjusted for exposure time, as described in Section 3.4.1, will be reported.

The following descriptive summaries will be provided by SOC, PT and treatment group separately for the ST, ST+LT and randomised withdrawal periods:

- Any SAE
- Any SAE, up to Week 32 (ST+LT period only)
- Any SAE excluding AEs following rescue medication use (sensitivity analysis)
- Any SAE related to study drug (not related, related [including SAEs with missing relationship to study drug])
- Any SAE leading to leading to discontinuation of study medication

For the combined ST+LT period, SAEs will also be summarised by treatment group received at the time of SAE onset. For placebo subjects re-randomised to switch to dapagliflozin (or saxagliptin), SAEs will be analysed in the placebo group to the beginning of the randomised withdrawal period and in the dapagliflozin (or saxagliptin) group if the event onset occurs during the randomised withdrawal period. SAEs PTs will be presented as incidence rate adjusted for exposure, as described in Section 3.4.1.

In addition, all SAEs will also be summarised for the post-study visit at Week 104 for the Treated Subjects Data Set regardless of rescue medication initiation. For the randomised withdrawal period, subjects going through the third randomisation will be presented using the Randomised Withdrawal Subjects Data Set and will be summarised separately for the three treatment comparisons described in Section 4.1.5.

Listings of all SAEs (including pre-treatment events or post-treatment events) by subject will be provided for the ST+LT period. A separate listing will be provided for SAEs reported at the post-study visit at Week 104.

4.7.1.4 Adverse events leading to discontinuation of study medication

Adverse events with an onset during treatment for which the action taken was "drug permanently discontinued" will be summarised by SOC, PT, and treatment group for both the primary (including data regardless of rescue medication initiation) and sensitivity safety analyses (excluding data after rescue). This summary will include all hypoglycaemia events and all DKA events that are reported as SAEs and will be presented for the ST, ST+LT and randomised withdrawal periods. Note that, when summarising AEs leading to discontinuation, no upper cut-off day windows (i.e., 4 days and 30 days from last dosing date for AEs and SAEs respectively) will be applied. For ST period analyses, the only upper cut-off date will be the start date of the LT period.

A subject listing of discontinuation of study medication due to AEs will be provided for the ST+LT period.

4.7.2 Other safety analyses

4.7.2.1 Amputation

All amputation events will be summarised for the ST+LT period. The number and proportion of subjects with amputation, type of event (trauma by accident, surgical amputation, spontaneous/non-surgical amputation), amputation lateral side, location of amputation, condition and underlying conditions that triggered amputation, and smoker status will be presented.

A listing of all amputation events will be provided for the ST+LT period.

4.7.2.2 Adjudicated Diabetic ketoacidosis (DKA)

All suspected DKA events sent for adjudication will be included in summaries for the ST, ST+LT and randomised withdrawal periods if their onset falls between the start of IP treatment and the cut-off dates defined for each period in Table 8.

The proportion of subjects with suspected DKA events sent for adjudication, regardless of rescue medication initiation, will be tabulated by treatment group per adjudication category (definite DKA, probable DKA, possible DKA, not DKA) for the ST, ST+LT and randomised withdrawal periods. The proportion of subjects with suspected DKA events sent for adjudication leading to discontinuation per adjudication category will also be summarised for the ST+LT period. When summarising suspected DKA events leading to discontinuation of study medication, no upper cut-off day windows are applied.

Furthermore, suspected DKA events sent for adjudication will be summarised for the ST, ST+LT and randomised withdrawal periods by treatment group per adjudication category for number of subjects with each sign and symptom and separately, risk factors.

Suspected DKA events sent for adjudication will also be presented ST, ST+LT and randomised withdrawal periods by treatment group per adjudication category and preferred term. This analysis for the ST+LT period will be repeated for the subgroup of subjects on a stable baseline dose of metformin IR or XR (with or without insulin).

A listing of suspected DKA events sent for adjudication will be generated for adjudication results, signs and symptoms, and risk factors with an onset date/time from the start date/time for the ST+LT period. For the ST+LT + Week 104 period, the listing will include all data collected up to Week 104.

4.7.2.3 Cardiovascular and hepatic adjudicated events

Cardiovascular and hepatic events sent for adjudication will be listed only.

4.7.2.4 Hypoglycaemia

Hypoglycaemic events will be included in summaries for the ST, ST+LT and randomised withdrawal periods if their onset falls between the start of IP treatment and the cut-off dates defined for each period in Table 8. The primary analysis will be based on data including

hypoglycaemia events occurring prior to rescue medication initiation; sensitivity analyses will include data after rescue medication initiation.

The number and proportion of subjects with hypoglycaemic events (including those reported as SAEs) will be tabulated in each treatment group by ADA and ISPAD categories (see Section8.9) for:

- The ST period and the combined ST+LT period, prior to rescue medication initiation (as primary analyses).
- The ST period and the combined ST+LT period, regardless of rescue medication initiation (as sensitivity analyses).
- The combined ST+LT period, up to Week 32, prior to rescue medication initiation (as primary analyses).
- The combined ST+LT period, up to Week 32, regardless of rescue medication initiation (as sensitivity analyses).
- The randomised withdrawal period. The events, with a date onset occurring on or after the randomised withdrawal prior to rescue medication initiation, will be summarised separately for the three treatment comparisons described in Section 4.1.5 using the Randomised Withdrawal Subjects Data Set.

The ST+LT period prior to rescue medication initiation analysis will also be repeated for the subgroup of subjects on a stable baseline dose of metformin IR or XR (with or without insulin).

Hypoglycaemic events that do not fulfil the ADA or ISPAD categories will be presented as 'Not classified'.

All information (symptoms, risk factors etc.) collected in the separate CRF pages for hypoglycaemic events (whether or not they fulfilled SAE criteria) will be summarised by treatment group and listed for the ST+LT period. For the ST+LT + Week 104 period, the listing will include all data collected up to Week 104.

Hypoglycaemic events meeting SAE criteria will also be presented in the listing.

4.7.3 Laboratory evaluations

Safety laboratory evaluations performed by central laboratories will be included in summary tables and both central and local laboratory evaluations will be included in the listings. The laboratory data will be presented in Conventional (US) Units and additional presentations for changes from baseline will be repeated using SI units.

Summaries of laboratory data will include assessments up to the cut-off dates defined for each period and parameter in Table 8. Visit windows are provided in Section 4.1.7.1 in order to link each laboratory test to a scheduled visit. All continuous laboratory parameters specified in

Section 3.4.4 will be summarised at each scheduled time point by treatment group using descriptive statistics (including data regardless of rescue medication initiation) during:

- The combined ST+LT period. Observed and change from baseline values will be summarised by treatment group based on the treatment received during the ST period (dapagliflozin/saxagliptin/placebo) using the Treated Subjects Data Set.

- The combined ST+LT period, up to Week 32. Observed and change from baseline values will be summarised by treatment group based on the treatment received during the ST period (dapagliflozin/saxagliptin/placebo) using the Treated Subjects Data Set.

- The randomised withdrawal period. Observed and change from withdrawal baseline values will be summarised for the first two treatment comparisons described in Section 4.1.5 using the Randomised Withdrawal Subject Data Set.

Additionally, eGFR will also be described by age group (using the randomisation strata) for the ST+LT and randomised withdrawal periods using SI units.

Marked abnormality laboratory assessment will be summarised using central laboratories assessments during the ST, the combined ST+LT and randomised withdrawal periods for both conventional and SI units.

Haematology, chemistry and urinalysis laboratory data for the ST+LT period will be listed using both conventional and SI units where applicable. For the ST+LT + Week 104 period, the listing will include all data collected up to Week 104. Flags will be applied to values falling outside reference ranges (which will be explicitly noted on these listings where applicable). Treatment at the time of a laboratory assessment will be included in the listings and will correspond to the last dose received by a subject up to and including the date/time of the laboratory assessment.

Laboratory data values of the form of "< x" (i.e., below the lower limit of quantification) or > x (i.e., above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "< x" or "> x" in the listings. For determining if the values are out of range or falling within the MA lab criteria, if a value is reported as "<x" or ">x" where x is the lower or upper criteria respectively, then this will be reported as "low" or "high" respectively for the reference range indicator and as meeting the MA criteria.

Note that prior to database lock and unblinding, analysis data for urinary glucose, and urinary glucose: creatinine ratio will be based on dummy values (to preserve the blind).

4.7.3.1 Safety laboratory parameters over time

For all continuous laboratory parameters listed in Section 3.4.4, absolute values and changes from baseline during the ST+LT and randomised withdrawal periods will be summarised by treatment group using descriptive statistics (including data regardless of rescue medication initiation). Visit windows are provided in Section 4.1.7.1 in order to link each laboratory test to a scheduled visit.

Unless otherwise specified, laboratory data obtained after the start of study medication dosing up to and including 4 days (30 days for liver function laboratory tests) after the last dosing date (or up to and not including the start of the LT treatment period, whichever comes first, for ST period) will be considered as obtained respectively during ST and the LT period. For the randomised withdrawal period, laboratory data collected on and after the withdrawal baseline up to and including 4 days (30 days for liver function laboratory tests) after the last dosing date in the randomised withdrawal period will be considered for the randomised withdrawal period. Laboratory data obtained from the day after the Week 56 visit up to the last visit date of the follow-up period will be considered as obtained during the follow-up period.

Shift tables (in SI units) of subjects with values in categories of low, normal, and high (based on normal ranges provided by the central laboratory) will be summarised by treatment group using the lowest values (for parameters with a lower normal range defined) and the highest values (for parameters with an upper normal range defined) obtained during the ST and ST+LT periods. In order to identify the lowest or highest post-baseline values in a subject all assessments will be considered, even if they do not correspond to a visit-based summary. For the shift tables, the last observation, regardless of post-randomisation rescue, prior to Week 26 or Week 52 will be used if no Week 26 or Week 52 measurement is available, respectively.

Additional shift table summaries for each period compared to baseline will be provided for the following:

- Subjects with electrolytes (Sodium, Potassium, Calcium, Phosphate, and Magnesium) categories of low, normal, and high (based on normal range of central laboratory) will be summarised by treatment group using the highest and lowest values obtained during the period.
- Subjects with Urine Albumin Excretion Categories (UACR) assessments, will be presented for the values at Week 26 (for ST period) or Week 52 (for ST+LT period) versus baseline, based on the following urine albumin to creatinine ratios: 0 - < 30 mg/g (3.4 g/mol) [normoalbuminuria], ≥ 30 mg/g (3.4 g/mol) - < 300 mg/g (33.9 g/mol) [microalbuminuria], ≥ 300 mg/g (33.9 g/mol) [macroalbuminuria]. If the value at Week 26 or Week 52 is not available, the LOCF observation will be used instead.

4.7.3.2 Elevated liver function tests

The following three criteria will be summarised by treatment group for the ST, ST+LT and randomised withdrawal periods in examination of elevated aminotransferases (AT) (ALT and/or AST) and TB:

- (AST or ALT > 3X upper limit of normal [ULN]) and (bilirubin > 1.5X ULN within 14 days on or after AT elevation)
- (AST or ALT > 3X ULN) and (bilirubin > 2X ULN within 14 days on or after AT elevation)
- (AST or ALT > 3X ULN) and {(bilirubin > 2X ULN and no ALP ≥ 2X ULN) within 14 days on or after AT elevation)}.

This analysis will be conducted regardless of rescue medication initiation. The summaries will include all data collected up to the cut-offs defined in Table 8. No comparison vs. baseline will be done.

A listing of all AST, ALT and TB results will be provided for subjects with AST or ALT ≥ 3× ULN and TB ≥ 1.5× ULN at any point during the study. For these summaries, liver test data obtained after the start of study medication dosing up to and including 30 days after the last blind dosing date (or up to and not including the start of the LT period, whichever comes first, for ST period) will be considered as obtained respectively during ST and the LT the period.

4.7.3.3 Elevated liver tests and/or reported hepatic adverse events

A summary of subjects with elevated liver tests (as defined in Appendix Section 8.7.1) and/or hepatic AEs will be provided by treatment group for the ST, ST+LT and randomised withdrawal periods. The summary will include subjects with AST and/or ALT elevation, TB elevation, combined AT and TB elevation, and ALP elevation. Hepatic AEs (defined prior to database lock) will be summarised by PT, in decreasing frequency of PT according to the overall active arm. A listing of all Hepatic AEs will be presented for the ST+LT period.

4.7.3.4 Marked laboratory abnormalities

Laboratory abnormalities will be evaluated based on MA values for selected parameters (see pre-defined criteria detailed in Appendix Section 8.7.1 to identify MAs). If both the baseline and on-treatment values of a parameter are beyond the same MA limit for the parameter, then the on-treatment value will be considered a MA only if it is more extreme (farther from the limit, e.g. worsens) than was the baseline value. If the baseline value is beyond the low MA limit, and the post-baseline value is beyond the high MA limit (or vice-versa), then the post-baseline value will be considered a MA. If baseline value is missing and the post-baseline value is beyond the MA limit, then the post-baseline value will be considered a MA.

Laboratory MAs occurring during the ST, ST+LT, and ST+LT up to Week 32 periods based on Treated Subjects Data Set will be summarised by treatment group. In addition, laboratory MAs will be summarised for the Randomised Withdrawal period based on the Randomised Withdrawal Subjects Data Set, separately for the three treatment comparisons described in Section 4.1.5. The summaries will be presented for both the primary and sensitivity safety analyses. The primary analyses of MAs will include data regardless of rescue medication initiation. Additional sensitivity analyses will be provided for MAs occurring prior to rescue medication initiation.

For the ST+LT analysis, incidence rates of marked abnormalities will also be presented.

In addition, laboratory MAs will be summarised using incidence rates by treatment group received at the time of MA onset for the ST+LT period. For placebo subjects re-randomised to switch to dapagliflozin (or saxagliptin), MAs will be analysed in the placebo group to the beginning of the randomised withdrawal period and in the dapagliflozin (or saxagliptin) group if the event onset occurs during the randomised withdrawal period.

The direction of change (high or low) in MA will be indicated in the tables.

In addition, a weighted analysis for the laboratory MAs will also be provided based on the ST+LT period, as described in Section 4.7, to account for the randomised withdrawal design.

Additionally, for each subject with a post-baseline MA for a parameter, all the subject's values of that parameter over the treatment period and the follow-up period, where applicable, will be listed.

4.7.3.5 Fasting lipid panel

Summaries of cholesterol, triglycerides, high density lipoproteins (HDL) cholesterol, and calculated low density lipoproteins (LDL) cholesterol will be provided by treatment group for baseline, Week 26, and Week 52 (ST+LT period analysis) with corresponding changes from baseline, regardless of rescue medication initiation. Lipid panel assessments will also be listed for the ST+LT period. For the ST+LT + Week 104 period, the listing will include all data collected up to Week 104.

4.7.3.6 Pregnancy test results

By-subject listings of pregnancy test results will be provided for the ST+LT period using HCG and serum pregnancy test results from the central laboratory. For the ST+LT + Week 104 period, the listing will include all data collected up to Week 104.

4.7.4 Vital signs

Vital sign measurements for diastolic blood pressure, systolic blood pressure and heart rate at baseline, Week 6, Week 12, Week 14, Week 20, Week 26, Week 32, Week 40, Week 52 and changes from baseline at each visit will be summarised by treatment group using descriptive statistics (including data regardless of rescue medication initiation) for the ST+LT period. In addition, this analysis will also be performed for the randomised withdrawal period using the Randomised Withdrawal Subjects Data Set for the first two treatment comparisons described in Section 4.1.5. Summaries of vital signs data will include assessments up to the cut-off dates defined for each period in Table 8. Visit windows are provided in Section 4.1.7.1 in order to link each vital sign measurement to a scheduled visit.

A listing of vital signs will be provided for the ST+LT period. For the ST+LT + Week 104 period, the listing will include all data collected up to Week 104.

4.7.5 Electrocardiograms

The normality/abnormality (further classified by clinical significance) of the overall ECG interpretation, as determined by the investigator, will be summarised by treatment group based on observed data regardless of rescue medication initiation using frequency tables on number of subjects who have a normal/abnormal ECG tracing at each scheduled time of assessment for the analysis period, overall and by the ECG tracing at baseline. These analyses will be performed for ST+LT treatment period using the LOCF approach.

In addition, a weighted analysis for the normality/abnormality of the overall ECG interpretation will also be provided based on the ST+LT period, as described in Section 4.7, to account for the randomised withdrawal design.

All ECG data will be listed for the ST+LT period.

4.7.6 Body weight, height and BMI

Body weight (kg), height (cm) and BMI (kg/m^2) measurements at baseline, Week 6, Week 12, Week 20, Week 26, Week 32, Week 40, Week 52, Week 104 and changes from baseline at each visit will be summarised using descriptive statistics, regardless of rescue medication initiation. Summaries will include assessments performed up to the cut-off dates defined for each period in Table 8. Visit windows are provided in Section 4.1.7.1 in order to link each measurement to a scheduled visit. In addition, normalised height, body weight and BMI expressed as a z-score adjusted for age at the assessment and sex using CDC (see details in Section 3.4.8) will be also be summarised using the same approach.

In addition, body weight, height, and BMI will also be summarised during the randomised withdrawal period using the Randomised Withdrawal Subjects Data Set for the first two treatment comparisons described in Section 4.1.5, and for post-study visit at Week 104 using the Treated Subjects Data Set.

A listing of body weight, height and BMI along with z-scores by subject will be provided. For the ST+LT period this listing will include all data collected up to the end of the LT period. For the ST+LT + Week 104 period, the listing will include all data collected up to Week 104.

4.7.7 Measures of growth and maturity

4.7.7.1 Tanner stages

Tanner stages will be summarised based on observed data, regardless of rescue medication initiation. Summaries of descriptive statistics will be provided for baseline, Week 26, Week 52, and for the post-study visit at Week 104 using the LOCF approach in the period. Changes from baseline at these time points will be provided using shift tables and by visit according to baseline status. Also, change from Week 26 status to Week 52 and change from Week 52 status to Week 104 according to baseline status will be presented. A weighted analysis, as described in Section 4.7, to account for the randomised withdrawal design may also be presented.

In addition, Tanner staging will also be summarised as above during the randomised withdrawal period, using the Randomised Withdrawal Subjects Data Set for the first two treatment comparisons described in Section 4.1.5. Summaries of descriptive statistics will be provided for withdrawal baseline, Week 52 and Week 104 using the LOCF approach. Changes from withdrawal baseline at Week 52 and Week 104 will be provided using shift tables, for Week 52 and Week 104 according to withdrawal baseline status and also for Week 104 according to Week 52 status.

4.7.7.2 Puberty status

Puberty status (as defined in Appendix Section 8.10.3) will be summarised regardless of rescue medication initiation at Week 26 and Week 52, where the height velocity is based on change from baseline, and Week 104, where the height velocity is based on change from Week 52.

4.7.7.3 Growth and maturity markers

Summaries of growth and maturation markers (see Section 3.4.9) in SI and conventional units will be based on observed data, regardless of rescue medication initiation. Descriptive summaries of absolute values and changes from baseline (where applicable) will be provided for baseline, Week 26, Week 52, and for the post-study visit at Week 104 using the LOCF approach. For the Week 104 analyses, change from Week 52 will also be presented.

In addition, growth and maturation markers will also be summarised during the randomised withdrawal period using the Randomised Withdrawal Subjects Data Set for the first two treatment comparisons described in Section 4.1.5. Descriptive summaries of absolute values and changes from withdrawal baseline (where applicable) will be provided for withdrawal baseline, Week 52 and Week 104 using the LOCF approach.

A categorical change from baseline summary will also be produced by treatment group, age category (≥ 10 and < 15 years, ≥ 15 and < 18 years) using the randomisation strata, and puberty status at Week 26, Week 52 and Week 104 (as defined in Appendix Section 8.10.3) for Week 26, Week 52, and for the post-study visit at Week 104 using the LOCF approach. Similarly, a categorical change from withdrawal baseline summary will also be produced for the Randomised Withdrawal Subjects Data Set for Week 52 and Week 104 using the LOCF approach.

A listing of the growth and maturation markers along with the Tanner stages by subject will be provided. For the ST+LT period this listing will include all data collected up to the end of the LT period. For the ST+LT + Week 104 period, the listing will include all data collected up to Week 104.

4.7.7.4 Bone biomarkers

Summaries of bone biomarkers (see Section 3.4.9) in SI and conventional units will be based on observed data, regardless of rescue medication initiation. Descriptive summaries of absolute values and changes from baseline (where applicable) will be provided for baseline, Week 26, Week 52, and for the post-study visit at Week 104 using the LOCF approach. For the Week 104 analyses, change from Week 52 will also be presented.

In addition, bone biomarkers will also be summarised as above for subjects going through the third randomisation using the Randomised Withdrawal Subjects Data Set for the first two treatment comparisons described in Section 4.1.5.

A categorical change from baseline summary will also be produced by treatment group, age category (≥ 10 and < 15 years, ≥ 15 and < 18 years) using the randomisation strata, and puberty status at Week 26, Week 52, and Week 104 (as defined in Appendix Section 8.10.3) for Week

26, Week 52, and for the post-study visit at Week 104 using the LOCF approach. Similarly, a categorical change from withdrawal baseline summary will also be produced for the Randomised Withdrawal Subjects Data Set for Week 52 and Week 104 using the LOCF approach.

A listing of the bone biomarkers along with the Tanner stages by subject will be provided. For the ST+LT period this listing will include all data collected up to the end of the LT period. For the ST+LT + Week 104 period, the listing will include all data collected up to Week 104.

4.8 Pharmacokinetic analyses

Plasma samples will be analysed for dapagliflozin, saxagliptin, and its metabolite 5-OH-saxagliptin by validated assays. Plasma concentration values for dapagliflozin, saxagliptin and 5-OH-saxagliptin will be summarised for the ST period using descriptive statistics by visit and time point for the Pharmacokinetic Analysis Data Set. For each analyte, descriptive summaries will include the n, number of subjects having a value below the Lower Limit of quantification (LLOQ) [n < LLOQ], arithmetic mean, SD, geometric mean, geometric SD, CV%, median, minimum and maximum values will be presented. A listing of plasma concentration values will be presented for the ST period.

The plasma concentration values may be used in population PK and/or population PK/pharmacodynamic analyses that will be reported separately from the CSR.

4.9 Pharmacodynamic analyses

Pharmacodynamic analyses will include but will not be limited to analysis of DPP-4 activity and FPG. The analyses will be reported separately from the CSR.

4.10 Site 4910

Due to concerns with the data collected at site 4910 and following further investigation by AstraZeneca it was decided that all of the tables, figures, and listings outlined above will be produced excluding the data from site 4910.

In addition, the following analyses will be produced including subjects from site 4910:

- Subject disposition during the ST+LT period as outlined in Section 4.2.1
- Demographics and baseline characteristics as outlined in Section 4.2.3
- All summaries and analyses associated with the primary and secondary efficacy endpoints as outlined in Sections 4.4.1, 4.5.2, 4.5.3, 4.5.4, 4.5.5, 4.5.6, 4.5.7, 4.5.8, 4.5.9, 4.5.10, 4.5.11, 4.5.12 (no sensitivity analyses will be performed)
- The overall summary of TEAEs during the ST+LT period, regardless of rescue, as outlined in Section 4.7.1.1
- TEAEs by SOC and PT during the ST+LT period, regardless of rescue, as outlined in Section 4.7.1.1

- Deaths during the ST+LT period as outlined in Section 4.7.1.2
- SAEs during the ST+LT period, regardless of rescue, as outlined in Section 4.7.1.3
- MA labs during the ST+LT period, regardless of rescue, as outlined in Section 4.7.3.4
- Pregnancy during the ST+LT period as outlined in Section 4.7.3.6
- Vital signs during the ST+LT period, regardless of rescue, as outlined in Sections 4.7.4 and 4.7.6

5. INTERIM ANALYSES (NOT APPLICABLE)

6. CHANGES OF ANALYSIS FROM PROTOCOL

Table 12 Changes of analysis from protocol

Section of SAP Affected (If applicable)	Change	Rationale
Section 2.2.7	A PK analysis data set was defined in the SAP, but this isn't mentioned in the study protocol.	It is necessary to have an analysis set defined for the PK data.
Section 4.1.1	The definition of the withdrawal baseline differs between the study protocol and the SAP.	This change was made to align the withdrawal baseline with how we define dose at onset and how to handle scenarios where the randomisation was done on a different date to the main visit.
Section 4.1.10	Fisher's exact test is used instead of logistic regression where there are <5 responders per treatment group.	This analysis was not mentioned in the protocol.
Section 4.1.12	The "wash-out" imputation method is used where there is insufficient data from "retrieved drop-outs".	This analysis was not mentioned in the protocol.

Section of SAP Affected (If applicable)	Change	Rationale
Sections 4.4 and 4.5	The primary efficacy endpoint was updated to use overall treatment and the secondary efficacy endpoints were updated to follow the order/hierarchy of overall, followed by low-dose/high-dose regimen testing, followed by low-dose regimen.	This was due to protocol amendment #6.
Section 4.7.1.1	The protocol states that additional safety analyses will be performed on the Treated Subjects Data Sets on all DKA events but in the SAP, we only present the analysis for adjudicated DKA SAEs.	Additional analyses were only done on confirmed DKAs.
Section 4.10	It was decided that all the TFLs will be produced excluding data collected from Site 4910. In addition, a few analyses will be produced including subjects from Site 4910.	This was due to loss of access to the source data of subjects at Site 4910. This decision was made following investigation by AstraZeneca.
Appendix 8.13	The protocol states that "separate analyses will be performed for subjects respectively randomized to the dapagliflozin or saxagliptin group" while in the SAP, we combine the randomised withdrawal treatment into one analysis table.	Presenting the data this way was more informative.

7. REFERENCES

1. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, Heller SR, Rodriguez H, Rosenzweig J, Vigersky R. Hypoglycaemia and diabetes: a report of a workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care. 2013 May; 36(5):1384-95

2. Clarke W, Jones T, Rewers A, Dunger D, Klingensmith G. ISPAD Clinical Practice Consensus Guidelines 2009 Compendium Assessment and management of

hypoglycaemia in children and adolescents with diabetes. Paediatric Diabetes 2009; 10: 134-145.

3. A SAS Program for the 2000 CDC Growth Charts (ages 0 to <20 years), available at: https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm

4. Ratitch B, Lipkovich I, O'Kelly M. Combining Analysis Results from Multiply Imputed Categorical Data. PharmaSUG 2013 - Paper SP03, available at: https://pharmasug.org/proceedings/2013/SP/PharmaSUG-2013-SP03.pdf

5. Danne T, Philotheou A, Goldman D, et al. A randomised trial comparing the rate of hypoglycaemia – assessed using continuous glucose monitoring – in 125 preschool children with type 1 diabetes treated with insulin glargine or NPH insulin. Paediatric Diabetes 2013: 14: 593–601.

6. Jones KL, Arslanian S, Peterokova VA, Park J-S, Tomlinson MJ. Effect of Metformin in Paediatric Patients with Type 2 Diabetes. Diabetes Care 25:89-94, 2002.

8. APPENDIX

8.1 Flow chart/time and events schedule

Table 13 Screening procedural outline (CV181375 [D1680C00019])

Procedure	Screening Maximum 6 months[a]	Lead-in Wk –2[b]	Notes
Eligibility Assessments			
Informed Consent	X		
Obtain written Assent (If applicable)	X		
Inclusion/Exclusion Criteria	X		
Medical History	X		
Review Concomitant Medication	X	X	
ECG		X	
Safety Assessments			
Physical Examination		X	
Targeted Physical Examination	X		
Tanner Staging (Investigator determined/Self-reported)		X	See Appendix Section 8.10.1
Vital Signs	X	X	
Height	X		
Body Weight	X		
BMI	X		
Serious Adverse Events Assessment	X	X	
Adverse Events Assessment		X	

Procedure	Screening Maximum 6 months[a]	Lead-in Wk –2[b]	Notes
Laboratory Tests			
Standard Safety Laboratory Panel (Blood/Urine)	X		See Appendix Section 8.7
GAD/IA2 Autoantibodies	X		
C-peptide	X		C-peptide will only be performed in otherwise eligible GAD and IA2 antibody-positive subjects
HbA1c	X		
Pregnancy Test (WOCBP only)	X		For WOCBP only urine test with reflex serum test, if positive.
TSH	X		An abnormal TSH value at enrolment will be further evaluated by free T4
Hepatitis Screening Panel	X		Includes Hepatitis Screen Panel (anti-HAV [IgM], HBsAg, and anti-HCV)
Study Drug / IXRS			
Contact IXRS	X	X	
General			
Provide Dietary and Exercise Counselling		X	
Provide glucose meter and supplies / instructions		X	
Provide logs / instructions		X	
Assessment of signs and symptoms of hypoglycaemia episodes		X	

[a] The screening period lasts a maximum of 6 months. Any screening procedures and assessments can be retested as determined by the Investigators during the 6-month screening period if subjects fail to meet the eligibility criteria at the first attempt and the Investigators believe that subjects may meet the eligibility criteria within 6 months. Any additional tests should be recorded as unscheduled assessments in the EDC system.

[b] The lead-in period should start within 6 weeks after completion of the screening visit, and may start as early as 2 weeks after completion of the screening visit if all laboratory results have been received.

Table 14 Short-term procedural outline (CV181375 [D1680C00019])

Procedure	Day 1[a]	Wk 2[a,b]	Wk 6[a]	Wk 12[a]	Wk 14[a,c]	Wk 20[a]	Wk 26 /ETD (early discontinuation of IP)/ Rescue[a,c]	Notes
Eligibility Assessments								
Inclusion/Exclusion Criteria	X							
Review concomitant medications / procedures	X	X*	X	X	X	X	X	*Assessed by phone
Safety Assessments								
Physical Examination							X	
Targeted Physical Examination	X		X	X		X		
Tanner Staging (Investigator determined/Self-reported)							X	See Appendix Section 8.10.1
Vital Signs	X		X	X	X	X	X	
Height	X		X	X		X	X	
Body Weight	X		X	X		X	X	
ECG							X	
Assessment of signs and symptoms of hypoglycaemia episodes	X	X*	X	X	X	X	X	*Assessed by Phone
Serious Adverse Event Assessment	X	X*	X	X	X	X	X	*Assessed by Phone
Adverse Events Assessment	X	X*	X	X	X	X	X	*Assessed by Phone
Laboratory Tests								
Standard Safety Laboratory Panel (Blood/Urine)	X		X	X		X	X	See Appendix Section 8.7
Fasting Lipid panel	X						X	Total cholesterol, triglycerides, HDL, and LDL

Procedure	Day 1[a]	Wk 2[a,b]	Wk 6[a]	Wk 12[a]	Wk 14[a,c]	Wk 20[a]	Wk 26 /ETD (early discontinuation of IP)/ Rescue[a,c]	Notes
Fasting Plasma Glucose (FPG)[d]	X		X	X		X	X	On Day 1, the FPG sample will be collected pre-dose only. At the Wk 6, 12, 20 and 26 visits FPG samples will be collected pre-dose and approximately 2 hours post-dose (± 1 hour) All samples will be drawn in the fasting condition.
HbA1c	X		X	X		X	X	Results masked following IP administration on Day 1 until after study completion
Pregnancy Test (WOCBP only)	X		X	X	X	X	X	WOCBP must have a negative serum or urine pregnancy test within 24 hours prior to the start of study drug. Home pregnancy kits will be provided.
Spot Urine Glucose	X		X	X		X	X	Results blinded to the Sponsor, Investigator, site, and subject for the duration of the study following IP administration on Day 1 until after study completion
Growth, bone and maturation markers	X						X	Thyroid-stimulating hormone (TSH), free thyroxine, luteinizing hormone (LH), follicle-stimulating hormone (FSH), oestradiol, total testosterone, insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), calcitonin, 25-hydroxy vitamin D, bone alkaline phosphatase, osteocalcin, parathyroid hormone (PTH) and carboxyterminal cross-linked telopeptide of Type 1 collagen (CTX-1)
Plasma samples for analysis of dapagliflozin, saxagliptin and its metabolite 5-OH-saxagliptin[d]			X	X		X	X#	Samples will be collected pre-dose and approximately 2 hours post-dose (± 1 hour) Samples will be drawn in the fasting condition.

Procedure	Day 1[a]	Wk 2[a,b]	Wk 6[a]	Wk 12[a]	Wk 14[a,c]	Wk 20[a]	Wk 26 /ETD (early discontinuation of IP)/ Rescue[a,c]	Notes
								# No samples will be drawn at Week 26 visit following Early Treatment Discontinuation Visit
Plasma samples for DPP-4 activity[d]	X		X	X		X	X	On Day 1 plasma samples for DPP-4 activity will be drawn pre-dose only. At the Weeks 6, 12, 20 and 26 visits, plasma samples for DPP-4 activity will be drawn at 2 hours (± 1 hour) post-dose only. Samples will be drawn in the fasting condition.
Study Drug / IXRS								
Contact IXRS	X		X		X	X	X	
First randomisation	X							
Second randomisation					X			
Dispense Study Drug	X		X		X	X	X*	* No study drug dispensed during ETD or Rescue visit. Rescued subjects will continue with their current assigned IP regimen.
Study Drug Compliance Review			X		X	X	X	
General								
Provide diet and exercise counselling	X	X*	X	X	X	X	X	*Assessed by Phone
Dispense meter supplies	X		X	X		X	X	
Review daily diary of finger-stick glucose values	X	X*	X	X	X	X	X	*Assessed by Phone
Provide logs / instructions	X		X	X		X	X	
Assess Rescue			X	X	X	X	X	

[a] Visits may be scheduled ± 7 days (of original schedule) to allow flexibility of scheduling. Week 12 and Week 14 visits should be scheduled at least 7 days apart. The visit window for the rescue visit assessments starts at the site's receipt of the HbA1c alert or FPG confirmation.

[b] Phone assessments.

[c] In case the Week 14 visit is delayed, subsequent visits should be delayed to maintain an interval of at least 12 weeks between the Week 14 and Week 26 visits. Short- and long-term period study visits can be delayed by a maximum of 11 months in total.. If the duration of IP administration is longer than 52 (+1) weeks, the safety follow-up period should be shortened such that the complete study duration does not exceed 104 weeks (+7 days).

[d] Samples will be drawn at the times shown in Table 17 Sampling Schedule.

Table 15 Long-term procedural outline (CV181375 [D1680C00019])

Procedure	Wk 32[a,c]	Wk 36[a,b]	Wk 40[a,c]	Wk 46[a,b]	Wk 52 / early discontinuation of IP / Rescue[a]	Wk 56[a,c]	Quarterly between Wk 56 and Wk 104	Wk 104 Post-study visit[d]	Notes
Eligibility Assessments									
Review concomitant medications/procedures	X	X*	X	X*	X				*Assessed by Phone
Safety Assessments									
Physical Examination					X				
Targeted Physical Examination	X		X						
Tanner Staging (Investigator determined/Self-reported)					X			X	See Appendix Section 8.10.1
Vital Signs	X		X		X				
Height	X		X		X			X	
Body Weight	X		X		X			X	
ECG					X				
Assessment of signs and symptoms of hypoglycaemia episodes	X	X*	X	X*	X				*Assessed by Phone
Serious Adverse Event Assessment	X	X*	X	X*	X	X*	X*	X	*Assessed by Phone
Adverse Events Assessment	X	X*	X	X*	X	X*	X*	X	*Assessed by Phone
Laboratory Tests									
Standard Safety Laboratory Panel (Blood/Urine)	X		X		X				See Appendix Section 8.7
Fasting Lipid panel					X				Total cholesterol, triglycerides, HDL, and LDL

Procedure	Wk 32[a, c]	Wk 36 [a,b]	Wk 40[a, c]	Wk 46[a,b]	Wk 52 / early discontinuation of IP / Rescue[a]	Wk 56[a,c]	Quarterly between Wk 56 and Wk 104	Wk 104 Post-study visit[d]	Notes
Fasting Plasma Glucose (FPG)	X		X		X				
HbA1c	X		X		X				Results masked following IP administration on Day 1 until after study completion
Pregnancy Test (WOCBP only)	X	X*	X	X*	X				*Parent will provide result over the phone. Home pregnancy kits will be provided.
Growth, bone and maturation markers					X			X	Thyroid-stimulating hormone (TSH), free thyroxine, luteinizing hormone (LH), follicle-stimulating hormone (FSH), oestradiol, total testosterone, insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), calcitonin, 25-hydroxy vitamin D, bone alkaline phosphatase, osteocalcin, parathyroid hormone (PTH) and carboxyterminal cross-linked telopeptide of Type 1 collagen (CTX-1)
Study Drug / IXRS									
Contact IXRS	X		X		X				

Procedure	Wk 32[a, c]	Wk 36 [a,b]	Wk 40[a, c]	Wk 46[a,b]	Wk 52 / early discontinuation of IP / Rescue[a]	Wk 56[a,c]	Quarterly between Wk 56 and Wk 104	Wk 104 Post-study visit[d]	Notes
Third randomisation	X		X*						The third randomisation will apply only to subjects who are eligible for randomised withdrawal of background medication (i.e., subjects who have background medication with metformin only and HbA1c < 7.5% at Week 26 or Week 32 ***Randomisation at Week 40 only for eligible subjects not randomised at Week 32**
Instruction regarding metformin withdrawal	X		X*						Subjects withdrawn from background medication with metformin following the third randomisation will be reminded to stop taking metformin. ***Only subjects randomised at Week 40**
Dispense Study Drug	X		X						No drug dispensed during ETD or Rescue visit. Rescued subjects will continue with their current assigned IP regimen.
Study Drug Compliance Review	X		X		X				
General									
Provide diet and exercise counselling	X	X*	X	X*					*Assessed by Phone
Dispense Meter Supplies	X		X						

Procedure	Wk 32[a, c]	Wk 36 [a,b]	Wk 40[a, c]	Wk 46[a,b]	Wk 52 / early discontinuation of IP / Rescue[a]	Wk 56[a,c]	Quarterly between Wk 56 and Wk 104	Wk 104 Post-study visit[d]	Notes
Review daily diary of finger-stick glucose values	X	X*	X	X*	X				*Assessed by Phone
Provide logs / instructions	X		X						
Assess Rescue	X	X*	X	X*					*Assessed by Phone
Telephone contact with subject/parent (follow-up reminder calls)							X		

[a] Visits may be scheduled ± 7 days (of original schedule) to allow flexibility of scheduling. The visit window for the rescue visit assessments starts at the site's receipt of the HbA1c alert or FPG confirmation.

[b] Phone assessments.

[c] In case the third randomization visit (at Week 32 or Week 40) is delayed, subsequent visits should be delayed to maintain an interval of at least 12 weeks between this visit and the Week 52 visit. Short- and long-term study period visits can be delayed by a maximum of 11 months in total. If the duration of IP administration is longer than 52 (+1) weeks, the safety follow-up period should be shortened such that the complete study duration does not exceed 104 weeks (+7 days).

[d] Visit may be scheduled at any time between Day -28 to +7 days of the original scheduled date to allow flexibility of scheduling.

Table 16 Early treatment discontinuation (ETD) follow-up non-treatment phase

Procedure	Non-treatment Follow-up, up to and including Wk-26 Office Visit[a,b]	Non-treatment Follow-up, past Wk 26 and including Wk-52 Office Visit[a,b]	Non-treatment Follow-up Phone Assessment (Day 1 up to and including Wk 56)[b,c]	Quarterly between Wk 56 and Wk 104	Wk 104 Post-study Visit[c]	Notes
Safety Assessments						
Targeted physical examination	X	X				
Vital signs	X	X				
Body weight & height	X	X			X	
Review concomitant medications	X	X	X			
Serious Adverse Events Assessment	X	X	X	X	X	
Adverse Events Assessment	X	X	X	X	X	
Standard safety laboratory panel (Blood)	X	X				See Appendix Section 8.7
Fasting Plasma Glucose (FPG)	X	X				
HbA1c	X	X				
Telephone reminder calls				X		

Procedure	Non-treatment Follow-up, up to and including Wk-26 Office Visit[a,b]	Non-treatment Follow-up, past Wk 26 and including Wk-52 Office Visit[a,b]	Non-treatment Follow-up Phone Assessment (Day 1 up to and including Wk 56)[b,c]	Quarterly between Wk 56 and Wk 104	Wk 104 Post-study Visit[c]	Notes
Safety Assessments						
Tanner Staging	X*	X*			X	See Appendix Section 8.10.1; *only at time points corresponding to originally scheduled Week 26 and Week 52 visits
Growth, bone and maturation markers	X	X			X	Thyroid-stimulating hormone (TSH), free thyroxine, luteinizing hormone (LH), follicle-stimulating hormone (FSH), oestradiol, total testosterone, insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), calcitonin, 25-hydroxy vitamin D, bone alkaline phosphatase, osteocalcin, parathyroid hormone (PTH) and carboxyterminal cross-linked telopeptide of Type 1 collagen (CTX-1)

[a] In-office assessments to occur at time points corresponding to originally scheduled Day 1 to Week 26 (Short-term) and past Week 26 to Week 52 (Long-term) visits.

[b] Phone assessments only to occur at time points corresponding to originally scheduled that is not identified above as an in-office visit.

[c] Visit may be scheduled at any time between Day -28 to +7 days of the original scheduled date to allow flexibility of scheduling. Short- and long-term period study visits can be delayed by a maximum of 11 months in total. If the duration of IP administration is longer than 52 (+1) weeks, the safety follow-up period should be shortened such that the complete study duration does not exceed 104 weeks (+7 days).

Table 17 Pharmacokinetic/Pharmacodynamic sampling schedule

Study Day	Time (Relative to Dosing) Hour[a]	PK Blood Sample[b]	Plasma Glucose[b]	Plasma DPP-4[b]
Day 1	Pre-dose		X	X
Week 6	0 (Pre-dose)	X	X	
Week 6	2 (± 1 hr)	X	X	X
Week 12	0 (Pre-dose)	X	X	
Week 12	2 (± 1 hr)	X	X	X
Week 20	0 (Pre-dose)	X	X	
Week 20	2 (± 1 hr)	X	X	X
Week 26	0 (Pre-dose)	X	X	
Week 26	2 (± 1 hr)	X[c]	X	X

[a] Pre-dose samples may be collected up to 1 hour pre-dose

[b] All samples will be collected in a fasting condition

[c] PK samples will not be collected at the Week 26 Visit following the Early Treatment Discontinuation Visit

8.2 Handling missing or partial event dates

For data summaries, in case of missing or partial dates and/or times imputation rules will be applied in order to classify AEs, hypoglycaemic events, and DKA as on treatment-emergent and to slot the event to an appropriate analysis period.

Partial dates

- For partial onset dates:

  - Calculate a surrogate date as the first non-missing valid date from the following list (in order of precedence):
    - First active study medication date
    - Informed consent date
    - If a valid non-missing date is not available for any of these dates, the surrogate date will be set to missing.
  - Based on the information provided, set the derived date to the earliest possible date. If only the year is provided, impute onset date as 1st January of that year. If the year and month are provided, impute onset date as 1st day of that month and year.
  - If the surrogate date is non-missing then:
    i. If the derived date is on or after the surrogate date, use the derived date as calculated
    ii. 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
    iii. 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 three dates used to determine the surrogate date are missing, then based on the information provided, set the derived date to the earliest possible date. If only a year is provided, set the derived date to January first of that year. If a year and month is provided, set the derived date to the first day of that month.

- For partial stop dates:

  - If only the year is provided, impute stop date as 31st December of that year, or end of study date for that subject or death date, whichever is earlier.
  - If the year and month are provided, impute stop date as the last day of that month and year, or end of study date for that subject or death date, whichever is earlier.

If the above rules result in illogical dates, the imputation should be updated accordingly, also considering which of the two dates (onset or stop) is more complete. For example, if the imputed start date is later than the imputed stop date, and the stop date is more complete, then the start date should be imputed to be the same as the stop date. This derived date will not be reported in summary tables or listings.

Missing dates

- 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
  - Informed 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.
- Events with missing onset and stop dates will be considered on-treatment.
- For events with missing onset and non-missing stop dates (imputed if partial as described above), if the stop date is earlier than the treatment start date (Day 1) the event will be considered as having started prior to treatment; otherwise the event will be considered on-treatment.

8.3 Handling missing or partial medication dates (excluding rescue insulin)

In order to classify medications as prior or concomitant and to slot the medication to an appropriate analysis period, partial missing or invalid start and stop dates will be imputed where possible as follows:

- If the reported start date is missing or invalid and the informed consent date is not missing or invalid, then the imputed start date is set equal to the informed consent date. If the informed consent date is missing or invalid and the birth date is not missing or invalid, then the imputed start date is set equal to the birth date. If the start date, the informed consent date and the birth date are all invalid or missing, then the imputed start date is set equal to missing.
- If the reported start date is partially entered, then the imputed start date is set equal to the earliest possible reported start date based on the partial entered reported start date.
- If the reported end date is missing, continuing, unknown or invalid, then the imputed end date is set equal to the last possible reported end date based on the reported end dates.
- If the reported end date of the medication is partial, then the imputed end date is set equal to the last possible reported end date based on the partial entered reported end date.

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

8.4 Handling missing or partial medication dates (rescue insulin only)

In order to select the date of rescue medication initiation and to derive the total daily dose of rescue insulin, partial start and stop dates will be imputed as follows:

- For partial start dates:
    - Calculate a surrogate date as the first rescue visit start date. If there is no available rescue visit start date, the surrogate date will be set to missing.
    - Based on the information provided, set the derived date to the earliest possible date. If only the year is provided, impute onset date as 1st January of that year. If the year and month are provided, impute onset date as 1st day of that month and year.
    - If the surrogate date is non-missing then:
        i. If the derived date is on or after the surrogate date, use the derived date as calculated
        ii. If the derived date is prior to the surrogate date, then use the surrogate date as the derived date.
    - If the surrogate date is missing, then use the derived date.
- For partial stop dates:
    - If only the year is provided, impute stop date as 31st December of that year, or end of study date for that subject or death date, whichever is earlier.
    - If the year and month are provided, impute stop date as the last day of that month and year, or end of study date for that subject or death date, whichever is earlier.

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

8.5 Handling missing or partial T2DM diagnosis dates

If the T2DM diagnosis date 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, or date of informed consent, whichever is earlier.
- Missing day and month, but year is present: the day and month will be imputed as 30 June of the year, or date of informed consent, whichever is earlier.
- 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 informed consent date, then the diagnosis date will be taken as equal to the informed consent date.

8.6 Deriving age at each visit

8.6.1 Age used to derive normalised height, body weight and BMI expressed as z-score

For baseline assessment, age at the time of the assessment used for baseline will be used. At Week 6, Week 12, Week 20, Week 26, Week 32, Week 40, Week 52, premature end of treatment visit, non-treatment follow-up visit, and Week 104 the age (months) will be derived as:

(Visit date – birth date +1) / 30.5;

If only year part of date of birth is available, this will be imputed to 30th of June. If imputed date of birth results in the derived age being less than the IWRS age at screening, then use IWRS age.

8.7 Clinical laboratory variables

8.7.1 Marked abnormality criteria for safety laboratory variables

Clinical laboratory variables will be summarised and listed using the units listed here. The criteria for marked abnormality for each variable are listed in the following table. Note that a post-baseline laboratory value will be considered a MA only if it satisfies the specified criteria as described in Section 4.7.3.4.

Table 18 Marked laboratory abnormalities

Conventional (US) Units:

Clinical Laboratory variables	Units	Marked Abnormality Criteria	
		Low	High
Hematology			
Haematocrit	%	< 20.0%	> 55.0%
Haematocrit	%		> 60.0%
Haemoglobin	g/dL	< 6 g/dL	> 18 g/dL
Haemoglobin	g/dL		> 20 g/dL
Blood Chemistry			
Protein, total	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
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
Bilirubin, total	mg/dL		> 1.5X ULN if PreTx ≤ ULN
Bilirubin, total	mg/dL		> 2X ULN if PreTx > 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
Creatinine	mg/dL		≥ 1.5X PreTx CREAT
Creatinine	mg/dL		≥ 2.5 mg/dL
Calcium	mg/dL	< 7.5 mg/dL	≥ 1 mg/dL from ULN **and** ≥ 0.5 mg/dL from PreTx CA
Magnesium	mEq/L	< 1 mEq/L	> 4 mEq/L
PO4 (Phosphate)	mg/dL	Age 17-65: ≤ 1.8mg/dL	Age 17-65: ≥ 5.6 mg/dL
Urine			
UACR (Urinary Albumin to Creatinine Ratio)	mg/g		> 1800 mg/g

Standard International Units

Clinical Laboratory variables	Units	Marked Abnormality Criteria	
		Low	High
Hematology			
Haematocrit	ratio	< 0.20	> 0.55
Haematocrit	ratio		> 0.60
Haemoglobin	g/L	< 60 g/L	> 180 g/L
Haemoglobin	g/L		> 200 g/L
Blood Chemistry			
Protein, total	g/L		> 100 g/L
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
Bilirubin, total	µmol/L		> 1.5X ULN if PreTx ≤ ULN
Bilirubin, total	µmol/L		> 2X ULN if PreTx > 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
Creatinine	µmol/L		≥ 1.5X PreTx CREAT
Creatinine	µmol/L		≥ 221 µmol/L
Calcium	mmol/L	< 1.88 mmol/L	≥ 0.25 mmol/L from ULN **and** ≥ 0.13 mmol/L from PreTx CA
Magnesium	mmol/L	< 0.5 mmol/L	> 2 mmol/L
PO4 (Phosphate)	mmol/L	Age 17-65: ≤ 0.58 mmol/L	Age 17-65: ≥ 1.81 mmol/L
Urine			
UACR (Urinary Albumin to Creatinine Ratio)	g/mol		> 203.62 g/mol

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:

- (AST or ALT > 3X ULN) and (Bilirubin > 1.5X ULN within 14 days on or after AT elevation),
- (AST or ALT > 3X ULN) and (Bilirubin > 2X ULN within 14 days on or after AT elevation),

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

8.8 Subgroups

Table 19 Subgroups analyses

Group variable	Subgroups
Race	White Non-White
Ethnicity	Hispanic or Latino Not Hispanic or Latino
Sex*	Male Female
Subject age*	≥ 10 and < 15 years ≥ 15 and < 18 years
Baseline HbA1c	< 8% ≥ 8%
Geographic region	North America Latin America Europe Asia/Pacific
Antidiabetic background medication*	Metformin only Insulin only Metformin + Insulin
Baseline body mass index	< 30 kg/m^2 ≥ 30 kg/m^2

** based on randomisation strata.*

8.9 Classification of hypoglycaemia episodes

Table 20 Classification of hypoglycaemia episodes

Category	Derivation (based on CRF Hypoglycaemia page)
ADA Classification	
Glucose alert value. A glucose alert value of 70 mg/dl (3.9 mmol/l) or less.	Lowest blood glucose value ≤ 70 mg/dl (3.9 mmol/l) and must be not missing.

Category	Derivation (based on CRF Hypoglycaemia page)
Clinically important hypoglycaemia. A glucose level of < 54 mg/dl (< 3.0 mmol/l) is sufficiently low to indicate serious, clinically important hypoglycaemia.	Lowest blood glucose value < 54 mg/dl (3.0 mmol/l) and must be not missing.
Severe hypoglycaemia. Severe hypoglycaemia, as defined by the ADA (6,7), denotes severe cognitive impairment requiring external assistance for recovery.	"Was third party intervention required for this episode of hypoglycaemia?" must be Yes
ISPAD Classification	
Mild/moderate hypoglycaemia The child or parent is aware of, responds to, and treats the hypoglycaemia orally after documenting a blood glucose level of ≤ 3.9 mmol/L (70 mg/dL), where the ADA has suggested using the terminology of 'Documented Symptomatic Hypoglycaemia' for this category. Or the child is not symptomatic with hypoglycaemia but the blood glucose is documented to be ≤ 3.9 mmol/L (70 mg/dL), where the ADA has suggested using the terminology of 'Asymptomatic Hypoglycaemia' for this category.	EITHER: ["Any Symptoms?" must be Yes. Lowest Blood Glucose Value ≤ 70 mg/dl (3.9 mmol/l) and must be not missing. Required Treatment must be Yes, and the treatment must be "Oral Treatment" or "Glucose Treatment" only.] OR ["Any Symptoms?" must be No. Lowest Blood Glucose Value ≤ 70 mg/dl (3.9 mmol/l) and must be not missing.]
Severe hypoglycaemia The child is having altered mental status and cannot assist in their care, is semiconscious or unconscious, or in coma± convulsions and may require parenteral therapy (glucagon or i.v. glucose).	"Any Symptoms?" must be Yes. "Was third party intervention required for this episode of hypoglycaemia?" must be Yes. "Required treatment" must be Yes.

8.10 Puberty status and height velocity used to categorise growth and maturation markers as well as bone biomarkers

8.10.1 Tanner staging

Table 21 Tanner staging criteria

Classification of Sex Maturity Stages in Girls		
Stage	**Pubic Hair**	**Breasts**
1	Preadolescent	Preadolescent
2	Sparse growth of long, slightly pigmented downy hair, straight or only slightly curled; appears chiefly along the labia	Breast bud stage; elevation of breast and papilla as a small mound; enlargement of areola diameter
3	Darker, beginning to curl, increased amount	Further enlargement of breast and areola with no separation of their contours
4	Resembles adult type but the area covered is still considerably smaller than in most adults; no spread to the medial surface of the thighs	Projection of areola and papilla form a secondary mound above the level of the breast
5	Adult in quantity and type, spread to medial surface of thighs	Mature; projection of papilla only due to recession of the areola to the general contour of the breast
Classification of Sex Maturity Stages in Boys		
Stage	**Pubic Hair**	**Genitalia**
1	None	Preadolescent
2	Sparse growth of long, slightly pigmented downy hair, straight or only slightly curled; appears chiefly at the base of the penis	Scrotum and testes have enlarged; change in texture of the scrotal skin with some reddening
3	Darker, coarser, and more curled; spreads sparsely over the junction of the pubes	Growth of the penis, mainly in length but with some increase in breadth; further growth of testes and scrotum
4	Resembles adult type but the area covered is still considerably smaller than in most adults; no spread to the medial surface of the thighs	Penis further enlarged in length and breadth with development of glans. Testes and scrotum further enlarged with further darkening of the scrotal skin
5	Adult in quantity and type, spread to medial surface of thighs	Adult size and shape. No further enlargement of testes and scrotum

8.10.2 Height velocity

The height velocity is defined as the change from baseline, or the previous measurement, to Week t in height (cm) standardised to 26 weeks (183 days) or 52 weeks (365 days). For example, change from Week 52 to Week 104.

The number of actual days between baseline, or the previous measurement, and Week t will be used to derive height velocity.

In case of missing Week t (Week 26, 52, or 104) height, an average change in height (in days) will be derived based on the actual day of the two closest non-missing observations (Week a and Week b, where Week a is the earlier of the two visits) to the planned visit. For missing Week 104, this will be the previous two observations collected. The average change in height per day will be multiplied by the number of days between the day of the Week a and Week t target date, and added to the height value of Week a to derive an imputed Week t value.

8.10.3 Puberty status

Puberty status will be defined, by visit, using the Tanner stage at that visit along with height velocity (as defined Section 8.10.1) as follow:

- Early/mid puberty: Tanner stage 1 or Tanner stage 2 or Tanner stage 3, or Tanner stage 4 with height velocity $\geq$ 1.5 cm/26 weeks = $\geq$ 3 cm/52 weeks,
- Late puberty and young adult: Tanner stage 4 with height velocity < 1.5 cm/26 weeks = < 3 cm/52 weeks, or Tanner stage 5.

8.11 Geographical regions

Table 22 Geographic Regions

Geographic Region	Countries
North America	Canada United States
Latin America	Argentina, Colombia Brazil, Mexico Chile
Europe	Ukraine, Russia Poland, Italy United Kingdom Finland, Romania Israel, Turkey
Asia/Pacific	Australia, Taiwan, Philippines, South Korea India, Thailand Malaysia, New Zealand

8.12 Reporting conventions

Reporting conventions will follow AZ's style guide, wherever applicable.

For summary statistics, the mean and median will be displayed to one decimal place greater than the original value and the measure of variability (e.g. SD, standard error [SE]) will be displayed to two decimal places greater than the original value. Minimum and maximum will be reported to the same decimal places as the original value. Least-square mean estimates will be rounded to two decimal places greater than the original value. Odds ratios will be rounded to one decimal place.

All values will be presented to a maximum 4 decimal places.

P-values ≥0.001 will be reported to three decimal places; p-values less than 0.001 will be reported as <0.001. For frequency tabulations, percentages will be presented with one decimal place. Percentages less than 0.1% will be presented as '<0.1%'. If the frequency and percentage are zero they will be presented as '0' (instead of 0 (0.0)). Non-estimable SDs or SEs will be replaced with a dash ('-'). Confidence intervals will be reported to the same number of decimal places as the associated estimate. The nominal alpha defined for the study is 0.05 (two-sided).

8.13 Treatment presentation for tables and figures

Treatment label	Explanation	Analysis purpose
First randomised / actual treatment (Day 1)		Disposition, Demographics, Safety, Exposure
Total Dapagliflozin	All subjects 1st randomised to / actual treatment to dapagliflozin 5mg	
Total Saxagliptin	All subjects 1st randomised to / actual treatment saxagliptin 2.5mg	
Placebo	All subjects 1st randomised to / actual treatment placebo	
Treatment regimen		By regimen outputs: Disposition, Efficacy
Dapagliflozin 5mg/10mg	Low/high dose regimen dapagliflozin	
Dapagliflozin 5mg	Low dose regimen dapagliflozin	
Saxagliptin 2.5mg/5mg	Low/high dose regimen saxagliptin	
Saxagliptin 2.5mg	Low dose regimen saxagliptin	
Placebo	All subjects 1st randomised to placebo	
Second randomisation (Week 14)		Up-titration subjects analysis set outputs: Disposition, Demographics, Efficacy
Dapagliflozin 5mg	All subjects randomised at Week 14 to remain on dapagliflozin 5mg	
Dapagliflozin 10mg	All subjects randomised at Week 14 to up-titrate to dapagliflozin 10mg	
Saxagliptin 2.5mg	All subjects randomised at Week 14 to remain on saxagliptin 2.5mg	
Saxagliptin 5mg	All subjects randomised at Week 14 to up-titrate to saxagliptin 5mg	
Third randomisation (Week 32 or 40)		Randomised withdrawal subjects analysis set outputs: Disposition, Demographics, Efficacy, Safety

Treatment label	Explanation	Analysis purpose
Dapagliflozin 10mg monotherapy	All subjects randomised at Week 32/40 to withdraw background metformin and either up-titrate to dapagliflozin 10mg (if previously randomised to dapagliflozin 5mg) or to stay on dapagliflozin 10mg (if previously up-titration randomised to high-dose) or switch from placebo to dapagliflozin 10mg	
Dapagliflozin 5mg or 10mg + Metformin	All 1st randomisation dapagliflozin subjects randomised at Week 32/40 to remain on background metformin	
Saxagliptin 5mg monotherapy	All subjects randomised at Week 32/40 to withdraw background metformin and either up-titrate to saxagliptin 5mg (if previously randomised to saxagliptin 2.5mg) or to stay on saxagliptin 5mg (if previously up-titration randomised to high-dose) or switch from placebo to saxagliptin 5mg	
Saxagliptin 2.5mg or 5mg + Metformin	All 1st randomisation saxagliptin subjects randomised at Week 32/40 to remain on background metformin	
Placebo + Metformin	All 1st randomisation placebo subjects randomised at Week 32/40 to remain on background metformin	
Last randomised/actual treatment		Disposition, Demographics, Safety
Dapagliflozin 10mg monotherapy	All subjects whose last randomised/actual treatment was dapagliflozin and the	

Treatment label	Explanation	Analysis purpose
	subject was randomised to withdraw background metformin	
Dapagliflozin 5mg or 10mg	All subjects whose last randomised/actual treatment was dapagliflozin and the subject remained on background metformin (if eligible for third randomisation)	
Saxagliptin 5mg monotherapy	All subjects whose last randomised/actual treatment was saxagliptin and the subject was randomised to withdraw background metformin	
Saxagliptin 2.5mg or 5mg	All subjects whose last randomised/actual treatment was saxagliptin and the subject remained on background metformin (if eligible for third randomisation)	
Placebo	All subjects whose last randomised/actual treatment was placebo and the subject remained on background metformin (if eligible for third randomisation)	
Dose at onset / actual dose and treatment taken		Dose at onset outputs: Safety (exposure, AEs, labs)
Dapagliflozin 5mg	All subjects on dapagliflozin 5mg per treatment assignments in Section 4.1.6	
Dapagliflozin 10mg	All subjects on dapagliflozin 10mg per treatment assignments in Section 4.1.6	
Total Dapagliflozin	All subjects who took Dapagliflozin based on all three randomisations	
Saxagliptin 2.5mg	All subjects on saxagliptin 2.5mg per treatment assignments in Section 4.1.6	

Treatment label	Explanation	Analysis purpose
Saxagliptin 5mg	All subjects on saxagliptin 5mg per treatment assignments in Section 4.1.6	
Total Saxagliptin	All subjects who took Saxagliptin based on all three randomisations	
Placebo	All subjects on placebo per treatment assignments in Section 4.1.6	
Highest dose taken in ST period		PK outputs
Dapagliflozin 5mg	All subjects whose highest actual dose in the ST period was dapagliflozin 5mg	
Dapagliflozin 10mg	All subjects whose highest actual dose in the ST period was dapagliflozin 10mg	
Saxagliptin 2.5mg	All subjects whose highest actual dose in the ST period was saxagliptin 2.5mg	
Saxagliptin 5mg	All subjects whose highest actual dose in the ST period was saxagliptin 5mg	

8.14 Overview of primary and sensitivity efficacy analyses

Table 23 Overview of primary and sensitivity efficacy analyses

Subgroup includes race, ethnicity, sex, age group using the randomisation strata, geographical region, baseline antidiabetic treatment, baseline HbA1c, baseline BMI.

Short term period

Parameter	Assessment	Overall drug treatment dapagliflozin (or saxagliptin) vs placebo	Low-dose/High-dose regimen dapagliflozin (or saxagliptin) vs placebo	Low-dose regimen dapagliflozin (or saxagliptin) vs placebo	Low-dose vs high-dose dapagliflozin (or saxagliptin)
HbA1c	Change from baseline to Week 26	**P1, primary** MI followed by ANCOVA ITT estimand MNAR Randomised Subjects Dataset	**S1, primary** MI followed by weighted ANCOVA ITT estimand MNAR Randomised Subjects Dataset	**S2, primary** MI followed by weighted ANCOVA ITT estimand MNAR Randomised Subjects Dataset	**S9, primary** MI followed by ANCOVA ITT estimand MNAR Up-titration Randomised Subjects Dataset
		P1, supportive Figure LS means by visit up to Week 26 MI followed by ANCOVA Randomised Subjects Dataset	**S1, supportive** Figure LS means by visit up to Week 26 MI followed by weighted ANCOVA Randomised Subjects Dataset	**S2, SA1** Prior rescue or discontinuation MI (MAR) followed by weighted ANCOVA Randomised Subjects Dataset	**S9, SA1** Prior rescue or discontinuation MI (MAR) followed by ANCOVA Up-titration Randomised Subjects Dataset
		P1, SA1 Prior rescue or	**S1, SA1** Prior rescue or	**S2, subpopulation**	**S9, subpopulation**

Parameter	Assessment	Overall drug treatment dapagliflozin (or saxagliptin) vs placebo	Low-dose/High-dose regimen dapagliflozin (or saxagliptin) vs placebo	Low-dose regimen dapagliflozin (or saxagliptin) vs placebo	Low-dose vs high-dose dapagliflozin (or saxagliptin)
		discontinuation MI (MAR) followed by ANCOVA Randomised Subjects Dataset	discontinuation MI (MAR) followed by weighted ANCOVA Randomised Subjects Dataset	MI followed by weighted ANCOVA ITT estimand MNAR Randomised Subjects Dataset	MI followed by ANCOVA ITT estimand MNAR Up-titration Randomised Subjects Dataset
		P1, SA2 Prior rescue or discontinuation or RPD onset MI (MAR) followed by ANCOVA Evaluable Subjects Dataset	**S1, subgroup analysis** MI followed by weighted ANCOVA ITT estimand MNAR Randomised Subjects Dataset		
		P1, SA3 Tipping point analysis	**S1, subpopulation**		

Parameter	Assessment	Overall drug treatment dapagliflozin (or saxagliptin) vs placebo	Low-dose/High-dose regimen dapagliflozin (or saxagliptin) vs placebo	Low-dose regimen dapagliflozin (or saxagliptin) vs placebo	Low-dose vs high-dose dapagliflozin (or saxagliptin)
		MI followed by ANCOVA (same as P1) Randomised Subjects Dataset	MI followed by weighted ANCOVA ITT estimand MNAR Randomised Subjects Dataset		
		P1, subpopulation MI followed by ANCOVA ITT estimand MNAR Randomised Subjects Dataset			
		P1, subgroup analysis MI followed by ANCOVA ITT estimand MNAR			

Parameter	Assessment	Overall drug treatment dapagliflozin (or saxagliptin) vs placebo	Low-dose/High-dose regimen dapagliflozin (or saxagliptin) vs placebo	Low-dose regimen dapagliflozin (or saxagliptin) vs placebo	Low-dose vs high-dose dapagliflozin (or saxagliptin)
		Randomised Subjects Dataset			
	Proportion of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7% at Week 26	**S6, primary** MI followed by Logistic regression ITT estimand Randomised Subjects Dataset	**S7, primary** MI followed by weighted Logistic regression ITT estimand Randomised Subjects Dataset	**S8, primary** MI followed by weighted Logistic regression ITT estimand Randomised Subjects Dataset	**S11, primary** MI followed by logistic regression ITT estimand MNAR Up-titration Randomised Subjects Dataset
		S6, SA1 Regardless of baseline value MI followed by Logistic regression ITT estimand	**S7, SA1** Regardless of baseline value MI followed by weighted Logistic regression ITT estimand	**S8, SA1** Regardless of baseline value MI followed by weighted Logistic regression ITT estimand	

Parameter	Assessment	Overall drug treatment dapagliflozin (or saxagliptin) vs placebo	Low-dose/High-dose regimen dapagliflozin (or saxagliptin) vs placebo	Low-dose regimen dapagliflozin (or saxagliptin) vs placebo	Low-dose vs high-dose dapagliflozin (or saxagliptin)
		Randomised Subjects Dataset	Randomised Subjects Dataset	Randomised Subjects Dataset	
		S6, subpopulation MI followed by Logistic regression ITT estimand Randomised Subjects Dataset	**S7, subpopulation** MI followed by weighted Logistic regression ITT estimand Randomised Subjects Dataset	**S8, subpopulation** MI followed by weighted Logistic regression ITT estimand Randomised Subjects Dataset	**S11, subpopulation** MI followed by logistic regression ITT estimand MNAR Up-titration Randomised Subjects Dataset
FPG	Change from baseline to Week 26	**S3, primary** MI followed by ANCOVA ITT estimand MNAR Randomised Subjects Dataset	**S4, primary** MI followed by weighted ANCOVA ITT estimand MNAR Randomised Subjects Dataset	**S5, primary** MI followed by weighted ANCOVA ITT estimand MNAR Randomised Subjects Dataset	**S10, primary** MI followed by ANCOVA ITT estimand MNAR Up-titration Randomised

Parameter	Assessment	Overall drug treatment dapagliflozin (or saxagliptin) vs placebo	Low-dose/High-dose regimen dapagliflozin (or saxagliptin) vs placebo	Low-dose regimen dapagliflozin (or saxagliptin) vs placebo	Low-dose vs high-dose dapagliflozin (or saxagliptin)
					Subjects Dataset
		S3, supportive Figure LS means by visit up to Week 26 MI followed by ANCOVA Randomised Subjects Dataset	**S4, supportive** Figure LS means by visit up to Week 26 MI followed by weighted ANCOVA Randomised Subjects Dataset	**S5, SA1** Prior rescue or discontinuation MI (MAR) followed by weighted ANCOVA Randomised Subjects Dataset	**S10, SA1** Prior rescue or discontinuation MI (MAR) followed by ANCOVA Up-titration Randomised Subjects Dataset
		S3, SA1 Prior rescue or discontinuation MI (MAR) followed by ANCOVA Randomised Subjects Dataset	**S4, SA1** Prior rescue or discontinuation MI (MAR) followed by weighted ANCOVA Randomised Subjects Dataset	**S5, subpopulation** MI followed by weighted ANCOVA ITT estimand MNAR Randomised Subjects Dataset	**S10, subpopulation** MI followed by ANCOVA ITT estimand MNAR Up-titration Randomised Subjects Dataset

Parameter	Assessment	Overall drug treatment dapagliflozin (or saxagliptin) vs placebo	Low-dose/High-dose regimen dapagliflozin (or saxagliptin) vs placebo	Low-dose regimen dapagliflozin (or saxagliptin) vs placebo	Low-dose vs high-dose dapagliflozin (or saxagliptin)
Glycaemic rescue medication or discontinuing study medication due to lack of efficacy	Proportion of subjects	**E1** Logistic regression Randomised Subjects Dataset			
		E1, subpopulation Logistic regression Randomised Subjects Dataset			
	Time to Glycaemic rescue medication or discontinuing study medication	**E2** Cox proportional hazards Randomised Subjects Dataset			

Parameter	Assessment	Overall drug treatment dapagliflozin (or saxagliptin) vs placebo	Low-dose/High-dose regimen dapagliflozin (or saxagliptin) vs placebo	Low-dose regimen dapagliflozin (or saxagliptin) vs placebo	Low-dose vs high-dose dapagliflozin (or saxagliptin)
	due to lack of efficacy				
		E2 Kaplan-Meier Randomised Subjects Dataset			
		E2, subpopulation Cox proportional hazards Randomised Subjects Dataset			
		E2, subpopulation Kaplan-Meier Randomised Subjects Dataset			

Parameter	Assessment	Overall drug treatment dapagliflozin (or saxagliptin) vs placebo	Low-dose/High-dose regimen dapagliflozin (or saxagliptin) vs placebo	Low-dose regimen dapagliflozin (or saxagliptin) vs placebo	Low-dose vs high-dose dapagliflozin (or saxagliptin)
	Percentage of subjects who initiate rescue medication	**E2, supportive** Descriptive statistics Randomised Subjects Dataset			
		E2, subpopulation Descriptive statistics Randomised Subjects Dataset			

P=Primary. S=Secondary. SA=Sensitivity Analysis. E=Exploratory.

Subpopulation: subgroup of subjects on background medication metformin +/- insulin.

Short term + long term period

Parameter	Assessment	Overall drug treatment [dapagliflozin or saxagliptin] vs placebo	
		Without considering the third randomisation (up to Week 52)	**Excluding subjects randomised to withdrawal (up to Week 52)**
HbA1c	Mean change from baseline to Week 52	**E3** MI MAR followed by ANCOVA Randomised Subjects Dataset	**E3, supportive** MI MAR followed by weighted ANCOVA Randomised Subjects Dataset excluding subjects randomised to withdrawal
		E3, supportive Line plot by visit MI MAR followed by ANCOVA Randomised Subjects Dataset	
	Proportion of subjects who had baseline ≥ 7% who achieve an HbA1c level < 7% at Week 52	**E4** MI MAR followed by logistic regression Randomised Subjects Dataset	**E4, supportive** MI MAR followed by logistic regression Randomised Subjects Dataset excluding subjects randomised to withdrawal
FPG	Mean change from	**E3**	**E3, supportive**

Parameter	Assessment	Overall drug treatment [dapagliflozin or saxagliptin] vs placebo	
		Without considering the third randomisation (up to Week 52)	**Excluding subjects randomised to withdrawal (up to Week 52)**
	baseline at Week 52	MI MAR followed by ANCOVA by visit Randomised Subjects Dataset	MI MAR followed by weighted ANCOVA Randomised Subjects Dataset excluding subjects randomised to withdrawal
		E3, supportive Line plot by visit MI MAR followed by ANCOVA Randomised Subjects Dataset	
Glycaemic rescue medication or discontinuing study medication due to lack of efficacy	Proportion of subjects at Week 52	**E1** Logistic regression Randomised Subjects Dataset	
	Time to Glycaemic rescue medication or	**E2** Cox proportional hazards	

Parameter	Assessment	Overall drug treatment [dapagliflozin or saxagliptin] vs placebo	
		Without considering the third randomisation (up to Week 52)	**Excluding subjects randomised to withdrawal (up to Week 52)**
	discontinuing study medication due to lack of efficacy	Randomised Subjects Dataset	
		E2 Kaplan-Meier Randomised Subjects Dataset	
	Percentage of subjects who initiate rescue medication at Week 52	**E2, supportive** Descriptive statistics Randomised Subjects Dataset	
		E2, subpopulation Descriptive statistics Randomised Subjects Dataset	

E=Exploratory.

Subpopulation: subgroup of subjects on background medication metformin +/- insulin.

Randomised withdrawal period

Parameter	Assessment	For subjects initially randomised the dapagliflozin (or saxagliptin) group: Dapagliflozin (or saxagliptin) vs Dapagliflozin (or saxagliptin) + Metformin	For subjects initially randomised to the placebo group: High-dose dapagliflozin (or saxagliptin) vs Placebo + Metformin
HbA1c	Mean change from withdrawal baseline to Week 52	**E5** Descriptive statistics No imputation Randomised Withdrawal Subjects Dataset	**E5** Descriptive statistics No imputation Randomised Withdrawal Subjects Dataset
	Percentage of subjects who achieve an HbA1c level < 7% at Week 52	**E5, supportive** Descriptive statistics No imputation Randomised Withdrawal Subjects Dataset	**E5, supportive** Descriptive statistics No imputation Randomised Withdrawal Subjects Dataset
FPG	Mean change from withdrawal baseline to Week 52	**E5** Descriptive statistics No imputation Randomised Withdrawal Subjects Dataset	**E5** Descriptive statistics No imputation Randomised Withdrawal Subjects Dataset

Parameter	Assessment	For subjects initially randomised the dapagliflozin (or saxagliptin) group: Dapagliflozin (or saxagliptin) vs Dapagliflozin (or saxagliptin) + Metformin	For subjects initially randomised to the placebo group: High-dose dapagliflozin (or saxagliptin) vs Placebo + Metformin
Glycaemic rescue medication or discontinuing study medication due to lack of efficacy	Time to Glycaemic rescue medication or discontinuing study medication due to lack of efficacy	**E5, supportive** Kaplan-Meier Randomised Withdrawal Subjects Dataset	**E5, supportive** Kaplan-Meier Randomised Withdrawal Subjects Dataset
	Percentage of subjects who initiate rescue medication at Week 52	**E5, supportive** Descriptive statistics No imputation Randomised Withdrawal Subjects Dataset	**E5, supportive** Descriptive statistics No imputation Randomised Withdrawal Subjects Dataset

E=Exploratory.

8.15 Overview of primary and sensitivity safety analyses

Table 24 Overview of primary and sensitivity safety analyses

Subgroup includes race, ethnicity, sex, age group using the randomisation strata, region, baseline antidiabetic treatment, baseline HbA1c, baseline BMI.

Parameter	**Assessment**	**Short term period**	**Short term + Long term period**	**Withdrawal period:** **1) For subjects initially randomised the dapagliflozin (or saxagliptin) group: High-dose dapagliflozin (or saxagliptin) vs High-dose dapagliflozin (or saxagliptin) + Metformin** **2) For subjects initially randomised to the placebo group: High-dose dapagliflozin (or saxagliptin) vs Placebo + Metformin** **3) Based on third randomisation (regardless of prior treatments)**	**Post-study visit Week 104**
AEs	Overall AEs	Descriptive statistics + incidence rates Regardless of rescue Treated Subjects Data Set	Descriptive statistics + incidence rates Regardless of rescue Treated Subjects Data Set	Descriptive statistics + incidence rates Regardless of rescue Randomised Withdrawal Subjects Data Set *For treatment regimens 1, 2 and 3*	
		Sensitivity Descriptive statistics + incidence rates Prior to rescue Treated Subjects Data Set	**Sensitivity** Descriptive statistics + incidence rates Prior to rescue Treated Subjects Data Set	**Sensitivity** Descriptive statistics + incidence rates Prior to rescue Randomised Withdrawal Subjects Data Set *For treatment regimens 1, 2 and 3*	
			Up to Week 32 Descriptive statistics + incidence rates Regardless of rescue		

Parameter	Assessment	Short term period	Short term + Long term period	Withdrawal period: 1) For subjects initially randomised the dapagliflozin (or saxagliptin) group: High-dose dapagliflozin (or saxagliptin) vs High-dose dapagliflozin (or saxagliptin) + Metformin 2) For subjects initially randomised to the placebo group: High-dose dapagliflozin (or saxagliptin) vs Placebo + Metformin 3) Based on third randomisation (regardless of prior treatments)	Post-study visit Week 104
			Treated Subjects Data Set		
			Excluding subjects randomised to withdrawal Weighted analysis Treated Subjects Data Set		
			Subgroup Descriptive statistics + incidence rates Regardless of rescue Treated Subjects Data Set		
			Subgroup - Sensitivity Descriptive statistics + incidence rates Prior to rescue Treated Subjects Data Set		

Parameter	**Assessment**	**Short term period**	**Short term + Long term period**	**Withdrawal period:** **1) For subjects initially randomised the dapagliflozin (or saxagliptin) group: High-dose dapagliflozin (or saxagliptin) vs High-dose dapagliflozin (or saxagliptin) + Metformin** **2) For subjects initially randomised to the placebo group: High-dose dapagliflozin (or saxagliptin) vs Placebo + Metformin** **3) Based on third randomisation (regardless of prior treatments)**	**Post-study visit Week 104**
			Subpopulation Descriptive statistics + incidence rates Regardless of rescue Treated Subjects Data Set		
			By treatment at onset of AE Incidence rates Regardless of rescue Based on treatment received at onset of AE Treated Subjects Data Set		
	Any AE by SOC + PT	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Randomised Withdrawal Subjects Data Set *For treatment regimens 1, 2 and 3*	Descriptive statistics Regardless of rescue Treated Subjects Data Set

Parameter	Assessment	Short term period	Short term + Long term period	Withdrawal period: 1) For subjects initially randomised the dapagliflozin (or saxagliptin) group: High-dose dapagliflozin (or saxagliptin) vs High-dose dapagliflozin (or saxagliptin) + Metformin 2) For subjects initially randomised to the placebo group: High-dose dapagliflozin (or saxagliptin) vs Placebo + Metformin 3) Based on third randomisation (regardless of prior treatments)	Post-study visit Week 104
		Sensitivity Descriptive statistics Prior to rescue Treated Subjects Data Set	**Sensitivity** Descriptive statistics Prior to rescue Treated Subjects Data Set		
			Up to Week 32 Descriptive statistics Regardless of rescue Treated Subjects Data Set		
			Excluding subjects randomised to withdrawal Descriptive statistics weighted analysis Regardless of rescue Treated Subjects Data Set		
		Subgroup [Only for subgroups: age group, sex, race, baseline antidiabetic treatment]	**Subgroup** [Only for subgroups: age group, sex, race, baseline antidiabetic treatment]	**Subgroup** [Only for subgroups: age group, sex, race, baseline antidiabetic treatment] Descriptive statistics	

Parameter	Assessment	Short term period	Short term + Long term period	Withdrawal period: 1) For subjects initially randomised the dapagliflozin (or saxagliptin) group: High-dose dapagliflozin (or saxagliptin) vs High-dose dapagliflozin (or saxagliptin) + Metformin 2) For subjects initially randomised to the placebo group: High-dose dapagliflozin (or saxagliptin) vs Placebo + Metformin 3) Based on third randomisation (regardless of prior treatments)	Post-study visit Week 104
		Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Regardless of rescue Randomised Withdrawal Subjects Data Set *For treatment regimens 1, 2 and 3*	
		Subpopulation Descriptive statistics Regardless of rescue Treated Subjects Data Set	**Subpopulation** Descriptive statistics Regardless of rescue Treated Subjects Data Set	**Subpopulation** Descriptive statistics Regardless of rescue Randomised Withdrawal Subjects Data Set *For treatment regimens 1, 2 and 3*	
			By treatment at onset of AE Incidence rates Regardless of rescue Based on treatment received at onset of AE Treated Subjects Data Set		
	Any AE by SOC, PT and	Descriptive statistics Regardless of rescue	Descriptive statistics Regardless of rescue	Descriptive statistics Regardless of rescue	

Parameter	Assessment	Short term period	Short term + Long term period	Withdrawal period: 1) For subjects initially randomised the dapagliflozin (or saxagliptin) group: High-dose dapagliflozin (or saxagliptin) vs High-dose dapagliflozin (or saxagliptin) + Metformin 2) For subjects initially randomised to the placebo group: High-dose dapagliflozin (or saxagliptin) vs Placebo + Metformin 3) Based on third randomisation (regardless of prior treatments)	Post-study visit Week 104
	maximum intensity	Treated Subjects Data Set	Treated Subjects Data Set	Randomised Withdrawal Subjects Data Set *For treatment regimens 1, 2 and 3*	
	Any AE related to study drug by SOC and PT	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Randomised Withdrawal Subjects Data Set *For treatment regimens 1, 2 and 3*	
	Any AE by SOC and PT for common PTs >5%	Descriptive statistics + number of events Regardless of rescue Treated Subjects Data Set	Descriptive statistics + number of events Regardless of rescue Treated Subjects Data Set	Descriptive statistics + number of events Regardless of rescue Randomised Withdrawal Subjects Data Set *For treatment regimens 1, 2 and 3*	
		Subpopulation Descriptive statistics + number of events Regardless of rescue Treated Subjects Data Set			

Parameter	Assessment	Short term period	Short term + Long term period	Withdrawal period: 1) For subjects initially randomised the dapagliflozin (or saxagliptin) group: High-dose dapagliflozin (or saxagliptin) vs High-dose dapagliflozin (or saxagliptin) + Metformin 2) For subjects initially randomised to the placebo group: High-dose dapagliflozin (or saxagliptin) vs Placebo + Metformin 3) Based on third randomisation (regardless of prior treatments)	Post-study visit Week 104
	Any non-serious AE by SOC and PT	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Randomised Withdrawal Subjects Data Set *For treatment regimens 1, 2 and 3*	
	Leading to discontinuation of study medication	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Randomised Withdrawal Subjects Data Set *For treatment regimens 1, 2 and 3*	
		Sensitivity Descriptive statistics Prior to rescue Treated Subjects Data Set	**Sensitivity** Descriptive statistics Prior to rescue Treated Subjects Data Set	**Sensitivity** Descriptive statistics Prior to rescue Randomised Withdrawal Subjects Data Set *For treatment regimens 1, 2 and 3*	
	AEOSI by PT	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Randomised Withdrawal Subjects Data Set *For treatment regimens 1, 2 and 3*	

Parameter	Assessment	Short term period	Short term + Long term period	Withdrawal period: 1) For subjects initially randomised the dapagliflozin (or saxagliptin) group: High-dose dapagliflozin (or saxagliptin) vs High-dose dapagliflozin (or saxagliptin) + Metformin 2) For subjects initially randomised to the placebo group: High-dose dapagliflozin (or saxagliptin) vs Placebo + Metformin 3) Based on third randomisation (regardless of prior treatments)	Post-study visit Week 104
SAEs	Any SAE by SOC and PT	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Randomised Withdrawal Subjects Data Set *For treatment regimens 1, 2 and 3*	Descriptive statistics Regardless of rescue Treated Subjects Data Set
		Sensitivity Descriptive statistics Prior to rescue Treated Subjects Data Set	**Sensitivity** Descriptive statistics Prior to rescue Treated Subjects Data Set	**Sensitivity** Descriptive statistics Prior to rescue Randomised Withdrawal Subjects Data Set *For treatment regimens 1, 2 and 3*	
			Up to Week 32 Descriptive statistics Regardless of rescue Treated Subjects Data Set		
			By treatment at onset of AE Descriptive statistics		

Parameter	**Assessment**	**Short term period**	**Short term + Long term period**	**Withdrawal period:** **1) For subjects initially randomised the dapagliflozin (or saxagliptin) group: High-dose dapagliflozin (or saxagliptin) vs High-dose dapagliflozin (or saxagliptin) + Metformin** **2) For subjects initially randomised to the placebo group: High-dose dapagliflozin (or saxagliptin) vs Placebo + Metformin** **3) Based on third randomisation (regardless of prior treatments)**	**Post-study visit Week 104**
			Regardless of rescue Based on treatment received at onset of AE Treated Subjects Data Set		
	Any SAE related to study drug by SOC and PT	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Randomised Withdrawal Subjects Data Set *For treatment regimens 1, 2 and 3*	
	Any SAE leading to discontinuation of study medication by SOC and PT	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Randomised Withdrawal Subjects Data Set *For treatment regimens 1, 2 and 3*	Descriptive statistics Regardless of rescue Treated Subjects Data Set
Amputation	Any amputations		Descriptive statistics Regardless of rescue		

Parameter	Assessment	Short term period	Short term + Long term period	Withdrawal period: 1) For subjects initially randomised the dapagliflozin (or saxagliptin) group: High-dose dapagliflozin (or saxagliptin) vs High-dose dapagliflozin (or saxagliptin) + Metformin 2) For subjects initially randomised to the placebo group: High-dose dapagliflozin (or saxagliptin) vs Placebo + Metformin 3) Based on third randomisation (regardless of prior treatments)	Post-study visit Week 104
			Treated Subjects Data Set		
Adjudicated DKA	Any adjudicated DKA events by adjudication category	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Randomised Withdrawal Subjects Data Set *For treatment regimens 1 and 2*	
	Any adjudicated DKA events, signs, symptoms and risk factors by adjudication category	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Randomised Withdrawal Subjects Data Set *For treatment regimens 1 and 2*	
	Any adjudicated DKA events leading to discontinuation by adjudication category		Descriptive statistics Regardless of rescue Treated Subjects Data Set		

Parameter	Assessment	Short term period	Short term + Long term period	Withdrawal period: 1) For subjects initially randomised the dapagliflozin (or saxagliptin) group: High-dose dapagliflozin (or saxagliptin) vs High-dose dapagliflozin (or saxagliptin) + Metformin 2) For subjects initially randomised to the placebo group: High-dose dapagliflozin (or saxagliptin) vs Placebo + Metformin 3) Based on third randomisation (regardless of prior treatments)	Post-study visit Week 104
	Any serious adjudicated DKA events by adjudication category and PT	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Randomised Withdrawal Subjects Data Set *For treatment regimens 1 and 2*	
Hypoglycaemia	Any hypoglycaemic events	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Randomised Withdrawal Subjects Data Set *For treatment regimens 1,2, and 3*	
		Sensitivity Descriptive statistics Prior to rescue Treated Subjects Data Set	**Sensitivity** Descriptive statistics Prior to rescue Treated Subjects Data Set		
			Up to Week 32 Descriptive statistics Regardless of rescue Treated Subjects Data Set		

Parameter	**Assessment**	**Short term period**	**Short term + Long term period**	**Withdrawal period:** **1) For subjects initially randomised the dapagliflozin (or saxagliptin) group: High-dose dapagliflozin (or saxagliptin) vs High-dose dapagliflozin (or saxagliptin) + Metformin** **2) For subjects initially randomised to the placebo group: High-dose dapagliflozin (or saxagliptin) vs Placebo + Metformin** **3) Based on third randomisation (regardless of prior treatments)**	**Post-study visit Week 104**
			Up to Week 32, Sensitivity Descriptive statistics Prior to rescue Treated Subjects Data Set		
Labs	Lab tests over time		Observed and change from baseline Regardless of rescue Treated Subjects Data Set	Observed and change from baseline Regardless of rescue Randomised Subjects Data Set *For treatment regimens 1 and 2*	
			Up to Week 32 Descriptive statistics Observed and change from baseline Regardless of rescue Treated Subjects Data Set		
		Shift table Based on LOCF values	Shift table Based on LOCF values		

Parameter	Assessment	Short term period	Short term + Long term period	Withdrawal period: 1) For subjects initially randomised the dapagliflozin (or saxagliptin) group: High-dose dapagliflozin (or saxagliptin) vs High-dose dapagliflozin (or saxagliptin) + Metformin 2) For subjects initially randomised to the placebo group: High-dose dapagliflozin (or saxagliptin) vs Placebo + Metformin 3) Based on third randomisation (regardless of prior treatments)	Post-study visit Week 104
		Treated Subjects Data Set	Treated Subjects Data Set		
	eGFR over time by age group		Observed and change from baseline Regardless of rescue Treated Subjects Data Set	Observed and change from baseline Regardless of rescue Randomised Subjects Data Set *For treatment regimens 1 and 2*	
	Elevated liver function tests	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Randomised Subjects Data Set *For treatment regimens 1 and 2*	
	Hepatic AEs by PT	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Randomised Subjects Data Set *For treatment regimens 1 and 2*	
	MA labs	Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Incidence rate Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Treated Subjects Data Set *For treatment regimen 1, 2 and 3*	
		Sensitivity	**Sensitivity**	**Sensitivity**	

Parameter	**Assessment**	**Short term period**	**Short term + Long term period**	**Withdrawal period:** **1) For subjects initially randomised the dapagliflozin (or saxagliptin) group: High-dose dapagliflozin (or saxagliptin) vs High-dose dapagliflozin (or saxagliptin) + Metformin** **2) For subjects initially randomised to the placebo group: High-dose dapagliflozin (or saxagliptin) vs Placebo + Metformin** **3) Based on third randomisation (regardless of prior treatments)**	**Post-study visit Week 104**
		Descriptive statistics Prior to rescue Treated Subjects Data Set	Descriptive statistics Incidence rate Prior to rescue Treated Subjects Data Set	Descriptive statistics Prior to rescue Treated Subjects Data Set *For treatment regimen 1, 2 and 3*	
			Up to Week 32 Descriptive statistics Treated Subjects Data Set		
			Excluding subjects randomised to withdrawal Weighted analysis Regardless of rescue Treated Subjects Data Set		
			By treatment at onset of MA Incidence rates Regardless of rescue		

Parameter	Assessment	Short term period	Short term + Long term period	Withdrawal period: 1) For subjects initially randomised the dapagliflozin (or saxagliptin) group: High-dose dapagliflozin (or saxagliptin) vs High-dose dapagliflozin (or saxagliptin) + Metformin 2) For subjects initially randomised to the placebo group: High-dose dapagliflozin (or saxagliptin) vs Placebo + Metformin 3) Based on third randomisation (regardless of prior treatments)	Post-study visit Week 104
			Based on treatment received at onset of MA Treated Subjects Data Set		
	Fasting lipid panel		Observed and change from baseline Regardless of rescue Treated Subjects Data Set		
Vital signs	Vital signs over time		Observed and change from baseline Regardless of rescue Treated Subjects Data Set	Observed and change from baseline Regardless of rescue Randomised Withdrawal Subjects Data Set *Treatment regimens 1 and 2*	
ECG	ECGs interpretation over time		Descriptive statistics Regardless of rescue Based on LOCF values		

Parameter	**Assessment**	**Short term period**	**Short term + Long term period**	**Withdrawal period:** **1) For subjects initially randomised the dapagliflozin (or saxagliptin) group: High-dose dapagliflozin (or saxagliptin) vs High-dose dapagliflozin (or saxagliptin) + Metformin** **2) For subjects initially randomised to the placebo group: High-dose dapagliflozin (or saxagliptin) vs Placebo + Metformin** **3) Based on third randomisation (regardless of prior treatments)**	**Post-study visit Week 104**
			Treated Subjects Data Set		
			Excluding subjects randomised to withdrawal Descriptive statistics Weighted analysis Regardless of rescue Based on LOCF values Treated Subjects Data Set		
Body weight, height and BMI	Body weight, height and BMI (including normalised values) over time		Descriptive statistics Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Randomised Withdrawal Subjects Data Set *Treatment regimens 1 and 2*	**Short term + Long term + Week 104:** Descriptive statistics Regardless of rescue Treated Subjects Data Set

Parameter	**Assessment**	**Short term period**	**Short term + Long term period**	**Withdrawal period:** **1) For subjects initially randomised the dapagliflozin (or saxagliptin) group: High-dose dapagliflozin (or saxagliptin) vs High-dose dapagliflozin (or saxagliptin) + Metformin** **2) For subjects initially randomised to the placebo group: High-dose dapagliflozin (or saxagliptin) vs Placebo + Metformin** **3) Based on third randomisation (regardless of prior treatments)**	**Post-study visit Week 104**
Measures of growth and maturity	Tanner stages		Descriptive statistics Based on LOCF values Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Based on LOCF values Randomised Withdrawal Subjects Data Set *Treatment regimens 1 and 2*	**Short term + Long term + Week 104:** Descriptive statistics **Short term + Long term + Week 104:** Based on LOCF values Regardless of rescue Treated Subjects Data Set
		Shift table from baseline to Week 26 Regardless of rescue Treated Subjects Data Set	Shift table from baseline to Week 52 Based on LOCF values Regardless of rescue Treated Subjects Data Set	Shift table from withdrawal baseline to Week 52 Based on LOCF values Regardless of rescue Treated Subjects Data Set *Treatment regimens 1 and 2*	**Short term + Long term + Week 104:** Shift table from baseline to Week 104 Based on LOCF values Regardless of rescue Treated Subjects Data Set

Parameter	**Assessment**	**Short term period**	**Short term + Long term period**	**Withdrawal period:** **1) For subjects initially randomised the dapagliflozin (or saxagliptin) group: High-dose dapagliflozin (or saxagliptin) vs High-dose dapagliflozin (or saxagliptin) + Metformin** **2) For subjects initially randomised to the placebo group: High-dose dapagliflozin (or saxagliptin) vs Placebo + Metformin** **3) Based on third randomisation (regardless of prior treatments)**	**Post-study visit Week 104**
			Categorical change from Week 26 to Week 52 by baseline status Based on LOCF values Regardless of rescue Treated Subjects Data Set	Categorical change from withdrawal baseline to Week 52 by baseline status Based on LOCF values Regardless of rescue Randomised Withdrawal Subjects Data Set *Treatment regimens 1 and 2*	**Short term + Long term + Week 104:** Categorical change from Week 52 to Week 104 by baseline status Based on LOCF values Regardless of rescue Treated Subjects Data Set
			Excluding subjects randomised to withdrawal Descriptive statistics Weighted analysis Based on LOCF values Regardless of rescue Treated Subjects Data Set		

Parameter	**Assessment**	**Short term period**	**Short term + Long term period**	**Withdrawal period:** **1) For subjects initially randomised the dapagliflozin (or saxagliptin) group: High-dose dapagliflozin (or saxagliptin) vs High-dose dapagliflozin (or saxagliptin) + Metformin** **2) For subjects initially randomised to the placebo group: High-dose dapagliflozin (or saxagliptin) vs Placebo + Metformin** **3) Based on third randomisation (regardless of prior treatments)**	**Post-study visit Week 104**
	Growth and maturity markers		Descriptive statistics Based on LOCF values Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Based on LOCF values Randomised Withdrawal Subjects Data Set *Treatment regimens 1 and 2*	**Short term + Long term + Week 104:** Descriptive statistics Regardless of rescue Based on LOCF values Treated Subjects Data Set
				Categorical change from withdrawal baseline by age and puberty status Regardless of rescue Randomised Withdrawal Subjects Data Set *Treatment regimens 1 and 2*	**Short term + Long term + Week 104:** Categorical change from baseline by age and puberty status Regardless of rescue Treated Subjects Data Set

Parameter	**Assessment**	**Short term period**	**Short term + Long term period**	**Withdrawal period:** **1) For subjects initially randomised the dapagliflozin (or saxagliptin) group: High-dose dapagliflozin (or saxagliptin) vs High-dose dapagliflozin (or saxagliptin) + Metformin** **2) For subjects initially randomised to the placebo group: High-dose dapagliflozin (or saxagliptin) vs Placebo + Metformin** **3) Based on third randomisation (regardless of prior treatments)**	**Post-study visit Week 104**
	Bone biomarkers		Descriptive statistics Based on LOCF values Regardless of rescue Treated Subjects Data Set	Descriptive statistics Regardless of rescue Based on LOCF values Randomised Withdrawal Subjects Data Set *Treatment regimens 1 and 2*	**Short term + Long term + Week 104:** Descriptive statistics Regardless of rescue Based on LOCF values Treated Subjects Data Set
				Categorical change from withdrawal baseline by age and puberty status Regardless of rescue Randomised Withdrawal Subjects Data Set *Treatment regimens 1 and 2*	**Short term + Long term + Week 104:** Categorical change from baseline by age and puberty status Regardless of rescue Treated Subjects Data Set

Subpopulation: subgroup of subjects on background medication metformin +/- insulin.