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

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Clinical Protocol CV181375
(AZ study number: D1680C00019)

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

Revised Protocol Number: 06
Incorporates global amendments: 01, 02, 03, 04, 05 and 06

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

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 06	07-Feb-2022	Incorporates Global Amendment 06
Amendment 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 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,

Document	Date of Issue	Summary of Change
		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.
Revised Protocol 05	24-Sep-2020	Incorporates Global Amendment 05
Amendment 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 randomization visit (for subjects undergoing third randomization) and the Week 52 visit in case the Week 14 or third randomization 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 randomization at Week 32, or the HbA1c collection at Week 32 and the third randomization at Week 40, the subject should not go through this randomization as the HbA1c value would no longer be reliable to ascertain eligibility for the third randomization.

Document	Date of Issue	Summary of Change
		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 04	27-Jun-2019	Incorporates Global Amendment 04
Amendment 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 maturations 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 harmonization across all AstraZeneca clinical study protocols.
Revised Protocol 03	04-Oct-2018	Incorporates Global Amendment 03
Amendment 03	04-Oct-2018	Based on recommendations provided by the Food and Drug Administration (FDA), the protocol has been revised to reflect modifications in the study design, i.e., the addition of a randomized withdrawal of background medication in a subset of eligible subjects from the active treatment arms, and randomized 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 02	04-Apr-2017	Incorporates Global Amendment 02
Amendment 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 United States FDA review. A post-study visit has also been added at Week 104.
Revised Protocol 01	11-Oct-2016	Incorporates Global Amendment 01
Amendment 01	11-Oct-2016	Subsequent to recent Health Authority feedback, the original study design has been entirely revised in accordance with the FDA-specified preferred study objectives and design.
Original Protocol	02-Mar-2016	Not applicable

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SYNOPSIS

Clinical Protocol CV181375 (AZ study number: D1680C00019)

Protocol 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.

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Dapagliflozin 5 mg, dapagliflozin 10 mg, saxagliptin 2.5 mg, saxagliptin 5 mg tablets administered orally once daily for the 26-week double-blinded treatment period and the 26-week site and subject-blinded long-term (LT) extension.

Throughout this protocol, reference to 26 weeks of treatment should be interpreted as treatment received until the Week 26 visit. Likewise, 52 weeks of treatment should be interpreted as treatment received until the Week 52 visit.

Study Phase: 3b

Research Hypothesis:

In pediatric Type 2 Diabetes Mellitus (T2DM) subjects on diet and exercise and metformin, or insulin, or metformin and insulin:

The primary research hypothesis for dapagliflozin is whether the addition of dapagliflozin results in a greater mean reduction from baseline in glycosylated hemoglobin (HbA1c) as compared to placebo when each are administered over 26 weeks of oral double-blind add-on treatment.

The primary research hypothesis for saxagliptin is whether the addition of saxagliptin results in a greater mean reduction from baseline in HbA1c as compared to placebo when each are administered over 26 weeks of oral double-blind add-on treatment.

Objectives:

Primary Objective:

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 to placebo in pediatric 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.

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 glycemic target of HbA1c < 7% at 12 weeks) compared to placebo in pediatric 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 pediatric 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 pediatric 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 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 of saxagliptin (2.5 mg or 5 mg [all doses and regimens combined]) compared to placebo in

pediatric 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.

e) To determine if there will be a greater mean reduction from baseline in 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 glycemic target of HbA1c <7% at 12 weeks) compared to placebo in pediatric 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.

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 pediatric 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 pediatric 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 < 7.0% after 26 weeks of oral double-blind add-on therapy of dapagliflozin (5 mg or 10 mg [all doses and regimens combined]) or of saxagliptin (2.5 mg or 5 mg [all doses and regimens combined]) compared to placebo in pediatric 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.

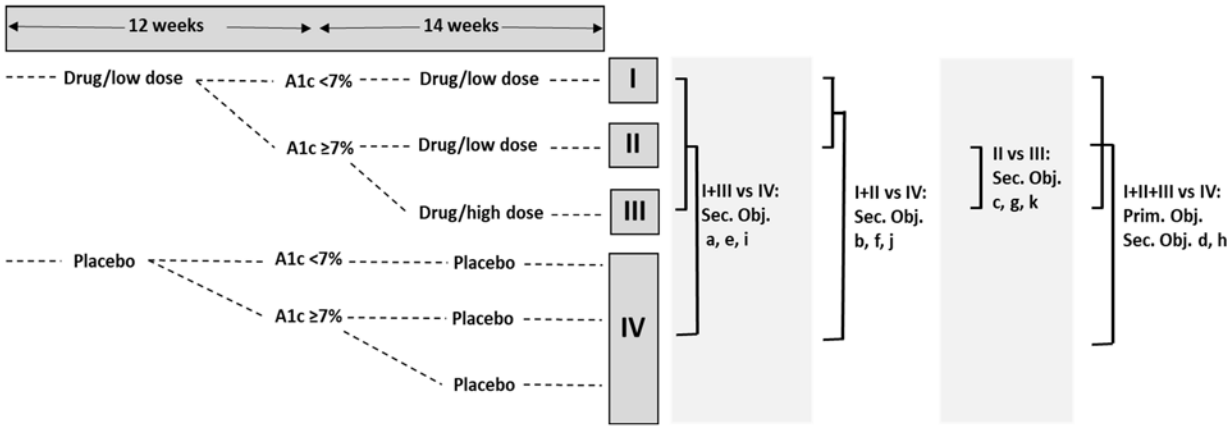
i) To compare the percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7.0% after 26 weeks of oral double-blind add-on therapy of dapagliflozin 5 mg or saxagliptin 2.5 mg (with titration to the high-dose for those who do not achieve the glycemic target of HbA1c <7% at 12 weeks) versus placebo in pediatric 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.

j) To compare the percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7.0% after 26 weeks of oral double-blind add-on therapy of dapagliflozin 5 mg or saxagliptin 2.5 mg versus placebo in pediatric 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 pediatric 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 < 7.0% 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 labeled numerically in Section 8.4.2.2 and the statistical analysis plan.

Figure 1: Schematic of group comparisons in study Primary & Secondary Objectives



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 schematized above.

Safety Objectives:

- To assess the safety and tolerability, including the incidence of adverse events (AEs) and events of hypoglycemia, 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 pediatric 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 pediatric 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 pediatric 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 pediatric subjects who are randomized to withdraw background metformin.

Exploratory Objectives:

- To compare the percentage of subjects requiring glycemic 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 pediatric 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 glycemic 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 pediatric 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 pediatric 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 pediatric 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 < 7.0% after 52 weeks of oral blinded add-on therapy with dapagliflozin versus placebo or saxagliptin versus placebo in pediatric 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 randomized to withdraw background metformin relative to dapagliflozin+metformin (and separately saxagliptin+metformin) and relative to placebo+metformin during the randomized withdrawal period using change in HbA1c, change in FPG, achievement of therapeutic glycemic response (HbA1c < 7%) and time to rescue or discontinuation due to lack of glycemic control.

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.

Study Design: The proposed study is a 26-week Phase 3b, multicenter, randomized, 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 pediatric subjects with T2DM, and an additional post-study visit at Week 104 for assessment of measures of growth and maturity. Approximately 243 pediatric subjects will be randomized in a 1:1:1 ratio to receive dapagliflozin 5 mg, saxagliptin 2.5 mg, or placebo. Approximately 81 subjects will be randomized to each treatment arm.

The primary efficacy endpoint will be assessed at the end of the initial 26-week double-blind treatment period (referred to as the ST period [from Day 1 to end of Week 26]). The ST period will be followed by a 26-week, double-blind safety extension period (the LT treatment period [from Week 27 to end of Week 52]). Dapagliflozin and, separately, saxagliptin will be compared against the single shared placebo comparator.

Safety monitoring will continue following the Week 52 end-of-treatment visit until the Week 104 post-study visit. Measures of growth and maturity will be assessed at the Week 104 post-study visit.

Screening procedures are expected to last 6 to 8 weeks. If, however, at initial screening, one or more laboratory values are not in the eligibility range, but the Investigators determine they are amenable to correction within a reasonable time frame, the screening period can be extended to a maximum of 6 months. At screening, all procedures and assessments should be completed and reviewed by the Investigators. Retesting/reassessment of failed variables can be performed as determined by the Investigators during the 6-month screening period. Retesting/reassessment frequencies are at the discretion of the Investigators, but should occur at least once every 3 months. In cases when a subject does not meet one or more criteria the first time and is later reassessed to see if he/she will meet that criteria, the Investigator should ensure that other criteria are still met (and have not become disqualifying during the interim time period) before accepting that the subject meets all eligibility criteria. Subjects who fail to meet the eligibility criteria after the 6-month screening period should be considered as screen failures and withdrawn from the study. Screen-failed subjects, however, can be re-screened a maximum of two more times at a later time. For re-screening, subjects must be re-consented and all the screening procedures and assessments must be repeated. Subjects are not able to be re-screened if they turn 18 years of age during the screening period.

Prior to randomization on Day 1, subjects will be required to have been treated with diet and exercise and a stable dose of at least 1000 mg metformin (IR or XR) for a minimum of 8 weeks, or a stable baseline dose of insulin for a minimum of 8 weeks, or a stable combination of at least 1000 mg metformin and insulin for a minimum of 8 weeks. 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 subjects will be between the ages of 10 and 14 years and at least one third, but no more than two thirds, female subjects.

During the 2-week lead-in 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 (2-week lead-in, 26-week double-blind ST treatment period, and the 26-week blinded safety extension LT treatment period), unless they are randomized to withdraw background medication with metformin at Week 32 or Week 40, until Week 52. If applicable, investigators will encourage subjects to keep their insulin doses stable. Down-titration of insulin will be allowed only as necessary to prevent hypoglycemia and will be at the discretion of the Investigator. Insulin will be up-titrated or added as rescue as warranted by a hyperglycemic state. Home glucose meters to monitor glucose control will be dispensed to subjects and self-blood glucose monitoring requirements and procedures will be explained. Subjects will also be instructed on the use of the subject diary to record self-monitoring glucose levels and daily insulin dose, if applicable. Subjects will also receive a blood ketone meter for testing when DKA is suspected.

After the lead-in period, eligible subjects with HbA1c of 6.5% to 10.5% at screening will be randomized 1:1:1 to receive oral, double-blind, dapagliflozin 5 mg (approximately 81 subjects), saxagliptin 2.5 mg (approximately 81 subjects), or placebo (approximately 81 subjects). Day 1 Randomization 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 baseline combination of metformin and insulin), gender, and age at randomization (10 to below 15 years of age, 15 to below 18 years of age).

Samples for analysis of plasma levels of dapagliflozin, saxagliptin and its metabolite 5-OH-saxagliptin will be collected up to 1 hour pre-dose and approximately 2 hours post-dose (± 1 hour) during the Week 6, 12, 20, and 26 visits.

Samples for analysis of FPG will be collected up to 1 hour pre-dose during the Day 1 visit, and up to 1 hour pre-dose and approximately 2 hours post-dose (± 1 hour) during the Week 6, 12, 20, and 26 visits.

Plasma samples for analysis of dipeptidyl-peptidase-4 (DPP-4) activity will be collected up to 1 hour pre-dose during the Day 1 visit, and at 2 hours post-dose (± 1hr) during the Week 6, 12, 20, and 26 visits.

All plasma samples will be drawn in the fasting condition.

HbA1c results will be blinded following IP administration on Day 1 until after study completion. A blinded HbA1c assessment will be performed at Week 12 for all subjects. A second randomization will be performed at the Week 14 visit, based on the Week 12 HbA1c assessment. All subjects with Week 12 HbA1c values $< 7\%$ will remain on previously assigned low-dose randomized treatment (dapagliflozin 5 mg, or saxagliptin 2.5 mg, or placebo) after the Week 12 assessment. Subjects assigned to the dapagliflozin treatment arm at Day 1 Randomization with Week 12 HbA1c values $\geq 7\%$ will be re-randomized in a 1:1 ratio to continue on the low-dose treatment (dapagliflozin 5 mg) or to up-titrate to the high-dose treatment (dapagliflozin 10 mg) after the Week 12 assessment. Similarly, subjects assigned to the saxagliptin treatment arm at Day 1 Randomization with Week 12 HbA1c values $\geq 7\%$ will be re-randomized in a 1:1 ratio to continue on the low-dose treatment (saxagliptin 2.5 mg) or to up-titrate to the high-dose treatment (saxagliptin 5 mg) after the Week 12 assessment. Subjects assigned to the placebo treatment arm at Day 1 Randomization with Week 12 HbA1c values $\geq 7\%$ will continue on placebo treatment. 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 second randomization process that will be indistinguishable (for the subjects and site personnel) from the actual second randomization. During the Week 14 visit, blinded study drug will be dispensed to all subjects in accordance with the treatment assignments based on Week 12 HbA1c assessments.

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 randomization) will continue with their randomized 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 randomization (randomized withdrawal of background medication) at either Week 32 or Week 40. Eligibility for randomized withdrawal from background medication will be restricted to subjects who are receiving background treatment with metformin only, and who have HbA1c $< 7.5\%$ at Week 26 or Week 32 provided they have not initiated rescue glycemic control therapy or been withdrawn from study drug. Subjects who are receiving background medication with metformin only, who do not qualify for the third randomization at Week 32 due to an HbA1c $\geq 7.5\%$ at Week 26, may qualify for the third randomization at Week 40 if HbA1c $< 7.5\%$ at

Week 32. Subjects who have passed Week 40 will not be included in the randomized withdrawal of background medication. During the third randomization:

- Eligible subjects who are receiving active treatment will be grouped into two separate strata for saxagliptin and dapagliflozin, and then randomized 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 randomized to withdraw background treatment 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 randomized 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 randomized 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.

Discontinuation of background metformin will occur in an unblinded manner. Exposure to monotherapy in subjects undergoing randomized withdrawal of metformin will last from the start of metformin withdrawal for that subject (following randomization at Week 32 or Week 40) until the end of Week 52, when all subjects will discontinue study medications. After Week 52, all subjects will take the most appropriate medication at the discretion of the treating physician.

Rescued subjects and subjects who discontinue IP will not be eligible for randomized withdrawal of background medication at Week 32 or Week 40.

Subjects with HbA1c $\geq$ 7.5% at Week 26 and Week 32 and subjects who are receiving background treatment with either insulin only, or insulin+metformin, including those randomized to receive placebo, will continue their randomized study medication (assigned after the Week 12 assessment) in the double-blind LT treatment period.

Adverse events and serious adverse events (SAEs) will be assessed during a Week 56 phone visit.

In case a visit is delayed for any reason, subsequent visits should be scheduled such that an interval of at least 12 weeks is maintained between the:

- Week-14 visit and the Week-26 visit.
- Third randomization (for subjects undergoing third randomization; occurring at the Week-32 or the Week-40 visit) and the Week-52 visit.

If more than 12 weeks elapse between the HbA1c collection at Week 26 and the third randomization at Week 32, or the HbA1c collection at Week 32 and the third randomization at Week 40, the subject should not go through this randomization, as the HbA1c value would no longer be reliable to ascertain eligibility for the third randomization. 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). A window period of -28 days to +7 days from the original scheduled date will be allowed for the Week-104 visit.

Subjects who discontinue study drug 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. Subjects will attend a post-study visit at Week 104, for assessment of measures of growth and maturity. This visit should be completed without delay at 104 weeks (+7 days) from Day 1, regardless of whether any other study visits were delayed.

All subjects with HbA1c > 8.0% at and after Week 26 will be rescued.

Discontinued subjects will still be evaluated for rescue and will not be replaced.

The Investigator, Sponsor, site and subject will be blinded to the subjects' HbA1c results following administration of IP on Day 1 until after study completion. 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.

During the course of the trial, subjects may be eligible for the addition of open-label rescue medication to their blinded treatment regimen in order to treat ongoing hyperglycemia. Insulin may be used as rescue, at the Investigator's discretion. Any permanent changes in dose of basal insulin should be done after evaluation of rescue criteria, including both self-monitoring blood glucose (SMBG) and central laboratory FPG values.

Pre-specified glycemic criteria (see Table 1 below), based upon SMBG, FPG, or single central laboratory FPG and repeat confirmatory FPG have been established during the treatment period, starting at Week 6, and up to but not including the Week 52 visit, to determine eligibility for open-label rescue medication.

Table 1: Lack of Glycemic Control Criteria for Initiation of Rescue Medication

Study week	Rescue criterion
Week 6 visit up to and not including Week 26 visit	FPG>13.3 mmol/L (240 mg/dl) based on 3 consecutive fasting SMBG values followed by a confirmatory central laboratory FPG or Single central laboratory FPG followed by a confirmatory central laboratory FPG
Week 26 visit up to and not including Week 52 visit	FPG>10 mmol/L (180 mg/dl) based on SMBG for 3 consecutive days followed by a confirmatory central laboratory FPG or Single central laboratory FPG followed by a confirmatory central laboratory FPG or HbA1c > 8.0% (while HbA1c values will remain blinded throughout the study, sites will be notified to allow rescue if values exceed this threshold)

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

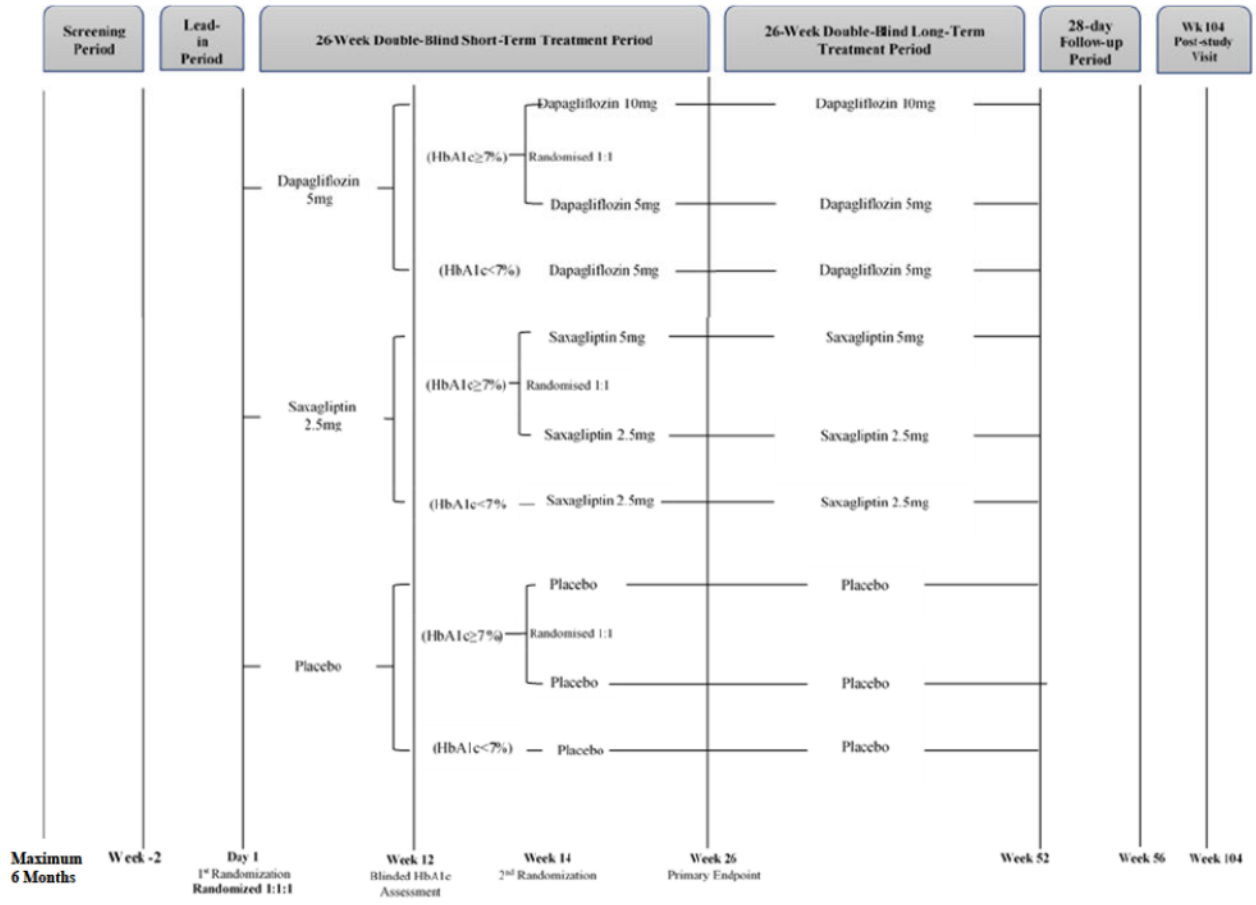
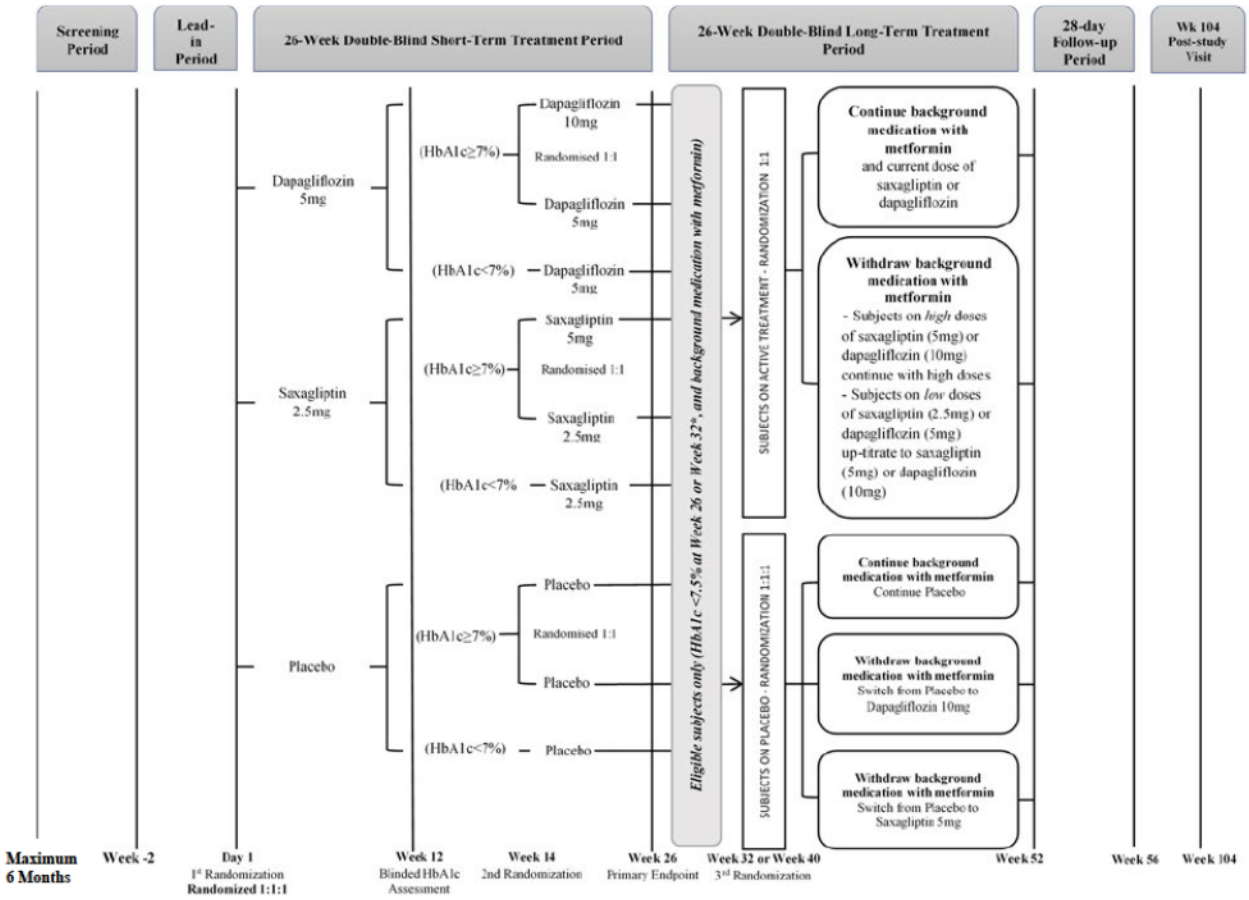


Figure 3: **Study design schematic for subjects undergoing randomized withdrawal of background medication at Week 32 or Week 40**



*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.

Study Population:

For entry into the study, the following key inclusion criteria MUST be met. The full inclusion/exclusion criteria are found in Section 3.3of the protocol.

Inclusion Criteria:

1) Target Population

   a) Previously diagnosed with T2DM by World Health Organization/ADA criteria

   b) HbA1c ≥ 6.5% and ≤ 10.5% obtained during the 6-month screening period

   c) Currently on diet and exercise and stable dose of at least 1000 mg metformin (IR or XR) for a minimum of 8 weeks, or stable dose of insulin for a minimum of 8 weeks, or a stable combination of at least 1000 mg metformin (IR or XR) and insulin for a minimum of 8 weeks prior to Day 1 Randomization

   d) Male and female subjects eligible if reached 10 years of age at screening, and up to but not including 18 years of age at randomization. At least 30% of total subjects will be between the ages of 10 and 14 years and at least one third but no more than two thirds, female subjects.

Exclusion Criteria:

1) Target Disease Exceptions

   a) Presence of Type 1 diabetes, as demonstrated by:

      - Preexisting diagnosis of Type 1 diabetes,

   OR

      - Positivity at screening of either antibodies to glutamic acid decarboxylase (GAD) or protein tyrosine phosphatase-like protein antibodies (IA-2) AND abnormally low levels of C-peptide. GAD and IA-2 antibody testing will be performed in all screened subjects, C-peptide only in otherwise eligible, antibody-positive subjects. All instances of antibody-positive subjects with normal or elevated C-peptide values will be discussed by the Investigator with the study medical monitors and Sponsor's study director to confirm study eligibility.

   b) Previous diagnosis of monogenic etiology of Type 2 diabetes such as maturity onset diabetes of the young (MODY), genetic disorders with strong associations with insulin resistance/diabetes and/or obesity such as Turner's Syndrome and Prader-Willi, or secondary diabetes (steroid use, Cushing's disease, acromegaly), secondary diabetes mellitus, or diabetes insipidus.

   c) Diabetes ketoacidosis within 6 months of screening

   d) Current use of the following medications for the treatment of diabetes, or use within the specified timeframe prior to screening for the main study:

      i. Eight weeks: sulfonylureas, alpha glucosidase inhibitors, metiglinide, oral or injectable incretins or incretin mimetics, other anti-diabetes medications not otherwise specified

      ii. Sixteen weeks: thiazolidinediones. DPP-4 inhibitors (with no reported medication related AEs related to DPP-4 inhibitors), sodium glucose cotransporter-2 (SGLT-2) inhibitors (with no reported medication related AEs related to SGLT-2 inhibitors)

Study Drug: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Table 2: Study Drug for BMS-477118 AND BMS-512148

Medication	Potency	IP/Non-IP
Saxagliptin	2.5 mg	IP
Saxagliptin	5 mg	IP
Dapagliflozin	5 mg	IP
Dapagliflozin	10 mg	IP
Placebo Matching Saxagliptin 2.5 mg/5mg	0 mg	IP
Placebo Matching Dapagliflozin 5 mg	0 mg	IP
Placebo Matching Dapagliflozin 10 mg	0 mg	IP

Statistical Considerations:

Sample Size:

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

Dapagliflozin and saxagliptin will be compared with placebo separately. 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 2-sided alpha level of 0.05.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 versus placebo assuming a standard deviation of 1.7%.

Day 1 Randomization 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), gender, and age (10 to below 15 years of age, 15 to below 18 years of age).

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

Endpoints:

Primary Endpoint:

Change from baseline in HbA1c at Week 26

Secondary Endpoints:

- Change from baseline in FPG at Week 26
- Percentage of subjects with baseline HbA1c $\geq$ 7% who achieve an HbA1c level < 7.0% at Week 26

Exploratory Endpoints:

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

- Percentage of subjects who require glycemic rescue medication or discontinue the study medication due to lack of efficacy during the 26-week treatment period

- Time to initiation of glycemic rescue medication or discontinuation of study medication due to lack of efficacy during the 26-week treatment period

Exploratory efficacy endpoints for long-term assessment of saxagliptin and dapagliflozin:

- 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 an HbA1c level < 7% at Week 52
- Time to initiation of glycemic rescue medication or discontinuation of study medication due to lack of efficacy during the 52-week treatment period

Exploratory efficacy endpoints for monotherapy assessment of saxagliptin and dapagliflozin:

- Change in HbA1c during the randomized withdrawal period
- Change in FPG during the randomized withdrawal period
- Percentage of subjects who achieve or maintain a HbA1c level < 7.0% at the end of the randomized withdrawal period
- Time to initiation of glycemic rescue medication or discontinuation of study medication due to lack of efficacy using the start time of randomized withdrawal as the reference point

Safety Endpoints:

Safety endpoints consist of the incidence of AEs, SAEs, hypoglycemic 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.

Analyses:

Dapagliflozin and saxagliptin will be summarized separately. A common placebo group will be included in each summary.

In addition, within the analyses of dapagliflozin and saxagliptin, 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 and saxagliptin regimens within each treatment will be combined into one subgroup and compared to the corresponding (common) placebo subgroup. P-values corresponding to subgroup comparisons will be reported for the primary and secondary efficacy endpoints, and will be reported at the nominal significance level.

All efficacy analyses will be performed using the Randomized Subjects Data Set (all randomized subjects who receive at least one dose of study medication during the treatment period) unless otherwise specified. Furthermore, to account for randomization withdrawal, analyses dedicated to monotherapy assessment will be performed on the Randomized Withdrawal Subjects Data Set.

The following treatment regimens are considered for analysis:

- Low-dose/high-dose: Initial treatment of the low-dose followed by up-titrating to the high-dose for those who do not achieve the glycemic target of HbA1c < 7% at Week 12 and continuing treatment with the low-dose for those achieving the glycemic target of HbA1c<7% at Week 12
- Low-dose: Initial treatment of the low-dose followed by continuing treatment on the low-dose drug for those who do not achieve the glycemic target of HbA1c <7% at Week 12 and continuing treatment with the low-dose for those achieving the glycemic target of HbA1c < 7% at Week 12

Following the third randomization:

- Subjects initially randomized to dapagliflozin (or saxagliptin) with metformin as background therapy will be re-randomized in a 1:1 ratio to either dapagliflozin (or saxagliptin) alone or to dapagliflozin (or saxagliptin) with metformin as background therapy
- Subjects initially randomized to placebo with metformin as background therapy will be re-randomized in a 1:1:1 ratio to dapagliflozin alone or saxagliptin alone or placebo with metformin as background therapy

For each drug, the comparison vs placebo will be tested at a two-sided alpha level of 0.05.

The primary efficacy analysis will be performed using an analysis of covariance (ANCOVA). For this analysis, all dose levels for a treatment will be combined into one treatment group for each drug. Separate models will be used for saxagliptin and dapagliflozin analyses, and each analysis will include the (common) placebo control. Each model will have terms for baseline value, treatment group, and randomization strata. Point estimates and 95% confidence intervals will be calculated based on maximum likelihood for the adjusted mean changes within each treatment group as well as for the differences in adjusted mean changes between treatment groups.

The intent-to-treat estimand (which will be estimated using all available data regardless of premature treatment discontinuation and regardless of rescue therapy initiation) will be evaluated as the primary estimand. Missing values for Week 26 will be imputed using a multiple imputation method assuming the data are not missing at random. Multiple imputation using retrieved drop-outs 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 26 HbA1c value. The details of the imputation methods will be presented in the statistical analysis plan.

To assess the robustness of the primary efficacy analysis for the change in HbA1c from baseline to Week 26, additional sensitivity analysis may be performed using the Evaluable Subjects Data Set if > 10% of the subjects in any treatment group in the Randomized Subjects Data Set have relevant protocol deviations.

The primary endpoint will also be compared between the low-dose/high-dose treatment regimen and placebo, separately for both dapagliflozin and saxagliptin. In addition, up-titrating to high-dose and continuing on low-dose will be compared in the subset of dapagliflozin and saxagliptin subjects who had HbA1c ≥ 7% at Week 12. These analyses are described under secondary efficacy analyses.

Secondary efficacy 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.

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 (all doses and regimens combined) 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 ≥7% who achieve an HbA1c level < 7.0% at Week 26 between overall drug treatment (all doses and regimens combined) and placebo
7. Comparison of the percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7.0% at Week 26 between the low-dose/high-dose treatment regimen and placebo
8. Comparison of the percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7.0% 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 ≥ 7% who achieve an HbA1c level < 7.0% 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, a weighted ANCOVA will be performed for the change from baseline in HbA1c at Week 26 to compare the placebo and the low-dose/high-dose treatment regimen. For this analysis, all dapagliflozin and saxagliptin subjects who had HbA1c <7% at Week 12 and remained on the low-dose will get a weight of one. The dapagliflozin and saxagliptin subjects who had HbA1c ≥ 7% at Week 12 and continued on the low-dose will get a weight of 0. The dapagliflozin and saxagliptin subjects who had HbA1c ≥ 7% at Week 12 and received the high-dose will get a weight of 2. All subjects who do not undergo the second randomization and all placebo subjects will get a weight of one.

For each drug, a weighted ANCOVA will be performed for the change from baseline in HbA1c at Week 26 to compare the placebo and the low-dose treatment regimen. For this analysis, all dapagliflozin and saxagliptin subjects who had HbA1c < 7% at Week 12 and remained on the low-dose will be get a weight of one. The dapagliflozin and saxagliptin subjects who had HbA1c ≥ 7% at Week 12 and continued on the low-dose will get a weight of 2. The dapagliflozin and saxagliptin subjects who had HbA1c ≥ 7% at Week 12 and received the high-dose will get a weight of 0. All subjects who do not undergo the second randomization and all placebo subjects will get a weight of one.

For subjects on dapagliflozin and saxagliptin who had HbA1c ≥ 7% at Week 12, the change from baseline HbA1c at Week 26 (ST) will be compared between the subjects re-randomized to remain on the low-dose and the subjects who are re-randomized to the high-dose using an ANCOVA. This analysis will be based on the Up-titration Randomized Subjects Data Set.

Change from baseline at Week 26 (ST) in FPG will be analyzed similarly as the analyses of change from baseline in HbA1c at Week 26.

The proportion of subjects achieving HbA1c < 7.0% at Week 26 (ST) will be analyzed using weighted logistic regression with adjustment for the baseline HbA1c measurement and the randomization strata. Weighting for the subjects will be applied similarly to a weighting in the analysis of change from baseline in HbA1c. Subjects with missing a response at Week 26 will be imputed by dichotomizing the imputed values of HbA1c at Week 26.

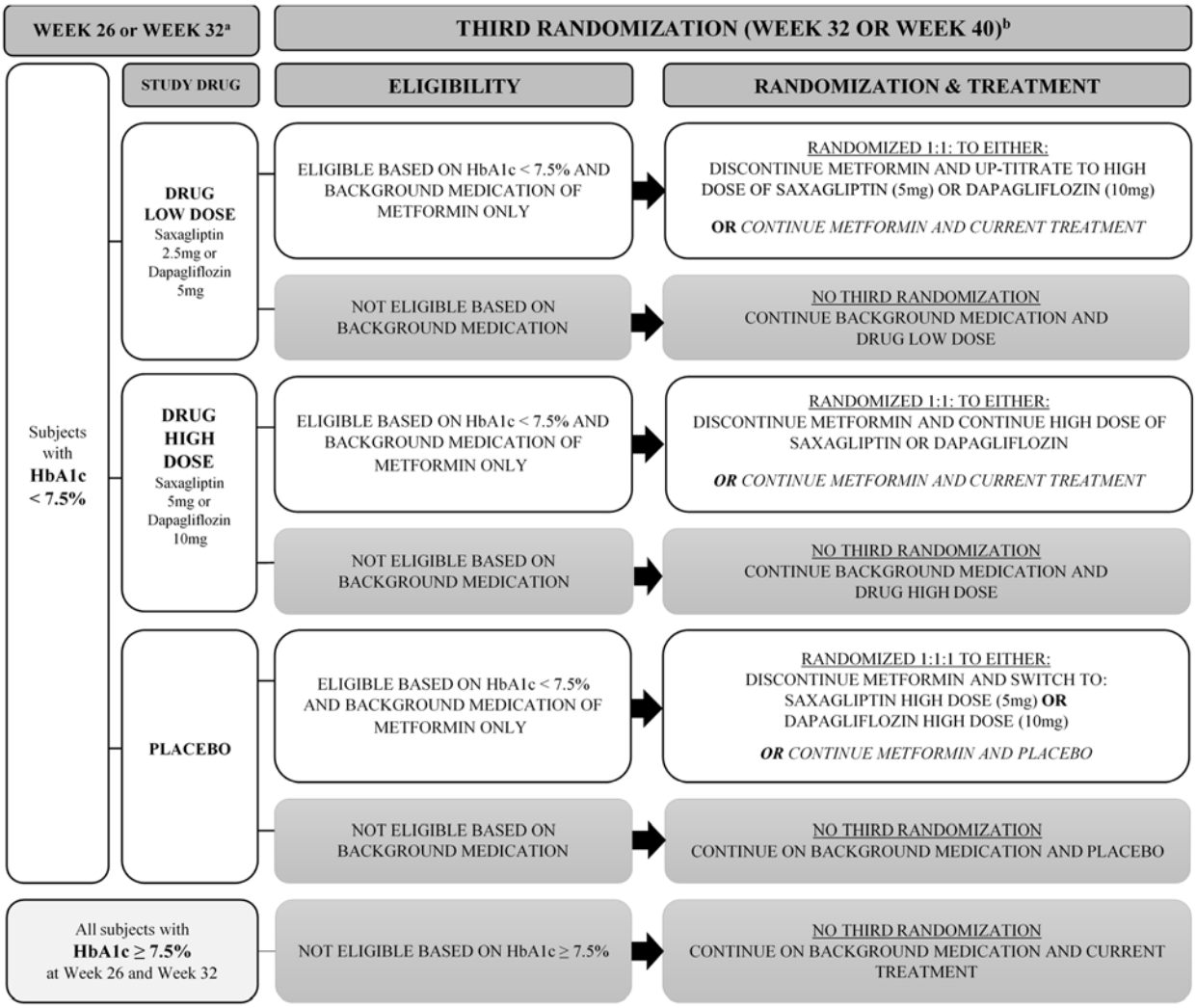
The assessment of safety will be based on the analyses of AEs, vital signs, physical examinations, electrocardiograms, hypoglycemia events, DKA events, safety laboratory evaluations, and measures of growth and maturity. Dapagliflozin and saxagliptin will be summarized separately. Both low-dose and high-dose saxagliptin and dapagliflozin groups, respectively, will be combined for saxagliptin and dapagliflozin to provide the safety summary for overall saxagliptin and overall dapagliflozin compared to placebo. A common placebo group will be included in each summary.

Measures of growth, bone, and maturation markers will be summarized for ST and the combined ST+LT treatment periods. Exploratory analyses will be performed for overall saxagliptin and overall dapagliflozin separately, by combining all low-dose and high-dose treatment groups as appropriate. All analyses will be conducted on the Randomized Subjects Data Set.

Exploratory analyses for the monotherapy period will include only subjects who are on background medication with metformin and have HbA1c measurement < 7.5% at Week 26 or Week 32.

The monotherapy safety assessment will include standard safety assessments occurring during the randomized withdrawal period. These analyses will be conducted during the randomized withdrawal period using the Randomized Withdrawal Subject Data Set. Exploratory efficacy and safety analyses will include short and long-term assessment of saxagliptin and dapagliflozin, and monotherapy assessment.

Figure 4: Subgroups following the third randomization at Week 32 or Week 40



[a] Subjects who fail to qualify for the third randomization 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 randomization at Week 32, and subjects who meet the eligibility criteria at Week 32 will undergo the third randomization at Week 40. Subjects who have passed Week 40 of the study will not be eligible for the third randomization.

1 INTRODUCTION AND STUDY RATIONALE

Type 2 diabetes is a complex and multifactorial metabolic disorder with contributions from genetic, behavioral, and environmental risk factors. Despite a wealth of information concerning Type 2 diabetes in adults, data unique to the pediatric age group regarding the pathophysiology of and therapy for Type 2 diabetes are limited.[1]

As in adults, Type 2 diabetes in children is characterized by hyperglycemia associated with initial relative insufficiency of insulin secretion and increased insulin resistance, and is ultimately often followed by pancreatic β-cell failure.[2,3,4] A potentially important difference between adults and pediatric patients with Type 2 diabetes is that in the natural course of Type 2 diabetes in pediatric patients, the glucose dysregulation may develop over a much more rapid time frame than is seen in adults.[5] This may be a contributing factor to the tendency for poorer prognosis for microvascular and macrovascular diabetic complications for pediatric patients with Type 2 diabetes, as they become adults.[6] An additional factor unique to the development of Type 2 diabetes in the pediatric age range is the potential additive contribution and impact of the insulin resistance of puberty, which, although a natural phenomenon during pubertal development, may have a negative influence on and potentially exacerbate glycemic dysregulation in susceptible children.[5]

As with adults, it is expected that children and adolescents with Type 2 diabetes are at risk for eventually developing diabetes-related micro- and macrovascular complications with higher glycemic levels.[1] Data from a number of small studies conducted in limited ethnic groups have confirmed an increased risk of microvascular complications[1,7] in pediatric patients with Type 2 diabetes compared with children and adolescents without diabetes. For example, microalbuminuria, macroalbuminuria, and hypercholesterolemia have all shown an increased tendency to develop in Pima Indian children with Type 2 diabetes. Among Japanese pediatric patients, retinopathy has been observed at a similar rate in those with Type 1 and Type 2 diabetes, although it appears to be less common in pediatric patients compared with adults with Type 2 diabetes. A study in Australia found that pediatric patients with Type 2 diabetes have significantly higher rates of microalbuminuria and hypertension than those with Type 1 diabetes, despite shorter duration of disease and lower glycosylated hemoglobin (HbA1c).[8] Additional small studies have shown an increased occurrence of renal disease (Japanese), non-alcoholic fatty liver disease (the Manitoba Cree), and cardiovascular mortality associated with hypertension and dyslipidemia in pediatric patients with Type 2 diabetes.[9]

There is evidence in adults from the UK Prospective Diabetes Study (UKPDS) that normalization of blood glucose substantially decreases the frequency of microvascular complications of Type 2 diabetes (UKPDS Group 1998), consistent with what has been noted with Type 1 diabetes.[10] It is assumed that a management regimen based on adequate glycemic control, via lifestyle changes with modification of diet and physical activity and, as appropriate, medical treatment, should help to reduce the risk of complications in younger persons as well as adults with the disease.

Current therapeutic agents have limited efficacy and are associated with side effects including hypoglycemia, weight gain, edema and gastrointestinal effects. While there are several oral glucose-lowering medications approved for adults with Type 2 diabetes, the only oral

glucose-lowering medication approved for use in pediatric patients age 10 and older is metformin. Agents with new mechanisms of action for the treatment of Type 2 diabetes are being studied.

Given the need for additional oral glucose-lowering therapy options for pediatric patients with Type 2 diabetes, it is appropriate to test the hypothesis that saxagliptin, an orally active dipeptidyl-peptidase-4 (DPP-4) inhibitor, and dapagliflozin, an orally active sodium glucose cotransporter-2 (SGLT-2) inhibitor, will confer the therapeutic benefit of glucose-lowering, without adding the risk of hypoglycemia, in this population. In addition, the risk of weight gain is not expected with saxagliptin, while dapagliflozin is expected to confer some weight loss. This program will investigate the pharmacokinetics (PK), efficacy, safety, and tolerability of saxagliptin versus placebo, and separately, dapagliflozin versus placebo for the treatment of Type 2 diabetes in pediatric patients aged from 10 to < 18 years.

1.1 Study Rationale

This is a Phase 3b study performed as part of the development programs for saxagliptin and dapagliflozin to improve glycemic control as an adjunct to diet and exercise and treatment with metformin immediate release (IR) or extended release (XR), insulin, or metformin (IR or XR) and insulin. This protocol will be performed to meet the pediatric post-marketing requirements for Onglyza, Kombiglyze XR, Farxiga, and Xigduo XR as required by the Pediatric Research Equity Act (PREA), and Onglyza Pediatric Investigational Plan.

Saxagliptin and dapagliflozin have demonstrated, both individually and in combination with insulin or metformin, a favorable safety and tolerability profile in the adult development programs. They have demonstrated a low propensity for hypoglycemia, and both drugs have either demonstrated weight neutrality (saxagliptin) or modest weight reduction (dapagliflozin). Both dapagliflozin and saxagliptin have also demonstrated persistent effects on HbA1c over 2 years of therapy. Given the need for additional oral glucose-lowering therapy options for pediatric patients with Type 2 diabetes, it is appropriate to test the hypothesis that saxagliptin, an orally active DPP-4 inhibitor, and dapagliflozin, an orally active SGLT-2 inhibitor, will confer the therapeutic benefit of glucose-lowering in this population.

The additional randomized withdrawal of background medication in a subset of eligible patients from the treatment arms based on HbA1c < 7.5% at Week 26 or Week 32, and the switch to active treatment in a subset of eligible patients from the placebo arm starting at Week 32 or Week 40 will provide information on patients being treated with monotherapy. The HbA1c criteria for patients to be included in the randomized withdrawal group (HbA1c < 7.5%) is the current HbA1c goal recommended by the American Diabetes Association (ADA) in diabetic patients across all pediatric ages (ADA SOC 2018)[11].

Throughout this protocol, reference to 26 weeks of treatment should be interpreted as treatment received until the Week 26 visit. Likewise, 52 weeks of treatment should be interpreted as treatment received until the Week 52 visit.

1.2 Research Hypotheses

In pediatric Type 2 Diabetes Mellitus (T2DM) subjects on diet and exercise and metformin (IR or XR), or insulin, or metformin (IR or XR) and insulin:

- The primary research hypothesis for dapagliflozin is whether addition of dapagliflozin results in a greater mean reduction from baseline in HbA1c as compared to placebo when each are administered over 26 weeks of oral double-blind add-on treatment.
- The primary research hypothesis for saxagliptin is whether addition of saxagliptin results in a greater mean reduction from baseline in HbA1c as compared to placebo when each are administered over 26 weeks of oral double-blind add-on treatment.

1.3 Objectives

1.3.1 Primary Objective

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 to placebo in pediatric 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.

1.3.2 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 glycemic target of HbA1c < 7% at 12 weeks) compared to placebo in pediatric 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 pediatric 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 pediatric 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 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 of saxagliptin (2.5 mg or 5 mg [all doses and regimens combined]) compared to placebo in pediatric 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.

e) To determine if there will be a greater mean reduction from baseline in 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 glycemic target of HbA1c <7% at 12 weeks) compared to placebo in pediatric 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.

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 pediatric 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 pediatric 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 < 7.0% after 26 weeks of oral double-blind add-on therapy of dapagliflozin (5 mg or 10 mg [all doses and regimens combined]) or of saxagliptin (2.5 mg or 5 mg [all doses and regimens combined]) compared to placebo in pediatric 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.

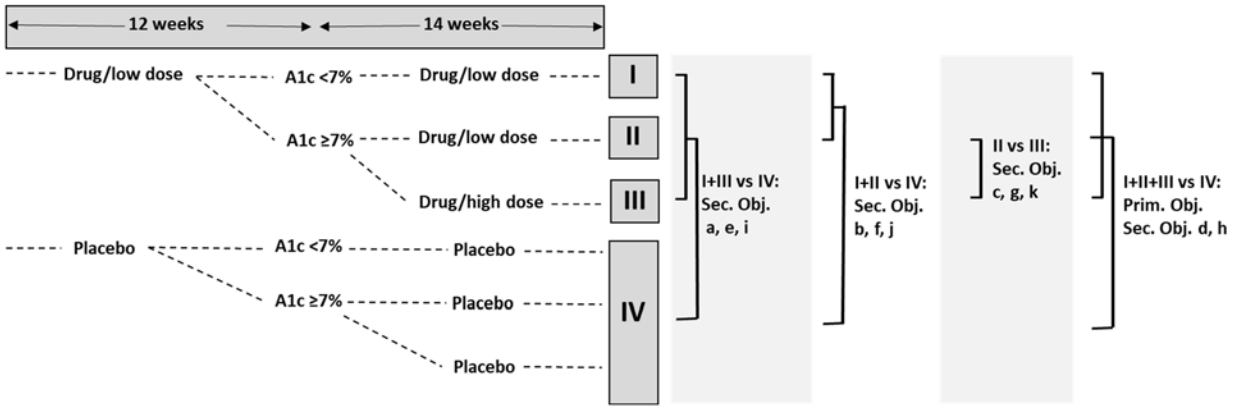
i) To compare the percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7.0% after 26 weeks of oral double-blind add-on therapy of dapagliflozin 5 mg or saxagliptin 2.5 mg (with titration to the high-dose for those who do not achieve the glycemic target of HbA1c < 7% at 12 weeks) versus placebo in pediatric 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.

j) To compare the percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7.0% after 26 weeks of oral double-blind add-on therapy of dapagliflozin 5 mg or saxagliptin 2.5 mg versus placebo in pediatric 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 pediatric 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 < 7.0% 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 labeled numerically in Section 8.4.2.2 and the statistical analysis plan.

Figure 1.3.2-1: Schematic of group comparisons in study Primary & Secondary Objectives



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 schematized above.

1.3.3 Safety Objectives

- To assess the safety and tolerability, including the incidence of adverse events (AEs) and events of hypoglycemia, 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 pediatric 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 pediatric 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 pediatric 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 pediatric subjects who are randomized to withdraw background metformin.

1.3.4 Exploratory Objectives

- To compare the percentage of subjects requiring glycemic 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 pediatric

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 glycemic 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 pediatric 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 pediatric 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 pediatric 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 < 7.0% after 52 weeks of oral blinded add-on therapy with dapagliflozin versus placebo, or saxagliptin versus placebo in pediatric 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 randomized to withdraw background metformin relative to dapagliflozin+metformin (and separately saxagliptin+metformin) and relative to placebo+metformin during the randomized withdrawal period using change in HbA1c, change in FPG, achievement of therapeutic glycemic response (HbA1c < 7%), and time to rescue or discontinuation due to lack of glycemic control.

1.3.5 Pharmacokinetic/Pharmacodynamic Objective

- To explore the 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.

1.4 Product Development Background

Saxagliptin (BMS-477118) is a highly potent, selective, reversible, and competitive DPP-4 inhibitor. Dipeptidyl-peptidase-4 is the enzyme responsible for the inactivation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide. By inhibiting the enzyme DPP-4, saxagliptin potentiates active endogenous GLP-1 concentrations, augmenting the physiological mechanism of insulin secretion and suppressing glucagon release, thereby reducing postprandial and fasting glucose levels in patients with T2DM.

The results from the adult saxagliptin development program support the oral dose of saxagliptin 5 mg once daily in a wide range of patients with T2DM, as either monotherapy, add-on

combination therapy with metformin, a thiazolidinedione, a sulfonylurea (SU), insulin, or initial combination therapy with metformin. The results from the adult Phase 3 studies confirmed clinically meaningful benefits of saxagliptin 5 mg on HbA1c, as well as FPG, postprandial glucose (PPG), insulin, C-peptide, and glucagon levels. In an extensive Phase 2b/3 program, most reported AEs were non-serious and did not require discontinuation of treatment. The safety profile was comparable to placebo and generally consistent when saxagliptin was given as monotherapy, as add-on combination treatment to metformin, to insulin (with or without background metformin), and as initial therapy in combination with metformin. Treatment with saxagliptin led to rates of hypoglycemia that were generally similar compared to placebo, except in combination with insulin or an SU.

Dapagliflozin is a rationally designed, stable, competitive, reversible, highly selective and orally active inhibitor of SGLT-2, the major transporter responsible for renal glucose reabsorption. Dapagliflozin inhibits human SGLT-2 (Ki = 0.55 nM) selectively (1400-fold selective), and is also highly selective versus other facilitative glucose transporters. Dapagliflozin's mechanism of action is different and complementary to the mechanisms of currently available antidiabetic medicines, resulting in the direct and insulin-independent elimination of glucose by the kidney. Further, as SGLT-2 is almost exclusively expressed in the kidney, the highly selective nature of dapagliflozin minimizes the risk of off target (i.e., non-kidney) effects. As such, dapagliflozin offers an important additional strategy for improving glycemic control in patients with T2DM.

Dapagliflozin has been shown to be effective in lowering HbA1c in adult patients with T2DM, when studied as monotherapy and in combination with insulin or oral antidiabetic medications. Results from secondary glycemic efficacy endpoints (including FPG, 2-hour PPG, and change in HbA1c in patients with baseline HbA1c $\geq$ 9.0%) are consistent with the main HbA1c results and further support the role of dapagliflozin as a glucose-lowering agent. Importantly, dapagliflozin has been shown to improve glycemic control with a low intrinsic risk for hypoglycemia. Furthermore, the steady excretion of glucose due to SGLT-2 inhibition results in a continual loss of calories that ultimately leads to a decrease in weight and adiposity. The inhibition of sodium and glucose transport in the proximal tubule also causes a mild diuretic effect, leading to a modest lowering of blood pressure (BP). Overall, dapagliflozin has been shown to improve HbA1c with a low risk of hypoglycemia, while also demonstrating positive trends for common comorbidities (weight gain and systolic hypertension) associated with increased cardiovascular risk in T2DM adult patients.

1.5 Overall Risk/Benefit Assessment

Dapagliflozin and saxagliptin, have been approved as antidiabetic agents in many countries, including the United States (US) and the European Union for use in adults and children with T2DM.

Evaluation of the clinical safety and efficacy data accumulated indicates a positive risk/benefit profile for dapagliflozin and saxagliptin.

Saxagliptin

Prior to approval, saxagliptin was evaluated in 6 core Phase 3, randomized, double-blind controlled trials. Compared to control, treatment with saxagliptin at doses of 2.5 mg to 10 mg resulted in clinically relevant and statistically significant improvements in HbA1c, FPG, and 2 hour PPG. Reductions in HbA1c were seen across subgroups including age, gender, race and baseline body mass index (BMI).

Overall, saxagliptin has been well tolerated in clinical studies. The majority of AEs reported in clinical studies have been of mild intensity and few have required treatment discontinuation.

For an overall risk/benefit assessment of saxagliptin, see the Investigator's Brochure/package leaflet.

Dapagliflozin

Prior to approval, dapagliflozin was evaluated in 5 core Phase 2b studies, 16 core Phase 3 studies, and 3 regional Phase 3 studies. These studies established that dapagliflozin is effective in reducing HbA1c in a broad range of subjects, regardless of disease progression/duration or concomitant use of antidiabetic therapies. Dapagliflozin consistently demonstrated statistically and clinically significant mean reductions in HbA1c versus placebo among the three doses typically studied (2.5 mg, 5, mg and 10 mg). Overall, the dose of 10 mg provided better efficacy than the two lower doses. Effects on secondary glycemic efficacy parameters, including FPG and PPG, support the primary HbA1c efficacy findings. Dapagliflozin also resulted in a modest reduction in total body weight relative to placebo or comparator, largely attributable to a decrease in body fat mass, as well as reductions in systolic BP. Placebo-controlled data for up to 2 years indicate that the beneficial effects on glycemic and non-glycemic parameters were maintained.

Overall, dapagliflozin has been well tolerated in clinical studies.

For an overall risk/benefit assessment of dapagliflozin, see the Investigator's Brochure/package leaflet.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Council for Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor/designee immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the Investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (e.g., advertisements), and any other written information to be provided to subjects. The Investigator or Sponsor/designee should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The Investigator or Sponsor/designee should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

The Sponsor/designee will provide the Investigator with an appropriate (i.e., Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.

6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The Investigator, or a person designated by the Investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subject's signed informed consent form and where applicable the subject's signed Health Insurance Portability and Accountability Act of 1996 (HIPAA) Authorization. Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred. The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the subject in the informed consent form. The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from Regulatory Authorities. The consent form must also include a statement that the Sponsor/designee and Regulatory Authorities have direct access to subject records.

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the informed consent form approved for the study prior to clinical study participation. The explicit wish of a minor, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the Investigator.

Minors who are judged to be of an age of reason must also give their written assent.

Subjects unable to give their written consent may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the Investigator.

Subjects who are re-screened are required to sign a new informed consent form.

The rights, safety, and wellbeing of the study subjects are the most important considerations and should prevail over interests of science and society.

2.4 Handling of Human Biological Samples

A full chain of custody is maintained for all samples throughout their lifecycle. The investigator at each site keeps full traceability of collected biological samples from the subjects while in storage at the site until shipment or disposal/destruction (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed/destroyed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal/destroyed. AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers. Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

The study start date is the date on which the clinical study will be open for recruitment of subjects. The first act of recruitment is the first site open and will be the study start date. Throughout this protocol, reference to 26 weeks of treatment should be interpreted as treatment received until the Week 26 visit. Likewise, 52 weeks of treatment should be interpreted as treatment received until the Week 52 visit.

The proposed study is a 26-week Phase 3b, multicenter, randomized, 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 pediatric subjects with T2DM and an additional post-study visit at Week 104 for assessment of measures of growth and maturity. Approximately 243 pediatric subjects will be randomized in a 1:1:1 ratio to receive dapagliflozin 5 mg, saxagliptin 2.5 mg, or placebo. Approximately 81 subjects will be randomized to each treatment arm.

The primary efficacy endpoint will be assessed at the end of the initial 26-week, double-blind, treatment period (referred to as the short-term [ST] period [from Day 1 to end of Week 26]). The ST period will be followed by a 26-week, double-blind safety extension period (the long-term [LT] period [from Week 27 to end of Week 52]). Dapagliflozin and, separately, saxagliptin, will be compared against the single shared placebo comparator. Safety monitoring will continue following the Week 52 end-of-treatment visit until the Week 104 post-study visit.

Measures of growth and maturity will be assessed at the Week 104 post-study visit.

Screening procedures are expected to last 6 to 8 weeks. If, however, at initial screening, one or more laboratory values are not in the eligibility range, but the Investigators determine they are amenable to correction within a reasonable time frame, the screening period can be extended to a maximum of 6 months. At screening, all screening procedures and assessments should be completed and reviewed by the Investigators. Retesting/reassessment of failed variables can be

performed as determined by the Investigators during the 6-month screening period. Retesting/reassessment frequencies are at the discretion of the Investigators, but should occur at least once every 3 months. In cases when a subject does not meet one or more criteria the first time and is later reassessed to see if he/she will meet that criteria, the Investigator should ensure that other criteria are still met (and have not become disqualifying during the interim time period) before accepting that the subject meets all eligibility criteria. Subjects who fail to meet the eligibility criteria after the 6-month screening period should be considered as screen failures and withdrawn from the study. Screen-failed subjects, however, can be re-screened a maximum of two more times at a later time. For re-screening, subjects must be re-consented and all the screening procedures must be repeated. Subjects are not able to be re-screened if they turn 18 years of age during the screening period.

Prior to randomization on Day 1, subjects will be required to have been treated with diet and exercise and stable dose of at least 1000 mg metformin (IR or XR) for a minimum of 8 weeks, or a stable baseline dose of insulin for a minimum of 8 weeks, or a stable combination of at least 1000 mg metformin (IR or XR) and insulin for a minimum of 8 weeks. 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 subjects will be between the ages of 10 and 14 years and at least one third, but no more than two thirds, female subjects.

During the 2-week lead-in period, subjects will be instructed on a diet and exercise program (in accordance with the ADA or similar local guidelines) to be followed for the study duration. Subjects will maintain their baseline types and/or doses of antidiabetic therapy throughout the study (2-week lead-in, 26-week double-blind ST treatment period, and the 26-week blinded safety extension LT treatment period), unless they are randomized to withdraw background medication with metformin at Week 32 or Week 40, until Week 52. If applicable, investigators will encourage subjects to keep their insulin doses stable. Down-titration of insulin will be allowed only as necessary to prevent hypoglycemia and will be at the discretion of the Investigator. Insulin may be up-titrated or added as rescue as warranted by a hyperglycemic state. Home glucose meters to monitor glucose control will be dispensed to subjects and self-blood glucose monitoring requirements and procedures will be explained. Subjects will also be instructed on the use of the subject diary to record self-monitoring glucose levels and daily insulin dose, if applicable. Subjects will also receive a blood ketone meter for testing when DKA is suspected.

After the lead-in period, eligible subjects with HbA1c of 6.5% to 10.5% at screening will be randomized 1:1:1 to receive oral, double-blind, dapagliflozin 5 mg (approximately 81 subjects), saxagliptin 2.5 mg (approximately 81 subjects), or placebo (approximately 81 subjects). Day 1 Randomization 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 baseline combination of metformin (IR or XR) and insulin), gender, and age (10 to below 15 years of age, 15 to below 18 years of age).

Subjects will be instructed to ingest two blinded tablets daily, as per Table 3.1-1.

Table 3.1-1: Treatment Period to Week 14
Tablet components based on treatment arm assignment

Subjects randomized to Dapagliflozin 5 mg arm receive:	Active Dapagliflozin 5 mg tablet	Saxagliptin Placebo tablet
Subjects randomized to Saxagliptin 2.5 mg arm receive:	Dapagliflozin 5 mg Placebo tablet	Active Saxagliptin 2.5 mg tablet
Subjects randomized to Placebo arm receive:	Dapagliflozin 5 mg Placebo tablet	Saxagliptin Placebo tablet

Table 3.1-2: Treatment Period Week 14 to Week 52
Tablet components based on treatment arm assignment

Subjects designated to Dapagliflozin 10 mg arm receive:	Active Dapagliflozin 10 mg tablet and Dapagliflozin 5 mg Placebo tablet	Saxagliptin Placebo tablet
Subjects designated to Dapagliflozin 5 mg arm receive:	Active Dapagliflozin 5 mg tablet and Dapagliflozin 10 mg Placebo tablet	Saxagliptin Placebo tablet
Subjects designated to Saxagliptin 5 mg arm receive:	Dapagliflozin 5 mg Placebo tablet and Dapagliflozin 10 mg Placebo tablet	Active Saxagliptin 5 mg tablet
Subjects designated to Saxagliptin 2.5 mg arm receive:	Dapagliflozin 5 mg Placebo tablet and Dapagliflozin 10 mg Placebo tablet	Active Saxagliptin 2.5 mg tablet
Subjects designated to Placebo arm receive:	Dapagliflozin 5 mg Placebo tablet and Dapagliflozin 10 mg Placebo tablet	Saxagliptin Placebo tablet

HbA1c results will be blinded following IP administration on Day 1 until after study completion (Section 5.9). A blinded HbA1c assessment will be performed at Week 12 for all subjects. A second randomization will be performed at the Week 14 visit, based on the Week 12 HbA1c assessment. All subjects with Week 12 HbA1c values < 7% will remain on previously assigned low-dose randomized treatment (dapagliflozin 5 mg, or saxagliptin 2.5 mg, or placebo) after the Week 12 assessment. Subjects assigned to the dapagliflozin treatment arm at Day 1 Randomization with Week 12 HbA1c values ≥ 7% will be re-randomized in a 1:1 ratio to continue on the low-dose treatment (dapagliflozin 5 mg) or up-titrate to the high-dose treatment (dapagliflozin 10 mg) after the Week 12 assessment. Similarly, subjects assigned to the saxagliptin treatment arm at Day 1 Randomization with Week 12 HbA1c values ≥ 7% will be re-randomized in a 1:1 ratio to continue on the low-dose treatment (saxagliptin 2.5 mg) or up-titrate to the high-dose treatment (saxagliptin 5 mg) after the Week 12 assessment. Subjects assigned to the placebo treatment arm at Day 1 Randomization with Week 12 HbA1c values ≥ 7% will continue on placebo treatment 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 second randomization process that will be indistinguishable (for the subjects and site personnel) from the actual second randomization. During the Week 14 visit, blinded study drug will be dispensed to all subjects in accordance with the treatment assignments based on Week 12 HbA1c assessments. Subjects will be instructed to ingest three (3) tablets daily as per Table 3.1-2.

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 randomization) will continue with their randomized study medication assigned after the Week 12 assessment in the double-blind LT treatment period (Figure 3.1-1).

After completion of assessments at Week 26, a subset of eligible subjects who are receiving background medication with metformin only will undergo a third randomization (randomized withdrawal of background medication) at either Week 32 or Week 40. Eligibility for randomized withdrawal from background medication will be restricted to subjects who are receiving background treatment with metformin only, and who have HbA1c < 7.5% at Week 26 or Week 32, provided they have not initiated rescue glycemic control therapy or been withdrawn from study drug. Subjects who are receiving background medication with metformin only, who do not qualify for the third randomization at Week 32 due to an HbA1c ≥ 7.5% at Week 26, may qualify for the third randomization at Week 40 if HbA1c < 7.5% at Week 32. Subjects who have passed Week 40 will not be included in the randomized withdrawal of background medication. During the third randomization:

- Eligible subjects who are receiving active treatment will be grouped into two separate strata for saxagliptin and dapagliflozin, and then randomized 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 randomized to withdraw background treatment 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 randomized to continue background medication with metformin will continue with their current dose of either saxagliptin or dapagliflozin (Figure 3.1-2).
- Eligible subjects who are receiving placebo will be randomized 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 (Figure 3.1-2).

Discontinuation of background metformin will occur in an unblinded manner. Exposure to monotherapy in subjects undergoing randomized withdrawal of metformin will last from the start of metformin withdrawal for that subject (following randomization at Week 32 or Week 40) until the end of Week 52, when all subjects will discontinue study medications. After Week 52, all subjects will take the most appropriate medication at the discretion of the treating physician.

Rescued subjects and subjects who discontinue IP will not be eligible for randomized withdrawal of background medication at Week 32 or Week 40.

Subjects with HbA1c ≥ 7.5% at Week 26 and Week 32 and subjects who are receiving background treatment with either insulin only, or insulin+metformin, including those randomized to receive placebo, will continue their randomized study medication assigned after the Week-12 assessment in the double-blind LT treatment period.

Exploratory analyses for the monotherapy period will include only subjects who are on background medication with metformin and have HbA1c measurement < 7.5% at Week 26 or Week 32. Analyses will be performed using the HbA1c value at the withdrawal baseline. The reference time point to be used as 'withdrawal baseline' will be the closest time point on or before the third randomization. The period starting from this baseline to Week 52 will be referred to as the 'randomized withdrawal period'.

For subjects recruited into the study prior to the study site implementation of the third protocol amendment, participation in the third randomization (with possible withdrawal of background medication with metformin) will be at the subject's discretion.

Adverse events and serious adverse events (SAEs) will be assessed during a Week 56 phone visit.

In case a visit is delayed for any reason, subsequent visits should be scheduled such that an interval of at least 12 weeks is maintained between the:

- Week 14 visit and the Week 26 visit.
- Third randomization (for subjects undergoing third randomization; occurring at the Week 32 or the Week 40 visit) and the Week 52 visit.

If more than 12 weeks elapse between the HbA1c collection at Week 26 and the third randomization at Week 32, or the HbA1c collection at Week 32 and the third randomization at Week 40, the subject should not go through this randomization, as the HbA1c value would no longer be reliable to ascertain eligibility for the third randomization. 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). A window period of -28 days to +7 days from the original scheduled date will be allowed for the Week-104 visit.

Subjects who discontinue study drug 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. Subjects will attend a post-study visit at Week 104, for assessment of measures of growth and maturity. This visit should be completed without delay (at 104 weeks (+7 days) from Day 1, regardless of whether any other study visits were delayed.

All subjects with HbA1c > 8.0% at and after Week 26 will be rescued.

Discontinued subjects will still be evaluated for rescue and will not be replaced.

Glycemic rescue parameters are included for subjects who meet the criteria for lack of glycemic control in both the 26-week ST treatment period and the 26-week safety extension period. Investigators may use insulin as rescue at their discretion.

The Investigator, Sponsor, site and subject will be blinded to the subjects' HbA1c results following administration of IP on Day 1 until after study completion. In the event of an HbA1c result > 8.0% during the LT 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.

Rescued subjects will continue treatment on study drug until Week 52.

Samples for analysis of plasma levels of dapagliflozin, saxagliptin, and its metabolite 5-OH-saxagliptin will be collected up to 1 hour pre-dose and approximately 2 hours post-dose (± 1 hour) during the Week 6, 12, 20, and 26 visits.

Samples for analysis of FPG will be collected up to 1 hour pre-dose during the Day 1 visit, and up to 1 hour pre-dose and approximately 2 hours post-dose (± 1 hour) during the Week 6, 12, 20, and 26 visits (Section 5.5).

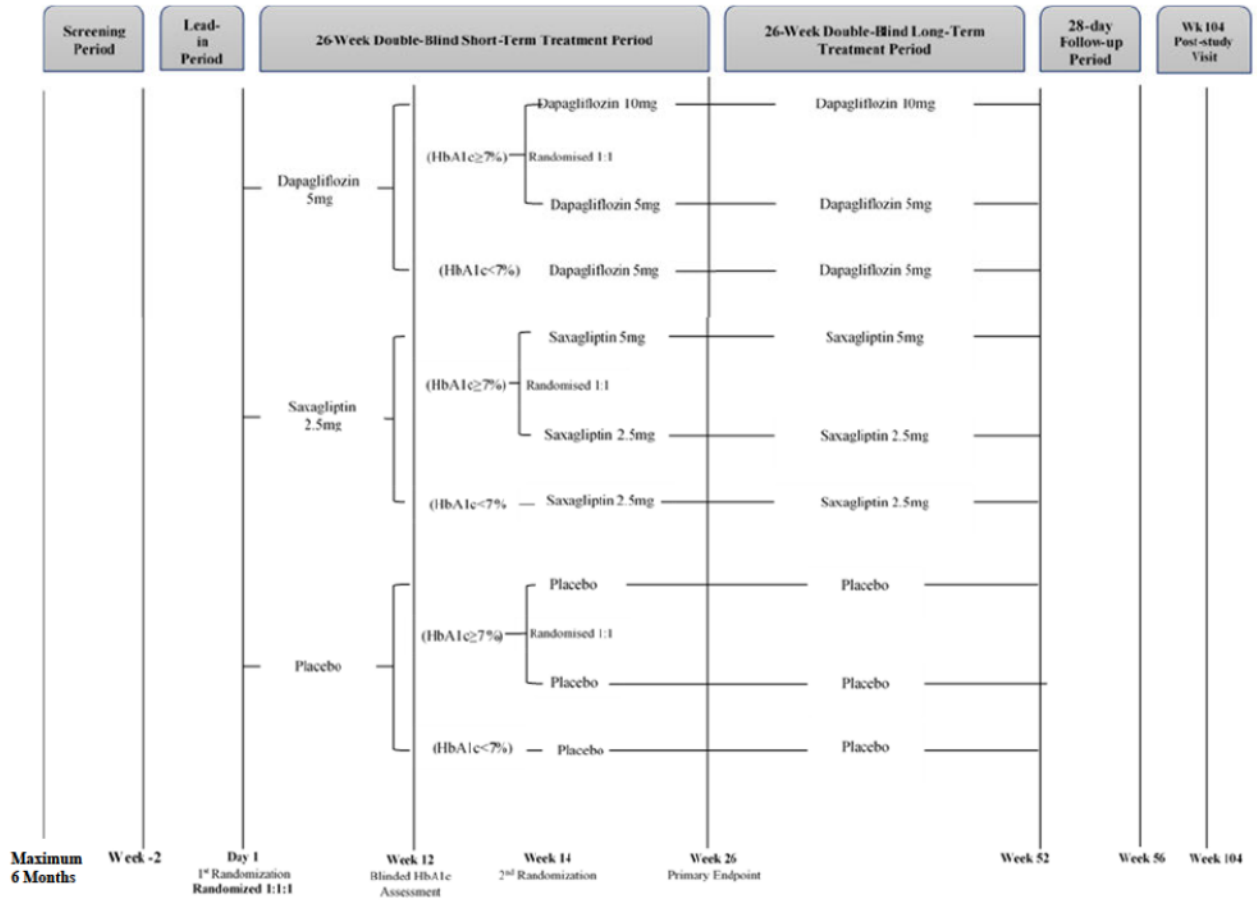
Plasma samples for analysis of DPP-4 activity will be collected up to 1 hour pre-dose during the Day 1 visit, and at 2 (± 1) hours post-dose during the Week 6, 12, 20, and 26 visits.

All plasma samples will be drawn in the fasting condition. Subjects should fast for at least 8 hours prior to sampling.

All study subjects will follow the schedules of assessments presented in Section 5.1.

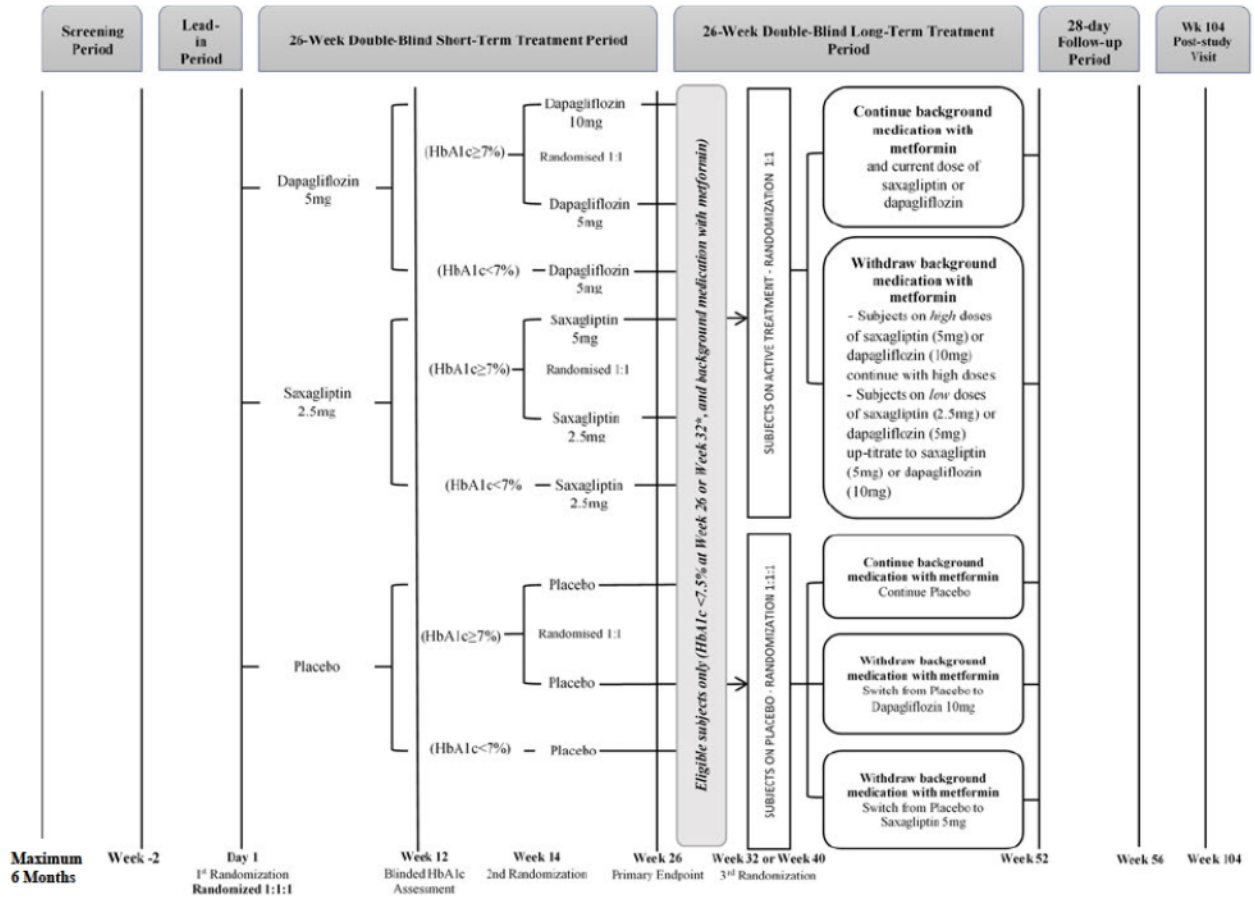
The study design schematic for all subjects not undergoing randomized withdrawal of background medication at Week 32 or Week 40 is presented in Figure 3.1-1.

Figure 3.1-1: Study design schematic for subjects not undergoing randomized withdrawal of background medication at Week 32 or Week 40



The study design schematic for subjects undergoing the third randomization (randomized withdrawal of background medication at Week 32 or Week 40) is presented in Figure 3.1-2.

Figure 3.1-2: Study design schematic for subjects undergoing randomized 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.

3.2 Post-Study Access to Therapy

At the end of the treatment period (Week 52 visit) or early discontinuation, the Sponsor/designee will not continue to provide Sponsor supplied study drug to subjects/investigators unless the Sponsor/designee chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

3.3 Study Population

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Subjects (or designee) must be willing and able to give signed and dated written informed consent. Minor's parent(s) or legally acceptable representatives must give fully informed

written consent. Assent should be obtained according to local regulations and if child is capable.

2. Target Population

a) Previously diagnosed with T2DM by World Health Organization/ADA criteria

b) HbA1c ≥ 6.5% and ≤ 10.5% obtained during the 6-month screening period

c) Currently on diet and exercise and stable dose of at least 1000 mg metformin (IR or XR) for a minimum of 8 weeks, or stable dose of insulin for a minimum of 8 weeks, or a stable combination of at least 1000 mg metformin (IR or XR) and insulin for a minimum of 8 weeks prior to Day 1 Randomization. For those children on insulin, investigators will confirm that attempts at removing insulin from the subject's therapeutic regimen had been previously made but had not been successful.

d) Subject re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (i.e., subject has not been randomized / has not been treated).

   i) If re-enrolled, the subject must be re-consented. All screening procedures will be repeated. Subjects may only be re-screened twice.

3. Age and Reproductive Status

a) Male and female subjects eligible if reached 10 years of age at screening, and up to but not including 18 years of age at randomization. At least 30% of total subjects will be between the ages of 10 and 14 years and at least one third, but no more than two thirds, female subjects.

b) Women of childbearing potential (WOCBP) must have a negative pregnancy test (minimum sensitivity 25 IU/L or equivalent units of beta-human chorionic gonadotropin) within 24 hours prior to the start of study drug.

c) Women must not be breastfeeding.

d) Women of childbearing potential must agree to follow instructions for method(s) of contraception for the duration of treatment with study drugs: saxagliptin, and dapagliflozin, plus 5 half-lives of study drugs or 30 days (whichever is longer), plus 30 days (duration of ovulatory cycle) for a total of 60 days post-treatment completion.

Women of childbearing potential who are continuously not heterosexually active are exempt from contraceptive requirements. However, they must still undergo pregnancy testing as described in Table 5.1-1.

Investigators shall counsel WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to use one highly effective method of contraception as listed below:

A. HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. Women of childbearing potential are expected to use one of the highly effective methods of contraception listed below. Contraception methods are as follows:

1. Progestogen only hormonal contraception associated with inhibition of ovulation
2. Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants and intrauterine devices (IUDs)
3. Nonhormonal IUDs
4. Bilateral tubal occlusion
5. Vasectomised partner with documented azoospermia 90 days after procedure
    a. Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
6. Intrauterine hormone-releasing system
7. Complete abstinence
    a. Complete abstinence is defined as the complete avoidance of heterosexual intercourse (refer to Glossary of Terms).
    b. Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus 5 half-lives of the investigational drug plus 30 days).
    c. It is not necessary to use any other method of contraception when complete abstinence is elected.
    d. Subjects who choose complete abstinence must continue to have pregnancy tests.
    e. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
    f. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

B. LESS EFFECTIVE METHODS OF CONTRACEPTION

1. Diaphragm with spermicide
2. Cervical cap with spermicide
3. Vaginal sponge with spermicide

4. Male or female condom with or without spermicide*[12,13]
5. Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.

* A male and a female condom must not be used together.

C. UNACCEPTABLE METHODS OF CONTRACEPTION

1. Periodic abstinence (calendar, symptothermal, post-ovulation methods)
2. Withdrawal (coitus interruptus)
3. Spermicide only
4. Lactation amenorrhea method

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Presence of Type 1 diabetes, as demonstrated by:

- Preexisting diagnosis of Type 1 diabetes,

OR

- Positivity at screening of either antibodies to glutamic acid decarboxylase (GAD) or protein tyrosine phosphatase-like protein antibodies (IA-2) AND abnormally low levels of C-peptide. GAD and IA-2 antibody testing will be performed in all screened subjects, C-peptide only in otherwise eligible, antibody-positive subjects. All instances of antibody-positive subjects with normal or elevated C-peptide values will be discussed by the Investigator with the study medical monitors and Sponsor's study director to confirm study eligibility.[14,15,16]

b) Previous diagnosis of monogenic etiology of Type 2 diabetes such as maturity onset diabetes of the young (MODY), genetic disorders with strong associations with insulin resistance/diabetes and/or obesity such as Turner's Syndrome and Prader-Willi, or secondary diabetes (steroid use, Cushing's disease, acromegaly), secondary diabetes mellitus, or diabetes insipidus

c) Diabetes ketoacidosis within 6 months of screening

d) Current use of the following medications for the treatment of diabetes, or use within the specified timeframe prior to screening for the main study:

i) Eight weeks: sulfonylureas, alpha glucosidase inhibitors, metiglinide, oral or injectable incretins or incretin mimetics, other anti-diabetes medications not otherwise specified.

ii) Sixteen weeks: thiazolidinediones, DPP-4 inhibitors (with no reported medication related AEs related to DPP-4 inhibitors), SGLT-2 inhibitors (with no reported medication related AEs related to SGLT-2 inhibitors)

e) Initiation or discontinuation of prescription or non-prescription weight loss drugs within 8 weeks of screening. Use of prescription or non-prescription weight loss drugs must be stable during the study.

2. Medical History and Concurrent Diseases

a) Pregnant, positive serum pregnancy test, planning to become pregnant during the clinical trials, or breastfeeding

b) History of unstable or rapidly progressive renal disease

c) History of unresolved vesico-ureteral reflux

d) History of or current, acute or chronic pancreatitis

e) History of hemoglobinopathy, with the exception of sickle cell trait or thalassemia minor; or chronic or recurrent hemolysis

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

g) Significant co-morbidity that, in the opinion of the Investigators, will increase the risk to the subject such as immunosuppression, or current treatment for cancer

h) Replacement or chronic systemic corticosteroid therapy, defined as any dose of systemic corticosteroid taken for > 4 weeks within 3 months prior to the Day 1 visit

NOTE: inhaled, nasal spray, or topical steroids if limited to minor surface area are allowed.

3. Physical and Laboratory Test Findings

a) Abnormal renal function, which is defined as an estimated glomerular filtration rate (eGFR) calculated by the Schwartz Formula < 80 mL/min/1.73 m^2 (1.33 mL/s)[17]

b) An abnormal thyroid-stimulating hormone (TSH) value at enrollment will be further evaluated for free T4. Subjects with abnormal free T4 values will be excluded.

(Note: In subjects who have had a prior diagnosis of a thyroid disorder and who are currently receiving thyroid replacement therapy, retest of TSH may be allowed, as determined by the Investigator, after a minimum of 6 weeks following the adjustment of thyroid hormone replacement therapy. Such cases should be discussed with the Sponsor prior to retesting. The subject must have all enrollment procedures and laboratory assessments performed as part of this retest, and all of these must meet enrollment eligibility criteria. The subject's number will however remain the same as initially assigned.)

c) Hematuria (confirmed by microscopy at screening) with no explanation as judged by the Investigator up to randomization.

d) Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2× upper limit of normal (ULN), or clinically significant hepatic disease.

e) Serum total bilirubin (TB) ≥ 2x ULN unless exclusively caused by Gilbert's syndrome

f) Positive serologic evidence of current infectious liver disease including anti-hepatitis A virus (HAV) (IgM), hepatitis B surface antigen (HBsAg), or anti-hepatitis C virus (HCV). Subjects who have isolated positive anti-hepatitis B surface antibodies may be included.

g) Anemia of any etiology defined as hemoglobin ≤ 10.7 g/dL (107 g/L) for females and ≤ 11.3 g/dL (113 g/L) for males. Subjects who are considered to have anemia according to local guidelines should be excluded.

h) Volume-depleted subjects. Subjects at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics, should carefully monitor their volume status.

i) Clinically significant abnormalities in any pre-Day 1 Randomization laboratory analyses or electrocardiogram (ECG) that, in the Investigator's opinion, would preclude randomization.

4. Allergies and Adverse Drug Reaction

a) Known allergy, sensitivity or contraindication to any study drug or its excipient/vehicle

5. Other Exclusion Criteria

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

b) Prisoners or subjects who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply and Sponsor/designee approval is required.)

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

d) Psychiatric or cognitive disorder that will, in the opinion of investigators, limit the subject's ability to comply with the study medications and monitoring.

e) Subjects who have contraindications to therapy as outlined in the saxagliptin and dapagliflozin Investigator Brochure or local package inserts.

f) Participation and receiving IP in another clinical study during the prior 3 months.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

A WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal.

3.4 Screen Failures

Screen failures are defined as subjects who signed the informed consent form to participate in the clinical study but are not subsequently randomly assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from Regulatory Authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened twice. A re-screened subject will be assigned a new subject number that is different from that assigned during the initial screening. Re-screening should be documented so that its effect on study results, if any, can be assessed.

These subjects should have the reason for study withdrawal recorded in the electronic case report form (eCRF).

3.5 Concomitant Treatments

3.5.1 Prohibited and/or Restricted Treatments

- Once consented subjects may not receive any prescription antihyperglycemic medication other than study drug, metformin and/or insulin.
- Once consented, subjects should not begin treatment with any systemic corticosteroid therapy lasting ≥ 5 days of therapy (inhaled, nasal, and topical are allowed). Subjects who require systemic corticosteroid therapy should be discussed with the Medical Monitor prior to starting therapy whenever possible.
- Once consented, subjects should not commence or modify therapy with any prescription or over-the-counter weight loss medications.
- Once consented, subjects should not undergo any bariatric surgery.
- Once consented, subjects should not commence therapy with potent cytochrome P450 3A4/3A5 (CYP3A4/5) inhibitors in countries where dose adjustment due to potent systemic CYP3A4/5 inhibitor use would be required by the saxagliptin label.

3.5.2 Other Restrictions and Precautions

- Subjects must comply with their prescribed dosing regimen to preserve study integrity and ensure subject safety.
- Subjects should be cautioned that any new prescription, over-the-counter or herbal/nutritional therapies should be discussed thoroughly with the Investigator as concomitant use could result

in alterations to their glycemic control and may place them at risk for significant hypoglycemic episodes.

- Medication other than those which are protocol prohibited as described above, considered necessary for the subject's safety and wellbeing, may be given at the discretion of the Investigator and must be recorded in the appropriate sections of the case report form (CRF).
- Subjects must make every attempt to adhere to the diet and exercise counseling and to the study flow chart/time and events schedule (see Section 5.1).
- Women of childbearing potential must immediately contact the Investigator if they suspect they might be pregnant and if they have changed or plan to change their birth control method.

3.6 Discontinuation of the Study

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the Regulatory Authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

3.7 Discontinuation of Investigational Product Following Any Treatment with Study Drug

Subjects MUST discontinue IP (and non-IP at the discretion of the Investigator) for any of the following reasons:

- Subject's request to stop study treatment
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by the Sponsor/designee

- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Unblinding a subject for any reason (emergency or non-emergency)
- Severe non-compliance to protocol, as judged by the Investigator and/or Sponsor/designee
- Safety reasons as judged by the Investigator and/or Sponsor/designee
- Pregnancy
- For subjects on metformin, development of contraindications to metformin therapy as per local label
- Subjects experiencing decreased renal function must be evaluated as per Investigator's discretion
    - Subjects with eGFR < 50 mL/min for sustained period of time (12 to 16 weeks) must be discontinued
- Subjects with a central laboratory ALT and/or AST > 3xULN will be scheduled for a follow-up visit within 3 days following the receipt of the result (see Appendix 1 and Appendix 2 for further guidance). Subjects should be discontinued from study drug if the initial and repeat laboratory tests meet any of the following criteria:
    - ALT and/or AST are > 3x ULN and TB > 2x ULN
    - ALT and/or AST are > 5x ULN for ≥ 14 consecutive days, at any time after initial confirmatory results
    - ALT and/or AST are ≥ 10x ULN

In the case of pregnancy, the Investigator must immediately notify the Sponsor Medical Monitor/designee of this event. The study drug will be permanently discontinued in an appropriate manner.

All subjects who discontinue IP early (prior to the Week 52 visit) will remain in the study and should comply with protocol-specified follow-up procedures including site visits and phone contacts as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a subject discontinues IP early (prior to the Week 52 visit), at the next visit the subject should be assessed according to the follow-up schedule for Early Treatment Discontinuation (ETD) (Table 5.1-4). The reason for early discontinuation must be documented in the subject's medical records and entered on the appropriate CRF page.

Subjects who discontinue IP early will still be evaluated for rescue.

After discontinuation of IP the management of the subject's diabetes will be under the care and direction of the Investigator.

3.7.1 Procedures for Handling Patients Incorrectly Enrolled or Randomized

Subjects who fail to meet the inclusion/exclusion criteria must not, under any circumstances, be enrolled or randomized. There can be no exceptions to this rule.

Subjects who are incorrectly enrolled, but are not yet randomized, should be withdrawn from the study. The procedures included in the protocol for the discontinuation of such subjects must be followed. Subjects should be further treated according to the Investigator's judgment and local therapy tradition.

If a subject not meeting the study criteria is randomized in error, and if the error is identified after Day 1 Randomization, a discussion must occur between the Sponsor Medical Monitor/designee and the Investigator regarding whether to continue or discontinue the subject from the study drug. If agreement to continue in the study is reached, the subject should complete the study unless there are safety concerns or if the subject withdraws the consent. In situations in which an agreement cannot be reached, the subject should have the randomized therapy stopped and be discontinued from the study. The procedures included in the protocol for the discontinuation of such subjects must be followed. The Sponsor Medical Monitor/designee is to ensure all such contacts with the Investigator and such decisions are appropriately documented.

Withdrawn subjects will not be replaced.

3.7.2 Rescue Guidelines for Subjects with Protocol-Defined Lack of Glycemic Control

During the course of the trial, subjects may be eligible for the addition of open-label rescue medication to their blinded treatment regimen in order to treat ongoing hyperglycemia. Insulin may be used as rescue, at the Investigator's discretion. Subjects who were already taking insulin at the start of the study may be switched to a flexible insulin dose following a Rescue Visit. For subjects on baseline insulin, persistently increased doses of insulin 20% or more above baseline dose, despite advice and counsel to keep the insulin dose stable, may be considered another potential manifestation of poor glycemic control, and should be evaluated for rescue. Only insulin may be used as rescue medication, but subjects can be rescued without the use of medication.

Pre-specified glycemic criteria (see Table 3.5.2-1), based upon self-monitoring blood glucose (SMBG) FPG, or single central laboratory FPG and repeat confirmatory FPG have been established during the treatment period, starting at Week 6, and up to, but not including, the Week 52 visit, to determine eligibility for open-label rescue medication. Any permanent changes in dose of basal insulin should be done after evaluation of rescue criteria, including both SMBG and central laboratory FPG values. To maintain study integrity, plasma glucose samples used to determine eligibility for rescue must reflect fasting values. Subjects who are not fasting at the time of sample collection will be asked to return when in a fasting state.

Table 3.5.2-1: Lack of Glycemic Control Criteria for Initiation of Rescue Medication

Study week	Rescue criterion
Week 6 visit up to and not including Week 26 visit	FPG>13.3 mmol/L (240 mg/dL) based on 3 consecutive fasting SMBG values followed by a confirmatory central laboratory FPG or Single central laboratory FPG followed by a confirmatory central laboratory FPG
Week 26 visit up to and not including Week 52 visit	FPG>10 mmol/L (180 mg/dL) based on SMBG for 3 consecutive days followed by a confirmatory central laboratory FPG or Single central laboratory FPG followed by a confirmatory central laboratory FPG or HbA1c >8.0% (while HbA1c values will remain blinded throughout the study, sites will be notified to allow rescue if values exceed this threshold)

Subjects must be rescued following one of these scenarios:

- Subjects with a SMBG FPG value meeting the lack of glycemic control criterion at any time during the pre-specified study period will be instructed to repeat FPG measurements on 2 further consecutive days. If all 3 daily values meet the relevant lack of glycemic control criterion subjects should be scheduled for a follow-up visit (within 1 - 5 days) to obtain a central laboratory FPG value and review of the subject's glucose meter readings. If the central laboratory FPG value meets the criterion, the subject must be rescued.
- Subjects with a central laboratory FPG value meeting the lack of glycemic control criterion at a pre-specified visit will be scheduled for a follow-up visit (within 3 - 5 days) to obtain a second central laboratory FPG value and review the subject's glucose meter readings. If the second central laboratory FPG value also meets the criterion, the subject must be rescued.
- Subjects with a central laboratory HbA1c value meeting the lack of glycemic control criterion at or following the pre-specified Week 26 visit must be rescued.

Subjects who meet rescue criteria must first complete the Rescue Visit procedures before receiving open-label rescue medication to ensure that important trial endpoint measurements are collected.

Following completion of the Rescue Visit, rescued subjects may initiate or up-titrate open-label insulin as rescue medication, at the discretion of the Investigators. Insulin should be initiated at the lowest starting dose and titrated in accordance with the approved product label in the applicable country at the discretion of the Investigator, in addition to their blinded study medication. Additional visits for titration of rescue medication should be scheduled as per the Investigator's judgment in accordance with the approved product label for that country and by the subject's

glycemic response. Rescued subjects will then continue in the study according to their original visit schedule.

Note: Rescue medication will NOT be provided by the Sponsor unless this is a local requirement.

3.7.3 Discontinuation Guidelines Due to Protocol-Defined Hypoglycemia Episodes

Subjects should not be discontinued from any treatment phase based on single episodes of hypoglycemia or symptoms of hypoglycemia unless clinically indicated. The assessment of a single finger-stick or central laboratory glucose value should not be the sole assessment used to determine subject discontinuation for hypoglycemia.

Clinical indications for discontinuation of blinded study drug because of hypoglycemia may include the following:

- Multiple occasions of episodes outlined below that, in the opinion of the Investigator, indicate that continued treatment with study therapy is not in the best interest of the subject. This includes, but is not limited to:
    - Severe hypoglycemia as defined by ADA criteria.[18]
    - Recurrent symptoms suggestive of hypoglycemia (e.g., sweating, shakiness, increased heart rate (HR), confusion, dizziness, light-headedness, or hunger) in the absence of environmental factors known to contribute to hypoglycemia (i.e., excess physical activity, concurrent illness, or missed or delayed meal).
    - Recurrent documented capillary or plasma blood glucose values < 54 mg/dL (< 3.0 mmol/L).
- A subject may also be discontinued from the study because of severe hypoglycemia as determined by the Investigator.

Subjects who discontinue blinded study drug due to hypoglycemia will continue to be followed in line with Section 5 until death or the conclusion of the study.

Down-titration of blinded study drug and/or background antihyperglycemic agent during the study

Down-titration of blinded study drug and/or background metformin will not be allowed at any time during the study. Subjects on background insulin treatment who experience multiple or severe episodes of hypoglycemia may down-titrate insulin treatment during the study. The down-titration should be minimized, but is at the Investigator's discretion.

3.7.4 Discontinuation Guidelines Due to Diabetic Ketoacidosis

There have been post-marketing reports of ketoacidosis, including DKA, in patients with Type 1 and Type 2 diabetes mellitus taking dapagliflozin and other SGLT-2 inhibitors, although a causal relationship has not been established. Dapagliflozin is not an approved treatment for Type 1 diabetes.

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

A subject with any symptoms that may be consistent with an event of DKA should contact the Investigator, have blood ketone levels measured and study drug interrupted. Subjects should continue in the study during the study drug interruption and undergo all scheduled assessments. Treatment with the study drug may resume when the symptoms resolve or at the Investigator's discretion. In the case of an established DKA, study drug should be interrupted until the event has resolved.

Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (e.g., Type 1 diabetes, history of pancreatitis, or pancreatic surgery), insulin dose reduction, reduced caloric intake, or increased insulin requirements due to infections, illness or surgery and alcohol abuse.

3.8 Post-Study Drug Follow-up

Post-study drug follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

Please note that after the discontinuation of study drug, the management of the subject's diabetes will be under the care and direction of the Investigator.

The only exception to any of these follow-up methods are when a subject withdraws consent for all study procedures, including post-treatment study follow-up or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

3.8.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. A subject who considers withdrawing from the study must be informed by the investigator about modified follow-up options (e.g., site visits with limited procedures, home nursing, phone calls, less frequent visits, or continuation in the study without further treatment).

Subjects should notify the Investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. A subject who withdraws consent will always be asked about the reason(s) and the presence of any AE. The withdrawal of consent should be explained in detail in the medical records by the Investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post-treatment study follow-up, and

entered on the appropriate CRF page. If deemed necessary, the Investigator will follow-up subjects as medically indicated.

If a subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a subject withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

Withdrawal of Informed Consent for donated biological samples

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

The investigator must ensure:

- Subject's withdrawal of informed consent to the use of donated samples is notified immediately to the Sponsor/designee.
- Biological samples from that subject, if stored at the study site, are immediately identified, destroyed, and the action documented.
- The laboratory holding the samples is informed about the withdrawn consent immediately and that samples are destroyed, and the action documented.
- The subject and Sponsor/designee are informed about the sample disposal.

3.8.2 Lost to Follow-up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If the Investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the Investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other data necessary to complete the follow-up portion of the study. The site staff and representative will conduct searches in a legally permissible manner that may include public records and database research, social media research, and genealogical research. Physical research of local municipal resources, as allowed by local laws and regulations, may be conducted. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the Investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial
- Other drugs administered as part of the study that are critical to claims of efficacy (e.g., background therapy, rescue medications).

Table 4-1: Study Drugs for CV181375: Product Description: Short-term Double-Blinded Treatment Period and Long-term Subject- and Site-Blinded Treatment Period

Product Description / Class and Dosage Form	Potency	IP / Non-IMP	Blinded or Open Label	Manufacturer	Packaging/ Appearance	Storage Conditions (per label)
Saxagliptin Film Coated Tablet (as the free base)	5 mg	IP	Blinded Label	AstraZeneca	Plain, yellow, biconvex, round, film coated tablet, HDPE bottle	Storage conditions (per label), printed on IP bottles
Saxagliptin Film Coated Tablet (as the free base)	2.5 mg	IP	Blinded Label	AstraZeneca	Plain, yellow, biconvex, round, film coated tablet, HDPE bottle	Storage conditions (per label), printed on IP bottles
Placebo for Saxagliptin Film Coated Tablets 2.5/5 mg	0 mg	IP	Blinded Label	AstraZeneca	Plain, yellow, biconvex, round, film coated tablet, HDPE bottle	Storage conditions (per label), printed on IP bottles
Dapagliflozin Film Coated Tablet 5 mg	5 mg	IP	Blinded Label	AstraZeneca	Green, plain, diamond shaped, film coated tablet, HDPE bottle	Storage conditions (per label), printed on IP bottles
Placebo for Dapagliflozin Film Coated Tablets 5 mg	0 mg	IP	Blinded Label	AstraZeneca	Green, plain, diamond shaped, film coated tablet, HDPE bottle	Storage conditions (per label), printed on IP bottles
Dapagliflozin Film Coated Tablet 10 mg	10 mg	IP	Blinded Label	AstraZeneca	Green, plain, diamond shaped, film coated tablet, HDPE bottle	Storage conditions (per label), printed on IP bottles
Placebo for Dapagliflozin Film Coated Tablets 10 mg	0 mg	IP	Blinded Label	AstraZeneca	Green, plain, diamond shaped, film coated tablet, HDPE bottle	Storage conditions (per label), printed on IP bottles

4.1 Investigational Product

An IP, also known as an IMP in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The IP should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that IP is only dispensed to study subjects. The IP must be dispensed only from official study sites by authorized personnel according to local regulations, except where the IP has to be sent directly to the subjects' homes due to the coronavirus disease 2019 (COVID-19) pandemic. Only subjects randomized in the study may receive IPs, and only authorized site staff may supply or administer IPs. Until dispensation to study participants, all IPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The IPs are described in Table 4-1. The tablets may contain lactose, which may cause discomfort in lactose intolerant individuals. Primary packaging of the IP will be carried out by AstraZeneca or their designee in accordance with Good Manufacturing Practice (GMP). Background therapy metformin (IR or XR) and insulin (as appropriate) will not be provided by the Sponsor unless this is a local requirement.

Labeling: Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local language according to the regional regulatory requirements.

4.2 Non-Investigational Product

Other medications used as support or rescue medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-IPs.

Subjects are expected to be on background medication of metformin (IR or XR) and/or insulin. Insulin, as per local labeling and standard of care, will be used for rescue as described in Section 3.6.

4.3 Storage and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the Sponsor/designee. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and the Sponsor/designee should be contacted immediately. All study drugs should be kept in a secure place under appropriate storage conditions. The IP label on the bottle specifies the appropriate storage. The Investigator and/or designee must confirm that appropriate temperature conditions have been maintained during transit for all study drugs received and any discrepancies are reported and resolved before use of the study drugs.

Study drug not supplied by the Sponsor will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by the Sponsor or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (e.g., required diluents, administration sets). The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study drugs are provided in Section 4.8.

4.4 Method of Assigning Subject Identification

At the screening visit each subject will be assigned a unique sequential subject number by the Interactive Web/Voice Response System (IXRS). This number will be used for identification throughout the study and will not be used for any other participant.

Randomized schedules will be generated and kept by the Sponsor/designee. Subjects will be randomly assigned to 1 of 3 blinded treatment groups by the IXRS in a 1:1:1 ratio. Day 1 Randomization will be stratified by gender, age at randomization (10 to below 15 years of age, 15 to below 18 years of age) and baseline medication (metformin alone, insulin±metformin).

Subjects entering the 2-week lead-in period

Following completion of the Screening activities, subjects who meet all the inclusion and none of the exclusion criteria will be registered by the IXRS into the lead-in period.

Subjects entering the 26-week double-blinded short-term treatment period

Following completion of the lead-in period, subjects who meet the criteria will be randomly assigned by the IXRS at the Day 1 Randomization visit, to one of the following three (3) double-blind treatment arms in a 1:1:1 ratio:

- Blinded dapagliflozin 5 mg
- Blinded saxagliptin 2.5 mg
- Blinded placebo

Subjects at Week 12 Blinded HbA1c Assessment

- A blinded HbA1c assessment will be performed at Week 12 for all subjects on treatment. HbA1c results will be blinded throughout the study until after study completion. A second randomization will be performed at Week 14, based on the Week 12 blinded HbA1c assessment. All subjects with Week 12 HbA1c values < 7% will remain on previously assigned randomized 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 Randomization with Week 12 HbA1c values ≥ 7% will be re-randomized 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 Randomization with Week 12 HbA1c values ≥ 7% will be re-randomized 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.
- Subjects assigned to the blinded placebo treatment arm at Day 1 Randomization with Week 12 HbA1c values ≥ 7% will continue on placebo 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 second randomization process that will be indistinguishable (for the subjects and site personnel) from the actual second randomization.
- During the Week 14 visit, blinded study drug will be dispensed to all subjects in accordance with the treatment assignments based on Week 12 HbA1c assessments.

Subjects entering the 26-week double-blind long-term extension period

Following completion of the 26-week double-blinded treatment period, subjects will enter the LT double-blind treatment period. All subjects will remain in their same randomization assignment based on their Week 12 randomization grouping.

Subjects eligible for randomized withdrawal of background medication (metformin) at Week 32 or Week 40

After completion of Week 26 assessments, a subset of eligible subjects will undergo randomized withdrawal of background medication at Week 32 (if HbA1c < 7.5% at Week 26) or Week 40 (if subject did not qualify at Week 26 and HbA1c ≥ 7.5% at Week 26 and < 7.5% at Week 32). Eligibility for randomized withdrawal of background medication is described in Section 3.1.

Eligible subjects who are receiving active treatment will be randomized 1:1 to either:

- Discontinue background treatment with metformin; subjects who are currently receiving high doses of saxagliptin (5 mg) or dapagliflozin (10 mg) will continue to receive the high doses. 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).
- Continue background medication with metformin; these subjects will continue with their current dose of either saxagliptin or dapagliflozin.

A subset of subjects from the placebo arm will be randomized 1:1:1 to either:

- Withdraw background medication and switch to active treatment with saxagliptin 5 mg
- Withdraw background medication and switch to active treatment with dapagliflozin 10 mg
- Remain on background medication with metformin and continue with placebo

During the third randomization visit, subjects will either be informed that they will remain on their current background medication or will be asked to discontinue background treatment with metformin and will be dispensed a new set of study drugs. Discontinuation of background metformin will occur in an unblinded manner.

If more than 12 weeks elapse between the HbA1c collection at Week 26 and the third randomization at Week 32, or the HbA1c collection at Week 32 and the third randomization at Week 40, the subject should not go through this randomization as the HbA1c value would no longer be reliable to ascertain eligibility for the third randomization. However, subjects not qualifying based on their HbA1c value at the Week 26 visit because more than 12 weeks elapsed between the Week 26 and Week 32 visits, may still be able to qualify based on the HbA1c value at the Week 32 visit, if no more than 12 weeks elapses between the Week 32 visit and the Week 40 visit and the subject otherwise meets criteria.

At all study visits when study drug is dispensed, each subject will be assigned unique Kit ID numbers by the IXRS. Kit ID numbers will be assigned non-sequentially and will correspond to the numbers printed on the bottles containing study drug, and will be recorded on the appropriate eCRF. The IXRS will be available 24 hours per day, 7 days a week.

4.5 Selection and Timing of Dose for Each Subject

Subjects successfully completing the lead-in period and meeting all eligibility criteria will be randomized (1:1:1) to receive either dapagliflozin 5 mg, or saxagliptin 2.5 mg or placebo (on top of background therapy).

Dapagliflozin 5 mg or 10 mg tablets or matching placebo tablets will be administered orally once daily during the blinded treatment periods. Subjects will be instructed to take one tablet from each bottle provided (2 bottles up to Week 14 [Table 3.1-1] and 3 bottles from Week 14 to Week 52 [Table 3.1-2].

Subjects initially randomized (Day 1 to Week 14) to the dapagliflozin 5 mg group will be administered one active dapagliflozin 5 mg tablet, and one saxagliptin placebo tablet. Subjects re-randomized (Week 14 to Week 52) to the dapagliflozin 5 mg group and subjects initially randomized to the dapagliflozin 5 mg group who did not qualify for the second randomization will be administered one active dapagliflozin 5 mg tablet, one dapagliflozin 10 mg placebo tablet and one saxagliptin placebo tablet. Subjects re-randomized (Week 14 to Week 52) to the dapagliflozin 10 mg group will be administered one active dapagliflozin 10 mg tablet, one dapagliflozin 5 mg placebo tablet and one saxagliptin placebo tablet.

Saxagliptin 2.5 mg or 5 mg tablets or matching placebo tablets will be administered orally once daily during the blinded treatment periods. Subjects initially randomized (Day 1 to Week 14) to the saxagliptin 2.5 mg group will be administered one active saxagliptin 2.5 mg tablet and one

dapagliflozin 5 mg placebo tablet. Subjects re-randomized (Week 14 to Week 52) to the saxagliptin 2.5 mg group and subjects initially randomized to the saxagliptin 2.5 mg group who did not qualify for the second randomization will be administered one active saxagliptin 2.5 mg tablet, one dapagliflozin 5 mg placebo tablet, and one dapagliflozin 10 mg placebo tablet. Subjects re-randomized (Week 14 to Week 52) to the saxagliptin 5 mg group will be administered one active saxagliptin 5 mg tablet, one dapagliflozin 5 mg placebo tablet, and one dapagliflozin 10 mg placebo tablet.

Saxagliptin and dapagliflozin matching placebo tablets will be administered orally once daily during the blinded treatment periods. Subjects initially randomized (Day 1 to Week 14) to the Placebo group will be administered one saxagliptin placebo tablet and one dapagliflozin 5 mg placebo tablet. After the second randomization (Week 14 to Week 52), placebo subjects will be administered one saxagliptin placebo tablet, one dapagliflozin 5 mg placebo tablet, and one dapagliflozin 10 mg placebo tablet (see Table 3.1-1 and Table 3.1-2).

The tablet components for each study treatment described in Table 3.1-2 will also apply for those subjects undergoing randomized withdrawal of background medication at Week 32 or Week 40.

4.6 Blinding/Unblinding

Blinding of treatment assignment is critical to the integrity of this clinical study.

Methods used to ensure blinding include:

- Investigational product will be labeled using a unique material kit ID, which is linked to the Day 1 randomization code, the Week 14 randomization code, and the Week 32/Week 40 randomization code.
- The IXRS will assign the bottle of study material to be dispensed to each subject.
- This is a double-blind study wherein each subject will receive either the active drug or matching placebo. The active drug and placebo tablets will be identical and presented in identical packaging to ensure blinding of the medication.

However, in the event of a medical emergency or pregnancy in an individual subject in which knowledge of the IP is critical to the subject's management, the blind for that subject may be broken by the Investigator. The subject's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual subject's treatment, the Investigator should determine that the unblinded information is necessary, i.e., that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not related to the IP, the problem may be properly managed by assuming that the subject is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the Investigator always has ultimate authority for the decision to unblind. The Principal Investigator should only call in for emergency unblinding AFTER the decision to discontinue the subject has been made.

For this study, the method of unblinding for emergency purposes is via the IXRS.

Any request to unblind a subject for non-emergency purposes should be discussed with the Medical Monitor.

The exception is for those personnel analyzing the PK data, the AstraZeneca Supply Chain Study Management (SCSM) team and the responsible personnel carrying out the packaging and labeling of IPs. The Day 1 Randomization 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 analyzed.

For subjects who are randomized to withdraw background metformin, the investigator may be partially unblinded to the subject's treatment assignment.

If a subject withdraws from the study, then his/her enrollment/randomization codes cannot be reused. Withdrawn subjects will not be replaced.

4.7 Treatment Compliance

Each time study medication is dispensed, compliance will be reinforced. When study medication is returned, compliance will be assessed based upon subject's interview and a count of the tablets returned. Compliance should be between ≥ 80% and ≤ 120% of that prescribed. The investigator (or designee) will record the amounts of study medication dispensed and returned at each visit, as well as document reasons for non-compliance in the source document. The dates of all study medication dosing, including interruptions, missed doses, medication errors, or overdose (see Section 6.5), must be recorded on the eCRF.

If the subject is not ≥ 80% compliant with study drug doses during the study, then the period of non-compliance should be noted as a significant protocol deviation and the Sponsor/designee should be notified. The subject should be re-educated regarding the importance of study drug compliance.

4.8 Destruction of Study Drug

For this study, study drugs (those supplied by the Sponsor or sourced by the Investigator) such as partially used study drug bottles, vials and syringes are to be destroyed locally at a site approved by the local Regulatory Authority in accordance with local regulations.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study drug bottles must be immediately destroyed as required for safety, or to meet local regulations (e.g., cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures (SOPs) and a copy provided to the Sponsor/designee upon request.

- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met, the responsible Study Monitor will make arrangements for return of study drug to the CRO Study Monitor.

4.9 Return of Investigational Product

It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.10 Retained Samples for Bioavailability/Bioequivalence

Not applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in Section 5.1.

The Investigator will ensure that data are recorded on the eCRFs. The electronic data capture (EDC) system will be used for data collection and query handling.

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

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study drug.

Adherence to the study design requirements, including those specified in Section 5.1, is essential and required for study conduct.

If scheduled visits at clinical sites will be significantly impacted by the COVID-19 pandemic (e.g., there is a risk that the subject may be exposed to COVID-19 when visiting the site), home visits by study site personnel/vendor are allowed in countries where this is logistically feasible and considered acceptable. Before such a visit, a risk assessment that considers the potential risks to both the subject and the study personnel has to be performed.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the informed consent form may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in Section 5.1.

Approximately 230 mL of blood will be collected from each subject. Repeat or unscheduled blood samples may be taken for safety reasons or due to technical issues with the samples.

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: 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 3
Vital Signs	X	X	
Height	X		
Body Weight	X		
BMI	X		
Serious Adverse Events Assessment	X	X	
Adverse Events Assessment		X	
Laboratory Tests			
Standard Safety Laboratory Panel (Blood/Urine)	X		See Appendix 1
GAD/IA2 Autoantibodies	X		

Table 5.1-1: Screening Procedural Outline (CV181375 [D1680C00019])

Procedure	Screening Maximum 6 months[a]	Lead-in Wk –2[b]	Notes
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 enrollment 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 Counseling		X	
Provide glucose meter and supplies / instructions		X	
Provide logs / instructions		X	
Assessment of signs and symptoms of hypoglycemia 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 5.1-2: 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 3
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 hypoglycemia 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 1
Fasting Lipid panel	X						X	Total cholesterol, triglycerides, HDL, and LDL

Table 5.1-2: 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
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.

Table 5.1-2: 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
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), estradiol, 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 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. # No samples will be drawn at the Rescue Visit or the 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.

Table 5.1-2: 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
Study Drug / IXRS								
Contact IXRS	X		X		X	X	X	
First randomization	X							
Second randomization					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 counseling	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 5.5-1 Sampling Schedule

Table 5.1-3: 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	Appendix 3
Vital Signs	X		X		X				
Height	X		X		X			X	
Body Weight	X		X		X			X	
ECG					X				
Assessment of signs and symptoms of hypoglycemia 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				Appendix 1

Table 5.1-3: 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
Fasting Lipid panel					X				Total cholesterol, triglycerides, HDL, and LDL
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), estradiol, 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				

Table 5.1-3: 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
Third randomization	X		X*						The third randomization will apply only to subjects who are eligible for randomized withdrawal of background medication (i.e., subjects who have background medication with metformin only and HbA1c < 7.5% at Week 26 or Week 32 ***Randomization at Week 40 only for eligible subjects not randomized at Week 32**
Instruction regarding metformin withdrawal	X		X*						Subjects withdrawn from background medication with metformin following the third randomization will be reminded to stop taking metformin. ***Only subjects randomized 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				

Table 5.1-3: 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
General									
Provide diet and exercise counseling	X	X*	X	X*					*Assessed by Phone
Dispense Meter Supplies	X		X						
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 (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 5.1-4: 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	*Assessed by Phone
Adverse Events Assessment	X	X	X	X*	X	*Assessed by Phone
Standard safety laboratory panel (Blood)	X	X				Appendix 1
Fasting Plasma Glucose (FPG)	X	X				
HbA1c	X	X				
Telephone reminder calls				X		
Tanner Staging	X*	X*			X	Appendix 3; *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), estradiol, 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

Table 5.1-4: 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						
						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).

5.1.1 Retesting/Reassessment During Screening or Lead-In Period

The laboratory parameters listed below may be repeated once in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

Retesting/reassessment of screening criteria are allowed if any of them does not meet eligibility criteria at initial screening, and the Investigators believe they may return within the eligibility range within 6 months. Retesting/reassessment frequencies of these variables are at the discretion of the Investigators, but should occur at least once every 3 months. The Investigators will ensure that all other eligibility criteria are still being met if a subject qualifies after retesting/reassessment.

If a subject turns 18 years of age during the screening period, he/she will be considered as screen failure and thus not eligible for the study.

Any new result will override the previous result (i.e., the most current result prior to Randomization) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

5.2 Study Materials

Study team will supply the sites with the following materials:

- Blood glucose meters. One (1) meter will be provided to each study subject at enrollment and one (1) meter will be provided to each investigative site.
- Glucose test strips
- Lancets
- Glucose control solutions
- Ketone meters and test strips
- Electronic eCRFs [SAE Forms, Pregnancy Surveillance Forms]
- Subject education and site support materials
- Subject alert cards
- Study drug inventory control forms
- Subject diary:
    - Use of the subject diary is mandatory for the study and will be maintained by each study subject for reporting of SMBG results, study medication dosing, ketone results, hypoglycemia episodes, if applicable, and WOCBP urine pregnancy results, if applicable.
        - Subjects are to record any hypoglycemic symptoms they may experience and SMBG values if they conducted the test when they have symptoms in their diaries. All events recorded in the subject diary are to be reviewed by site staff according to Section 5.3.1.

- Any other materials as locally required or agreed.
- The central laboratory will provide all laboratory-related materials including home pregnancy testing kits for WOCBP to the study sites.

5.3 Safety Assessments

Safety assessments will include AE reporting, as well as marked abnormalities in clinical laboratory tests. Please refer to Appendix 1 for details on central laboratory assessments.

The procedures described in the sections that follow will also be completed to ensure subjects' safety.

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

5.3.1 Self-Monitoring Blood Glucose and Guidance on Management and Reporting of Hypoglycemia Episodes

5.3.1.1 Self-Monitoring of Blood Glucose

Glucose meters will be supplied to each study site. At entry to the lead-in period (Week -2 visit), subjects will receive a glucose meter, supplies, and instruction on their use. Supplies will be provided to allow for approximately 60 blood glucose assessments per month for the duration of the study. Subjects should be encouraged to measure and record fasting blood glucose levels at least once per day. The investigator may require more frequent readings based on local clinical practice. Subjects should bring their glucose meter with them to each study visit to ensure that it is functioning properly. Subjects may keep the glucose meter at the end of the study, but the Sponsor will not continue to provide glucose meter supplies once the study is complete.

In the occurrence of hypoglycemic symptoms or in the event of an unusually high or low blood glucose value, subjects should contact the Investigator. In addition, study subjects should comply with site's instructions with regard to SMBG and should report to the site blood glucose values and/or signs and symptoms suggestive of a hypoglycemia episode.

The memory of the glucose meter should be reviewed to compare readings with the subject's hypoglycemia episode log, as applicable. The glucose values should be reviewed by the site to identify any unusual high or low values, and to confirm that the values (from the glucose meter's memory and/or from the subject's hypoglycemia log) were obtained for the subject. If finger-stick glucose values are discordant from glycemic control assessed by the central laboratory or with clinical symptoms, the subject's glucose meter should be tested and the procedure for using it reviewed with the subject.

5.3.1.2 Guidance on Management and Reporting of Hypoglycemia Episodes

Hypoglycemia may be an expected event in subjects who are treated for diabetes. Subjects and their family members must be aware of the possibility that hypoglycemia may occur and the

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

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

The Investigator is responsible for questioning the subject about all symptoms reported on the hypoglycemia portion of the diary and for determining if they meet the clinical definition of hypoglycemia. Only symptoms and/or blood glucose values deemed by the Investigator to meet the definition of hypoglycemia should be reported on the hypoglycemia eCRF pages. Signs and symptoms of hypoglycemia, hypoglycemia episode or discontinuation due to hypoglycemia should not be reported on the AE eCRF page, unless the event fulfills protocol criteria for an SAE (see Section 6.2), in which case an SAE form must be completed in addition to the hypoglycemia eCRF pages for hypoglycemia.

Hypoglycemia episodes will be classified in the Clinical Study Report (CSR) according to the ADA criteria[18] and the International Society for Pediatric and Adolescent Diabetes (ISPAD) criteria.[19]

5.3.2 Self-Monitoring Blood Ketone Testing and Guidance on Management and Reporting of Diabetic Ketoacidosis Episodes

Diabetic ketoacidosis has been identified as a potential risk in subjects with diabetes receiving SGLT-2 inhibitors. Subjects and their family members must be aware of the possibility that DKA may occur, and of the signs and symptoms and the dangers associated with DKA. Subjects will receive a separate blood ketone meter, a device similar to the blood glucose meter, and sufficient supplies for testing when DKA is suspected. Subjects will be trained in the procedure of conducting blood ketone testing according to the manufacturer's specifications, and will be instructed to measure their blood ketones using the ketone meter provided by the Sponsor:

- When experiencing potential symptoms/signs of DKA, including but not limited to excessive thirst, nausea and vomiting, frequent urination, weakness or fatigue, fever, fruity-scented breath, confusion, and/or consistently elevated blood glucose: at least once a day

Blood ketone test results, symptoms potentially associated with DKA and relevant risk factors (e.g., missed insulin injection, infection, etc.) should be recorded in the subject diary. As DKA may present differently and occur at lower glucose values than expected, particular attention should be paid to episodes of nausea and vomiting as indicative of DKA symptoms, particularly in subjects requiring insulin therapy. Subjects should contact the site for assistance with diabetes

management in the event that they develop such symptoms or when the blood ketone reading is 0.6 mmol/L or above, even if their blood glucose levels are not elevated at that time.

The action, follow-up and monitoring plan will be at the discretion of the Investigators and will depend on their judgment of severity based on signs/symptoms of DKA, risk factors, relevant contributing factors, and blood glucose level (with the caveat that the blood glucose level may be lower than would be otherwise expected given elevated ketone levels):

- Any elevated blood ketone value (≥ 0.6 mmol/L) should be thoroughly reviewed by the site, in the context of concomitant clinical symptoms of DKA, and of possible discordance between finger-stick blood values and glycemic control assessed by the central laboratory or with clinical symptoms.

In the presence of such discordance, the subject's glucose and ketone meters should be tested and the procedure for using it reviewed with the subject. Investigators will determine if any of the reported elevated ketone values are actually indicative of a DKA event. If yes, investigators will document all DKA related symptoms, relevant risk factors, and available laboratory test results (including blood ketone values and blood glucose values measured by the glucose/ketone meter) on the DKA eCRF pages and report this event to the Sponsor. Signs and symptoms associated with DKA events should not be reported on the AE eCRF page, unless the event fulfills protocol criteria for an SAE (see Section 6.1), in which case an SAE form must be completed in addition to the DKA eCRF pages.

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.

5.3.3 Guidance on Assessment of Urinary Infections and Hematuria

5.3.3.1 Guidance on Assessment of Urinary Tract Infections

The following is presented to assist in the classification and management of urinary tract infections (UTI). It is not intended to supplant investigators' clinical judgment.

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

It is recommended that a follow-up urine culture be obtained within 7 days of clinical recovery from all UTIs. Whether or not additional therapy is prescribed because of culture results should be determined by Investigator judgment, after consultation with the Medical Monitor.

It is the Investigator's responsibility to report, as applicable based on Investigator's judgment and subject's medical history, related AEs as defined in Section 6.

Additional information, including but not limited to completion of supplemental eCRFs or questionnaires may be requested for certain AEs and/or laboratory abnormalities which are reported/identified during the course of the study.

Asymptomatic bacteriuria

During enrollment, treatment, and follow-up of subjects in this trial, the Investigator may discover a subject with asymptomatic bacteriuria. Asymptomatic bacteriuria is defined as the presence of $\geq 10^5$ colony forming units/mL of bacteria, in a properly collected voided urine specimen, without signs or symptoms typically attributed to UTI. In this study, the central laboratory will report urinary dipstick test results for hemoglobin but will not routinely report the results of urinary dipstick tests for leukocyte esterase as a screening test for pyuria in surveillance urine examinations.

5.3.3.2 Guidance on Assessment of Hematuria

All events of hematuria (microscopic and/or macroscopic) during the study should be worked up for a possible cause as per local guidelines.

5.3.4 Guidance on Assessment of Cardiovascular Events

An independent Cardiovascular Adjudication Committee that is blinded to the treatment of the subjects will independently adjudicate all events of heart failure requiring hospitalization. An adjudication manual/charter of operations further defines and describes the procedure for the handling, reporting and classification of these events.

5.3.5 Guidance on Assessment of Hepatic Laboratory Abnormalities

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 events related or leading to death (occurring within 30 days before death)
- Liver laboratory abnormalities such as
    - AST and/or ALT ≥ 3x ULN and TB ≥ 2x ULN (within 14 days of the AST and/or ALT elevation)
    - AST and/or ALT ≥ 10x ULN

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

The following is presented to assist in the evaluation and management of hepatic laboratory values. It is not intended to supplant the Investigator's clinical judgment. Subjects who experience ALT and/or AST values > 3x ULN confirmed with a repeated test will have the following performed within 3 days of the confirmed laboratory results:

- Adverse event assessment
- Physical examination for jaundice and other signs of liver diseases

- Review of relevant risk factors and current history focusing on possible causes of the increased ALT and/or AST and/or TB, including:
    - Use of suspect concomitant medication (including over-the-counter [i.e., acetaminophen/paracetamol], herbal and vitamin preparations)
    - Recent alcohol consumption or recreational drug/narcotic use
    - Recent unaccustomed physical exertion
    - Occupational or environmental exposure to hepatotoxins
    - Other conditions which may cause liver diseases or which may cause abnormal test results
    - Specialized liver laboratory panel (see Appendix 1)

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

For subjects who are discontinued from study medication as a result of sustained elevated liver safety abnormalities, as described in Section 3.6, additional blood sampling must be done within 3 days of the confirmed laboratory results (see Appendix 1 and Appendix 2), in conjunction with an ETD visit, in addition to the procedures noted above. A referral consultation to a hepatologist or gastroenterologist (specializing in liver abnormalities) should be obtained.

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

5.3.6 Physical Examination

- A targeted physical examination should include cardiovascular, lungs, abdomen, and extremities, and any organ systems pertinent to the subject's signs, symptoms, or AEs.
- A complete physical examination should include general appearance, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdomen, lymph nodes, extremities, neurological, skin, and musculoskeletal.

The individual performing the physical examinations must be licensed by state law (or applicable local law) to perform this procedure.

5.3.7 Measures of Growth and Maturity

Measures of growth and maturity will include Tanner staging and laboratory evaluations of growth, bone and maturation markers.

Tanner staging (Appendix 3) will be determined by Investigator assessment and subjects' self-reports.

Growth, bone and maturation markers will include:

- Thyroid-stimulating hormone (TSH) and free thyroxine
- Luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and total testosterone
- Insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3)
- Calcitonin, 25-hydroxy vitamin D, bone alkaline phosphatase, osteocalcin, and PTH
- Carboxyterminal cross-linked telopeptide of Type 1 collagen (CTX-1)

5.3.8 Blood Pressure, Orthostatic Blood Pressure and Heart Rate

Blood pressure, orthostatic BP and HR measurements must be taken consistently throughout the study. Only the right or the left arm should be used consistently when measuring these parameters. Document which arm was used along with the observer's initials; the same arm should be used for each position and at each visit. The subject should be allowed at least 5 minutes of rest before measurement. Blood pressure should be measured with the subject's arm resting on a table, and with subject's back support and feet flat on the floor.

Blood pressure and HR will be determined from three replicate measurements obtained at least 1 minute apart; the time between these measurements should not exceed 15 minutes. The average BP and HR will be determined from these three replicate measurements and reported in the eCRF.

Orthostatic BP and HR measurements should be obtained following completion of seated BP and HR measurement.

The supine BP and HR must be measured prior to the standing BP. The subject should rest in the supine position for at least 5 minutes prior to measurement of BP and HR.

The subject will then stand for 2 to 3 minutes. After this time, measure the BP with the arm supported at the antecubital fossa at heart level. Standing BP and HR will be determined from three replicate measurements obtained at least 1 minute apart. The average BP and HR will be determined from these three replicate measurements and reported in the eCRF.

All measurements should occur at least 8 hours after the last ingestion of caffeine, alcohol, or nicotine.

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

5.3.9 Guidance on Volume Depletion

Dapagliflozin has a modest diuretic effect. The risk of volume depletion is enhanced when two diuretics are used in combination and in subjects that otherwise are at risk for volume depletion. Therefore, caution should be exercised when administering dapagliflozin to subjects at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics. These subjects should be carefully monitored for volume status, electrolytes, and renal function.

5.3.10 Supplemental Visits

5.3.10.1 Rescue Visit

Any subject who qualifies for rescue during the study periods must have all Rescue visit procedures performed before rescue therapy is initiated. The IXRS must be called to record the subject status (i.e., rescue status). All subjects who are rescued but have not undergone ETD should remain in the study, follow the visit schedule, and continue treatment with study drugs.

Subjects who discontinue IP early will still be evaluated for rescue and follow the visit schedule, but will continue the study without IP administration after the Rescue Visit.

After Rescue Visit, the subject will continue in the treatment period according to the regular visit schedule.

The Rescue supplemental eCRF will be completed to collect rescue-related endpoint data.

All prescribed rescue medication and dosage(s) along with any changes should also be recorded in the eCRF.

5.3.10.2 Early Treatment Discontinuation Visit

Any subject who discontinues during the study periods must have all ETD visit procedures performed before study discontinuation. The IXRS must be called to record the subject status (i.e., ETD status). All subjects who discontinue study drug should remain in the study.

After ETD visit procedures are performed, the subject will continue in the treatment period according to the Early Discontinued follow-up visit schedule (Table 5.1-4).

The ETD supplemental eCRF will need to be completed.

5.3.10.3 Other Supplemental (Unscheduled) Visits

At any time during the trial, the Investigator may at his/her discretion arrange for a subject to have an unscheduled (supplemental) assessment(s), especially in the case of AEs that require follow-up. If a subject is seen for an unscheduled assessment, the appropriate supplemental pages of the eCRF must be completed.

5.3.11 Imaging Assessment for the Study

Not applicable.

5.4 Efficacy Assessments

Assessments consist of the central laboratory measurement of HbA1c and other relevant laboratory tests, collected during the study.

5.5 Pharmacokinetic/Pharmacodynamic Assessments

Table 5.5-1: 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] Pharmacokinetic samples will not be collected at any visit following an Early Treatment Discontinuation Visit.

Blood samples for determination of plasma levels of dapagliflozin, saxagliptin and its metabolite 5-OH-saxagliptin, glucose and DPP-4 activity will be taken at the times presented in Table 5.5-1. Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the Sponsor, e.g., for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring. Samples will be collected, labeled, stored and shipped as detailed in the Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality.

All PK and pharmacodynamic (PD) samples will be collected in a fasting condition.

Samples for determination of drug concentration in plasma will be analyzed by an appointed laboratory on behalf of the Sponsor/designee using appropriate bioanalytical methods. The PK laboratory will be unblinded to treatment, and PK data will not be transferred until after database lock. Full details of the analytical methods used will be described in a separate bioanalytical report.

Only PK samples from subjects on relevant active study drug will be analyzed; these samples will not be collected after treatment discontinuation. Samples from subjects not dosed with the relevant active study treatment will only be analyzed on a 'for cause' basis, for example, if there is a suspicion that a subject has been dosed incorrectly.

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses. Pharmacokinetics and exposure-response relationship analysis may be summarized and reported separately from the CSR as needed.

All PK samples still within the known stability of the analyses of interest at the time of receipt by the bioanalytical laboratory will be analyzed.

Pharmacokinetic samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation may be reported separately from the CSR.

In addition, PK samples will be archived for potential metabolite analysis, if the need arises and to the extent possible.

Pharmacodynamic samples will be stored and processed as detailed in the Laboratory Manual. Only DPP-4 samples from subjects on relevant active study drug will be analyzed. All samples will be disposed of after testing has been completed by the analytical lab.

5.6 Biomarker Assessments

Not applicable

5.7 Outcomes Research Assessments

Not applicable

5.8 Other Assessments

5.8.1 Diet and Exercise Counseling

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

A registered dietitian, registered nurse, physician, Certified Diabetes Educator (CDE), nutritionist, or other qualified member of the study team who has appropriate documented training, will provide this counseling.

5.8.2 Weight, Height, and BMI

Body weight and height will be measured according to the schedule presented in the study flow chart/time and event schedule (see Section 5.1) and will be recorded in the eCRF.

The study-site staff should use a digital precision scale if possible and record the weight to the first decimal point (e.g., 69.3 kg). The subject should wear a standard hospital-type gown or equivalent light indoor clothing, shoes removed, and bladder empty for the body weight measurement at each visit. Subjects should be weighed on the same scale at all visits.

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

Body mass index is determined by weight (kg) divided by height (m) squared.

Method of BMI Calculation:

- Use actual height and weight
- To calculate BMI:
    - Convert pounds (lbs) to kilograms (kg = lb / 2.2)
    - Convert inches (in) to centimeters (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)

5.9 Results of Central Assessments

Blood and urine samples will be obtained at specified time points for laboratory evaluations (see Appendix 1). The central laboratory for this study will perform the analysis of all scheduled laboratory tests and will provide reference ranges for these tests. The central laboratory will provide specific instructions for collection, processing, packaging, and shipping of all samples.

The HbA1c values and urinary glucose values, including the urinary glucose:creatinine ratio will be blinded to the Sponsor, Investigator, site, and subject for the duration of the study following IP administration on Day 1 until after study completion. In the event of an HbA1c result > 8.0% during the LT 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. After study completion at Week 56 (and data locked and analysis completed), the above measurements will be unblinded and available to the Sponsor and Investigator.

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all AEs. The causal relationship can be one of the following:

- Related: There is a reasonable causal relationship between study drug administration and the AE.
- Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

The Sponsor/designee will be reporting AEs to Regulatory Authorities and Ethics Committees according to local applicable laws including European Directive 2001/20/EC and Food and Drug Administration Code of Federal Regulations 21 CFR Parts 312 and 320.

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

6.1 Serious Adverse Events

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization. Potential DILI is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and DILI are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as an SAE (see Section 6.1.1 for reporting details).

NOTE:

The following hospitalizations are not considered SAEs in this clinical study:

- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Elective surgery, planned prior to signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 28 days of discontinuation of dosing.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

Serious adverse events will also be collected quarterly from the Week 56 visit to the Week 104 post-study visit.

An SAE report must be completed for any event where doubt exists regarding its seriousness.

If the Investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship must be specified in the narrative section of the SAE Report Form.

Serious adverse events, whether related or not related to study drug, and pregnancies must be reported to Sponsor (or designee) within 24 hours of awareness of the event.

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

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

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

Serious adverse events must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: [redacted]

USA

SAE Telephone Number: [redacted]

SAE Facsimile Number: [redacted]

Other

SAE Facsimile Number: [redacted]

SAE Telephone Number: [redacted]

For studies capturing SAEs through EDC, electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on-site.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to the Sponsor (or designee) using the same procedure used for transmitting the initial SAE report.

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

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

Intensity will be graded according to the following definitions:

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Section 6.1. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Section 6.1.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects. Nonserious AE information will also be collected quarterly from the Week 56 visit to the Week 104 post-study visit.

After the initial nonserious AE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All nonserious AEs will be followed until resolution, stabilization, the event is otherwise explained, the subject is lost to follow-up, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that, wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the Investigator must immediately notify the Medical Monitor or appropriate AstraZeneca representative of this event and complete and forward a Pregnancy Surveillance Form to AstraZeneca or designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

If pregnant, the study drug shall be immediately discontinued.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive (above therapeutic range) and medically important (i.e., with clinical sequel). All occurrences of overdose must be reported as SAEs (see Section 6.1.1 for reporting details).

6.6 Potential Drug-Induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential DILI is defined as:

1. Aminotransferase (AT) (ALT or AST) elevation > 3 times ULN

AND

2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Medication Error

Medication errors with AstraZeneca IP are collected in all studies where medication error is possible.

If a medication error occurs in the course of the study, the Investigator or other site personnel informs the appropriate AstraZeneca representatives immediately, and no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (initially fatal/life-threatening or follow-up fatal/life-threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error (see Section 6.1.1) and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix 4.

6.8 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, ECG, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

For the purposes of regulatory reporting, the following events must be reported in 24 hours regardless of whether the events are classified as serious or non-serious:

Liver function test (LFT) abnormalities accompanied by jaundice or hyperbilirubinemia

This category of events includes all AEs where hepatocellular damage (with elevation of ALT or AST > 3x ULN) is combined with hepatic dysfunction (with elevation of TB > 2x ULN) or jaundice. With respect to LFT abnormalities, both central lab results and AEs will be monitored.

Opportunistic infections

This category of events includes infections of interest that are consistent with AIDS defining diagnoses and are specific for immunosuppression, including unusual infections caused by bacteria, mycobacteria, fungi, viruses and protozoa.

Severe Hypersensitivity

This category of events includes all cases of severe hypersensitivity including: angioedema, anaphylaxis, and Stevens-Johnson Syndrome.

When one of these events meets the criteria for a SAE, report the event using SAE reporting procedures (Section 6.1.1). When one of these events does not meet the criteria for a SAE, report the event within 24 hours as a non-serious event.

For each non-serious event in these three categories, notify the Medical Monitor within 24 hours to discuss the next steps in reporting.

6.8.1 Adverse Events of Interest

The following are possible safety concerns associated with DPP-4 inhibitors and/or SGLT-2 inhibitors, which should be considered adverse events of interest and must be captured when spontaneously reported: amputations/peripheral revascularizations, 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; necrotizing 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 hospitalization for heart failure); acute kidney injury, renal impairment and/or renal failure; volume depletion; bone fractures; hyperlipidemia; hypoglycemic events; hyperglycemic events; ketoacidosis; malignancies (including bladder cancer); and arthralgia.

For the purposes of regulatory reporting, based on whether AEs in the above categories meet the criteria for serious or nonserious AEs, they will be collected and reported according to the appropriate guidelines, as described above in Sections 6.1.1 and 6.2.1, respectively.

To ensure that data on amputations are systematically collected, amputations and underlying conditions relevant to amputation will be recorded on a specific eCRF page. The AE leading to amputation should be recorded in the eCRF as AE/SAE. Events potentially placing the subject at risk for a lower limb amputation ("preceding events") should also be recorded in the eCRF as AE/SAE whether or not an amputation has taken place. These will be collected on a dedicated eCRF page.

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

7.1 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) comprised of Pediatric 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.

7.2 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 hospitalization (see Section 5.3.4 for more details).

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

7.3 Hepatic Adjudication Committee

An independent Hepatic Adjudication Committee, blinded to the treatment of the subjects, will determine the probability that 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 AST and/or ALT with or without TB elevations (see Section 5.3.5 for more details).

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

7.4 Diabetic Ketoacidosis 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.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

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 2-sided alpha level of 0.05. 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 versus placebo assuming a standard deviation of 1.7%.

Day 1 Randomization will be stratified based on the baseline antidiabetic treatment regimen (stable baseline dose of metformin IR or XR, a stable baseline dose of insulin, or a stable combination of metformin and insulin), gender, and age (10 to below 15 years of age, 15 to below 18 years of age).

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

8.2 Populations for Analyses

- The Enrolled Subjects Data Set will consist of all subjects who sign informed consent.
- The Randomized Subjects Data Set is the primary efficacy dataset and will consist of all randomized 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 Randomized Subjects Data Set, subjects will generally be presented in the treatment group to which they were randomized at the start of the ST treatment period (even if the treatment they received is different).
- The Up-titration Randomized Subjects Data Set will consist of the subset of randomized subjects who are re-randomized because their HbA1c is greater than or equal to 7 at Week 12.
- The Evaluable Subjects Data Set will be a subset of the Randomized Subjects Data Set. All data points after a relevant protocol deviation will be excluded from this dataset. Relevant protocol deviations are defined as deviations which could potentially affect the interpretability of the study results. All decisions to exclude data from the Randomized 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 > 10% of subjects in any treatment group have relevant protocol deviations. All relevant protocol deviations will be finalized prior to the database lock.

- The Treated Subjects 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 randomized 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 randomized withdrawal of metformin.
- The Randomized Withdrawal Subjects Data Set will be a subset of the Randomized Subject Data Set and will consist of all subjects belonging to the metformin randomization strata of background therapy who will be re-randomized at Week 32 or Week 40 (as described in Section 3.1). This data set will be used to analyze efficacy and safety during the randomized withdrawal period using the treatment assignment from the third randomization.

8.3 Endpoints

8.3.1 Primary Endpoint

Change from baseline in HbA1c at Week 26

8.3.2 Secondary Endpoints

- Change from baseline in FPG at Week 26
- Percentage of subjects with baseline HbA1c ≥ 7%, who achieve an HbA1c level < 7.0% at Week 26

8.3.3 Exploratory Endpoints

8.3.3.1 Exploratory Efficacy Endpoints for Short-term Assessment of Saxagliptin and Dapagliflozin

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

8.3.3.2 Exploratory Efficacy Endpoints for Short-term plus Long-term Assessment of Saxagliptin and Dapagliflozin

- 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 an HbA1c level < 7% at Week 52
- Time to initiation of glycemic rescue medication or discontinuation of study medication due to lack of efficacy during the 52-week treatment period

8.3.3.3 Exploratory Efficacy Endpoints for Monotherapy Assessment of Saxagliptin and Dapagliflozin

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

8.3.3.4 Safety Endpoints

Safety endpoints consist of the incidence of AEs, SAEs, hypoglycemic 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.

8.4 Analyses

Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan will be developed and finalized before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the CSR.

Analysis of data will be performed after all subjects have completed or have been discontinued from the study. In addition, all relevant queries must be resolved, and the database must be locked prior to the final analysis.

Dapagliflozin and saxagliptin will be summarized separately. A common placebo group will be included in each summary.

In addition, within the analyses of dapagliflozin and saxagliptin, 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 and saxagliptin regimens within each treatment will be combined into one subgroup and compared to the corresponding (common) placebo subgroup. P-values corresponding to subgroup comparisons will be reported for the primary and secondary efficacy endpoints, and will be reported at the nominal significance level.

8.4.1 Demographics and Baseline Characteristics

Frequency distributions and summary statistics for demographic and other baseline characteristics (age, gender, race, ethnicity, body weight, BMI, and region), including diabetes-related characteristics (duration of T2DM, HbA1c, FPG, and Day 1 Randomization strata) will be summarized by treatment group based on first randomization and overall using the Randomized Subjects Data Set. The analyses will be repeated using the Randomized Withdrawal Subjects Data Set. No statistical test will be carried out for comparison of any baseline measurement among the treatment groups.

8.4.2 Efficacy Analyses

All efficacy analyses will be performed using the Randomized Subjects Data Set unless otherwise specified. In addition, the primary efficacy analysis will be performed using the Evaluable Subjects Data Set if > 10% of the subjects in any treatment group have relevant protocol deviations. Furthermore, to account for randomization withdrawal, analyses dedicated to monotherapy assessment will be performed on the Randomized Withdrawal Subjects Data Set.

The ITT estimand (which will be estimated by using data regardless of premature treatment discontinuation and regardless of rescue therapy initiation, with missing values assumed not missing at random, imputed based on all available data) will be evaluated as the primary estimand.

All subjects taking dapagliflozin or saxagliptin including those who are rescued will go through the second randomization if their HbA1c values are ≥ 7% at Week 12. After the second randomization, subjects will belong to one of the following treatment groups:

1. Subjects responding at Week 12 and remaining on the low-dose
2. Subjects not responding at Week 12 and re-randomized to the low-dose
3. Subjects not responding at Week 12 and re-randomized to the high-dose

For the placebo arm, these three groups will be combined into one placebo group.

The following treatment regimens are considered for analysis:

- Low-dose/high-dose: Initial treatment of the low-dose followed by up-titrating to the high-dose for those who do not achieve the glycemic target of HbA1c < 7% at Week 12 and continuing treatment with the low-dose for those achieving the glycemic target of HbA1c < 7% at Week 12 (Groups 1 & 3)
- Low-dose: Initial treatment of the low-dose followed by continuing treatment on the low-dose drug for those who do not achieve the glycemic target of HbA1c < 7% at Week 12 and continuing treatment with the low-dose for those achieving the glycemic target of HbA1c < 7% at Week 12 (Groups 1 & 2)

Following the third randomization:

- Subjects initially randomized to dapagliflozin (or saxagliptin) with metformin as background therapy will be re-randomized in a 1:1 ratio to either dapagliflozin (or saxagliptin) alone or to dapagliflozin (or saxagliptin) with metformin as background therapy

- Subjects initially randomized to placebo with metformin as background therapy will be re-randomized in a 1:1:1 ratio to dapagliflozin alone or saxagliptin alone or placebo with metformin as background therapy

When fitting models that involve the stratification variables, if the data are too sparse within one or more stratification cells, levels of stratification variables may be combined, and/or one or more stratification variables may be removed from the model. Details will be provided in the statistical analysis plan.

8.4.2.1 Primary Efficacy Analysis

The primary endpoint is the change from baseline to Week 26 of the ST treatment period in HbA1c.

The primary efficacy analysis will be performed using an analysis of covariance (ANCOVA). For this analysis, all dose levels for a treatment will be combined into one treatment group for each drug. 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 value, treatment group, and randomization strata. For each drug, the comparison vs placebo will be tested at a 2-sided alpha level of 0.05. Point estimates and 95% confidence intervals will be calculated based on maximum likelihood for the adjusted mean changes within each treatment group as well as for the differences in adjusted mean changes between treatment groups.

The ITT estimand (which will be estimated using all available data regardless of premature treatment discontinuation and regardless of rescue therapy initiation) will be evaluated as the primary estimand. Missing values for Week 26 will be imputed using a multiple imputation method assuming the data are not missing at random. Multiple imputation using retrieved drop-outs 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 26 HbA1c value. The details of the imputation methods will be presented in the statistical analysis plan. To assess the robustness of the primary efficacy analysis for the change in HbA1c from baseline to Week 26, additional sensitivity analysis may be performed using the Evaluable Subjects Data Set if > 10% of the subjects in any treatment group in the Randomized Subjects Data Set have relevant protocol deviations.

The primary endpoint will also be compared between the low-dose/high-dose treatment regimen and placebo, separately for both dapagliflozin and saxagliptin. In addition, up-titrating to high-dose and continuing on low-dose will be compared in the subset of subjects who had HbA1c $\geq$ 7% at Week 12. These analyses are described under secondary efficacy analyses.

8.4.2.2 Secondary Efficacy Analyses

Secondary efficacy 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.

1. Comparison of mean reduction in HbA1c from baseline at Week 26 between 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 (all doses and regimens combined) 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 ≥7% who achieve an HbA1c level < 7.0% at Week 26 between overall drug treatment (all doses and regimens combined) and placebo
7. Comparison of the percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7.0% at Week 26 between the low-dose/high-dose treatment regimen and placebo
8. Comparison of the percentage of subjects with baseline HbA1c ≥ 7% who achieve an HbA1c level < 7.0% 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 ≥ 7% who achieve an HbA1c level < 7.0% 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, a weighted ANCOVA will be performed for the change from baseline in HbA1c at Week 26 to compare the placebo and the low-dose/high-dose treatment regimen. For this analysis, all dapagliflozin and saxagliptin subjects who had HbA1c <7% at Week 12 and remained on the low-dose will get a weight of one. The dapagliflozin and saxagliptin subjects who had HbA1c ≥ 7% at Week 12 and continued on the low-dose will get a weight of 0. The dapagliflozin and saxagliptin subjects who had HbA1c ≥ 7% at Week 12 and received the high-dose will get a weight of 2. All subjects who do not undergo the second randomization and all placebo subjects will get a weight of one.

For each drug, a weighted ANCOVA will be performed for the change from baseline in HbA1c at Week 26 to compare the placebo and the low-dose treatment regimen. For this analysis, all dapagliflozin and saxagliptin subjects who had HbA1c < 7% at Week 12 and remained on the low-dose will get a weight of one. The dapagliflozin and saxagliptin subjects who had HbA1c ≥ 7% at Week 12 and continued on the low-dose will get a weight of 2. The dapagliflozin and saxagliptin subjects who had HbA1c ≥ 7% at Week 12 and received the high-dose will get a

weight of 0. All subjects who do not undergo the second randomization and all placebo subjects will get a weight of one.

For subjects on dapagliflozin and saxagliptin who had HbA1c ≥ 7% at Week 12, the change from baseline HbA1c at Week 26 (ST) will be compared between the subjects who are re-randomized to remain on the low-dose and the subjects who are re-randomized to the high-dose using an ANCOVA. This analysis will be based on the Up-titration Randomized Subjects Data Set.

Change from baseline at Week 26 (ST) in FPG will be analyzed similarly as the analyses of change from baseline in HbA1c at Week 26.

The proportion of subjects achieving HbA1c < 7.0% at Week 26 (ST) will be analyzed using a weighted logistic regression with adjustment for the baseline HbA1c measurement and the randomization strata. Weighting for the subjects will be applied similarly to the weighting in the analysis of change from baseline in HbA1c. Subjects with missing response at Week 26 will be imputed by dichotomizing the imputed values of HbA1c at Week 26.

8.4.2.3 Exploratory Efficacy Analyses

Exploratory analyses will be performed for overall saxagliptin and overall dapagliflozin separately, by combining all low-dose and high-dose treatment groups as appropriate.

As with the primary and secondary efficacy analyses, separate models will be used for saxagliptin and dapagliflozin analyses, and each analysis will include the (common) placebo group.

Additionally, subjects belonging to the randomization strata of background therapy metformin alone with HbA1c < 7.5% at Week 26 or Week 32 will be eligible for a third randomization:

- Subjects initially randomized to the active arm will be randomized 1:1 to either discontinuing background therapy with metformin or to continuing current treatment. For subjects randomized to withdraw metformin, those receiving the low-dose will be up-titrated to the high-dose whereas those receiving the high-dose will continue on the high-dose.
- These subjects will be used to assess the effect of dapagliflozin (or saxagliptin) monotherapy versus dapagliflozin (or saxagliptin) with metformin add-on therapy. This analysis will estimate the effect of metformin on efficacy in the presence of dapagliflozin (or saxagliptin) and indicate the effects that would be lost/gained if withdrawing metformin (and using only monotherapy).
- Subjects initially randomized to the placebo arm will be randomized 1:1:1 to either discontinue metformin and switch to the dapagliflozin high-dose, or to discontinue metformin and switch to the saxagliptin high-dose, or to continue with their current treatment (placebo+metformin).
- These subjects will be used to assess the effect of dapagliflozin (or saxagliptin) monotherapy versus metformin alone at steady state.

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

These analyses will be conducted on the Randomized Subjects Data Set.

Comparison of the percentage of subjects who require glycemic rescue medication or discontinue the study medication due to lack of efficacy at or prior to Week 26 will be performed between overall dapagliflozin (or saxagliptin) and placebo.

The proportion of subjects who require glycemic rescue medication or discontinue the study medication due to lack of efficacy at Week 26 will be analyzed using a logistic regression with adjustment for the baseline HbA1c measurement, treatment, and the randomization strata. Ninety five percent confidence intervals for the adjusted percentages/response rate within each treatment group as well as for the adjusted odds ratios for each treatment group and placebo, 95% confidence intervals, and p-value will be calculated with adjustment for baseline HbA1c measurement and randomization strata.

The analysis will use subjects in the primary efficacy data set (i.e., Randomized Subjects Data Set).

Time to glycemic rescue medication or discontinuation of study medication due to lack of efficacy during the 26-week treatment period will be analyzed using a Cox proportional hazards model with stratification factor as covariate. Estimates of the hazard ratio and 95% confidence interval will be provided. Kaplan-Meier estimates will be calculated and plotted by treatment group. For the analysis during the 26-week treatment, all subjects will be censored at the Week 26 visit date or last study date (for those withdrawing from the study prior to Week 26 visit), if rescue or treatment discontinuation due to lack of efficacy has not occurred by then.

These analyses will use subjects from the Randomized Subjects Data Set.

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

Change from baseline at Week 52 (LT) in HbA1c and, separately, FPG will be analyzed using an ANCOVA model.

Percentage of subjects with baseline HbA1c $\geq$ 7% achieving an HbA1c $<$ 7% at Week 52 (LT), will be analyzed using a logistic regression with adjustment for the baseline HbA1c measurement and the randomization strata.

Time to initiation of glycemic rescue medication or discontinuation of study medication due to lack of efficacy during the 52-week treatment period will be analyzed using a Cox proportional hazards model with stratification factors as covariates. Estimates of the hazard ratio and 95% confidence intervals will be provided. Kaplan-Meier estimates will be calculated and plotted by treatment group. For the analysis during the 52-week treatment period, all subjects will be censored at the Week 52 visit date or last study date (for those withdrawing from the study prior to Week 52 visit), if rescue or treatment discontinuation due to lack of efficacy has not occurred by then. These analyses will use subjects from the Randomized Subjects Data Set.

To account for the randomized withdrawal of background metformin at Week 32 or Week 40, additional weighted analyses of change in HbA1c, FPG, and the percentage of subjects with HbA1c $<$ 7% will be performed excluding subjects randomized to withdraw from metformin. For the weighted analyses, dapagliflozin (or saxagliptin) subjects who went through the third

randomization and withdrew metformin will get a weight of zero, and those randomized to stay on metformin will get a weight of 2. All other dapagliflozin (or saxagliptin) subjects will get a weight of 1. Placebo subjects randomized to withdraw metformin and switch to active treatment will get a weight of zero. Placebo subjects randomized to stay on metformin will get a weight of 3. All other placebo subjects will get a weight of 1. ANCOVA models will be utilized for the weighted analyses of change in HbA1c and FPG, and a logistic regression model will be used for the weighted analysis of the percentage of subjects with HbA1c < 7%.

Exploratory efficacy analysis for monotherapy assessment

These analyses will be conducted during the randomized withdrawal period using the Randomized Withdrawal Subjects Data Set.

The reference time point to be used as 'withdrawal baseline' will be the closest time point on or before the third randomization visit. The following endpoints will be assessed:

- Change from withdrawal baseline in HbA1c
- Change from withdrawal baseline in FPG
- Percentage of subjects who achieve or maintain a HbA1c level < 7.0% at the end of the withdrawal period
- Time to rescue therapy initiation or discontinuation of study medication due to lack of glycemic control during the withdrawal period using withdrawal baseline as the reference time point

The above endpoints will be summarized within each treatment group from the original randomization as follows:

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

The observed and change from withdrawal baseline in HbA1c and in FPG will be summarized. Percentage of subjects who achieve or maintain an HbA1c level < 7.0% at the end of the withdrawal period will also be summarized.

Time from baseline withdrawal (days) to initiation of glycemic rescue medication or discontinuation of study medication due to lack of efficacy during the randomized withdrawal period will be summarized using Kaplan-Meier estimates.

8.4.3 Safety Analyses

The assessment of safety will be based on the analyses of AEs, vital signs, physical examinations, ECGs, hypoglycemia events, DKA events, safety laboratory evaluations, and measures of growth and maturity.

Dapagliflozin and saxagliptin will be summarized separately. Both low-dose and high-dose saxagliptin and dapagliflozin groups, respectively, will be combined for saxagliptin and dapagliflozin to provide the safety summary for overall saxagliptin and overall dapagliflozin compared to placebo. A common placebo group will be included in each summary.

8.4.3.1 Short-term and Long-term Assessment

The number and percent of subjects with at least one AE will be summarized for each treatment group, including summaries of AEs, SAEs, and AEs leading to discontinuation. Summaries will include the number of subjects with events by system organ class and preferred term. In addition, the proportion of subjects experiencing at least one episode of hypoglycemia during the 26 weeks of ST treatment and 52 weeks of treatment (ST+LT) will be summarized by treatment group.

The incidence of marked laboratory abnormalities through 26 weeks (ST), and separately, through 52 weeks (ST+LT) will be summarized for each treatment group.

Values and changes from baseline at each scheduled time point for clinical laboratory parameters, body weight and vital signs, including seated BP and HR, will be summarized by treatment group using descriptive statistics. The normality/abnormality of ECG tracings, as determined by the Investigator, will be summarized by shift tables overall and by ECG tracing at baseline. Tanner staging and measures of growth will also be summarized by treatment group using descriptive statistics.

The Treated Subjects Data Set will be used for all safety analyses, including data after rescue (primary safety analysis). Additional sensitivity analyses on data collected prior to rescue will be performed for AEs, hypoglycemia events, and clinical laboratory marked abnormalities. The primary analyses of events of hypoglycemia will be performed excluding data after rescue. Safety analyses will be performed using data from the ST treatment period (at the time of the primary endpoint analysis) and then again at the final database lock (52 weeks) on the combined ST+LT treatment period.

Measures of growth, bone, and maturation markers will be summarized for ST and the combined ST+LT treatment periods.

For these analyses, safety data will be summarized by treatment group based on the treatment received (dapagliflozin/saxagliptin/placebo) using the Treated Subjects Data Set.

8.4.3.2 Additional Long-term Safety Assessment

Due to the randomized withdrawal design, additional safety analyses will be performed up to Week 32 along with modified analyses performed at Week 52 to account for the randomized withdrawal. These assessments of safety will be based on the safety parameters already described (Section 8.4.3).

Selected safety analyses performed during the ST and LT periods (Section 8.4.3.1) will also be conducted during the treatment period up to Week 32 to account for randomized withdrawal. This will include analyses of AEs, hypoglycemia events, DKA events, and clinical laboratory marked abnormalities. All safety data will be summarized by treatment group based on the treatment received (dapagliflozin/saxagliptin/placebo) using the Treated Subjects Data Set.

To assess the effects of dapagliflozin (or saxagliptin) versus placebo on safety endpoints for subjects on background medication (i.e., excluding subjects re-randomized to withdraw from metformin) a weighted analysis will be conducted for select safety parameters using the Treated Subjects Data Set using the original randomized groups.

Dapagliflozin (or saxagliptin) subjects who went through the last randomization and withdrew metformin will get a weight of zero and those randomized to stay on metformin will get a weight of 2.

Placebo subjects randomized to withdraw metformin and switched to active treatment will get a weight of zero. Placebo subjects randomized to stay on metformin will get a weight of 3. All other subjects will get a weight of 1.

Additional safety analyses will be performed on the Treated Subjects Data Set on AEs, DKA events, hypoglycemia events, and clinical laboratory marked abnormalities during the ST and LT treatment periods to compare safety endpoints per treatment received at the time of the event.

For placebo subjects re-randomized to switch to dapagliflozin (or saxagliptin), events and clinical laboratory marked abnormalities will be classified in the placebo group up to the beginning of the randomized withdrawal period and in the dapagliflozin (or saxagliptin) group during the randomized withdrawal period.

Furthermore, as the length of exposure in the treatment received following the re-randomization withdrawal process may be shorter for the subjects who switch from placebo to dapagliflozin (or saxagliptin); these events and marked abnormalities analyses will report incidence rates adjusted for exposure time.

8.4.3.3 Monotherapy Safety Assessment

The monotherapy safety assessment will include standard safety assessments (Section 8.4.3) occurring during the randomized withdrawal period. These analyses will be conducted during the randomized withdrawal period using the Randomized Withdrawal Subjects Data Set.

The reference time point to be used as 'withdrawal baseline' will be the closest time point on or before the third randomization visit.

The safety assessments will be compared within each treatment group from the original randomization as follows:

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

- For subjects initially randomized to the placebo group, the subjects re-randomized to switch to dapagliflozin (or saxagliptin) monotherapy will be compared to the subjects re-randomized to stay on placebo with add-on metformin. Separate analyses will be performed respectively for subjects re-randomized to the dapagliflozin group and for those re-randomized to the saxagliptin group, using those re-randomized to placebo as comparator.
- Additional analysis will also be performed to compare all subjects taking dapagliflozin (or saxagliptin) monotherapy vs those taking placebo with background metformin during the randomized withdrawal period (adding placebo subjects randomized to withdraw metformin and switched to dapagliflozin [or saxagliptin]) monotherapy to dapagliflozin (or saxagliptin) subjects randomized to withdraw metformin).

For assessment of events, only those with an onset date occurring on or after the randomized withdrawal will be included in these analyses.

8.4.3.4 Week 104 Assessment

Selected safety analyses described above at Week 52 (Sections 8.3.3.1, 8.3.3.2, and 8.3.3.3) can be repeated at Week 104 (using the same treatment groupings). Analyses will be performed on the Treated Subjects Data Set. Additionally, selected analyses will be performed on the Randomized Withdrawal Subjects Data Set to assess the effects of monotherapy.

The following parameters will be summarized:

- Measures of growth, bone, and maturation markers as well as Tanner stage assessment
- Height, body weight and BMI

8.4.4 Pharmacokinetic Analyses

Plasma samples will be analyzed for dapagliflozin, saxagliptin and its metabolite 5-OH-saxagliptin by validated assays.

Plasma concentration values for dapagliflozin, saxagliptin and 5-OH-saxagliptin will be summarized using descriptive statistics by visit and time point. The plasma concentration values may be used in population PK and/or population PK/PD analyses that will be reported separately from the CSR.

8.4.5 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.

8.4.6 Biomarker Analyses

Not applicable.

8.4.7 Outcomes Research Analyses

Not applicable.

8.4.8 Other Analyses

Not applicable.

8.5 Interim Analyses

Not applicable.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, the Sponsor/designee. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- The Sponsor/designee
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to the Sponsor/designee.

To prevent interruption of study drug administration, some changes from Amendment 05 were implemented before approval from the IRB/IEC due to the ongoing COVID-19 pandemic and only for subjects affected by the pandemic/local restrictions related to the pandemic, in accordance with the advice from Regulatory Authorities.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s). To prevent interruption of study drug administration, some changes from Amendment 05 were implemented after verbal informed consent was obtained from subjects affected by the pandemic/local restrictions related to the pandemic. Written consent will be obtained after approval of the informed consent form by applicable Regulatory Authorities/IRB(s)/IEC(s).

9.1.2 Monitoring

The Sponsor/designee representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of the Sponsor (or designee) must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable. Off-site monitoring visits and remote source data verification are allowed when restrictions due to the COVID-19 pandemic prevent on-site visits (e.g., monitors may not be able to access the sites in a timely manner). Should this occur, it should be documented and the reasons be available for review by the Sponsor and during inspections by any Regulatory Authorities. Remote monitoring should be focused on review of critical study site documentation and source data and the monitoring activities, including remote review of source documents, should be documented in the same level of detail as on-site monitoring activities. Any resulting actions to address issues identified from the remote source document review should be consistent with procedures and processes described in the study monitoring plan.

In addition, the study may be evaluated by the Sponsor (or designee) internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. The Sponsor (or designee) audit reports will be kept confidential.

The investigator must notify the Sponsor (or designee) promptly of any inspections scheduled by Regulatory Authorities, and promptly forward copies of inspection reports to the Sponsor/designee.

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), AE tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original. Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

9.1.3 Investigational Site Training

The Sponsor/designee will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the Sponsor/designee, whichever is longer. The investigator must contact the Sponsor/designee prior to destroying any records associated with the study.

The Sponsor/designee will notify the Investigator when the study records are no longer needed.

If the Investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Notice of such transfer will be given in writing to the Sponsor/designee.

9.2.2 Study Drug Records

It is the responsibility of the Investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include IPs. Any unused IP sent directly to subjects' homes should be returned to the site at the next on-site visit. Records or logs must comply with applicable regulations and guidelines and should include:

- Amount received and placed in storage area
- Amount currently in storage area
- Label identification number or batch number
- Amount dispensed to and returned by each subject, including unique subject identifiers
- Amount transferred to another area/site for dispensing or storage
- Nonstudy disposition (e.g., lost, wasted)
- Amount destroyed at study site, if applicable
- Amount returned to the Sponsor/designee
- Retain samples for bioavailability/bioequivalence, if applicable
- Dates and initials of person responsible for IP dispensing/accountability, as per the Delegation of Authority Form

The Sponsor/designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. Case report forms may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor/designee's EDC tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance Form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by the Sponsor/designee.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the Investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the Sponsor/designee's EDC tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet Sponsor/designee training requirements and must only access the Sponsor/designee's EDC tool using the unique user account provided by the Sponsor/designee. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

The CSR will be prepared after subjects have completed 52 weeks of randomized treatment and Week 56 follow-up data are available.

The post-study data (Week 104 data) will be reported separately.

A Signatory Investigator must be selected to sign the CSR.

For the CSR the Signatory Investigator will be selected as appropriate based on the following criteria:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee

- Subject recruitment (e.g., among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (e.g., among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to the Sponsor/designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to the Sponsor/designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

A description of this clinical study is available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of the study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the subject. This does not mean periodic abstinence (e.g., calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Women must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception's must be discussed in the event that the subject chooses to forego complete abstinence.

11 LIST OF ABBREVIATIONS

Term	Definition
5-OH-saxagliptin	5-hydroxy-saxagliptin
ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AT	aminotransferase
AZ	AstraZeneca
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
CFR	Code of Federal Regulations
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	Clinical Study Report
CTA	Clinical Trial Agreement
CTX-1	carboxyterminal cross-linked telopeptide of Type 1 collagen
CYP3A4/5	cytochrome P450 3A4/3A5
DILI	drug-induced liver injury
DKA	diabetic ketoacidosis
DMC	Data Monitoring Committee
DPP-4	dipeptidyl-peptidase-4
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ETD	early treatment discontinuation
FDA	Food and Drug Administration
FPG	fasting plasma glucose

Term	Definition
GAD	glutamic acid decarboxylase
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GMP	Good Manufacturing Practice
HAV	hepatitis A virus
HbA1c	glycosylated hemoglobin
HBsAg	hepatitis B surface antigen
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HR	heart rate
IA-2	protein tyrosine phosphatase-like protein
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGF-1	insulin-like growth factor-1
IGFBP-3	insulin-like growth factor binding protein-3
IMP	investigational medicinal product/
IND	Investigational New Drug Exemption
IP	investigational (medicinal) product
IR	immediate release
IRB	Institutional Review Board
ITT	intent-to-treat
LFT	liver function test
LT	long-term
IUD	intrauterine device
IXRS	Interactive Web/Voice Response System
MODY	maturity onset diabetes of the young
non-IMP	non-investigational medicinal product
non-IP	non-investigational (medicinal) product
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)

Term	Definition
PPG	postprandial glucose
PTH	parathyroid hormone
SAE	serious adverse event
SGLT-2	sodium glucose cotransporter-2
SMBG	self-monitoring blood glucose
SOP	standard operating procedures
ST	short-term
SU	Sulfonylurea
TB	total bilirubin
T2DM	type 2 diabetes mellitus
TSH	thyroid-stimulating hormone
UKPDS	United Kingdom Prospective Diabetes Study
ULN	upper limit of normal
US/USA	United States of America
UTI	urinary tract infection
WOCBP	women of childbearing potential
XR	extended release

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APPENDIX 1 CENTRAL LABORATORY ASSESSMENTS

Blood and urine samples will be obtained at specified time points for laboratory evaluations. The central laboratory for this study will perform the analysis of all scheduled laboratory tests and will provide reference ranges for these tests. The detailed methods for specimen collection, handling, processing, shipping, and storage will be supplied in the Investigator's Laboratory Manual provided by the Central Laboratory. All clinical laboratory tests will be performed by the Central Laboratory or designated reference laboratory.

The HbA1c values and urinary glucose values, including the urinary glucose:creatinine ratio will be blinded to the Sponsor, Investigator, site, and subject for the duration of the study until after study completion. In the event of an HbA1c result > 8.0% during the LT 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.

The following sections indicate the laboratory tests required for this study. For countries using conventional units, the results will be reported using conventional units. For countries using SI units, the results will be reported using SI units. In cases of differences in the units as listed in this protocol compared to the units on the central laboratory reports, the units from the central laboratory reports will be used.

PROTOCOL-SPECIFIC CENTRAL LABORATORY ASSESSMENTS:

- HbA1c (%, mmol/mol)
- FPG (mg/dL, mmol/L)
- Fasting serum lipid profile:
  - Total-C (mg/dL, mmol/L)
  - Calculated LDL-C (mg/dL, mmol/L)
    - *Except screening period, reflex testing will occur for Direct LDL-C if TG > 400 mg/dL (4.52 mmol/L)*
  - HDL-C (mg/dL, mmol/L)
  - TG (mg/dL, mmol/L)
- Anti-Glutamic acid decarboxylase (GAD) antibodies (nmol/L or U/mL)
  - *Note- this test may also be reported as either positive or negative*
- Anti-Protein tyrosine phosphatase-like protein (IA2) antibodies (nmol/L or U/mL)
  - *Note- this test may also be reported as either positive or negative*

Enrollment-Specific Reflex Testing

Reflex testing refers to specific tests which are only performed when the results of prior tests are outside a pre-determined range.

- Thyroid-stimulating hormone (TSH)
  - *Reflex testing: abnormal TSH value at enrollment will be further evaluated by free T4*
- Hepatitis Screen Panel:
  - Anti-hepatitis C virus antibody
  - Hepatitis B surface antigen
  - Anti-hepatitis A virus IgM
    - *Reflex testing: Low positive and positive results require confirmatory testing.*
- C-peptide
  - *Reflex testing will only be performed in otherwise eligible GAD and IA2 antibody-positive subjects*

Specialized Liver Panel:

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

- Hepatitis A IgM
- Hepatitis BsAg
- Hepatitis B Core Ab IgM
- Hepatitis C virus RNA or RIBA
- Hepatitis C Ab
- Hepatitis E IgM
- Epstein-Barr virus (EBV) IgM Ab
- Lactate dehydrogenase (LDH)
- Gamma-glutamyl-transpeptidase (GGT)
- Carbohydrate deficient transferrin (CDT)
- Prothrombin time (PT/INR)
- Iron Panel - iron, ferritin, total iron binding capacity (TIBC)

- Immunology panel including Antinuclear Antibody (ANA), Anti-Smooth Muscle Antibody (SMA) and Anti-Liver/Kidney Microsomal Antibody (Anti-LKM)
- Anti-tissue Transglutaminase Antibody

Liver Discontinuation Panel:

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

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

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

Standard Safety Laboratory Panels:

Table Appendix 1: Standard Safety Laboratory Panels

Hematology
• Hemoglobin (g/dL, g/L)
• Hematocrit (%, V/V)
• Red blood cell (RBC) ($x10^6$/UL, $x10^{12}$/L)
RBC count indices:
• Mean cell volume (MCV) (fL)
• Mean cell hemoglobin (MCH) (pg/cell)
• Mean cell hemoglobin concentration (MCHC) (gHb/dL, gHb/L)
• White blood cell count and differential
• Platelet count ($x10^9$/L)
Serum Chemistry
• AST (IU/L)

Table Appendix 1: Standard Safety Laboratory Panels

- ALT (IU/L)
- Alkaline phosphatase (ALK-P) (IU/L)
- Total bilirubin (mg/dL, µmol/L)
- Serum creatinine (Scr) used to calculate estimated glomerular filtration rate (eGFR) according to the Schwarz formula as follows: eGFR (ml/min/1.73m^2) = 0.413 *(height (cms)/serum creatinine (mg/dL):

*If serum creatinine concentration is measured in SI units (µmoles/L), divide this number by the conversion factor of 88.4 to get the SI units (mg/dl) before inserting into the Schwartz formula to calculate eGFR.

Results will be reported to the sites and the Sponsor.

- Sodium (mEq/L, mmol/L)
- Potassium (mEq/L, mmol/L)
- Chloride (mEq/L, mmol/L)
- Calcium (mg/dL, mmol/L)
- Magnesium (mEq/L, mmol/L)
- Phosphorus (mg/dL, mmol/L)
- Total protein (g/dL, g/L)
- Uric acid (mg/dL, µmol/L)

Table Appendix 1: Standard Safety Laboratory Panels

Urine Analyses

- Creatinine
- Calculated Urinary albumin:creatinine ratio (UACR)
- Urine human chorionic gonadotrophin (HCG) pregnancy test for women of childbearing potential (WOCBP) (HCG minimum sensitivity of 25 IU/L; performed at site or at home). *If a urine HCG test is positive, a blood specimen will be obtained and a serum pregnancy test will be performed by the central laboratory for confirmation.*

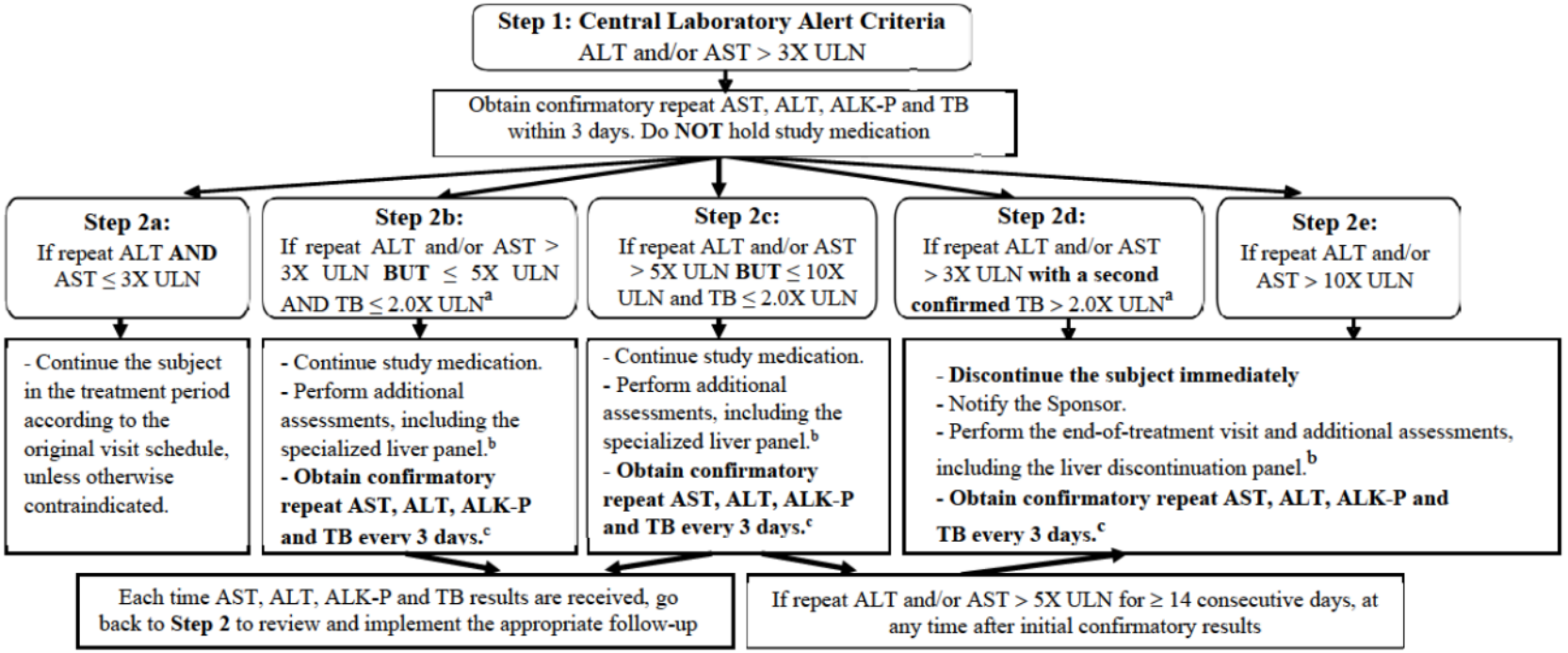
Spot urine:

- Urinary glucose:creatinine ratio

Urinalysis with microscopy:

- Hematuria

APPENDIX 2 SUSTAINED ELEVATED LIVER SAFETY ABNORMALITIES FLOW CHART



[a] In subjects with repeat ALT or AST > 3X ULN but ≤ 10X ULN, only subjects with TB ≤ 2.0X ULN at Step 1 should be followed according to Step 2b. Subjects with an initial TB and confirmatory repeat TB > 2.0X ULN should be followed according to Step 2d.

[b] Refer to section 5.3.4 for details on additional assessments to be performed (AE assessment, PE, review of current medical history including focused review of risk factors for liver diseases and collection of blood samples [specialized liver panel or liver discontinuation panel]).

[c] Confirmatory repeat AST, ALT, ALK-P and TB should be obtained every 3 days following receipt of prior laboratory results, until the ALT and AST are ≤ 2X ULN or until ALT and AST are at or below baseline levels. The frequency of retesting can decrease to once a week or less if abnormalities stabilize and the subject is asymptomatic.

APPENDIX 3 TANNER ASSESSMENT SCALE

The Tanner Scale (also known as Tanner Staging) is a measure of pubertal development (sexual maturation) in children and adolescents with components described for each sex, rated separately on a scale of stage one to stage five. The stages define physical measurement of development based on external primary and secondary sexual characteristics. Females are classified with regard to breast and pubic hair characteristics. Males are classified with regard to genitalia and pubic hair characteristics.

A qualitative determination of the subject's sexual maturity rating on a scale of 1 to 5 will be determined according to those criteria established by Tanner (summarized in Tables 1 and 2 below). Based on the level of comfort by the Investigator, caregiver, or study subject, the measure of sexual maturity may be obtained by 1) visually observing the level of development after the subject disrobes or 2) requesting the caregiver or subject point to the level of maturity from a description or selection of pictures that exhibit the various stages of maturity.

Table 1: 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

Table 2: 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

Table 2: Classification of Sex Maturity Stages in Boys

Stage	Pubic Hair	Genitalia
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

Additional materials to aid in the Tanner Stage assessment will be provided upon request.

APPENDIX 4 DEFINITION OF MEDICATION ERROR

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

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

Medication error includes situations where an error:

- occurred
- was identified and intercepted before the participant received the investigational product
- did not occur, but circumstances were recognized that could have led to an error

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

- Investigational product name confusion
- Dispensing error, e.g., medication prepared incorrectly, even if it was not actually given to the subject
- Investigational product not administered as indicated, e.g., wrong route or wrong site of administration
- Investigational product not taken as indicated, e.g., tablet dissolved in water when it should be taken as a solid tablet
- Investigational product not stored as instructed, e.g., kept in the fridge when it should be at room temperature
- Wrong subject received the medication (excluding IVRS/IWRS errors)
- Wrong investigational product administered to subject (excluding IVRS/IWRS errors)

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

- Errors related to or resulting from IVRS/IWRS - including those that lead to one of the above listed events that would otherwise have been a medication error
- Subject accidentally missed investigational product dose(s), e.g., forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Subject failed to return unused medication or empty packaging

- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AstraZeneca product
- Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error

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