Janssen Research & Development *

Clinical Protocol

A Randomized, Multicenter, Double-Blind, Parallel-Group, Placebo-Controlled Study to Investigate the Efficacy and Safety of Canagliflozin in Children and Adolescents (≥10 to <18 years) with Type 2 Diabetes Mellitus

Protocol 28431754DIA3018; Phase 3
AMENDMENT 4

JNJ-28431754 (canagliflozin)

CCI [redacted]

This compound is being investigated in Phase 3 clinical studies.

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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Prepared by: Janssen Research & Development, LLC
CCI [redacted]

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	19 December 2016
Amendment 1	27 March 2017
Amendment 2	25 August 2017
Amendment 3	25 June 2018
Amendment 4	14 August 2020

Amendments below are listed beginning with the most recent amendment.

Amendment 4 (14 August 2020)

The overall reason for the amendment:

Due to slower than expected recruitment in the study, a high rate of screen failures, and the goal of maintaining the study timeline, the power calculation was modified with the Food and Drug Administration's (FDA's) approval and without compromising the study's integrity, thus resulting in a reduced sample size. In addition, minor modifications to the inclusion and exclusion criteria have been made.

Applicable Section(s)	Description of Change(s)
Rationale: To reduce the sample size for the overall study and for subjects on background metformin, while maintaining adequate power.	
Synopsis (Overview of Study Design; Sample Size Determination); 3.1, Overview of Study Design; 4, Subject Population; 11.2, Sample Size Determination	Reduced the sample size from 172 subjects (86 per group) to 146 subjects (73 per group) for the overall study while maintaining adequate power (85%) for detecting differences between the treatment groups to address the study's primary objectives; and reduced the sample size for subjects on background metformin (with or without insulin), from 37 subjects per group to 33 subjects per group while maintaining adequate 85% power.
Rationale: To apply FDA's recommendation to remove the assessment of canagliflozin as add-on to diet and exercise only due to challenges in recruiting pediatric subjects with T2DM who are treatment-naïve (ie, on diet and exercise alone) for assessment of canagliflozin as monotherapy and to evaluate a population that is more representative of patients who will use canagliflozin.	
Synopsis (Sample Size Determination; Major Secondary Objectives; Secondary Hypotheses; Multiplicity Adjustment); 2.1, Objectives; 2.2, Hypotheses; 11.2, Sample Size Determination; 11.3.1 Primary Efficacy Endpoint; 11.3.2 Multiplicity Adjustment	Deleted the major secondary objective about assessing the effect of canagliflozin relative to placebo in the subset of subjects on a background of diet and exercise only on glycated hemoglobin (HbA_{1c}) after 26 weeks of treatment. Deleted the hypothesis for the major secondary objectives. Deleted that if results are significant, the analysis will then proceed to test the subset of subjects on a background of diet and exercise only. Deleted information related to the target sample of 20 subjects per group and 80% power to assess canagliflozin's efficacy. Deleted the relevant analysis for the subgroup. Deleted the test of the subset of subjects on a background of diet and exercise only.

Rationale: To add descriptions of the treatment effect (ie, estimand) per ICH E9(R1) addendum on estimands and sensitivity analysis in clinical trials.	
11.3.1 Primary Efficacy Endpoint	Added the descriptions of the estimand for the primary efficacy endpoint.
Rationale: To modify 3 inclusion/exclusion criteria to improve subject enrollment, by: 1) Increasing the upper limit of HbA_{1c} to be in line with other pediatric T2DM studies. 2) Changing the time frame for subjects on diet and exercise only, prior to screening. This allows for closer alignment with American Diabetes Association guidelines recommending that pharmacologic therapy should begin at the time of diagnosis. A reduced amount of time on diet and exercise only for subjects is preferable. 3) Increasing the upper limit of normal (ULN) for alanine aminotransferase (ALT) is justified because increased transaminases and nonalcoholic fatty liver disease are not uncommon in this study population (Nadeau 2005, Newton 2016), and there are no contraindications for canagliflozin in relation to ALT up to 5 times ULN. Therefore, the study population will be more representative of patients who would use canagliflozin.	
Synopsis (Objectives; Hypotheses; Overview of Study Design; Subject Population); 2.1, Objectives; 2.2, Hypotheses; 3.1, Overview of Study Design; 3.2, Study Design Rationale; 4.1, Inclusion Criteria	Revised Inclusion Criterion #5 by modifying the upper limit of HbA_{1c} from ≤10.5% to ≤11.0%.
4.1, Inclusion Criteria	Revised the Inclusion Criterion #5a for diet and exercise from at least 8 weeks prior to screening to at least 4 weeks prior to screening.
4.2, Exclusion Criteria	Revised Exclusion Criterion #10 for ALT from >2 times the ULN to>5 times the ULN.
Rationale: To include additional information regarding study visits.	
Time and Events Schedule (footnote a); 9.1.1.1, Visit Schedules and Visit Windows	Added that there may be exceptional cases where it is possible, with concurrence of the sponsor's medical monitor, that certain on-site study visits may be replaced by telemedicine visits (a remote visit that is done by video or phone call).
Rationale: To correct or clarify minor inconsistencies within the protocol.	
Time and Events Schedule (footnote y)	Clarified footnote "y" by deletion of fasting lipid panel at Screening and reminder to collect fasting lipid panel at Baseline visit/Day 1.
1.1, Background; 1.1.3, Efficacy/Safety Studies; 3.2, Study Design Rationale; 14.1, Physical Description of Study Drug(s)	Updated references to the Investigator's Brochure to Edition 18, May 2020.
1.2, Overall Rationale for the Study	Clarified that there are limited approved treatment options for T2DM in subjects ≥10 and <18 years of age.

3.1, Overview of Study Design; 9.1.5, Post-treatment Phase (Follow-up); 10.2.4, Comprehensive Follow-up at Scheduled Study Visits Following Premature Discontinuation of Study Drug	Aligned the list of specific data to be collected after a subject's early discontinuation of study drug.
3.2, Study Design Rationale	Deleted the reference to (Lu 2008) and added (Tahara 1993).
6.2.1, Background Antihyperglycemic Therapies	Clarified that the adjustment to the AHA regimen is permitted during prolonged fasting (ie, religious events) and should be carefully implemented so as to avoid events of hypoglycemia.
6.2.2, Glycemic Rescue Therapy: Criteria and Implementation	Clarified the rescue initiation process to indicate that any subject that qualifies for initiation of rescue therapy should return to the clinic/investigational site.
9.3, Self-Monitoring of Blood Glucose (Run-in Period Management)	Revised the number of times subjects should perform fasting self-monitoring of blood glucose (SMBG) measurements from at least 3 times per week to a minimum of 3 days during the 2-week run-in period.
9.3, Self-Monitoring of Blood Glucose (Double-blind Treatment Phase Glycemic Management)	Added information on the SMBG requirement so that, during the double-blind treatment phase, investigators will counsel subjects to perform regular fasting SMBG determinations a minimum of 3 days per week with additional measurements made as considered clinically appropriate by the investigator and per local guidelines.
9.8, Safety Evaluations (Clinical Laboratory Tests)	Revised the specimen assessment to indicate that if the subject cannot provide the morning void collection on the Week -2 visit, it must be provided prior to the Day 1 visit to assess whether the specimen is positive for protein.
10.3.1, Lost to follow-up	Clarified that a subject's contact information may be transferred to another study site.
12.2.1, All Adverse Events	Clarified that the comprehensive foot evaluation will occur at Day 1 instead of Screening.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, and/or spelling changes were made.

Amendment 3 25 June 2018

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The primary reason for this amendment is to have an independently powered subset of subjects on a background of diet and exercise only where superiority of canagliflozin vs placebo can be assessed.

Applicable Section(s)	Description of Change(s)
Rationale: To include analyses of the primary efficacy endpoint in an independently powered subset of subjects on a background of diet and exercise only.	
Synopsis; Section 2.1, Objectives; Section 2.2, Hypotheses; Section 11.2, Sample Size Determination; Section 11.3.1, Primary Efficacy Endpoint; 11.3.2, Multiplicity Adjustment	Added major secondary objective and hypothesis.
Rationale: To provide additional clarification on eligibility of subjects for study enrollment.	
Section 4.2, Exclusion Criterion (#14)	Changed the sentence "Current participation in a canagliflozin study" to "Previously been, or is currently being treated with an SGLT2 inhibitor, or the subject has participated or is currently participating in a canagliflozin study".
Rationale: Minor errors were noted	
Time Event Schedule Section 9.1.2, Pretreatment Phase	Clarification to the Screening Visit: A non-fasting blood sample may be collected during the screening visit.
Protocol Amendment Table	Typographical error occurred to the version date of Amendment 2. Date changed to reflect correct date of 25 August 2017.
Attachment 8	Edits were made to the table to include column headings.

Amendment 2 25 August 2017

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The primary reason for this amendment is to reflect recommendations from the United States (US) Food and Drug Administration (FDA) on the statistical analysis.

Applicable Section(s)	Description of Change(s)
Rationale: In the primary analysis of glycated hemoglobin (HbA_{1c}) change from baseline to Week 26, different weights will be assigned depending on the comparison, on the treatment assignment and re-randomization after Week 12.	
Synopsis Statistical Methods; Section 11, Statistical Methods	The weight will be considered in the analyses when comparing each dose of canagliflozin vs. placebo.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify that the requirement for a 24-hour urine sample collection after the first morning void at Week -2 is based on presence of "proteinuria" (assessed by dipstick) instead of "albuminuria" as previously stated.	
Time and Events Schedule (footnote cc); Section 9.8 Safety Evaluations; Attachment 7	If the first morning void on Week -2 visit shows a presence of proteinuria (ie, proteinuria +1 and above) based on the central laboratory urine dipstick, a 24-hour urine collection will be done during the run-in period. Subjects who require a 24-hour urine collection prior to randomization, will also be required to provide a 24-hour urine sample on Week 26 and Week 52. Subjects who had a Week -2 first morning void negative for protein and develop a positive first morning void after randomization are not required to obtain 24-hour urine samples.
Rationale: To clarify ketone measurement procedure.	
4.2 Exclusion Criteria (Criterion #8); Section 9.2 Ketone Monitoring; Section 9.2.1.1 Pre-specified Ketone Measurements During Run-in Period	Clarified that the routine capillary blood ketone measurements should be obtained in a non-fasting state. Clarified that for elevated capillary blood ketone levels (ie, ≥0.6 mmol/L) subjects will be required to record onto the study diary other pertinent information (concomitant blood glucose levels, signs/symptoms of illness, precipitating factors, etc). Revised the title of this section to "Pre-specified Ketone Measurements During Run-in Period" from "Ketone Measurement During the Run-in Period."
Rationale: To clarify text or reconcile inconsistencies.	
Synopsis Overview of Study Design; Section 3.1 Overview of Study Design; Section 4.1 Inclusion Criteria	Simplified eligibility criterion to align with the regions.
Time and Events Schedule	Modified the reference of Footnote "v".
Time and Events Schedule (footnote b); Section 9.1.1.1 Visit Schedules and Visit Windows; Section 9.1.2 Pre-treatment Phase	Clarified that the screening period and/or run-in period may be increased by 1 or 2 weeks to allow sufficient time for results of pancreatic autoimmunity testing (if needed) to be received by the site to assess subject's eligibility.
Synopsis Overview of Study Design; Section 9.1.4 Double-blind Treatment Phase	Clarified that subjects who are eligible for re-randomization based on Week 12 HbA_{1c} and an estimated glomerular filtration rate (eGFR) will be re-randomized in a 1:1 ratio.
Section 9.6.2 Analytical Procedures	Removed text to indicate that plasma pharmacokinetic (PK) samples may be stored for future analysis of the metabolic profile.
Section 15 Study-Specific Materials	Added ketone strips (blood and urine) and alcohol wipes; removed the manual of instructions regarding diabetic ketoacidosis (DKA) events from the study-specifics materials.

Applicable Section(s)	Description of Change(s)
Section 16.2.3 Informed Consent/Pediatric Assent	Clarified text regarding the informed consent form (ICF) for subjects who have become adults during the study.
Attachment 6	Clarified that the Tanner Staging must be performed by the investigator or site staff and not by the subject and parent or legally acceptable representative.
Attachment 7	Removed glucose, cholesterol, and triglycerides from the serum chemistry panel.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 1 27 March 2017

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: To modify the study design to allow the assessment of canagliflozin when used with and without titration which is more reflective of how canagliflozin may be used in this pediatric population, and to add ketone monitoring procedures.

Applicable Section(s)	Description of Change(s)
Rationale: This revised treatment strategy is more likely to represent real-world prescribing practices and is consistent with treatment guidelines for non-insulin titratable anti-hyperglycemic agents which consist of starting at a lower dose and re-assessing the need to increase the dose after at least 3 months of treatment when typically, near-maximal to maximal HbA_{1c}-lowering effect is observed. In the proposed revised study design, subjects will initially be treated with canagliflozin 100 mg (or placebo) and their HbA_{1c} will be evaluated after 12 weeks. Those who fail to achieve the HbA_{1c} goal of <7.0% will be re-randomized to either remain on canagliflozin 100 mg (or placebo) or to up-titrate to canagliflozin 300 mg (or placebo). This titration strategy, which is aligned with the canagliflozin prescribing information, will allow the evaluation of whether increasing the dose of canagliflozin is beneficial to pediatric patients.	
Synopsis Objectives and Hypotheses; 2.1 Objectives; Synopsis Hypotheses; 2.2 Hypotheses; Synopsis Overview of Study Design; 3.1 Study Design; 6. Dosage and Administration	To change the study design from a 3-arm study (placebo, canagliflozin 100 mg, and canagliflozin 300 mg) to a 2-arm study that compares placebo to canagliflozin administered at a starting dose of 100 mg and a re-randomization of subjects who fail to achieve a HbA_{1c} goal of <7.0% after 12 weeks of treatment and who have adequate renal function to either up-titrate to 300 mg (or matching placebo) or remain on 100 mg (or matching placebo).

Applicable Section(s)	Description of Change(s)
Rationale: Given the mechanism of action of canagliflozin it is possible that mild ketonemia might be detected especially with fasting in otherwise non-acutely ill subjects. According to the recent American Association of Clinical Endocrinologists (AACE) position statement (Handelsman 2016), daily or routine measurement of urine ketones is not recommended as this measurement can be misleading. Instead, measurement of blood ketones is preferred for diagnosis of diabetic ketoacidosis (DKA). Therefore, proposed ketone monitoring strategy employs the use of capillary ketone measurements to be obtained whenever subjects are ill, or may be at increased risk for ketosis (eg, non-compliance with insulin treatment, low-carb diet, etc). This "trigger-based monitoring" approach is expected to increase compliance in this population that is unlikely to adhere to daily monitoring with either urine or blood ketones.	
Synopsis Overview of Study Design; Synopsis Safety Evaluations; Time and Events Schedule; 3.1 Study Design; 3.2 Study Design Rationale; 4.2 Exclusion Criteria; 9.1.3 Single-Blind Placebo Run-In Visit (Week -2); 9.2 Ketone Monitoring; 9.8 Safety Evaluations; Attachment 1; Attachment 2	To add ketone monitoring procedures (capillary blood measurement on 3 days during the 2-week run-in period and in the case of intercurrent illness/stress or other precipitating factor) and related eligibility criteria, and to provide instructions on sick day management.
Rationale: To change requirement for fasting procedures/visits when no fasting samples are required to be collected, and to allow more flexibility with visits schedule windows.	
4.1 Inclusion Criteria; 4.2 Exclusion Criteria; 9.1.1. Overview; Attachment 7	Changed requirement for fasting procedures/visits.
Rationale: The glycemic rescue criteria have been revised based on feedback from the Pediatric Diabetes Consortium (PDC) that indicated that fasting plasma glucose (FPG) in this population is of limited value given the variability of this measurement that may lead to unnecessary rescue or to unnecessary unscheduled visits to obtain repeat measurements to confirm whether rescue criterion is met. Instead, the sponsor proposes to trigger rescue based on changes in HbA_{1c} from baseline. This will not only eliminate the "noise" of daily glucose fluctuation but will also likely significantly reduce the study burden to subjects, decrease the likelihood that subjects will drop-out, and increase compliance with study procedures as subjects will not be required to fast when attending study visits to obtain FPG measurements.	
Synopsis Glycemic Rescue; 3.1 Study Design; 6.2.2. Glycemic Rescue Therapy: Criteria and Implementation	Replaced the former glycemic rescue criteria of FPG and HbA_{1c}, with changes from baseline in HbA_{1c} to align with HbA_{1c} re-randomization criterion and with reduction of fasting visits.

Applicable Section(s)	Description of Change(s)
Rationale: Based on data from the PDC, many pediatric patients with T2DM have a baseline HbA_{1c} of <7.0% (Tamborlane 2016), especially those who are on diet and exercise alone and on metformin monotherapy, the latter of which will likely represent the largest proportion of subjects recruited into the canagliflozin pediatric study. In light of the anticipated low baseline HbA_{1c} values and the acknowledged recruitment difficulties and challenges for the study, the sponsor has re-examined the original statistical assumptions and believes that the current standard deviation (SD) of 1.0% for HbA_{1c} change from baseline should be lowered to 0.9%. Furthermore, due to the change in study design above, the sponsor proposes to evaluate the HbA_{1c} efficacy of canagliflozin by comparing all subjects who are randomized to canagliflozin to all subjects who are randomized to placebo. These 2 proposed changes will allow a reduction in sample size from 285 subjects to 172 subjects (86/group) and increases the likelihood of completing the study and evaluating the primary hypothesis.	
Synopsis Overview of Study Design, Statistical Methods; 3.1 Study Design; 4. Subject Population; 11.2. Sample Size Determination	Reduced the overall sample size and statistical testing order due to the change in study design.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A Randomized, Multicenter, Double-Blind, Parallel-Group, Placebo-Controlled Study to Investigate the Efficacy and Safety of Canagliflozin in Children and Adolescents (≥10 to <18 years) with Type 2 Diabetes Mellitus

OBJECTIVES AND HYPOTHESIS

Objectives

In children and adolescents (≥10 to <18 years) with type 2 diabetes mellitus (T2DM) who have inadequate glycemic control (ie, hemoglobin A_{1c} [HbA_{1c}] of ≥6.5% to ≤11.0%), either on diet and exercise only, or on diet and exercise and metformin monotherapy, or on diet and exercise and insulin monotherapy, or on diet and exercise and combination therapy with metformin and insulin:

Primary Objectives

- To assess the effect of canagliflozin relative to placebo on HbA_{1c} after 26 weeks of treatment.
- To assess the overall safety and tolerability of canagliflozin.

Major Secondary Objectives

- After 26 weeks of treatment, to assess the effect of canagliflozin relative to placebo in the subset of subjects on a background of metformin (with or without insulin) on HbA_{1c}
- After 26 weeks of treatment, to assess the effect of canagliflozin relative to placebo on:
  - Fasting plasma glucose (FPG)
  - Proportion of subjects with HbA_{1c} <7.5%, <7.0%, and <6.5%
  - Time to rescue therapy and proportion of subjects receiving rescue therapy
  - Body weight
- After 52 weeks of treatment, to assess the effect of canagliflozin relative to placebo on:
  - HbA_{1c} and FPG
  - Proportion of subjects with HbA_{1c} <7.5%, <7.0%, and <6.5%
  - Time to rescue therapy and proportion of subjects receiving rescue therapy
  - Body weight

Additional Secondary Objectives

- After 12 weeks of treatment to assess the effects of canagliflozin relative to placebo on HbA_{1c}
- After 26 weeks of treatment, to assess the effect of canagliflozin 100 mg relative to placebo on HbA_{1c}
- After 26 weeks of treatment, to assess the effect of canagliflozin 100 mg followed by a dose increase to 300 mg relative to placebo on HbA_{1c}
- After 26 weeks and 52 weeks of treatment, to assess the effect of canagliflozin relative to placebo on:
  - Body mass index (BMI)

- Fasting plasma lipids (ie, low-density lipoprotein-cholesterol [LDL-C], high-density lipoprotein-cholesterol [HDL-C], total cholesterol, non-HDL-C, LDL-C to HDL-C ratio, non-HDL-C to LDL-C ratio, and triglycerides)
- Systolic and diastolic blood pressure
- Growth velocity and Tanner Staging
- Markers of calcium and phosphate homeostasis, (calcium, magnesium, phosphate, parathyroid hormone [PTH], 25-hydroxy Vitamin D, calcitonin; urinary excretion of calcium and phosphate)
- Bone turnover markers (serum osteocalcin and serum collagen type 1 carboxy-telopeptide [CTx])
- Urinary albumin/creatinine ratio

Hypotheses

In children and adolescents (≥10 to <18 years) with T2DM who have inadequate glycemic control (ie, HbA_{1c} of ≥6.5% to ≤11.0%), either on diet and exercise only, or on diet and exercise and metformin monotherapy, on diet and exercise and insulin monotherapy or on diet and exercise and combination of metformin and insulin:

Primary Hypothesis

- After 26 weeks of treatment, canagliflozin reduces HbA_{1c} relative to placebo.

Secondary Hypotheses

- After 26 weeks of treatment, canagliflozin reduces HbA_{1c} relative to placebo in the subset of subjects on background of metformin (with or without insulin).

OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, 2-arm, parallel-group, multicenter study. At least 146 subjects with T2DM ≥10 and <18 years of age who have inadequate glycemic control (ie, HbA_{1c} of ≥6.5% to ≤11.0%) and who meet 1 of the criteria below will be eligible to be screened:

- Are on diet and exercise only for at least 4 weeks prior to screening,

or

- Are on diet and exercise and a stable dose of metformin monotherapy ≥1,000 mg per day or maximum tolerated dose (MTD) per day (defined by the investigator) for at least 8 weeks prior to screening,

or

- Are on diet and exercise and a stable insulin monotherapy regimen for at least 8 weeks prior to screening (stable dose is defined as no change in the insulin regimen [ie, type{s} of insulin] and ≤15% change in the total daily dose of insulin [averaged over 1 week to account for day to day variability]),

or

- Are on diet and exercise and a stable combination therapy with metformin and insulin for at least 8 weeks prior to screening.

Note: Subjects who are on diet and exercise and a stable dose of metformin extended release (XR) for at least 8 weeks prior to screening may be included in the study; however, they will be switched from metformin XR to metformin immediate release (IR) (at the same daily dose or nearest appropriate dose) at the single-blind placebo run-in visit and will be enrolled in the study if the metformin IR is well tolerated during the 2-week single-blind placebo run-in period prior to Visit 3/Day 1.

Eligible subjects will go directly into a 2-week single-blind placebo run-in period and may then be randomized if they meet all other enrollment criteria. The goal is to have at least 30% of participants that will be ≥10 to <15 years of age, 30% to <65% of participants that will be female in each age group (10 to <15 years and ≥15 to <18 years), and 30% of participants that will have ethnicity and lifestyle comparable to Europe.

Subjects who meet all enrollment criteria will be randomly assigned in a 1:1 ratio to once-daily administration of canagliflozin 100 mg or matching placebo and enter a 52-week double-blind placebo-controlled treatment phase consisting of a 26-week core double-blind treatment period, followed by a 26-week double-blind extension treatment period. Randomization will be stratified by antihyperglycemic agent (AHA) background (ie, diet and exercise only; metformin monotherapy; insulin monotherapy, or combination therapy of insulin and metformin) and age group [≥10 to <15 years old; ≥15 to <18 years old]. Subjects who at Week 12 have an HbA_{1c} of ≥7.0% and an estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73m^2 will be re-randomized in a 1:1 ratio to either remain on double-blind canagliflozin 100 mg (or matching placebo) or to up-titrate to double-blind canagliflozin 300 mg (or matching placebo).

The total duration of the study, including the 1-week screening phase, the 2-week single-blind placebo run-in period, the 52-week double-blind placebo-controlled treatment phase, and the 30-day follow-up post-treatment phase is approximately 59 weeks for each subject.

The key efficacy evaluations include HbA_{1c}, FPG, body weight, proportion of subjects reaching HbA_{1c} goals, and use of rescue medication.

Safety and tolerability evaluations will include the monitoring of adverse events, collection of hypoglycemia events, capillary blood ketone monitoring, physical examinations, measurement of body weight, vital sign measurements, clinical laboratory tests, self-monitoring of blood glucose (SMBG), bone turnover markers, markers of calcium and phosphate homeostasis, urinary albumin/creatinine ratio, growth velocity and Tanner Staging.

Early withdrawal evaluations will be performed in subjects who prematurely discontinue study drug and in subjects who withdraw from the study (either on their own and/or by parent[s]/legal guardian[s]). The early withdrawal visit evaluation should be performed as soon as possible after the last dose of study drug is taken. Subjects who discontinue study drug prematurely should continue to attend all subsequent study visits and be followed to the end of the study (Week 52).

All subjects, regardless of their study completion status, will have a follow-up telephone contact (or optional study visit, at the discretion of the investigator) approximately 30 days after their last dose of study drug is taken to collect information on any serious adverse events and adverse events of interest.

Subjects who discontinue the study during the double-blind treatment phase will not be replaced.

Re-randomization

At Week 12, subjects' glycemic status will be assessed by the central laboratory. Following the review of the Week 12 unmasked HbA_{1c} and eGFR values, the following will occur:

- Subjects with an HbA_{1c} value <7.0% or eGFR <60 mL/min/1.73m^2 will not undergo re-randomization and instead will continue their current treatment assignment (ie, canagliflozin 100 mg or matching placebo) for the remainder of the study.
- Subjects with an HbA_{1c} value ≥7.0% and eGFR ≥60 mL/min/1.73m^2 will be re-randomized (in a blinded fashion via the interactive web response system [IWRS]) to either
  - remain on their original treatment assignment (ie, canagliflozin 100 mg or matching placebo) **or**
  - up-titrate canagliflozin 100 mg to 300 mg (or matching placebo). To maintain the study blind, subjects randomized to placebo will undergo a mock up-titration.

For subjects with a Week 12 HbA_{1c} ≥7.0% and who are on insulin and have experienced recurrent (ie, at least 2 episodes within a 7-day period) episodes of hypoglycemia after randomization, consideration should be given to down-titrate insulin prior to the blinded up-titration (or mock up-titration) to canagliflozin 300 mg.

Since the unmasked central laboratory HbA_{1c} values will not be immediately available at the Week 12 visit, subjects (or their parent/legal guardian) will be informed whether the subject is eligible for re-randomization via a telephone contact. If the subject is eligible for re-randomization, then the subject and/or their parent/legal guardian will return to the site, preferably within 1 week from Week 12 to return any unused study drug and obtain new blinded study drug according to IWRS assignment. Although no additional study or laboratory procedures will occur at this visit, and the subject is not required to be physically present, the subject's attendance is highly encouraged to allow the site to provide new dosing instructions related to the double-blind treatment.

Management of double-blind study drug based on renal function:

- Subjects who have undergone re-randomization and subsequently have a confirmed eGFR <60 mL/min/1.73m^2 will undergo down-titration (or mock down-titration) of blinded study drug at an unscheduled down-titration visit; only those subjects who were re-randomized to the canagliflozin 300 mg dose will actually titrate down (in a blinded fashion via the IWRS). Subjects randomized to canagliflozin 100 mg or placebo will undergo a mock down-titration and will continue on their randomized treatment.
- If at any time during the study, a subject has an eGFR of <45 mL/min/1.73m^2 that is confirmed within 1 week, the subject must be discontinued from study drug. Subjects discontinued from study drug and who do not withdraw consent will remain in the study and will be followed for post-treatment evaluations for the duration of the study.
- Prior to down-titrating or discontinuing canagliflozin due to eGFR <60 mL/min/1.73m^2 or <45 mL/min/1.73m^2, respectively, a repeat determination should be performed within 1 week and study drug down-titrated or discontinued if the repeat determination confirms that the value still meets the criteria (unless a reversible acute cause is identified [eg, short-term illness or transient volume depletion] in which case an additional repeat determination can be performed after resolution of the illness).
- All subjects will receive a new medication kit assignment through the IWRS at the unscheduled down-titration visit. The investigator, or qualified assigned designee, will provide the subject with double-blind treatment medication, updated instructions on dosing and a new subject diary. The subject will be instructed to continue with the diet and exercise regimen and the completion of the study diary.

Note: Once a subject has up-titrated to canagliflozin 300 mg, down-titration is not allowed unless for confirmed eGFR <60 mL/min/1.73m^2. Therefore, if after up-titration to canagliflozin 300 mg a subject

experiences recurrent hypoglycemia (ie, at least 2 episodes within a 7-day period), consideration should be given to down-titrate background AHA(s) such as insulin (or metformin).

Glycemic Rescue

Subjects who meet the protocol-specified glycemic rescue criteria, despite reinforcement of compliance with background AHA therapy, study drug and lifestyle counseling, may return to the clinic for a rescue visit, per the investigator's judgment, where he/she may either alter background AHA therapy (ie, metformin and/or insulin) or initiate an approved AHA for the pediatric population as per the local label. Rescued subjects will continue in the study on double-blind study drug.

SUBJECT POPULATION

Eligible subjects must be between the ages of ≥10 and <18 years at the time of screening, have a diagnosis of T2DM before screening, with C-peptide at screening >0.6 ng/mL (>0.2 nmol/L) and an HbA_{1c} of ≥6.5% to ≤11.0%. At the time of screening, subject may be on diet and exercise only, or on stable dose of metformin monotherapy ≥1,000 mg per day or MTD per day, or on a stable insulin monotherapy regimen, or on a stable combination therapy with metformin and insulin.

Note: Subjects who are on diet and exercise and a stable dose of metformin XR for at least 8 weeks prior to screening may be included in the study, however they will be switched from metformin XR to metformin IR (at the same daily dose or nearest appropriate dose) at the single-blind placebo run-in visit and will be enrolled in the study if the metformin IR is well tolerated during the 2-week placebo run-in period prior to Visit 3/Day 1.

DOSAGE AND ADMINISTRATION

Single-Blind Study Drug

During the 2-week single-blind placebo run-in period, subjects will take 1 placebo tablet matching canagliflozin 100 mg once-daily before the first meal of the day.

Double-Blind Study Drug

During the first 12 weeks of the double-blind treatment phase, subjects will take 1 tablet of canagliflozin 100 mg or matching placebo once-daily before the first meal of the day.

At Week 13, subjects who have a Week 12 HbA_{1c} of ≥7.0% and eGFR ≥60 mL/min/1.73m^2 will be re-randomized in a 1:1 ratio to either remain on double-blind canagliflozin 100 mg (or matching placebo) or to up-titrate to double-blind canagliflozin 300 mg (or matching placebo). A double-dummy approach will be used to maintain the blind to dose-assignments as indicated below:

- Subjects initially randomized to placebo and undergoing re-randomization at Week 13 will continue receiving 1 tablet of placebo matching canagliflozin 100 mg and will **ADD** 1 tablet of placebo matching canagliflozin 300 mg for the remainder of the double-blind treatment period.
- Subjects initially randomized to canagliflozin 100 mg and re-randomized to remain on canagliflozin 100 mg at Week 13 will continue receiving 1 tablet of canagliflozin 100 mg and will **ADD** 1 tablet of placebo matching canagliflozin 300 mg for the remainder of the double-blind treatment period.
- Subjects initially randomized to canagliflozin 100 mg and re-randomized to up-titrate to canagliflozin 300 mg at Week 13 will switch to 1 tablet of placebo matching canagliflozin 100 mg and will **ADD** 1 tablet of canagliflozin 300 mg for the remainder of the double-blind treatment period.

Subjects **not** undergoing re-randomization (ie, HbA_{1c} of <7.0% or eGFR <60 mL/min/1.73m^2) at Week 13 will continue to receive 1 tablet of canagliflozin 100 mg or matching placebo for the remainder of the double-blind treatment period.

A summary of study drug administration is provided in the table that follows.

Summary of dose level and number of tablets by study period and treatment.

Study Period	Criteria for re-randomization	Treatment Group: canagliflozin	Treatment Group: placebo
Day 1 to re-randomization	Not applicable	1 tablet of canagliflozin 100 mg	1 tablet of placebo matching canagliflozin 100 mg
Re-randomization to Week 52	**NOT eligible for re-randomization if**: HbA_{1c}< 7.0% or eGFR <60 mL/min/1.73m^2	1 tablet of canagliflozin 100 mg	1 tablet of placebo matching canagliflozin 100 mg
Re-randomization to Week 52	**Eligible for re-randomization if**: HbA_{1c} ≥7.0% and eGFR ≥60 mL/min/1.73m^2	1 tablet of canagliflozin 100 mg **AND** 1 tablet of placebo matching canagliflozin 300 mg **or** 1 tablet of canagliflozin 300 mg **AND** 1 tablet of placebo matching canagliflozin 100 mg	1 tablet of placebo matching canagliflozin 100 mg **AND** 1 tablet of placebo matching canagliflozin 300 mg

EFFICACY EVALUATIONS/ENDPOINTS

Primary Efficacy Endpoint

The primary efficacy endpoint will be the change in HbA_{1c} from baseline to Week 26.

Major Secondary Efficacy Endpoints

Key secondary endpoints will include the change from baseline to Week 26 and change from baseline to Week 52 in FPG, body weight, and proportion of subjects with an HbA_{1c} <7.5%, <7.0% and <6.5%, and time to rescue and proportion of subjects receiving rescue therapy.

Additional Secondary Efficacy Endpoints

Additional secondary endpoints include change from baseline to Week 12 in HbA_{1c}, and change from baseline to Week 52 of BMI, fasting lipid profile, systolic and diastolic blood pressure, and HbA_{1c}.

PHARMACOKINETIC EVALUATIONS

Venous blood samples of 4 mL will be collected at Week 12, Week 26, end-of-treatment (EOT Week 52), and at early withdrawal visit for determination of plasma trough concentrations of canagliflozin in all subjects. On the days when pharmacokinetic (PK) blood samples are collected, subjects will be instructed to refrain from taking the study drug before the clinic visit and to bring the study drug to the clinic visit. The subjects will be instructed to take the dose of study drug immediately before the subject's next meal. The subjects will record the time that the study drug was taken on the day preceding the clinic visit. The

exact dates and times of blood sampling must be recorded in the electronic case report form (eCRF) or laboratory requisition form.

ARCHIVE SAMPLES FOR EXPLORATORY RESEARCH AND SPECIMEN FOR BIOMARKER ASSESSMENT

Fasting plasma, serum, and urine archive samples will be collected (where local regulations permit) to allow for biomarker analyses and exploratory research related to canagliflozin or T2DM and obesity.

SAFETY EVALUATIONS

Safety and tolerability evaluations, according to the time points provided in the Time and Events Schedule will include:

- Collection/monitoring of adverse events
- Collection of potential hypoglycemic episodes (eg, from the subject diary provided to subjects)
- Ketone monitoring
- Physical examinations
- Body weight
- Vital signs (blood pressures and pulse rates)
- Safety laboratory tests (including chemistry, hematology, urinalysis)
- SMBG
- Bone turnover markers (serum osteocalcin and serum collagen type 1 CTx)
- Markers of calcium and phosphate homeostasis (calcium, magnesium, phosphate, PTH, 25-hydroxy Vitamin D, calcitonin, urinary excretion of calcium and phosphate)
- Urinary albumin/creatinine ratio
- Assessment of growth velocity and Tanner Staging

STATISTICAL METHODS

Analysis Sets

The full analysis set (FAS) population includes all subjects who are randomly assigned to a treatment group, have received at least one dose of study drug and have a baseline HbA_{1c} measurement. The per protocol (PP) analysis set consists of all FAS subjects who complete the 26-week double-blind treatment phase and have no major protocol deviations that may affect the interpretation of the primary efficacy endpoint. Major protocol deviations will be defined in the Statistical Analysis Plan (SAP).

The safety analysis set will include randomized subjects who take at least 1 dose of study drug.

The primary efficacy analyses, to demonstrate the superiority of canagliflozin compared with placebo, will be based on the FAS population. Supportive analyses include the PP analysis set, which will also be performed for the primary endpoint of HbA_{1c}.

Efficacy data will be analyzed according to the initial randomization assignment, regardless of the actual treatment received. Safety data will be analyzed according to the predominant treatment received, in the event that subjects received a treatment other than that to which they were randomly assigned to receive. The approach used to handle study deviations will be detailed in the SAP.

Sample Size Determination

The primary hypothesis of the study is that canagliflozin is superior to placebo in glycemic control, as measured by the change from baseline to Week 26 in HbA_{1c}. The sample size calculation is based on the 2-stage randomization design using a 2-sample, 2-sided t-test with Type 1 error rate of 0.05. Based on the following assumptions on treatment effect (0.4 to 0.5%) and an associated common standard deviation of 0.9% and assuming 50% of the subjects will meet the re-randomization criteria at Week 12, it is estimated that at least 66 subjects per group will be required to achieve approximately 85% power to meet the study's primary objectives. To account for attrition due to study discontinuation in a longitudinal analysis, a 10% sample size inflation factor is employed, and a total of at least 146 subjects (73 per arm) will be randomized in this study.

Treatment group	Meeting re-randomization criteria at Week 12	Placebo-subtracted group difference in change in HbA_{1c} from baseline to Week 26
canagliflozin 100 mg to canagliflozin 100 mg	No	0.5%
canagliflozin 100 mg to canagliflozin 100 mg	Yes	0.4%
canagliflozin 100 mg to canagliflozin 300 mg	Yes	0.5%

For the subjects who are on background metformin (with or without insulin), it is estimated with the following assumptions that at least 33 subjects per group (after accounting for attrition due to study discontinuation) will be required to achieve approximately 85% power to assess the efficacy of canagliflozin on a background of metformin.

Treatment group (add-on to metformin)	Meeting re-randomization criteria at Week 12	Placebo-subtracted group difference in change in HbA_{1c} from baseline to Week 26
canagliflozin 100 mg to canagliflozin 100 mg	No	0.75%
canagliflozin 100 mg to canagliflozin 100 mg	Yes	0.65%
canagliflozin 100 mg to canagliflozin 300 mg	Yes	0.75%

Safety Analyses

Subjects in the safety analysis set (defined as subjects who are randomized and dosed) will be included in the denominators for the summaries of adverse events, exposure, and concomitant medication data. There will be no imputation of missing values for clinical safety laboratory test results, vital sign measurements, and evaluations in the safety analyses.

All safety analyses (except hypoglycemia) will be summarized regardless of the use of rescue medication; given the potential confounding due to rescue medication, analyses related to hypoglycemia will only be presented prior to rescue medication.

Efficacy Analyses

The primary efficacy endpoint will be the change in HbA_{1c} from baseline at Week 26.

Estimand

The primary efficacy estimand is described according to the following attributes:

- Population: children and adolescents (≥10 to <18 years) with T2DM who have an HbA1c ≥6.5% to ≤11.0%
- Variable: change in HbA1c from baseline to Week 26
- Treatments: canagliflozin vs placebo

- Intercurrent event (events that preclude observation of the variable or affects its interpretation): treatment discontinuation or initiation of rescue medication, variable is used regardless of early treatment discontinues or initiation of rescue medication
- Treatment policy strategy: the measurements of the variable of interest are used regardless of the occurrence of the intercurrent event
- Population-level summary for the variable: the placebo-subtracted difference (ie, canagliflozin versus placebo) in least-squares mean change of HbA1c from baseline at Week 26 along with the 2-sided 95% CI

This estimand targets the effect of canagliflozin on the variable measured and follows an "ITT principle" strategy.

The main analysis of the primary efficacy outcome will be based on all HbA_{1c} measurements (regardless of the occurrence of treatment discontinuation or initiation of rescue medication) and will employ pattern mixture modelling using multiple imputation methods. The imputed datasets will be analyzed using analysis of covariance (ANCOVA) with terms for treatment, stratification factors, and baseline HbA_{1c}. Additional details will be specified in the SAP.

The following sensitivity analyses will be performed:

- The primary efficacy endpoint will be analyzed using a mixed model for repeated measures (MMRM) based on restricted maximum likelihood. The analysis will use the observed data and will include the fixed, categorical effects of treatment, stratification factors (ie, background AHA and age group), visit, and treatment-by-visit interaction, as well as the fixed, continuous covariates of baseline and baseline-by-visit interaction. An unstructured covariance will be used to model the within-patient errors. This sensitivity analysis will constitute the primary analysis based on a specific health authority request.
- The change from baseline in HbA_{1c} will be analyzed using an ANCOVA model with treatment and the stratification factors as fixed effects and baseline HbA_{1c} value as a covariate. The treatment differences in the least-squares means and the 2-sided 95% CI will be estimated based on this model. The last-observation-carried-forward (LOCF) method will be applied when the Week 26 values are missing.

The following supplementary analysis will be performed using the primary estimand:

- A re-randomization test (Proschan 2011) (utilizing the MMRM as described above) will be used to determine the p-value for the primary efficacy comparison (ie, comparing all subjects who are randomized to canagliflozin to all subjects who are randomized to placebo). The re-randomization test will fix the observed HbA1c data, regenerate treatment assignments for the entire study using the same minimization algorithm employed in the study and compute the test statistics corresponding to the primary efficacy comparison. This process will be repeated at least 1,000 times. The p-value for the primary efficacy comparison will be defined as the proportion of re-randomized studies whose test statistic for that comparison is at least as extreme as that of the original treatment assignment.

The primary efficacy endpoint will also be performed in the FAS in the subset of subjects on a background of metformin (with or without insulin) using the main analysis methods described above. Analyses for the other AHA subgroups in the FAS may also be performed.

Additional details on the data handling rules (including the data window used for analysis) will be described in the SAP.

Multiplicity Adjustment

To strongly control the family-wise error rate at the 5% significance level, a sequential testing procedure will be applied first in testing the primary endpoint for all subjects (ie, FAS). If the results are significant (2-sided alpha level of 0.05), it will then proceed to test the subset of subjects on a background of metformin (with or without insulin) to placebo.

The comparisons by canagliflozin dose to placebo will be presented and analyzed using the weights in the analyses described below.

- When comparing the subjects who initially receive canagliflozin 100 mg with no dose increase to 300 mg to placebo: All subjects start with a weight of 1. After Week 12, subjects with an HbA_{1c} ≥7.0% and eGFR ≥60 mL/min/1.73m^2 who are re-randomized to continue canagliflozin 100 mg will have a weight of 2. The subjects who are re-randomized to up-titrate to canagliflozin 300 mg will have a weight of 0.
- When comparing the subjects who initially receive canagliflozin 100 mg followed by a dose increase to 300 mg to placebo: All subjects start with a weight of 1. After Week 12, subjects with an HbA_{1c} ≥7.0% and eGFR ≥60mL/min/1.73m^2 who are re-randomized to continue canagliflozin 100 mg will have a weight of 0 and those who are re-randomized to up-titrate to canagliflozin 300 mg will have a weight of 2.

Secondary Efficacy Endpoints

The categorical secondary efficacy endpoint of maintaining HbA_{1c} <7.0% (and HbA_{1c} <6.5% and HbA_{1c} <7.5%) will be analyzed longitudinally using a generalized linear mixed model in the FAS population. The model will include the fixed, categorical effects of treatment, stratification factors (ie, background AHA and age group), visit, and treatment-by-visit interaction, as well as the fixed, continuous covariates of baseline and baseline-by-visit interaction. An unstructured covariance will be used to model the within subject errors. The odds ratio and 2-sided 95% CI for the treatment comparisons at Week 26 (canagliflozin compared to placebo) will be estimated based on this model.

Continuous endpoints (except for triglycerides) will be analyzed with an MMRM model described before in the FAS population. For the endpoints with post-baseline assessments taken only at Week 26 and Week 52, an ANCOVA model similar to the primary efficacy endpoint will be used at Week 26. The least-squares means for the treatment comparisons and their 2-sided 95% confidence intervals will be estimated based on this model. The analysis of percent change in triglycerides may be based on nonparametric methods (given the anticipated skewed nature of this parameter) or alternative methods, to be further described in the SAP.

TIME AND EVENTS SCHEDULE

	Pretreatment Phase			Double-blind Treatment Phase[a]										Post-treatment
	Screening Visit	2-week SB PBO Run-In	Baseline											
	Wk -3	Wk -2[b]	Day 1	Wk 3 TC	Wk 6	Wk 12	Wk 13[c]	Wk 20	Wk 26	Wk 34	Wk 42	Wk 52/EOT /Early Withdrawal[d]	Rescue Visit	Telephone call at Wk 56 or 30 days post last dose[e]
Screening/Administrative														
Informed consent	X[f]													
Child or adolescent assent	X[f]													
Inclusion/Exclusion criteria[g]	X	X	X											
Medical history and demographics	X													
Prestudy therapy[h]	X													
Concomitant therapy[i]	X	X	X	X	X	X		X	X	X	X	X	X	
Randomization			X											
Assess eligibility for re-randomization[j]						X								
Re-randomization of eligible subjects							X[c]							
Study Drug Administration														
Dispense single-blind placebo		X												
Assess for single-blind placebo compliance			X											
Dispense double-blind study drug			X		X	X	X[k]	X	X	X	X			
Drug Accountability					X	X	X	X	X	X	X	X	X	
Assess/Reinforce double-blind study drug compliance				X	X	X	X	X	X	X	X		X	
Review thresholds for potential need for rescue medication[l]				X	X	X		X	X	X	X		X	

	Pretreatment Phase			Double-blind Treatment Phase[a]									Post-treatment
	Screening Visit	2-week SB PBO Run-In	Baseline										
	Wk -3	Wk -2[b]	Day 1	Wk 3 TC	Wk 6	Wk 12	Wk 13[c]	Wk 20	Wk 26	Wk 34	Wk 42	Wk 52/EOT /Early Withdrawal[d]	Rescue Visit	Telephone call at Wk 56 or 30 days post last dose[e]
Clinical Procedures														
Vital signs[m]	X		X		X	X		X	X	X	X	X	X	
Body weight[n]	X		X		X	X		X	X	X	X	X	X	
Height[o]	X		X		X	X		X	X	X	X	X	X	
Tanner Staging[p]			X						X			X	X	
Physical examination[q]			X						X			X	X	
Subject Counseling and Ongoing Review/Assessments														
Diet/exercise counseling[r]		X												
Diet/exercise monitoring and re-enforcement			X	X	X	X		X	X	X	X	X	X	
Counseling for hypoglycemia and recognition & treatment of ketosis-related medically important events[r]		X	X	X	X	X		X	X	X	X		X	
Review of subject diary[s]			X	X	X	X		X	X	X	X	X	X	
Record hypoglycemic episodes[t] and ketone levels		X	X	X	X	X		X	X	X	X	X	X	
Dispense glucose/ketone meter & test strips, urine ketone strips, and subject diary (as needed)[u]		X	X		X	X		X	X	X	X		X	
Safety Evaluations														
Foot examination[v]			X						X			X	X	
Record adverse events[w]		X	X	X	X	X	X	X	X	X	X	X	X	X[e]
Laboratory Assessments														
Fasting plasma glucose[x]			X						X			X	X	
Hemoglobin A_{1c}	X		X		X	X		X	X	X	X	X	X	
Site fingerstick glucose			X											
Random C- peptide	X													
Fasting C-peptide[x]			X						X			X	X	
Hematology[y]	X		X						X			X		
Serum chemistry panel[y]	X		X			X			X			X	X	

	Pretreatment Phase			Double-blind Treatment Phase[a]										Post-treatment
	Screening Visit	2-week SB PBO Run-In	Baseline	Wk 3 TC	Wk 6	Wk 12	Wk 13[c]	Wk 20	Wk 26	Wk 34	Wk 42	Wk 52/EOT /Early Withdrawal[d]	Rescue Visit	Telephone call at Wk 56 or 30 days post last dose[e]
	Wk -3	Wk -2[b]	Day 1											
Blood ketones			X			X			X			X		
Fasting serum lipid profile[x,y]			X						X			X		
Urinalysis[y]			X									X		
Serum pregnancy test [z]	X													
Urine pregnancy test [z]									X			X		
First morning void urine for Urinary albumin/creatinine ratio [aa,bb,cc]		X[cc]							X[cc]			X[cc]		
GAD and islet cell antigen 2 [IA2] antibody test[dd]	X													
Pharmacokinetic Evaluations														
Pharmacokinetics blood sample[ee]						X			X			X		
Bone turnover markers (serum osteocalcin and serum collagen type 1 carboxy-telopeptide [CTx])			X						X			X		
Markers of calcium and phosphate homeostasis (calcium, magnesium, phosphate, parathyroid hormone (PTH), 25-hydroxy Vitamin D, calcitonin; urinary excretion of calcium and phosphate)			X						X			X		
Archived sample (plasma, serum, and urine samples) for exploratory analyses [x]			X						X			X		

Key: EOT= end-of-treatment; Wk= week; SB PBO= single-blind placebo; TC= telephone contact

a. All visits will be scheduled based on the date of randomization (Day 1). The study visits should generally occur within a 7-day recommended window (ie, ±7 days) around the protocol-specified visit schedule during the double-blind treatment phase. There may be exceptional cases where it is possible, with the concurrence of the sponsor's medical monitor, that certain on-site study visits may be replaced by telemedicine visits (a remote visit that is done by video or phone call).
b. The run-in start visit should generally be 1 week after the screening visit (with a recommended window of +/- 4 days). Subjects who at screening may require testing of pancreatic autoimmunity (ie, GAD-65 and/or IA antibodies) or who require a repeat of other screening procedures may have the duration of the screening period and/or run-in period increased by 1 to 2 weeks to allow sufficient time for the assessments to be obtained.
c. Subjects who have a Week 12 HbA_{1c} of ≥7.0% and eGFR ≥60 mL/min/1.73m^2 will be re-randomized to either remain on double-blind canagliflozin 100 mg (or matching placebo) or to up-titrate to double-blind canagliflozin 300 mg (or matching placebo). See Section 9.1.4.3, Re-randomization.
d. Early withdrawal visit evaluations will be performed in subjects who prematurely discontinue study drug (see Section 10.2, Study Drug Treatment Premature Discontinuation, Reinstitution, and Follow-up) and in subjects who withdraw consent from the study (either on their own and/or by their parents[s]/legal guardian[s]). See Section 10.3, Withdrawal from the Study). The early withdrawal visit evaluation should be performed as soon as possible after the last dose of study drug is taken.
e. A telephone follow-up contact (or optional study visit, at the discretion of the investigator) will be conducted for all subjects approximately 30 days after the last dose of study drug to collect serious adverse events and adverse events of interest since the last visit unless the subject has died, has been lost to follow-up, or has withdrawn consent. If a telephone contact or study visit is not possible, follow-up information may be collected via email or other electronic means. This follow-up is not required in subjects who discontinue study drug prematurely and continue to attend all subsequent study visits. At this telephone contact, investigators should ask subjects about any foot problems and remind them about routine preventative foot care and early intervention for foot problems.
f. The informed consent form for the parent(s)/legal guardian(s) (and the assent form for minor subjects, as described in Section 16.2.3, Informed Consent/Pediatric Assent) must be signed before any study procedure is performed.
g. Inclusion/Exclusion criteria must be reviewed at all visits up to and including the baseline visit/Day 1. Eligibility cannot be confirmed until the results of screening procedures and all screening laboratory test results are returned and reviewed.
h. Record any medications taken from up to 30 days before screening (and up to 6 months before screening for AHAs) until the first dose of double-blind study drug on Day 1 (baseline) as prestudy therapy in the corresponding eCRF.
i. Concomitant therapy includes all medications since the first dose of study drug on Day 1; after study drug discontinuation, use of AHA therapies will be recorded at the final visit or contact.
j. Eligibility for re-randomization will be based on HbA_{1c} and eGFR values obtained at Week 12. At this visit sites should schedule appointment for Week 13 for ALL subjects and confirm or cancel by phone upon review of laboratory results.
k. Only those subjects who qualify for re-randomization will return to the site at Week 13 where the site personnel will dispense new bottles of study drug and provide new dosing instructions. Subjects not undergoing re-randomization will not return to the site at Week 13.
l. See Section 6.2.2, Glycemic Rescue Therapy: Criteria and Implementation, for additional details for subjects meeting the protocol-specified glycemic rescue criteria.
m. Three consecutive blood pressure readings will be taken. (see Attachment 3, Method of Blood Pressure Measurement). Pulse rate will be measured once after subject has been sitting for at least 5 minutes at each clinic visit.
n. Whenever possible, body weight will be measured using the same calibrated scale at each visit. Subjects will be weighed at approximately the same time of day on the same scale wearing underwear and a gown and without shoes. **Note**: if disrobing for weighing is logistically impossible, the subject must be dressed as lightly as possible, with consistency from visit to visit. Subjects will be instructed to empty their bladders before being weighed.
o. Height will be measured using a stadiometer. (see Attachment 5, Guideline for Collecting Height Measurements).
p. See Attachment 6: Tanner Staging for guidance on Tanner Staging. **Note**: once subjects have reached Stage 5, no later assessments are required.
q. Physical examinations will include a review of body systems (head and neck, eyes, chest and lungs, cardiovascular, extremities and back, and abdomen examination). Significant findings that are present must be documented in the source and eCRF.
r. Subjects should be counseled to maintain a diet and exercise regimen consistent with those outlined in treatment guidelines for T2DM (eg, the American Diabetes Association guideline). Subjects will receive information regarding the signs and symptoms of and treatment for hypoglycemia (see Attachment 4, Hypoglycemia: Definitions, Symptoms, and Treatment) and the signs and symptoms of DKA (see Attachment 1, Instructions on Ketone Monitoring and Sick Day Management).
s. Subjects will be instructed to return with their completed diaries to the study site for review by study-site personnel at each clinic visit (eg, for review of hypoglycemic events, insulin dosage changes [only for subjects who are on insulin], self-monitoring of blood glucose values, ketone levels, concomitant medications, timing of study drug taken and any missed doses of study drug).

t. Hypoglycemic episodes should be recorded on the hypoglycemia eCRF and also on the adverse event eCRF if considered as an adverse event by the investigator (see Attachment 4 Hypoglycemia: Definitions, Symptoms, and Treatment).
u. Subjects will be provided with and instructed on the use of a home blood glucose/ ketone monitoring system. Subjects will also be instructed on how to measure urine ketones (to be only used as a back-up procedure in case capillary ketones cannot be assessed). Blood glucose and blood and urine ketone testing supplies will also be provided as necessary.
v. Consistent with standard diabetes treatment guidelines, all study participants should be provided with routine preventative foot care and early intervention for foot problems (see Section 12.2.1, All Adverse Events for further detail).
w. Adverse events will be monitored throughout the study from the time of signing the informed consent form until the end of the study (see Section 12.2.1, All Adverse Events).
x. Specific details about specimen collection, storage, packaging, and shipping will be provided in the laboratory manual. For FPG, fasting C-peptide, and lipids, subjects must be fasting for at least 8 hours before blood sample collection, except for the screening visit when non-fasting blood samples may be collected. A set of plasma, serum, and urine samples will be collected at each specified time point. The urine collections for routine urinalyses and exploratory specimens should be obtained from a spot urine specimen in the clinic.
y. Hematology and serum chemistry are performed at the screening visit and should ***not*** be repeated at baseline, unless the screening visit was performed more than 4 weeks before the baseline visit. No fasting lipid panel will be collected at the Screening Visit; please ensure to collect fasting lipid panel at the Baseline visit/Day 1.
z. Serum (β-human chorionic gonadotropin [β-hCG] pregnancy testing will be performed for all female subjects of childbearing potential at the screening visit. Additional urine (or serum) pregnancy tests may be conducted throughout the study in sufficient number, as determined by the investigator or required by local regulations, to establish the absence of pregnancy during the study. Serum pregnancy test must be performed and the result reviewed before randomization.
aa. The urine sample for albumin/creatinine ratio should not be collected if the subject is menstruating, has exercised vigorously in the past 24 hours, or had a fever or an active infection within the past 2 days of the clinic visit.
bb. Subjects will be given urine collection containers at each of the clinic visits preceding the first morning urine collection time points. The subject will provide a urine specimen from the first morning void on the morning of the clinic visit. If the subject does not provide the morning void collection on the day of the visit, the subject may bring a first morning void specimen to the investigational site during the subsequent week. For subjects who have atypical sleep patterns, the collection should be made at the end of the subject's usual sleep period. Study research staff is encouraged to contact the subject before this clinic visit as a reminder to the subject that he/she will need to provide a urine specimen at a particular visit (only 1 urine specimen is necessary at the indicated visit for the determination of albumin/creatinine ratio).
cc. If the first morning void on Week -2 visit shows a presence of proteinuria (ie, proteinuria +1 and above) based on the central laboratory urine dipstick, 24-hour urine collection will be done during the run-in period. Subjects who require a 24-hour urine collection prior to randomization, will also be required to provide a 24-hour urine sample on Week 26 and Week 52. Subjects who had a Week -2 first morning void negative for protein and develop a positive first morning void after randomization are not required to obtain 24-hour urine samples. Instead, in these subjects first morning urine sample will be collected for the remainder of the study.
dd. Only required in subjects with no documented history of absence of pancreatic autoimmunity.
ee. Subjects will be instructed to refrain from taking the study drug the morning of the clinic visit. The subject will be instructed to take the dose of study drug before the subject's next meal, after the study visit. The subject will record the time that the study drug was taken on the day preceding the clinic visit. Refer to laboratory manual for further information regarding the collection, handling, shipment and labeling of pharmacokinetic samples.

ABBREVIATIONS

ACR	albumin/creatinine ratio
ADA	American Diabetes Association
ADR	adverse drug reaction
AHA	antihyperglycemic agent
AUC	area under the curve
BMD	bone mineral density
BMI	body mass index
CANVAS	Canagliflozin Cardiovascular Assessment Study
CI	confidence interval
CRF	case report form (paper or electronic as appropriate for this study)
CSR	clinical study report
CV	cardiovascular
CTx	carboxy-telopeptide
DKA	diabetic ketoacidosis
DXA	dual energy X-ray absorptiometry
eCRF	electronic case report form
eDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	end-of-treatment
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GAD	glutamic acid decarboxylase
GCP	Good Clinical Practice
HbA_{1c}	glycated hemoglobin
hCG	human chorionic gonadotropin
HDL-C	high-density lipoprotein-cholesterol
IA2	islet cell antigen 2
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	identification
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IR	immediate release
IRB	Institutional Review Board
IWRS	interactive web response system
LADA	latent autoimmune diabetes of adulthood
LC-MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
LCT	Leydig cell tumors
LDL	low-density lipoprotein-cholesterol
LH	Luteinizing hormone
LOCF	last-observation-carried-forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MODY	Maturity-Onset Diabetes of the Young
MSRC	Medical Safety Review Committee
MTD	maximum tolerated dose
PD	pharmacodynamics
PDC	Pediatric Diabetes Consortium
PG	plasma glucose
PI	package insert
PK	pharmacokinetic

PP	per protocol
PPG	post-prandial plasma glucose
PQC	product quality complaint
PTH	parathyroid hormone
RT_G	renal threshold for glucose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SGLT2	sodium-glucose co-transporter 2
SU	sulphonylurea
SMBG	self-monitoring of blood glucose
SUSAR	suspected unexpected serious adverse reaction
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
UGE	urinary glucose excretion
UGT	UDP-glucuronosyltransferases
ULN	upper limit of normal
US	United States
UTI	urinary tract infection
XR	extended release

DEFINITIONS OF TERMS

C_{max}	maximum plasma drug concentration
t_{max}	time to reach the maximum observed plasma concentration
$t_{1/2}$	elimination half-life (to be used in one or noncompartmental model)

1. INTRODUCTION

Canagliflozin (JNJ-28431754) is an inhibitor of the sodium-glucose co-transporter 2 (SGLT2) that has been developed as an oral antihyperglycemic agent (AHA) for the treatment of adults with type 2 diabetes mellitus (T2DM). It has been approved by several Health Authorities, including the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Canagliflozin is used as an adjunct to diet and exercise to improve glycemic control in adults with T2DM; to reduce the risk of major adverse cardiovascular (CV) events in adults with T2DM and established CV disease; and to reduce the risk of end-stage kidney disease, doubling of serum creatinine, CV death, and hospitalization for heart failure in adults with T2DM and diabetic nephropathy with albuminuria. (Not all indications are approved in all markets.)

Type 2 diabetes mellitus is a chronic, progressive disorder that occurs across a broad age range, is rarely seen in children <10 years of age and occurs with rising incidence as age increases. Once diet and exercise are no longer sufficient, children, adolescents, and adults with T2DM may initially have adequate glycemic control with a single oral agent, usually metformin. Over time, however, maintaining good glycemic control requires the use of combinations of oral agents, then insulin in combination with oral agents, and finally the implementation of a multi-injection per day insulin regimen. Recent clinical treatment guidelines published by the American Academy of Pediatrics state that all youth with newly diagnosed T2DM should be treated immediately with insulin, if pre-specified criteria are met. In all other cases, treatment with metformin should be initiated (Copeland 2013). Thus, treatment-naïve patients, managed only with diet and exercise, are very uncommon. Currently, in addition to insulin, the only FDA and EU approved oral agent in children and adolescents ≥10 years of age with T2DM is metformin. Therefore, there is an unmet need for additional options to treat children and adolescents ≥10 years of age with T2DM.

The present study will examine the efficacy and safety of canagliflozin in children and adolescents ≥10 and <18 years of age. This is a 52-week randomized, double-blind, placebo-controlled, parallel-group study, consisting of a 26-week core double-blind treatment period followed by a 26-week extension double-blind treatment period. Eligible subjects will be either on diet and exercise alone, on diet and exercise and a stable dose of metformin monotherapy, on diet and exercise and a stable insulin monotherapy regimen, or on diet and exercise and a stable combination therapy with metformin and insulin. The results of this study plus the available extensive data in the adult population with T2DM as well as model-based analyses on exposure-response pharmacokinetics/pharmacodynamics (PK/PD) in adults and children/ adolescents, is expected to provide sufficient information to assess the benefit/risk ratio of canagliflozin in pediatric subjects with T2DM.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

For more detailed and current information regarding the preclinical characterization of canagliflozin PK (ie, absorption, distribution, metabolism, and excretion) and toxicology, and clinical study results in adults, refer to the current version (Edition 18) of the Investigator's Brochure (IB) for canagliflozin (IB JNJ-28431754 2020). One Phase 1 PK/PD study of canagliflozin (DIA1055) in subjects 10 to <18 years of age has been completed. Data from 17 subjects enrolled in Study DIA1055 indicate that the safety, PK, and PD of canagliflozin in the adolescent T2DM population is comparable to that observed in diabetic adults for both the canagliflozin 100 mg and 300 mg doses and consequently no dose-adjustment is necessary for this population ([Clinical Study Report CSR] JNJ-28431754 DIA1055 2016).

In a juvenile rat oral toxicity study (beginning dosing interval corresponds to a developmental age of approximately 2 years old in human infants) with canagliflozin (4, 20, 65, 100 mg/kg/day) administered orally for 10 weeks (day 21 to 90 postnatal) followed by a 4-week recovery period, renal and bone findings in immature rats were consistent with those in adult rats in the repeat-dose toxicity studies. There was a dose-related increase in the incidence and severity of renal tubular and pelvic dilatation, with a similar incidence and severity as for adult rats at the same doses. At the end of 4-week recovery, renal tubular dilatation was fully reversible, whereas renal pelvic dilatation was partially reversible in males at ≥20 mg/kg and fully reversible in the other dose groups. Dose-related hyperostosis observed was consistent with effects at the same dose levels in adult rats and was fully reversible at the end of the 4-week recovery. In general, findings were consistent with those in the 3- and 6-month repeat-dose studies in adult rats, and there were no new or unexpected effects. At the no-observed adverse effect level (NOAEL) of 4 mg/kg/day, area under the curve (AUC) values were up to 2.4x and 0.6x the AUC for the 100 and 300 mg doses in humans, respectively.

1.1.1. Pharmacokinetics

In adults, canagliflozin exhibits similar PK in healthy subjects and subjects with T2DM. The mean absolute oral bioavailability of canagliflozin was 65% following single-dose administration of the canagliflozin 300 mg tablet in healthy subjects. In healthy subjects (25 to 1,600 mg once-daily and subjects with T2DM (50 mg to 300 mg once-daily and 300 mg twice-daily), after oral administration of single and multiple doses, mean canagliflozin area under the curve $(AUC)_{0-\infty}$ increased in an approximately dose-proportional manner whereas mean maximum plasma concentration (C_{max}) increased in an approximately dose-proportional manner up to 1,200 mg. Following oral administration of canagliflozin, the median time to reach maximum plasma concentration (t_{max}) was approximately 1 to 2 hours. The mean terminal plasma elimination half-life ($t_{1/2}$) of canagliflozin was 10 and 13 hours with canagliflozin doses of 100 and 300 mg, respectively. The t_{max} was independent of dose. After repeated dosing with 50 to 300 mg canagliflozin, steady-state was reached by 4 to 5 days. Minimal accumulation of canagliflozin was observed at steady-state across 50, 100, and 300 mg doses with mean accumulation ratios ranging from 1.3 to 1.4 in subjects with T2DM. Bioavailability of canagliflozin was not affected after co-administration of canagliflozin 300 mg with food in

healthy subjects indicating that the canagliflozin tablet formulation may be taken without regard to meals.

O-glucuronidation is the major metabolic elimination pathway for canagliflozin in humans. In human plasma, 2 non-pharmacologically active O-glucuronide conjugates of unchanged drug, M5 (formed by UDP-glucuronosyltransferases [*UGT2B4]*) and M7 (formed by *UGT1A9*), were present. Co-administration with rifampin, a nonselective inducer of several uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes, decreased canagliflozin AUC by 51%, which may decrease efficacy. There was an increase in the AUC and C_{max} of digoxin when co-administered with canagliflozin 300 mg. Subjects taking concomitant digoxin should be monitored appropriately. The C_{max} of canagliflozin was not meaningfully altered by renal impairment.

Based on in vitro data and the clinical drug-drug interaction studies conducted to date, the potential for clinically significant CYP450 based PK interactions appears to be low.

The Phase 1, multiple-dose, PK study (Study DIA1055), conducted in subjects with T2DM who were ≥10 to <18 years of age and on a stable dose of metformin, demonstrated that plasma canagliflozin concentrations increased rapidly following administration of both treatments. Mean t_{max} for canagliflozin after 14 days of once-daily 100- or 300-mg dose administration ranged from 1.64 to 2.44 hours (range of 1 to 4 hours) across both treatments. Mean C_{max} and AUC_{τ} values in the 9 pediatric T2DM subjects receiving canagliflozin 300 mg once-daily were higher than the 8 pediatric T2DM subjects receiving canagliflozin 100 mg once-daily. Mean $t_{1/2}$ for canagliflozin after 14 days of once-daily 100- or 300-mg dose administration ranged from 11.3 to 15.2 hours (range of 8.0 to 29.3 hours) across both treatments. In general, the pharmacokinetics observed in the 8 pediatric T2DM subjects receiving 100 mg once-daily and the 9 pediatric T2DM subjects receiving 300 mg once-daily doses of canagliflozin were consistent with those of adult subjects.

1.1.2. Pharmacodynamics

In adult subjects with T2DM following single and multiple oral doses (30 to 600 mg once-daily and 300 mg twice-daily), canagliflozin treatment dose dependently increased urinary glucose excretion $(UGE)_{0\text{-}24h}$, with mean $UGE_{0\text{-}24h}$ of approximately 100 g/day typically observed with doses of 100 mg once-daily or higher.

In subjects with T2DM, canagliflozin treatment with 100 mg and 300 mg once-daily lowered renal threshold for glucose (RT_G) to approximately 70 to 90 mg/dL (3.9 to 5.0 mmol/L), respectively. Because RT_G remains above plasma glucose (PG) levels associated with hypoglycemia and because very little UGE occurs whenever PG is below the RT_G, canagliflozin, itself, is not expected to pose a risk for hypoglycemia.

In Study DIA1055, conducted in subjects with T2DM who were ≥10 to <18 years of age and on a stable dose of metformin, both doses of canagliflozin lowered the RT_G, increased UGE, and

lowered PG concentrations in a manner that is consistent with the relationship defined by adult subjects with T2DM.

1.1.3. Efficacy/Safety Studies

The canagliflozin clinical program was designed to assess the efficacy and safety of canagliflozin in individuals with T2DM.

In the Phase 3 studies in adults, canagliflozin has been assessed as monotherapy, as add-on therapy with metformin, sulphonylurea (SU), metformin and SU, metformin and a peroxisome proliferator-activated receptor (PPARγ) agonist (pioglitazone), and as add-on therapy with insulin (with or without other AHAs). The Phase 3 program also included studies in special populations of subjects with T2DM: subjects with renal impairment (estimated glomerular filtration rate [eGFR] ≥30 to <50 mL/min/1.73m^2), subjects with or at high risk for CV complications, and older subjects. The latter 2 studies also included subjects on incretin-based therapies, including dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) agonists.

Efficacy

Results of the Phase 3 studies demonstrated the efficacy of canagliflozin in reducing HbA_{1c} in a broad range of adult subjects with T2DM, both with recent onset as well as long-standing diabetes and on a range of different background AHAs. A clinically meaningful improvement in glycemic control was seen when canagliflozin was given as monotherapy and when given in dual combinations (add-on to metformin or to SU agents), in triple oral AHA combinations (add-on to metformin plus an SU agent or metformin plus pioglitazone), in combination with insulin (alone or in combination with other agents), or as an add-on to existing diabetes therapy (any approved oral or parenteral therapy). In the monotherapy study, HbA_{1c} reductions of -0.91% and -1.16% relative to placebo for canagliflozin 100 mg and 300 mg, respectively, were observed. In the studies examining specific add-on combination uses, the efficacy of canagliflozin in lowering HbA_{1c}, relative to placebo, was generally consistent ranging from -0.62% to -0.74% with the 100-mg dose and from -0.73% to -0.92% with the 300-mg dose. Across all studies, the 300-mg dose consistently provided greater HbA_{1c} lowering relative to the 100-mg dose. Because reduction in diabetic microvascular complications is continuous with improvements in glycemic control, the additional glucose-lowering efficacy with the 300-mg dose is considered likely to be clinically relevant.

Results of subgroup analyses performed in a pooled population of the placebo-controlled Phase 3 studies found no important differences when comparing the effect of canagliflozin in change from baseline in HbA_{1c} based on baseline demographic characteristics (age, sex, race, and ethnicity), body mass index (BMI), or geographic region. Greater reductions in HbA_{1c} relative to placebo were observed with canagliflozin among subjects with higher baseline HbA_{1c} and higher eGFR values compared with subjects with lower baseline values. In subjects with moderate renal impairment (ie, baseline eGFRs between 30 to 60 mL/min/1.73m^2), the mean placebo-subtracted reduction in HbA_{1c} was 0.38% and 0.47% on canagliflozin 100 mg and 300 mg, respectively. A

total of 24% and 32% of subjects achieved a target HbA_{1c} <7.0% at the end-of-treatment (EOT) on canagliflozin 100 mg and 300 mg, respectively compared to 17% of subjects on placebo.

With regard to other glycemic endpoints, canagliflozin provided improvements in FPG as well as in the post-prandial glucose (PPG) excursion. Canagliflozin also provided improvements in beta-cell function and a reduction in beta-cell stress as reflected by a decrease in the proinsulin/ C-peptide ratio. The improvement in beta-cell function and reduction in beta-cell stress is consistent with the sustained effect of canagliflozin on both HbA_{1c} and FPG observed in the 52-week studies.

Weight and Blood Pressure Effects

In addition to the observed glycemic improvements, treatment with canagliflozin resulted in consistent, statistically significant reductions in total body weight relative to placebo. Weight loss with canagliflozin appeared dose-related (with -1.4% to -2.7% reductions with 100 mg and -1.8% to -3.7% reductions with 300 mg, relative to placebo). Results of specialized body composition investigations using dual energy X-ray absorptiometry (DXA) in 2 of the Phase 3 studies showed that the body weight reduction with canagliflozin was attributable to a greater decrease in body fat mass relative to lean body mass.

Reductions in systolic blood pressure were observed with canagliflozin in Phase 3 studies (ranging from -2.2 to -5.7 mm Hg of systolic blood pressure with canagliflozin 100 mg dose, and -1.6 to -7.9 mm Hg with the 300-mg dose, relative to placebo, in placebo-controlled 26-week studies), and were generally statistically significantly greater for both doses relative to placebo, and also greater relative to comparator agents (glimepiride and sitagliptin).

Safety

For a complete review of the adverse drug reactions (ADRs) and laboratory findings associated with canagliflozin, please refer to the current version (Edition 18) of the canagliflozin IB (IB JNJ-28431754 2020).

The safety and tolerability profile that emerges from the development program for canagliflozin shows a medication that is overall well tolerated. The incidence of discontinuations due to adverse events was slightly higher than seen in the control group, though generally low. The small increase in discontinuations due to adverse events were generally related to specific ADRs, described below, with each particular ADR infrequently leading to discontinuations; there was no increase in serious adverse events or deaths in the canagliflozin treatment groups relative to control groups.

Adverse drug reactions were observed that relate to the osmotic diuretic effect of canagliflozin, with increases in UGE leading to a diuretic action; this included ADRs of pollakiuria (increased urinary frequency), polyuria (increased urinary volume), and thirst. Adverse drug reactions related to reduced intravascular volume were observed including postural dizziness, orthostatic hypotension, and hypotension. Risk factors for volume-related adverse events on canagliflozin treatment were ≥75 years of age, eGFR of 30 to 60 mL/min/1.73m^2 and use of loop diuretics.

These adverse events were generally considered as mild or moderate in intensity, and infrequently led to discontinuation. No increase in serious adverse events related to reduced intravascular volume were seen with canagliflozin treatment. The reduction in intravascular volume also led to reversible reductions in eGFR that generally attenuated with continued treatment.

In men, the genital mycotic infections (including balanitis and balanoposthitis) occurred predominantly in uncircumcised individuals and in those with a past history of genital mycotic infections, generally did not lead to discontinuation from the study. Circumcision was performed in 17/3,569 (0.5%) and 3/1,924 (0.2%) of men treated with canagliflozin and control, respectively. In women, genital mycotic infections (including candidal vulvovaginitis) occurred more commonly with a prior history of genital mycotic infections and did not generally lead to discontinuation. A modest increase in the incidence of adverse events of urinary tract infection (UTI) (mostly lower UTIs) was observed with canagliflozin relative to control, without an increase in serious adverse events of UTI.

Based on the observations from the 2-year rat carcinogenicity study (findings of renal tubular cell cancers, Leydig cell tumors [LCTs], and pheochromocytomas), an extensive preclinical toxicology program was conducted that demonstrated that these tumors related to effects of canagliflozin in rats, not seen in humans (including rises in luteinizing hormone [LH] associated with LCT, and carbohydrate malabsorption leading to associated metabolic effects, including marked hypercalciuria, inducing renal tubular tumors and pheochromocytomas). In the clinical program, there were no reports of LCT or pheochromocytoma and no imbalance in the low incidence across groups of renal cell cancers.

In preclinical studies in rats, hyperostosis (increased trabecular bone) was observed. Mechanistic toxicology studies demonstrated that hyperostosis, like the tumors discussed above, related to carbohydrate malabsorption in rats treated with canagliflozin, with consequent marked hypercalciuria (which is not seen in human). Overall, no meaningful changes in serum and urinary calcium and serum parathyroid hormone [PTH] and 1,25-dihydroxyvitamin D were seen in subjects treated with canagliflozin. Unlike the findings in rats, modest increases in markers of bone turnover, including serum collagen type 1 carboxy-telopeptide (CTx) and osteocalcin, were seen in subjects with T2DM treated with canagliflozin. Based on the lack of carbohydrate malabsorption or alterations in calcium metabolism in humans treated with canagliflozin, hyperostosis seen in rats treated with canagliflozin is considered to be of no relevance to human safety. A detailed analysis of bone safety was conducted in the Phase 3 program, including an assessment using DXA in a dedicated Phase 3 study (a study conducted in older subjects [ages ≥55 and ≤80 years] with T2DM) and a cross-program assessment of fracture incidence. Bone mineral density (BMD) was examined at 4 sites: at the lumbar spine, total hip, distal radius, and femoral neck. Minimal changes in BMD from baseline to Week 104 were seen in the lumbar spine (a cancellous bone region), femoral neck (a mixed cancellous and cortical bone region), and distal forearm. A decrease in BMD from baseline to Week 104 in the total hip, a site comprised of mixed cortical and cancellous bone (like the femoral neck), was observed for both canagliflozin treatment groups (-0.9% and -1.2% in the canagliflozin 100 mg and 300 mg

groups, respectively, placebo-adjusted). Using a data-cutoff of May 2013, in a cardiovascular study of 4,327 adult subjects with known or at high risk for cardiovascular disease (Study DIA3008), the incidence rates of bone fracture were 1.6, 1.6, and 1.1 per 100 subject-years of exposure to canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively, with the fracture imbalance initially occurring within the first 26 weeks of therapy. In other T2DM studies with canagliflozin, which enrolled a general diabetes population of approximately 5,800 adult subjects, no difference in fracture risk was observed relative to control.

Increases in low-density lipoprotein-cholesterol (LDL-C) were observed in a pooled analysis of placebo-controlled 26-week studies with canagliflozin, increases in LDL-C relative to placebo were 4.4 mg/dL (0.11 mmol/L) and 8.2 mg/dL (0.21 mmol/L) at the 100-mg and 300-mg doses, respectively. Relative increases in Apolipoprotein B, non-high-density lipoprotein-cholesterol (HDL-C), and LDL particle number were approximately half as large as the rise in LDL-C. The changes in the CV risk profile with canagliflozin include reductions in systolic blood pressure and increases in LDL-C, both established CV risk factors, and validated as surrogate endpoints. Improvements in other endpoints associated with CV risk, but not established as surrogate endpoints for CV benefit, such as body weight, glycemic control, HDL-C, and triglycerides (TG) were also observed with canagliflozin. The cross-program CV meta-analysis (including results from the dedicated CV safety study) observed a hazard ratio of 0.91 for a pre-specified composite endpoint of CV death, non-fatal myocardial infarction (MI), non-fatal stroke, and hospitalized unstable angina (95% confidence interval [CI]: 0.68, 1.22), showing no signal for an increase in the CV risk.

In the adult Phase 3 program, treatment with canagliflozin was associated with a dose-dependent, reversible reduction in eGFR that was maximal at the first post-baseline visit and was either stable or attenuated with continued treatment. Analyses of eGFR post-discontinuation showed reversibility of the initial reductions in eGFR observed with canagliflozin. To assess the effects of canagliflozin on the progression of diabetic nephropathy, the proportion of subjects with categorical progression of albuminuria based upon the urinary albumin/creatinine ratio (ACR) was assessed in 4 Phase 3 studies (DIA3004, DIA3005, DIA3008, and DIA3009). Numerically greater mean and median reductions in urinary ACR with both doses of canagliflozin (100 mg and 300 mg) relative to placebo or comparator were observed in all 4 studies.

As of 11 May 2015, in the T2DM clinical development program, incidence rates of unblinded serious adverse events of diabetic ketoacidosis (DKA), ketoacidosis, metabolic acidosis, and acidosis were 0.0522 (0.07%, 4/5,337), 0.0763 (0.11%, 6/5,350), and 0.0238 (0.03%, 2/6,909) per 100 subject-years with canagliflozin 100 mg, canagliflozin 300 mg, and comparator, respectively. Of the 12 subjects with serious adverse events of DKA, ketoacidosis, metabolic acidosis, or acidosis (all of whom were hospitalized), 6 subjects on canagliflozin (3 on canagliflozin 100 mg and 3 on canagliflozin 300 mg), and none on comparator were reported to have autoimmune diabetes (latent autoimmune diabetes of adulthood [LADA] or type 1 diabetes [T1DM]) or tested positive for glutamic acid decarboxylase (GAD) 65 antibodies after being diagnosed with a serious DKA-related event. Eight of the 10 subjects on canagliflozin were

receiving insulin therapy. The blood glucose values around the time of admission in 9 of 10 subjects on canagliflozin ranged from 347 to 571 mg/dL (9.3 to 31.7 mmol/L). The remaining subject had blood glucose values ranging from 148 to 320 mg/dL (8.2 to 17.8 mmol/L). Diabetic ketoacidosis has also been reported during post-marketing surveillance and has occurred in patients with blood glucose values <250 mg/dL (<13.9 mmol/L). As a result, DKA is considered a rare ADR.

An increased risk of lower limb amputations associated with canagliflozin use compared with placebo was observed in the Canagliflozin Cardiovascular Assessment Study (CANVAS) (5.9 vs 2.8 events per 1000 patient-years) and CANVAS-Renal (7.5 vs 4.2 events per 1000 patient-years), 2 randomized, placebo-controlled trials evaluating adults with type 2 diabetes who had either established CV disease or were at risk for CV disease. The risk of lower limb amputations was observed at both the 100-mg and 300-mg once-daily dosage regimens. Infections were the events most commonly associated with amputations, and most amputations were of the toe. The factors associated with the greatest risk for amputation included prior amputation, peripheral vascular disease, and neuropathy.

A recently completed, dedicated renal study (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial [CREDENCE]; DNE3001) evaluated canagliflozin as a treatment to reduce the progression of diabetic nephropathy in adult subjects with T2DM, Stage 2 or 3 chronic kidney disease and macroalbuminuria, receiving background standard of care, including a maximum tolerated labeled daily dose of an angiotensin converting enzyme inhibitor or angiotensin II receptor blockers. In the CREDENCE Dataset, there were a total of 133 subjects who experienced an atraumatic lower limb amputation, 70 subjects (87 events) and 63 subjects (96 events) in the canagliflozin and placebo groups, respectively. The exposure-adjusted incidence rate of lower limb amputations was comparable between the 2 groups: 1.23 and 1.12 per 100 subject-years in the canagliflozin and placebo groups, respectively.

In Study DIA1055, conducted in subjects with T2DM who were ≥10 to <18 years of age and on a stable dose of metformin, 17 subjects received study drug (canagliflozin 100 mg [N=8] or canagliflozin 300 mg [N=9]) for 14 days. Overall, 52.9% of subjects reported at least 1 adverse event. The most frequently reported adverse event (≥2 subjects) was nausea. There were no deaths or serious adverse events reported during the study. None of the subjects discontinued the study drug due to an adverse event. Overall, no new, unexpected, or unusual safety signals were reported in the study.

1.2. Overall Rationale for the Study

The present study will examine the efficacy and safety of canagliflozin in children and adolescents ≥10 and <18 years of age. This is a 52-week randomized, double-blind, placebo-controlled, parallel-group study, consisting of a 26-week core double-blind treatment period, followed by a 26-week extension double-blind treatment period. There are limited treatment options for T2DM in subjects ≥10 and <18 years of age, and as the prevalence of T2DM in the pediatric population is increasing over time (Copeland 2013), there is a substantial unmet need

for treatment options in this population. The current study will evaluate efficacy and safety of canagliflozin in pediatric subjects with T2DM.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

In children and adolescents (≥10 to <18 years) with T2DM who have inadequate glycemic control (ie, HbA_{1c} of ≥6.5% to ≤11.0%), either on diet and exercise only, or on diet and exercise and metformin monotherapy, on diet and exercise and insulin monotherapy, or on diet and exercise and a combination therapy with metformin and insulin:

Primary Objectives

- To assess the effect of canagliflozin relative to placebo on HbA_{1c} after 26 weeks of treatment.
- To assess the overall safety and tolerability of canagliflozin.

Major Secondary Objectives

- After 26 weeks of treatment, to assess the effect of canagliflozin relative to placebo for the subset of subjects on a background of metformin (with or without insulin) on HbA_{1c}
- After 26 weeks of treatment, to assess the effect of canagliflozin relative to placebo on:
  - FPG
  - Proportion of subjects with HbA_{1c} <7.5%, <7.0% and <6.5%
  - Time to rescue therapy and proportion of subjects receiving rescue therapy
  - Body weight
- After 52 weeks of treatment, to assess the effect of canagliflozin relative to placebo on:
  - HbA_{1c} and FPG
  - Proportion of subjects with HbA_{1c} <7.5%, <7.0% and <6.5%
  - Time to rescue therapy and proportion of subjects receiving rescue therapy
  - Body weight

Additional Secondary Objectives

- After 12 weeks of treatment to assess the effects of canagliflozin relative to placebo on HbA_{1c}
- After 26 weeks of treatment, to assess the effect of canagliflozin 100 mg relative to placebo on HbA_{1c}
- After 26 weeks of treatment, to assess the effect of canagliflozin 100 mg followed by a dose increase to 300 mg relative to placebo on HbA_{1c}
- After 26 weeks and 52 weeks of treatment, to assess the effect of canagliflozin relative to placebo on:

- BMI
- Fasting plasma lipids (ie, LDL-C, HDL-C, total cholesterol, non-HDL-C, LDL-C to HDL-C ratio, non-HDL-C to LDL-C ratio, and triglycerides)
- Systolic and diastolic blood pressure
- Growth velocity and Tanner Staging
- Markers of calcium and phosphate homeostasis, (calcium, magnesium, phosphate, PTH, 25-hydroxy Vitamin D, calcitonin; urinary excretion of calcium and phosphate)
- Bone turnover markers (serum osteocalcin and serum collagen type 1 CTx)
- Urinary ACR

2.2. Hypotheses

In children and adolescents (≥10 to <18 years) with T2DM who have inadequate glycemic control (ie, HbA_{1c} of ≥6.5% to ≤11.0%), either on diet and exercise only, or on diet and exercise and metformin monotherapy, on diet and exercise and insulin monotherapy, or on diet and exercise and a combination of metformin and insulin:

Primary Hypothesis

- After 26 weeks of treatment, canagliflozin reduces HbA_{1c} relative to placebo.

Secondary Hypotheses

- After 26 weeks of treatment, canagliflozin reduces HbA_{1c} relative to placebo in the subset of subjects on background of metformin (with or without insulin).

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled, 2-arm, parallel-group, multicenter study. Subjects with T2DM ≥10 and <18 years of age who have inadequate glycemic control (ie, HbA_{1c} of ≥6.5% to ≤11.0%) and who meet 1 of the criteria below will be eligible to be screened:

- Are on diet and exercise only for at least 4 weeks prior to screening,

or

- Are on diet and exercise and a stable dose of metformin monotherapy ≥1,000 mg per day or maximum tolerated dose (MTD) per day (defined by the investigator) for at least 8 weeks prior to screening,

or

- Are on diet and exercise and a stable insulin monotherapy regimen for at least 8 weeks prior to screening (stable dose is defined as no change in the insulin regimen (ie, type[s]) of insulin) and ≤15% change in the total daily dose of insulin [averaged over 1 week to account for day to day variability]),

or

- Are on diet and exercise and a stable combination therapy with metformin and insulin for at least 8 weeks prior to screening as described above.

Note: Subjects who are on diet and exercise and a stable dose of metformin extended release (XR) for at least 8 weeks prior to screening may be included in the study; however, they will be switched from metformin XR to metformin IR (at the same daily dose or nearest appropriate dose) at the single-blind placebo run-in visit and will be enrolled in the study if the metformin IR is well tolerated during the 2-week single-blind placebo run-in period prior to Visit 3/Day 1.

Eligible subjects will go directly into a 2-week single-blind placebo run-in period and may then be randomized if they meet all other enrollment criteria. The goal is to have at least 30% of participants that will be ≥10 to <15 years of age, 30% to <65% of participants that will be female in each age group (≥10 to <15 years and ≥15 to <18 years), and 30% of participants that will have ethnicity and lifestyle comparable to Europe.

At least 146 subjects who meet all enrollment criteria will be randomly assigned in a 1:1 ratio to once-daily administration of canagliflozin 100 mg, or placebo and enter a 52-week double-blind placebo-controlled treatment phase consisting of a 26-week core double-blind treatment period, followed by a 26-week double-blind extension treatment period. Randomization will be stratified by AHA background (ie, diet and exercise only; metformin monotherapy; insulin monotherapy; or combination of insulin and metformin) and age group (≥10 to <15 years old; ≥15 to <18 years old). Subjects who at Week 12 have an HbA_{1c} of ≥7.0% and an eGFR ≥60 mL/min/1.73m^2 will be re-randomized in a 1:1 ratio to either remain on double-blind canagliflozin 100 mg (or matching placebo) or to up-titrate to double-blind canagliflozin 300 mg (or matching placebo).

Study Phases

- Pretreatment phase
  - Screening visit (Week -3)
  - Single-blind placebo run-in period: 2 weeks (Week -2 visit to baseline [Day 1])
- Double-blind treatment phase: 52 weeks including a 26-week core double-blind treatment period and a 26-week double-blind extension treatment period
  - Starting at the baseline (Day 1) visit and completing at the Week-52 visit (or the EOT visit for subjects discontinuing study drug early).
- Post-treatment phase: 30-day follow-up contact
  - Telephone follow-up contact (or optional study visit, at the discretion of the investigator) 30 days after the last dose of study drug.

The total duration of the study, including the 1-week screening phase, the 2-week single-blind placebo run-in period, the 52-week double-blind placebo-controlled treatment phase and the 30-day follow-up post-treatment phase, is approximately 59 weeks for each subject.

The key efficacy evaluations include HbA_{1c}, FPG, body weight, proportion of subjects with HbA_{1c} <7.5%, <7.0%, and <6.5%, and use of rescue medication. For a complete list of efficacy measures and endpoints, see Section 9.5, Efficacy Evaluations.

Safety and tolerability evaluations will include the monitoring of adverse events, collection of potential hypoglycemic events (eg, from the subject diary provided to subjects), capillary blood ketone monitoring, physical examinations, body weight, vital signs (blood pressures and pulse rates), safety laboratory tests (including chemistry, hematology, urinalysis), self-monitoring of blood glucose (SMBG), bone turnover markers (serum osteocalcin and serum collagen type 1 CTx), markers of calcium and phosphate homeostasis (calcium, magnesium, phosphate, PTH, 25-hydroxy Vitamin D, calcitonin, urinary excretion of calcium and phosphate), urinary ACR, growth velocity, and Tanner Staging.

An internal Medical Safety Review Committee (MSRC), and an IDMC, will review data from this study. Refer to Section 9.4, Study Management: Committees, for details.

Subjects who prematurely discontinue study drug will require an immediate EOT assessment (either on the day of study drug discontinuation or as soon as possible following study drug discontinuation). It is the intent that subjects who discontinue study drug will continue in the study according to the visit schedule described in the Time & Events Schedule. After early discontinuation of study drug, subjects will continue to be followed up for specific data collection, including vital signs, body weight, laboratory assessments, serious adverse events, adverse events of interest, and adverse events of special interest for the duration of the study. See Section 10.2.4, Comprehensive Follow-up at Scheduled Study Visits Following Premature Discontinuation of Study Drug, for more detail. (Refer to Section 12, Adverse Event Reporting for a list of adverse events of special interest that will be collected). All subjects, regardless of their completion status, will have a follow-up telephone contact (or optional study visit, at the discretion of the investigator) approximately 30 days after their last dose of study drug is taken to collect information on any serious adverse events and adverse events of interest.

Subjects who discontinue the study during the double-blind treatment phase will not be replaced.

Re-randomization

At Week 12, subjects' glycemic status will be assessed through an HbA_{1c} level determined by the central laboratory. Following the review of the Week 12 unmasked HbA_{1c} and eGFR results, subjects may be eligible to be re-randomized at Week 13 to either remain on their original treatment assignment (ie, canagliflozin 100 mg or matching placebo) **or** up-titrate canagliflozin 100 mg to 300 mg (or matching placebo). Refer to Section 9.1.4.3, Re-randomization, for details.

Glycemic Rescue

Subjects who meet the protocol-specified glycemic rescue criteria, despite reinforcement of compliance with background AHA therapy, study drug and lifestyle counseling, will initiate an approved AHA for the pediatric population as per the local label and will continue in the study

on double-blind study drug (see Section 6.2.2, Glycemic Rescue Therapy: Criteria and Implementation).

A diagram of the study design is provided.

Figure 1: Schematic Overview of the Study

Screening
Age ≥10 and <18 years with T2DM with HbA_{1c} ≥6.5% to ≤11.0% and ANY of the following conditions:

- On diet and exercise only for ≥4 weeks prior to screening

OR

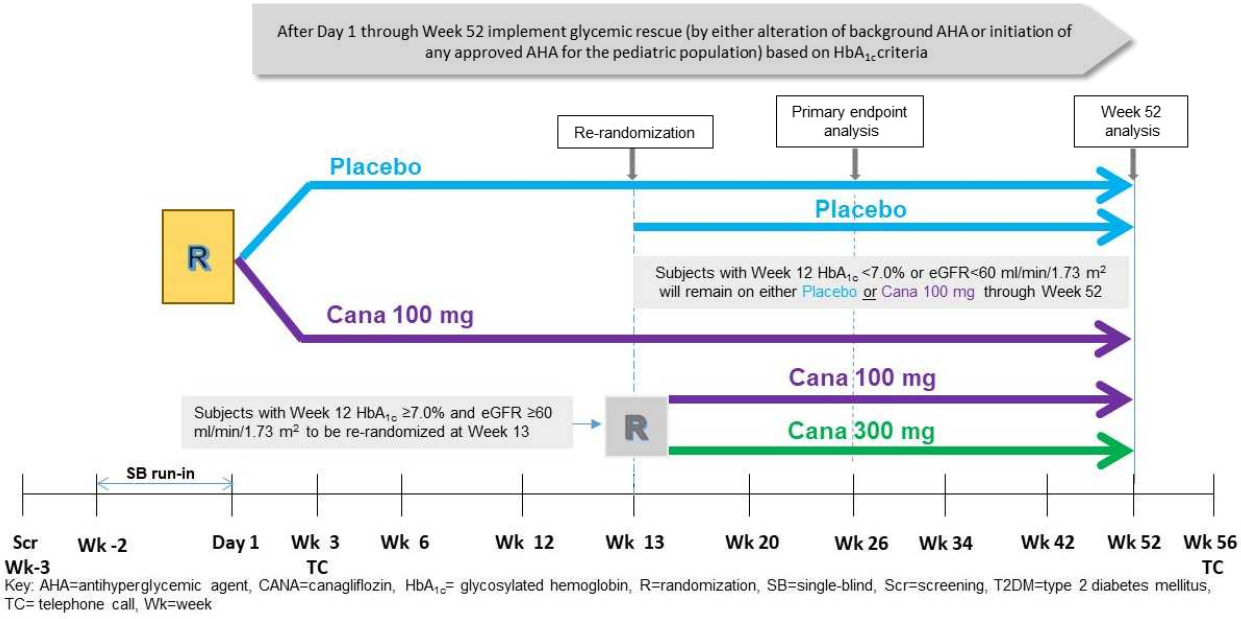
- On any stable dose of metformin monotherapy ≥1000 mg/day for ≥8 weeks prior to screening

OR

- On a stable insulin monotherapy regimen for ≥8 weeks prior to screening

OR

- On a stable combination therapy of metformin ≥1000 mg/day + insulin for ≥8 weeks prior to screening



Key: AHA=antihyperglycemic agent, CANA=canagliflozin, HbA_{1c}= glycosylated hemoglobin, R=randomization, SB=single-blind, Scr=screening, T2DM=type 2 diabetes mellitus, TC= telephone call, Wk=week

3.2. Study Design Rationale

The goal of this study is to investigate the efficacy and safety of canagliflozin for the treatment of children and adolescents (≥10 to <18 years) with T2DM with inadequate glycemic control (ie, HbA_{1c} of ≥6.5% to ≤11.0%), as monotherapy, or as add-on to metformin and/or insulin.

Blinding, Control, Study Phase/Periods, Treatment Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment. Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

The 2-week single-blind placebo run-in period before randomization will allow sufficient time for investigators to assess whether subjects demonstrate compliance with study procedures, including compliance with administration of study drug. The single-blind placebo run-in period also helps to assure that subjects entering the study will have no difficulty with administration of the study drug.

The 52-week double-blind treatment phase (with the primary endpoint analysis conducted at Week 26) should allow sufficient time to fully evaluate the effect of canagliflozin on the primary glycemic endpoint, provide sufficient time to assess secondary efficacy endpoints, and to assess safety and tolerability of this agent, relative to placebo, in pediatric subjects. Hemoglobin A_{1c}, the primary efficacy endpoint of the study, reaches full steady-state after approximately 12 to 16 weeks following a change in glycemic control (Tahara 1993).

Dosage Selection, Route of Administration, Dose Interval

Canagliflozin has been approved by several Health Authorities including the FDA and EMA as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. As per the US Package Insert (USPI) and EU Summary of Product Characteristics (SmPC), the recommended starting dose of canagliflozin in adults with T2DM is 100 mg. The dose can be increased to 300 mg in patients requiring additional glycemic control. The formulation and route of administration proposed for use in the pediatric population is the same as that used for the adult population, ie, tablet for oral use. The sponsor believes the current canagliflozin tablet formulation is age appropriate for the ≥10 to <18 years old pediatric population.

The effects of canagliflozin when administered using an up-titration algorithm was evaluated in a randomized, placebo-controlled, parallel-group, 2-arm, 26-week multicenter study (DIA4004). In this study, adult subjects with T2DM who had inadequate glycemic control (HbA_{1c} ≥7.5% to ≤10.5%) on maximally or near-maximally effective dose metformin and sitagliptin 100 mg were randomized to the addition of either placebo or canagliflozin 100 mg. After 6 weeks or treatment, only subjects meeting pre-specified up-titration criteria were required to up-titrate to canagliflozin 300 mg (or matching placebo). At the end of the 26-week treatment period, canagliflozin had been up-titrated to 300 mg in 85% of subjects, and compared to placebo provided clinically important glycemic improvements (ie, HbA_{1c} change from baseline, proportion to <7.0% HbA_{1c} goal, and FPG change from baseline), and clinically important reduction in body weight and systolic blood pressure (SBP). In addition, canagliflozin treatment was associated with a safety and tolerability profile consistent with expectations, including an increased incidence of adverse events of genital mycotic infections. Adverse events related to osmotic-diuresis (eg, polyuria, pollakiuria, thirst) were similar but numerically increased in the canagliflozin group and perhaps lower than expected based on the rates observed in other studies with this agent at the 300-mg dose (CSR JNJ-28431754 DIA4004 2016)

Based on the above information, in this study canagliflozin will be administered using a titration strategy which is likely to be followed in common clinical practice. Subjects will initially be randomized to a starting dose of canagliflozin 100 mg (or placebo). Subjects who after 12 weeks of treatment fail to achieve the HbA_{1c} goal of <7.0% and have normal renal function (eGFR

≥60 mL/min/1.73m^2) are eligible to be re-randomized to either up-titrate to canagliflozin 300 mg (or placebo) or to remain on canagliflozin 100 mg (or placebo).

Choice of Efficacy Measures

The efficacy measures in this pediatric study are the same as those evaluated in the canagliflozin T2DM program in adults. The HbA_{1c} levels will be measured throughout the study to evaluate glycemic control, as it is an accepted endpoint for AHAs and is predictive of the risk for microvascular diabetic complications. Fasting plasma glucose, another important measure of glycemic control, is closely correlated with HbA_{1c} and will also be measured throughout the study. Hemoglobin A_{1c} provides information on glycemic control throughout the day, both fasting and post-meal, while FPG reflects only overnight glucose control before the first morning meal. Additional secondary measures of efficacy (ie, serum lipids, blood pressure) will be evaluated to identify additional treatment effects of canagliflozin on comorbidities often seen in patients with T2DM.

Rescue Medication

To assure that subjects are not exposed to prolonged poor glycemic control, the investigator may apply progressively stricter glycemic rescue criteria based upon HbA_{1c} (or SMBG/FPG at their discretion). Rescue criteria can be found in Table 2 in Section 6.2.2, Glycemic Rescue Therapy: Criteria and Implementation.

Glycemic rescue procedures and therapies will be implemented as outlined in Section 6.2.2, Glycemic Rescue Therapy: Criteria and Implementation.

Rationale for Monitoring of Ketosis, Diabetic Ketoacidosis and Sick Day Management Algorithms

As described in Section 1.1.3, Efficacy/Safety Studies, treatment with canagliflozin may lead to an increased risk of DKA in subjects with T2DM. However, the risk of DKA and ketone-related adverse events in subjects with T2DM treated with canagliflozin is notably lower compared to the risk of DKA commonly observed in subjects with T1DM. Canagliflozin lowers blood glucose by increasing UGE, which is associated with potential increases in glycogenolysis, gluconeogenesis, and fatty acid oxidation. Based on its mechanism of action, it is possible that mild ketonemia might be detected especially with fasting in otherwise non-acutely ill subjects. In a Phase 3 study in Japanese subjects with T2DM involving canagliflozin as an add-on to existing therapy, the median total ketone body level increased to approximately 0.2 mmol/L within 4 to 8 weeks (reference range ≤0.13 mmol/L), but then declined to approximately 0.15 mmol/L in each of the groups by Week 24, and then remained stable thereafter. Total ketone bodies were transiently increased in 22/1,297 subjects to ≥3.0 mmol/L and to ≥5.0 mmol/L in 6 subjects; no subjects developed DKA (Inagaki 2015).

Since canagliflozin lowers blood glucose in an insulin-independent fashion it is expected that subjects treated with insulin and receiving canagliflozin may require less insulin to avoid hypoglycemia in maintaining acceptable blood glucose control. As the insulin-to-glucagon ratio is a key determinant in controlling hepatic ketogenesis, a reduction in this ratio subsequent to a

decrease in the insulin dose could in turn increase a subject's susceptibility to developing DKA. In patients with T2DM who have an acute illness or other stressor, insulin resistance is increased, leading to a reduced insulin action and further reduction in the "functional" insulin-to-glucagon ratio.

It should be noted that given the glucosuric effect of canagliflozin, an atypical DKA presentation characterized by concomitant blood glucose levels that are lower (ie, <250 mg/dl or <13.9 mmol/L) than what would be expected in subjects with DKA treated with insulin alone could potentially delay the recognition of DKA. As subjects generally monitor blood glucose levels during an illness and are then prompted to check concomitant serum or urine ketones when blood glucose levels are elevated, the impetus (elevated blood glucose) to check for ketones may be missing, and patients and health care providers could fail to recognize the need to increase their insulin dose. Thus, the opportunity to treat DKA early in its course may be missed and the subject could be at risk to progress to a more advanced state of DKA.

To reduce the risk of subjects delaying the recognition of ketosis and/or progression to overt DKA, subjects will be counseled on when and how to measure ketone levels, recognize and monitor signs and symptoms of DKA, and receive instructions on when to contact the site or seek medical attention (see Attachment 1, Instructions to Patients on Ketone Monitoring and Sick Day Management, and Attachment 2, Suggested Algorithm for Ketone Monitoring and Findings of Elevated Ketones). In this study, the ketone level that will trigger procedures described in the attachments is ≥0.6 mmol/L. This cut-off was chosen as there is general consensus among investigators that normal serum levels of ketone bodies can be defined as <0.5 mmol/L. Hyperketonemia can be defined as levels in excess of 1.0 mmol/L and DKA can be defined as levels of in excess of 3.0 mmol/L (Laffel 1999).

Collection of Additional Information for Selected Adverse Events

The safety profile of canagliflozin has been well-established in the Phase 3 program, which included approximately 10,000 subjects from randomized, controlled clinical studies. (IB JNJ-28431754 2020) For adverse events of interest, investigators will be asked to provide additional information on separate electronic case report forms (eCRFs) (Refer to Section 12, Adverse Event Reporting for a list of adverse events of special interest that will be collected). The detailed information on collection and reporting of all adverse events is also described in Section 9.8, Safety Evaluations. Investigators may also be asked to provide additional information on other adverse events, based upon review by the MSRC, and the IDMC, (Section 9.4.1, Medical Safety Review Committee, Section 9.4.2, Independent Data Monitoring Committee).

Additional Safety Measures

The urinary albumin to creatinine ratio (from the first morning void) will be measured over the duration of the study.

Bone turnover markers (serum osteocalcin and serum collagen type 1 CTx), and markers of calcium and phosphate homeostasis (calcium, magnesium, phosphate, PTH, 25-hydroxy

Vitamin D, calcitonin; urinary excretion of calcium and phosphate) will also be measured over the duration of the study.

Pharmacokinetics

Blood samples (only at trough) for PK analysis will be collected to document the steady-state PK exposure of canagliflozin. The potential effects of demographic characteristics and other subject covariates on the PK of canagliflozin may be evaluated. In addition, the PK data from this study may be integrated with plasma concentration-time data collected across other clinical development studies and subjected to population PK analysis. Refer to Section 9.6, Pharmacokinetic Evaluations, for more detail.

Archive Samples for Exploratory Research and Specimens for Biomarker Assessment

Fasting plasma, serum, and urine archive samples will be collected (where local regulations permit) to allow for biomarker analyses and exploratory research related to canagliflozin or T2DM and obesity. Refer to the laboratory manual for further information regarding the collection and handling of exploratory blood and urine samples.

4. SUBJECT POPULATION

At least 146 subjects with T2DM will be randomly assigned to treatment in this study in a 1:1 ratio such that at least 73 subjects will be randomized to each treatment group. For a discussion of the statistical considerations, refer to Section 11.2, Sample Size Determination.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling the subject in the study.

Note: For laboratory test values, a one-time repeat measurement is allowed, at the discretion of the investigator, if the screening value is not consistent with prior values and the repeat is considered clinically appropriate. For more information, refer to Section 4.4, Repeat Testing and Subject Rescreening.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Male or female between the ages ≥10 to <18 years at the time of screening.
2. Diagnosis of T2DM.
3. Random C-peptide at screening >0.6 ng/mL (>0.2 nmol/L) as determined by the central laboratory.
   Note: If the C-peptide is ≤0.6 ng/mL (≤0.2 nmol/L) in the presence of low concomitant blood glucose (ie, <70 mg/dL [<3.9 mmol/L]), a repeat C-peptide measurement should be obtained to assess eligibility.

4. Absence of pancreatic autoimmunity (GAD, and islet cell antigen 2 [IA2] antibody negative) as confirmed by subject history (documented in medical records) or if not available, by central clinical laboratory evaluation at the time of screening.

5. HbA_{1c} of ≥6.5% to ≤11.0% and meets 1 of the inclusion criteria below:

   a. On diet and exercise only for at least 4 weeks prior to screening,

   b. On diet and exercise and a stable dose of metformin monotherapy ≥1,000 mg per day or MTD per day (defined by the investigator) for at least 8 weeks prior to screening,

   c. On diet and exercise and a stable insulin monotherapy regimen for at least 8 weeks prior to screening (stable dose is defined as no change in the insulin regimen [ie, type{s} of insulin] and ≤15% change in the total daily dose of insulin [averaged over 1 week to account for day to day variability]),

   d. On diet and exercise and a stable combination therapy with metformin and insulin for at least 8 weeks prior to screening, as described above.

   Note: Subjects who are on diet and exercise and a stable dose of metformin XR for at least 8 weeks prior to screening may be included in the study, however they will be switched from metformin XR to metformin IR (at the same daily dose or nearest appropriate dose) at the single-blind placebo run-in visit and will be enrolled in the study if the metformin IR is well tolerated during the 2-week single-blind placebo run-in period prior to Visit 3/Day 1.

6. Each subject (or their legally acceptable representative) must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study. Assent is also required of children capable of understanding the nature of the study (approximately 7 years of age and older) as described in Section 16.2.3, Informed Consent/Pediatric Assent.

7. Before randomization, a female subject must be either:

   a. Not of childbearing potential defined as:

      - premenarchal
      - permanently sterile (eg, bilateral tubal occlusion [which includes tubal ligation procedures as consistent with local regulations]), hysterectomy or bilateral salpingectomy, bilateral oophorectomy); or otherwise be incapable of pregnancy, or

   b. Of childbearing potential and

      - heterosexually active *and* practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) including combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral, injectable, or implantable; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner (provided that the partner is the sole sexual partner of the female subject of childbearing potential and the absence of sperm has been confirmed; if not, additional highly effective method of contraception should be used), and agrees to remain on a highly effective method

of contraception throughout the study and for at least 30 days after the last dose of study drug.

Note: Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

- not heterosexually active (ie, female subject agrees to refrain from heterosexual intercourse during the entire period of risk associated with the study drug).

  Note: Female subjects who are not heterosexually active at screening must agree to utilize a highly effective method of contraception if they become heterosexually active during their participation in the study.

8. Female subjects of childbearing potential must have a negative highly sensitive serum β-human chorionic gonadotropin (β-hCG) pregnancy test at the screening visit.
9. Adequate compliance with placebo single-blind run-in procedures, including ≥80% compliance (by tablet count) with single-blind placebo medication.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

Diabetes-Related/Metabolic

1. History of DKA, T1DM, pancreas or β-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy or maturity-onset diabetes of the young (MODY). See Attachment 8, Maturity-Onset Diabetes of the Young (MODY).
2. On any AHAs other than metformin, or injectable insulin within 8 weeks of the first dose of study drug (ie, Day 1).
3. Repeated (ie, 2 or more over a 1-week period) fasting SMBG glucose measurements >270 mg/dL (>15 mmol/L) during the pretreatment phase, despite reinforcement of diet and exercise counseling.

   Note: Subjects with fingerstick glucose >270 mg/dL (>15 mmol/L) may have their AHA regimen adjusted and be rescreened once on a stable regimen for at least 8 weeks.
4. Severe hypoglycemia (defined as an event for which the subject required assistance from another person, or which resulted in seizure or loss of consciousness) within 6 months prior to Day 1. (See Attachment 4, Hypoglycemia: Definition, Symptoms and Treatment).
5. History of hereditary glucose-galactose malabsorption or primary renal glucosuria.

Renal/Cardiovascular

6. Renal disease that required treatment with immunosuppressive therapy or a history of dialysis or renal transplant.

   Note: Subjects with a history of treated renal disease, without sequelae, may participate.

Gastrointestinal

7. Known significant liver disease (eg, acute hepatitis, chronic active hepatitis, cirrhosis).

Laboratory

8. Persistent elevation in capillary blood ketones ≥0.6 mmol/L in the absence of concomitant illness or other identified precipitating factor during the screening period. Persistent elevation is defined as capillary blood ketone values ≥0.6 mmol/L obtained on ≥2 consecutive days.

   Note: Subjects with capillary ketone levels ≥0.6 mmol/L in the presence of precipitating factors (eg, acute illness, non-compliance with insulin treatment) may have the screening or run-in period extended by up to 2 weeks if it is the investigator's opinion that precipitating factor/concomitant illness will be resolved and the subject will no longer meet the exclusion criterion. If, following resolution of the precipitating factor(s), the repeat assessment of capillary blood ketones shows values ≥0.6 mmol/L, the subject must be excluded.

   Note: To avoid the confounding effect of overnight fasting on ketogenesis, for the pre-specified ketone assessment procedures, the blood ketone measurements should be obtained in a non-fasting state. If non-symptomatic ketone elevations are found in the fasting state, subjects should be instructed to repeat the ketone measurement after breakfast.

9. eGFR is <60 mL/min/1.73m^2 as assessed by Schwartz formula (see Attachment 7, Clinical Laboratory Tests).

   Note: A one-time repeat measurement is allowed, at the discretion of the investigator, if the value for eGFR is not consistent with prior values.

10. Alanine aminotransferase level >5.0 times the upper limit of normal (ULN) or total bilirubin >1.5 times the ULN at screening (for elevations in bilirubin: if, in the opinion of the investigator and agreed upon by the sponsor's medical officer, the elevation in bilirubin is consistent with Gilbert's disease, the subject may participate).

Other Conditions

11. History of malignancy within 5 years before screening (eg, any evidence of active disease within 5 years, or diagnosis of malignancy within this period).

    Note: Subjects with squamous or basal cell carcinomas of the skin, carcinomas in situ of the cervix, or a malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence, may participate.

12. Major surgery (ie, requiring general anesthesia) within 12 weeks before screening, or has not fully recovered from surgery, or planned surgery during the participation of the current study.

    Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate.

13. History of non-traumatic amputation within past 12 months of screening, or an active skin ulcer, osteomyelitis, gangrene, or critical ischemia of the lower extremity within 6 months of screening.

Medications/Therapies

14. Previously been or is currently being treated with an SGLT2 inhibitor, or the subject has participated, or is currently participating in a canagliflozin study.
15. Known allergies, hypersensitivity, or intolerance to canagliflozin or its excipients (refer to the Investigator's Brochure).
16. Current use of corticosteroid medication or immunosuppressive agent, or likely to require treatment with a corticosteroid medication (for longer than 2 weeks in duration) or an immunosuppressive agent.

    Note: Subjects using inhaled, intranasal, intra-articular, or topical corticosteroids, or corticosteroids in therapeutic replacement doses may participate.
17. Current use of anticonvulsant medication or is likely to require treatment with anticonvulsant medication.
18. Received an active investigational drug (including vaccines) or used an investigational medical device within 12 weeks before the planned start of treatment.

General

19. History of drug or alcohol abuse within 3 years before screening.
20. Pregnant or breast-feeding or planning to become pregnant during the study.
21. Child or adolescent of an employee at the investigational study center, whose parent/legally accepted representative has direct involvement in the proposed study or other studies under the direction of that investigator or study center.
22. Any condition that in the opinion of the investigator or sponsor's medical monitor would make participation not in the best interest of the subject or could prevent, limit, or confound the protocol-specified assessments.

Investigators should ensure that all study enrollment criteria have been met and determine that the subject has not had any interval change in clinical status since screening. Before randomization, subjects whose status changes after screening, such that they now meet an exclusion criterion, should be excluded from participation. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

- Female subjects of childbearing potential who are heterosexually active, must remain on a highly effective method of birth control throughout their participation in the study and for at least 30 days after the last dose of study drug (refer to Section 4.1, Inclusion Criteria and refer to Section 12.2.3, Pregnancy, for instructions in cases of a positive pregnancy test).

- Prohibited medications include other SGLT2 inhibitors, or other AHAs that are not approved for use in pediatric population (including commercially available canagliflozin). Subjects must not take any other investigational agents during the study (if a subject prematurely discontinues the study drug but continues to participate in the post-treatment follow-up phase, entering another investigational study is discouraged but is not prohibited; however, entering another canagliflozin study is prohibited).
- Subjects should not collect first morning void urine specimens during acute illness with fever. The collection and respective visit should be postponed until the subject is recovered from the acute illness.
- Exceptionally strenuous exercise may affect urine protein excretion and other safety laboratory results; for this reason, strenuous exercise should be avoided within 72 hours before planned study visits.

4.4. Repeat Testing and Subject Rescreening

During the screening period and prior to initiation of the single-blind placebo run-in period at Week -2, a non-qualifying laboratory test value may be repeated one time, at the discretion of the investigator and where there is a clinical reason to do so. In subjects for whom a one-time repeat measure is deemed clinically appropriate, the repeat measure should be assessed within the screening period and prior to recording the subject as having failed screening.

Subjects who do not satisfy entry criteria based on a physical or laboratory measurement either during the initial screening assessment or following an allowable one-time repeat assessment will be reported as having failed screening and may be rescreened ***once***, at the discretion of the investigator and with concurrence of the sponsor's medical monitor. Additional rescreening may be discussed with the sponsor's medical monitor to evaluate eligibility into the study on a case by case basis. Rescreening will typically require that all screening parameters be repeated, including the signing of a new ICF and the completion of a full screening visit with a comprehensive central laboratory review. Rescreened subjects must meet all entry criteria to be considered eligible for the study.

5. TREATMENT ALLOCATION

Stratification

Dynamic randomization (ie, covariate-adjusted randomization) will be used in an effort to maintain balance between treatment groups with respect to the following stratification factors: AHA background (ie, diet and exercise only; metformin monotherapy; insulin monotherapy or combination of metformin and insulin) and age group (≥10 to <15 years old; ≥15 to <18 years old). The stratification process will be handled after logging on to the IWRS being used for the study.

Randomization and Blinding Procedures

In dynamic randomization, a new subject is sequentially assigned to a particular treatment group by taking into account the specific covariates and previous assignments of subjects. This approach uses the method of minimization by assessing the imbalance of sample size among the

covariates listed above. Subjects will be randomized to 1 of 2 treatment groups based on a computer-generated dynamic randomization algorithm prepared by or under the supervision of the sponsor before the study. This approach seeks to maintain balance between treatment groups with respect to the AHA background and age group. The goal is to have at least 30% of participants that will be ≥10 to <15 years of age, 30% to <65% of participants that will be female in each age group (≥10 to <15 years and ≥15 to <18 years), and 30% of participants that will have ethnicity and lifestyle comparable to Europe.

Based on this approach, the study drug will be packaged and labeled. Medication numbers will be preprinted on the study drug labels and assigned as subjects qualify for the study and are assigned to double-blind treatment. At baseline (Day 1), the randomization number, medication numbers, and the treatment code, which is linked to the dynamically-generated randomization schedule, will be assigned after logging on to the IWRS designated by the sponsor. The requestor must use his/her own user identification (ID) and personal identification number (PIN) when accessing the IWRS and will then enter the relevant subject details to uniquely identify the subject. Based on this information, the IWRS will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. As subjects are randomized to treatment, the IWRS will assign a study drug kit to be dispensed at that visit. New study drug kits will be assigned each time the IWRS is assessed for dispensing additional study drug.

At the baseline (Day 1) visit, all eligible subjects, regardless of the treatment assignment to canagliflozin 100 mg will be assigned canagliflozin 100 mg kits and matching placebo kits.

The dynamically-generated randomization code that links the randomization number assigned to the subject with a treatment group assignment will be maintained within the IWRS. This randomization code will not be provided to the investigator unless required, as described below, for unblinding in emergency situations.

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. However, the treatment blind may be broken to provide unblinded information to the study site only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by assessing the IWRS. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation before breaking the blind. The reason for unblinding is not captured through the IWRS. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the appropriate section of the eCRF, and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner (eg, sealed envelope) so as not to unblind the treatment assignment to the study site or sponsor personnel. The investigator is also advised not to reveal the study treatment assignment to the study site (except as necessary for the clinical management of the subject) or sponsor personnel.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. The translation of randomization codes into treatment and control groups will be disclosed only to those authorized.

To avoid the potential unblinding after randomization (Day 1), FPG values will be masked to the study sites and to sponsor. Similarly, HbA_{1c} values will be masked, except for (1) Day 1 value, (2) Week 12 value, and (3) after glycemic rescue therapy has been initiated.

In addition, unless required by urgent subject management, investigators should obtain all post-baseline urinalyses through the central laboratory and not by a local laboratory so as to avoid potential for unblinding related to urine glucose results (which will not be reported by the central laboratory). Investigators will be counseled to avoid performing local urinalysis with dipstick. If a urinalysis must be performed locally for appropriate subject management (eg, to evaluate a potential infection), investigators should request microscopic rather than dipstick urinalysis (if microscopic evaluation is considered clinically sufficient).

6. DOSAGE AND ADMINISTRATION

6.1. Blinded Study Drug

6.1.1. Single-Blind Placebo Study Drug

Upon completion of initial screening, all eligible subjects will receive 1 placebo tablet (1 placebo tablet matching canagliflozin 100 mg) prior to the first meal of the day for a total of 2-weeks to assess compliance.

Subjects will take the last dose of single-blind placebo study drug on the day prior to the baseline (Day 1) visit. The investigational site staff should avoid disclosing to the subject that the 2-week single-blind placebo run-in period drug is placebo.

6.1.2. Double-Blind Study Drug

On Day 1, subjects will be randomly assigned in a 1:1 ratio to 1 of 2 treatment groups: canagliflozin 100 mg, or matching placebo.

On Day 1, the first dose of double-blind study drug will be administered at the study site **after** all baseline procedures have been completed.

After Day 1, subjects will be counseled to take their dose of canagliflozin 100 mg or matching placebo, once daily, before the first meal of the day.

At Week 13, subjects who have a Week 12 HbA_{1c} of ≥7.0% and eGFR ≥60 mL/min/1.73m^2 will be re-randomized to either remain on double-blind canagliflozin 100 mg (or matching placebo) or to up-titrate to double-blind canagliflozin 300 mg (or matching placebo). A double-dummy approach will be used to maintain the blind to dose-assignments as indicated below:

- Subjects initially randomized to placebo and undergoing re-randomization at Week 13, will continue receiving 1 tablet of placebo matching canagliflozin 100 mg and will **ADD** 1 tablet of placebo matching canagliflozin 300 mg for the remainder of the double-blind treatment period.
- Subjects initially randomized to canagliflozin 100 mg and re-randomized to remain on canagliflozin 100 mg at Week 13, will continue receiving 1 tablet of canagliflozin 100 mg and will **ADD** 1 tablet of placebo matching canagliflozin 300 mg for the remainder of the double-blind treatment period.
- Subjects initially randomized to canagliflozin 100 mg and re-randomized to up-titrate to canagliflozin 300 mg at Week 13, will switch to 1 tablet of placebo matching canagliflozin 100 mg and will ADD 1 tablet of canagliflozin 300 mg for the remainder of the double-blind treatment period.

Subjects **not** undergoing re-randomization (ie, HbA_{1c} of <7.0% or eGFR <60 mL/min/1.73m^2) at Week 13 will continue to receive 1 tablet of canagliflozin 100 mg or 1 tablet of placebo matching canagliflozin 100 mg for the remainder of the double-blind treatment period.

A summary of study drug administration is provided in Table 1.

Table 1: Summary of Dose Level and Number of Tablets by Study Period and Treatment

Study Period	Criteria for re-randomization	Treatment Group: canagliflozin	Treatment Group: placebo
Day 1 to re-randomization	Not applicable	1 tablet of canagliflozin 100 mg	1 tablet of placebo matching canagliflozin 100 mg
Re-randomization to Week 52	**NOT eligible for re-randomization if:** • HbA_{1c} <7.0% or • eGFR <60 mL/min/1.73m^2	1 tablet of canagliflozin 100 mg	1 tablet of placebo matching canagliflozin 100 mg
Re-randomization to Week 52	**Eligible for re-randomization if:** • HbA_{1c} ≥7.0% and eGFR ≥60 mL/min/1.73m^2	1 tablet of canagliflozin 100 mg **AND** 1 tablet of placebo matching canagliflozin 300 mg **or** 1 tablet of canagliflozin 300 mg **AND** 1 tablet of placebo matching canagliflozin 100 mg	1 tablet of placebo matching canagliflozin 100 mg **AND** 1 tablet of placebo matching canagliflozin 300 mg

The study drug must be swallowed whole with liquid and not chewed, divided, dissolved, or crushed. If the subject does not take the study drug within 12 hours after the first meal of the day, the dose of study drug should be skipped for that day and the subject should be instructed to take the study drug on the following day before the first meal of the day.

Study drug treatment may be interrupted (eg, for safety and/or tolerability reasons such as hospitalizations for major surgical procedure or serious medical illness). In addition, study drug treatment should be interrupted in clinical situations known to predispose to ketoacidosis

(eg, prolonged fasting due to acute illness or surgery [see Section 9.2.2, Management of Blinded Study Drug During Ketonemia]).

For subjects who develop conditions that are associated with amputations, such as a lower-extremity infection, skin ulcer, osteomyelitis, gangrene, or critical limb ischemia, study drug should be interrupted until the condition has resolved in the opinion of the investigator. In the event of an amputation, restarting of dosing with canagliflozin should only be done after careful consideration of the individual risk:benefit and following discussion with the sponsor.

Study drug treatment interruption, occurring for any reason, will be documented on the eCRF. Study drug should be reinstituted once the subject has recovered and the safety and/or tolerability concern is no longer present.

Study-site personnel will instruct subjects on how to store study drug for at-home use as indicated for this protocol.

On the days of study visits when fasting blood samples are collected (refer to the Time and Events Schedule that follows the synopsis), subjects will be instructed to refrain from taking the study drug before the clinic visit. The subject will be instructed to take the dose of study drug before the subject's next meal.

6.2. Concomitant Open-Label Antihyperglycemic Therapies

6.2.1. Background Antihyperglycemic Therapies

Subjects should remain on a stable AHA regimen (doses and medications) from screening to Week 52, unless glycemic rescue criteria are met (refer to Section 6.2.2, Glycemic Rescue Therapy: Criteria and Implementation). Adjustment to the AHA regimen, including adjustments in insulin doses and insulin type and metformin, is permitted during prolonged fasting (eg, religious events), and should be carefully implemented so as to avoid events of hypoglycemia.

After initiation of rescue therapy, adjustment of AHA therapy will be performed by the investigator, consistent with standard diabetes guidance. Treatment may include reinforcement of lifestyle counseling, up-titration to maximum labeled doses of current AHAs, or the initiation and up-titration of any approved AHAs. Investigators should make all reasonable efforts to achieve and maintain the subject's individualized target glycemic control, and may add unscheduled visits, if clinically appropriate, to monitor glycemic control, and adjust the subject's regimen. All adjustments to the AHA regimen should be documented in the appropriate eCRF.

Use of AHAs and adjustments to the AHA regimen (dose or agents) should be consistent with the labeled use of the AHA within the country of the investigational site.

6.2.2. Glycemic Rescue Therapy: Criteria and Implementation

To assure that subjects are not exposed to prolonged poor glycemic control, the investigator may apply glycemic rescue criteria based upon HbA_{1c}. These criteria are designed such that they take into account changes in HbA_{1c} from baseline, with cut-offs that are progressively stricter with

increasing baseline HbA_{1c} values. In particular, subjects should be started on glycemic rescue if they meet the increases in HbA_{1c} relative to their individual Day 1/Baseline HbA_{1c} value as described in Table 2. Subjects should be counseled to increase the frequency of SMBG monitoring if they experience an increase in their usual fasting and/or post-meal glucose levels and to contact the site if they experience sustained hyperglycemia. Sustained hyperglycemia is defined as 80% of non-fasting SMBG values >300 mg/dL (>16.7 mmol/L) or fasting SMBG values >200 mg/dL (>11.1 mmol/L) over a 1-week period. If, after reinforcement of compliance with study drug, non-study drug AHA therapy and lifestyle counseling, the subject continues to experience sustained hyperglycemia, the subject may come into the clinic (at an unscheduled visit, if needed) to obtain an HbA_{1c} measurement and to determine eligibility for glycemic rescue therapy. If the HbA_{1c} value meets a rescue threshold, the investigational site will be alerted and receive the unmasked HbA_{1c} result. Once the protocol-specified glycemic rescue criterion has been met, the subject should return to the clinic for a rescue visit at which time, per the investigator's discretion, he/she may either alter background AHA therapy (ie, metformin and/or insulin) or initiate an approved AHA for the pediatric population as per the local label. Double-blind study drug is to be continued after initiation of rescue therapy.

It should be noted that if the subject does not meet HbA_{1c} rescue criterion (either at scheduled or unscheduled visit), the subject may be still rescued if it is the investigator's opinion, based on recent SBMGs/FPG values, that the subject's glycemic control is progressively deteriorating and unlikely to improve with reinforcement of compliance with background AHA therapy and diet and exercise counseling. If a subject has scheduling conflicts and cannot attend an unscheduled visit at the site to assess the HbA_{1c} criterion, the site may instruct the subject to obtain an HbA_{1c} assessment at a local laboratory.

Table 2: Glycemic Rescue Criteria

Baseline HbA_{1c}	**HbA_{1c} change from baseline**
<9.0%	>0.8%
≥9.0%	>0.5%

Key: HbA_{1c}=glycated hemoglobin

Any subject that qualifies for initiation of rescue therapy should return to the investigational site, per the investigator's judgment, after an overnight fast, for measurement of HbA_{1c}, FPG, and serum chemistry.

If new rescue therapy is initiated, it will be supplied locally by the sponsor or reimbursed by the sponsor as appropriate. Investigators must complete the appropriate eCRF (documenting initiation of therapy) for subjects starting on rescue medication.

For subjects rescued based on SMBG and/or FPG instead of HbA_{1c}, the most recent values supporting such decision will be documented into the appropriate eCRF.

Notes:

- Subjects who meet the protocol-specified glycemic rescue criteria ***prior to*** Week 12, despite reinforcement of compliance with background AHA therapy, study drug, and lifestyle counseling, will **NOT** undergo early re-randomization (via a re-randomization visit). Instead

subjects will initiate glycemic rescue therapy and be evaluated at Week 12 to determine if they meet eligibility for re-randomization.

- If rescue criterion is met based on the Week 12 HbA_{1c} value, then the subject will return to the site for the Week 13 visit to undergo re-randomization **AND** initiate concomitant rescue therapy.

7. TREATMENT COMPLIANCE

The investigator or designated study research staff will maintain a log of all drug dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study. Subjects who are poorly compliant with taking the study should receive counseling on the importance of dosing compliance and may continue in the study, at the investigator's discretion.

Subjects will receive clear instructions on compliance with study procedures at the screening visit. During the study, the investigator or designated study research staff will be responsible for providing additional instructions to reeducate any subject who is not compliant with taking the study drug or with completing the diary, as required.

Study drug interruption occurring for any reason will be documented on the appropriate eCRF.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy therapy includes any therapy used before the first dose of double-blind study drug. Concomitant therapy is any therapy used after the first dose of double-blind study drug is administered on Day 1.

Prestudy therapies administered up to 30 days before screening (and up to 6 months before screening for AHAs) and up to the time of the first dose of double-blind study drug must be recorded.

All therapies (prescriptions or over-the-counter medications, including vitamins and herbal supplements; non-pharmacologic therapies such as, special diets, exercise regimens) different from the study drug must be recorded as prestudy therapy (before the first dose of double-blind study drug) or concomitant therapy (after first dose of double-blind study drug) on the eCRF.

Disallowed Therapies

No other SGLT2 inhibitors (including commercially available canagliflozin), or other AHAs that are not approved for use in pediatric population, may be used as concomitant medications, and subjects should not take any other investigational agents during the study.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY PROCEDURES AND EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule that follows the synopsis summarizes the frequency and timing of efficacy, safety, and other measurements applicable to this study.

9.1.1.1. Visit Schedules and Visit Windows

A screening visit should occur approximately 1 week before the single-blind placebo run-in visit (Week -2). The single-blind placebo run-in period should be 2 weeks in length, with a recommended visit window of ±4 days.

Note: Subjects who at screening may require testing of pancreatic autoimmunity (ie, GAD-65 and/or islet cell antigen [IA] antibodies) or who require a repeat of other screening procedures may have the duration of the screening period and/or run-in period increased by 1 to 2 weeks to allow sufficient time for the assessments to be obtained.

Post-randomization (from Day 1) scheduled study visits should generally occur within a recommended 7-day window (ie, ±7 days) around the protocol-specified visit schedule (as provided in the Time and Events Schedule). All visits will be scheduled based on the date of randomization (Day 1). There may be exceptional cases where it is possible, with concurrence of the sponsor's medical monitor, that certain on-site study visits may be replaced by telemedicine visits (a remote visit that is done by a video or phone call.).

A telephone follow-up contact (or optional study visit, at the discretion of the investigator) will be conducted for all subjects approximately 30 days after the last dose of study drug. If a telephone contact or study visit is not possible, follow-up information may be collected via email or other electronic means.

In the event that it is impossible for a subject to make a scheduled clinic visit, telephone contacts may be conducted at the time of the missed visit, but a clinic visit should be scheduled as soon as possible thereafter. If a telephone contact or study visit is not possible, follow-up information may be collected via email or any other appropriate means. Details regarding discussions via telephone, email, or other such contacts must be properly documented in source records, including responses by the subject (or parent/guardian).

For study visits that are unable to be held within the protocol-recommended visit windows, the visit should be conducted as close as possible to the protocol-specified study visit timing. All subsequent visits should be scheduled based on the date of randomization, not the date of the rescheduled visit.

For subjects who prematurely discontinue study drug, but don't withdraw consent, study sites will be required to follow-up on subsequent scheduled visits, and to make a final contact

(eg, schedule the last follow-up visit). See Section 10.2.4, Comprehensive Follow-up at Scheduled Study Visits Following Premature Discontinuation of Study Drug, for more detail.

9.1.1.2. Visit Reminders- Telephone Contacts

Prior to each visit, subjects should be contacted and reminded of:

- The date and time of their clinic appointment.
- The requirement to fast for at least 8 hours prior to clinic visits on Day 1 (Randomization Visit), Week 26, Week 52, and unscheduled visit for initiation of glycemic rescue therapy.
- The requirement on the morning of clinic visits at Week 12, 26, and 52 to not take blinded study drug prior to coming to the clinic.

  Note: Non-study medications that are not AHAs should be taken as directed by the prescribing physician.
- The requirement to bring study drugs, glucometer, hypoglycemia assessment tool(s), any collected SMBG measurements and ketone information to the clinic visit.

9.1.1.3. Pregnancy Testing

A negative serum pregnancy test for females of childbearing potential is required at the screening visit. Additionally, urine (or serum) pregnancy tests will be performed at Weeks 26 and 52, or more frequently as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the study (refer to the Time and Events Schedule that follows the synopsis for further details regarding urine pregnancy testing).

9.1.1.4. Subject Diary: Collection of Self-Monitoring of Blood Glucose (SMBG), Ketones, and Possible Hypoglycemic Event Information

A standard, protocol-specified subject diary will be provided to each subject at Week-2 (and at subsequent visits, if needed). The purpose of this diary is to record routine SMBG measurements and those potentially leading to glycemic rescue, episodes of elevated ketone levels, and all episodes of possible hypoglycemia. In addition, this diary will be used to collect time and date of study drug administration on the days prior to PK sample collection, any missed doses of study drug and it may also be used to keep track of medications and/or medication changes at the investigator's discretion.

9.1.1.5. Archive Samples for Exploratory Research and Specimen for Biomarker Assessment

Fasting plasma, serum, and urine archive samples will be collected (where local regulations permit) to allow for biomarker analyses and exploratory research related to canagliflozin or T2DM and obesity. Subject participation in this component of the study is optional. Refusal to consent for this component does not exclude a subject from participation in the clinical study. Refer to Section 9.9, Exploratory Biomarker Evaluations, for further details. Additionally, refer to the laboratory manual for further information regarding the collection and handling of exploratory blood and urine samples.

9.1.1.6. Blood Collection

As summarized in Table 3 below, the estimated total blood volume that will be collected from a subject who completes the study (including all procedures outlined in the pretreatment and double-blind treatment phases over approximately 52 weeks) will be approximately 173 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 3: Estimated Volume of Blood to be Collected from Each Subject

Type of Sample	Volume per Sample (mL)	No. of Samples per Subject	Total Volume of Blood (mL)[a]
Fasting plasma glucose	2.0	4	8.0
Hemoglobin $_{A1c}$	2.0	7	14.0
C-peptide	2.0	5	10.0
Hematology	2.0	4	8.0
Serum chemistry	2.5	6	15.0
Fasting lipid panel	3.5	3	10.5
Serum β-hCG pregnancy tests	2.5	1	2.5
Pharmacokinetic samples	4.0	3	12.0
Bone turnover markers	10.0	3	30.0
Markers of calcium and phosphate homeostasis	10.0	3	30.0
Biomarkers (serum archived samples)[c]	5.0	3	15.0
Biomarkers (plasma collection)	6.0	3	18.0
Approximate Total [b, c]	**51.5**	**45**	**173.0**

[a] Calculated as number of samples multiplied by amount of blood per sample.
[b] Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.
[c] Approximate total volume of blood that would be collected from a subject who completed the study and had all blood tests performed (including Rescue and/or Down-Titration Visits). Total volume of blood collected will be lower in males, and in subjects who do not have a Rescue and/or Down-titration Visit during the study, or who do not consent to archive samples.

9.1.1.7. Other Routine Examinations

During the study, subjects should continue to have routine screening examinations for diabetes complications (eg, ophthalmologic and podiatric examinations) consistent with standard guidelines for the care of patients with diabetes along with appropriate management, based upon these evaluations.

9.1.2. Pretreatment Phase

Potential subjects will be seen at a screening visit at which informed consent and assent will be obtained. At the screening visit, a focused medical history and initial screening assessment of inclusion/exclusion criteria will be performed and samples for required central laboratory tests will be collected. Laboratory specimens will be obtained as described in the Time and Events Schedule. Vital signs (Attachment 3, Method of Blood Pressure Measurement) and height and weight (Attachment 5, Guideline for Collecting Height Measurements) will be measured and prestudy medicines will be reviewed. For FPG, fasting C-peptide, and lipids, subjects must be fasting for at least 8 hours before blood sample collection, except for the screening visit when non-fasting blood samples may be collected.

Eligible subjects who meet all enrollment criteria (see Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria) will be scheduled to return to the investigational site at Week -2 to begin the single-blind placebo run-in period.

Note: Subjects who at screening may require testing of pancreatic autoimmunity (ie, GAD-65 and/or IA antibodies) or who require a repeat of other screening procedures may have the duration of the screening period and/or run-in period increased by 1 to 2 weeks to allow sufficient time for the assessments to be obtained.

9.1.3. Single-Blind Placebo Run-In Visit (Week -2)

At the Week -2 visit, subjects will be 1) provided with a glucose meter and testing supplies and instructed on the performance of SMBG, and blood and urine ketone measurement; 2) provided with a standard, protocol-specific subject diary (for recording of information on hypoglycemia, SMBG readings and ketone measurements); 3) receive counseling regarding diet and exercise consistent with standard diabetes guidance recommendations (eg, American Diabetes Association [ADA]); 4) receive counseling regarding recognition and management of hypoglycemia, and will be instructed to record all possible hypoglycemic episodes in the subject diary along with concurrent fingerstick glucose measurements, 5) receive counseling regarding how to recognize and monitor signs and symptoms of ketosis-related important events and importance of ketone monitoring and sick day management; 6) provide a first morning void urine sample. At this visit, potential eligible subjects who are on diet and exercise and a stable dose of metformin XR for at least 8 weeks prior to screening will be switched from metformin XR to metformin IR (at the same daily dose or nearest appropriate dose).

Subjects who meet eligibility criteria will be dispensed a single-blind placebo tablet (through IWRS, refer to Section 5, Treatment Allocation) and enter the 2-week single-blind placebo run-in period. Potential eligible subjects will be counseled to take 1 tablet of single-blind placebo once-daily, before the first meal of the day, for the duration of 2 weeks. Subjects should be instructed to take their last dose of single-blind placebo study drug on the day prior to the baseline (Day 1) visit. The study-site staff should not disclose to the subjects that during the single-blind placebo run-in period subjects will receive placebo tablets.

An assessment of the subjects' adherence to protocol procedures during the single-blind placebo run-in period will be made at the end of the period (on Day 1), before randomization. Investigators should ensure adequate compliance with the single-blind placebo run-in period study procedures, including performance of the SMBG and blood ketone measurements (Section 9.2.1.1, Pre-specified Ketone Measurements During Run-in Period) with diary entries or documentation through glucose/ketone meter memory, and ≥80% compliance (by pill count).

Note: If the subject does not meet the eligibility criteria related to compliance with study procedures during the run-in period due to unforeseeable circumstances (eg, breakage or loss of the meter, or intercurrent illness that prevented the subject to be compliant with single-blind study drug, etc), at the discretion of the investigator and with concurrence of the sponsor's medical monitor, the duration of the run-in period may be extended to repeat the procedures and allow assessment of eligibility. In such cases, subjects may receive additional single-blind study drug.

Potential subjects who do not meet all entry criteria must be excluded from the study.

9.1.4. Double-Blind Treatment Phase

9.1.4.1. Day 1/Day of Randomization

Eligible subjects (ie, those who have taken ≥80% of the scheduled single-blind placebo tablets during the single-blind placebo run-in period) will return for the Day 1 (baseline) visit, at which time they will be stratified by AHA background (ie, diet and exercise only, metformin monotherapy, insulin monotherapy or combination of insulin and metformin) and age group [≥10 to <15 years old; ≥15 to <18 years old] and will be randomly assigned to 1 of 2 double-blind treatment groups (in a 1:1 ratio): canagliflozin 100 mg, or matching placebo.

Those subjects who were switched from metformin XR to metformin IR at the single-blind placebo run-in visit will only be randomized if the metformin IR is well tolerated during the 2-week single-blind placebo run-in period prior to Visit 3/Day 1.

The first dose of study drug will be administered at the study site on Day 1. Subjects will continue treatment until the study completes or the subject is prematurely withdrawn from double-blind study drug (refer to Section 10, Subject Completion, Premature Discontinuation of Treatment, or Withdrawal from the Study).

9.1.4.2. Visits Following Randomization

Subjects will be seen in the clinic at visits as described in the Time and Events Schedule. Procedures and clinical laboratory assessments for each visit or contact are outlined in the Time and Events Schedule.

9.1.4.3. Re-Randomization

At Week 12, subjects' glycemic status will be assessed by a central laboratory HbA_{1c}. Following the review of the Week 12 unmasked HbA_{1c} and eGFR results, the following will occur:

- Subjects with HbA_{1c} value <7.0% or eGFR <60 mL/min/1.73m^2 will not undergo re-randomization and instead will continue their current treatment assignment (ie, canagliflozin 100 mg or matching placebo) for the remainder of the study.
- Subjects with HbA_{1c} value ≥7.0% and eGFR ≥60 mL/min/1.73m^2 will be re-randomized in a 1:1 ratio (in a blinded fashion via the IWRS) to either
  - remain on their original treatment assignment (ie, canagliflozin 100 mg or matching placebo) **or**
  - up-titrate canagliflozin 100 mg to 300 mg (or matching placebo). In order to keep the study blind, subjects randomized to the placebo group will undergo a mock up-titration.

For subjects with a Week 12 HbA_{1c} ≥7.0% and who are on insulin and have experienced recurrent (ie, at least 2 episodes within a 7-day period) episodes of hypoglycemia after randomization, consideration should be given to down-titrate insulin prior to the blinded up-titration (or mock up-titration) to canagliflozin 300 mg.

Since the unmasked central laboratory HbA_{1c} values will not be available at the Week 12 visit, subjects (or their parent/legal guardian) will be informed whether the subject is eligible for re-randomization via phone contact. If the subject is eligible for re-randomization, the subject and/or parent/legal guardian will return to the site, preferably within 1 week from Week 12, to return any unused study drug and obtain new blinded study drug according to the IWRS assignment. Although no additional study or laboratory procedures will occur at this visit, and the subject is not required to be physically present, the subject's attendance is highly encouraged to allow the site to provide new dosing instructions related to the double-dummy treatment.

Management of double-blind study drug based on renal function

- Subjects who have undergone re-randomization and subsequently have a confirmed eGFR <60 mL/min/1.73m^2 will undergo down-titration (or mock down-titration) of blinded study drug at an unscheduled down-titration visit; only those who were up-titrated previously to the canagliflozin 300 mg dose will actually titrate down (in a blinded fashion via the IWRS). Subjects randomized to canagliflozin 100 mg or placebo will undergo a mock down-titration and continue their randomized treatment.
- If at any time during the study, a subject has a confirmed eGFR of <45 mL/min/1.73m^2, the subject must be discontinued from study drug as described in Section 10.2, Study Drug Treatment Premature Discontinuation, Reinstitution and Follow-up. Subjects discontinued from study drug and who do not withdraw consent will remain in the study and followed as described in Section 10.2. Study Drug Treatment Premature Discontinuation, Reinstitution, and Follow-up.
- Prior to down-titrating or discontinuing canagliflozin due to confirmed eGFR <60 mL/min/1.73m^2 or <45 mL/min/1.73m^2, respectively, a repeat determination should be performed within 1 week and study drug down-titrated or discontinued if the repeat determination confirms that the value still meet the criteria (unless a reversible acute cause is identified [eg, short-term illness or transient volume depletion] in which case an additional repeat determination can be performed after resolution of the illness).
- All subjects will receive a new medication kit assignment through the IWRS at the unscheduled down-titration visit. The investigator, or qualified assigned designee, will provide the subject with double-blind treatment medication with updated instructions on dosing and a new subject diary. The subject will be instructed to continue with the diet and exercise regimen and the completion of the study diary.

Note: Once a subject has up-titrated to canagliflozin 300 mg, down-titration is not allowed unless for confirmed eGFR <60 mL/min/1.73m^2. Therefore, if after up-titration to canagliflozin 300 mg a subject experiences recurrent hypoglycemia (ie, at least 2 episodes within a 7-day period), consideration should be given to down-titrate background AHA(s) such as insulin (or metformin).

9.1.5. Post-treatment Phase (Follow-Up)

All subjects should have a follow-up telephone contact (or optional study visit, at the discretion of the investigator) approximately 30 days after the last dose of study drug to collect any serious adverse events and adverse events of interest that occurred since the last visit, unless the subject has been lost to follow-up, has withdrawn consent, or has died. If serious adverse events are

obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the subject has died, the date and cause of death will be collected and documented on the eCRF.

All subjects who discontinue study drug prematurely should continue to attend all subsequent study visits in the same way as the subjects who are still on the study drug treatment, unless the subject (and/or the parents[s]/legal guardian[s]) has elected to withdraw his/her consent from the study.

Subjects who discontinue study drug early for any reason (other than withdrawal of consent for follow-up contacts) will be contacted according to the post-treatment visit (or more frequently if necessary based on the investigator's knowledge of the subject) until completion of the overall study, with the goal of collecting any information on vital signs, body weight, laboratory assessments, serious adverse events, adverse events of interest, and adverse events of special interest. See Section 10.2.4, Comprehensive Follow-up at Scheduled Study Visits Following Premature Discontinuation of Study Drug, for more detail.

9.2. Ketone Monitoring

Subjects will be provided with a capillary blood ketone meter and strips. It should be noted that capillary blood ketone testing is the preferred methodology for decision making, as it provides a quantitative measure of 3β-OH butyrate which accounts for approximately 75% of the ketones (Foster 1983) and represents a more sensitive marker to detect and monitor ketonemia. On the contrary, the urine ketone test provides a qualitative assessment of aceto-acetate and appears to be less sensitive in detecting early stages of ketosis and may be overestimating the degree of ketosis during its resolution phase.

Subjects and parents/legal guardians will be counseled on various aspects of sick day management and ketone monitoring aiming at early identification of elevated ketone levels and timely intervention in order to prevent or reduce the risk of progression to ketoacidosis. In particular, subjects will receive counseling on

- Importance of monitoring ketones any time the subject is ill or does not feel well, or has any potential precipitating factors for ketone elevation or DKA;
- Recognition of signs and symptoms of ketosis and DKA;
- Management of insulin and food intake during illness and/or in presence of elevated ketone levels.

See Attachment 1, Instructions on Ketone Monitoring and Sick Day Management and Attachment 2, Suggested Algorithm for Ketone Monitoring and Findings of Elevated Ketones.

During the study, subjects will return the diary containing information on ketone measurements and if applicable, action taken by the subject to treat elevated ketone levels. Study site personnel will be required to review the diaries and enter only the data of elevated ketones (ie, ≥0.6 mmol/L) along with other pertinent information (concomitant blood glucose levels, signs/symptoms of illness, precipitating factors, etc) on a specific eCRF. In addition, upon

review of the diaries, findings of elevated ketones considered by the investigator to be adverse events should also be reported in the adverse event eCRF. In addition, any illness considered to be a precipitating factor of the ketone elevation should be reported as an adverse event, if appropriate, on the adverse event eCRF.

9.2.1.1. Pre-specified Ketone Measurements During Run-in Period

Subjects will be required to measure and document in their study diary capillary blood ketones and blood glucose on a minimum of 3 days during the 2-week run-in period (to assess subject's pre-dose ketone levels and compliance with ketone management procedure). The measurements do not have to be made on 3 consecutive days.

To avoid the confounding effect of overnight fasting on ketogenesis, for the pre-specified ketone assessment procedures, the blood ketone measurements should be obtained in a non-fasting state. If non-symptomatic ketone elevations are found in the fasting state, subjects should be instructed to repeat the ketone measurement after breakfast.

9.2.1.2. Ketone Measurements During Periods of Increased Risk of Ketonemia

It is paramount that subjects and parents/legal guardians are educated on obtaining ketone measurements whenever they experience potential causes of ketone elevation that might lead to ketoacidosis if not identified and treated in time.

These possible precipitating factors include, but are not limited to:

- Acute illness
- Significant and/or sudden reduction in insulin dose (eg, non-compliance with insulin treatment regimen)
- Prolonged fasting or low carbohydrate diet
- Dehydration and/or a marked increase in physical activity
- Increased alcohol consumption
- Undergoing a minor procedure (eg, dental extraction)
- Significant physiologic stress

Subjects and parents/legal guardians will be instructed to test their ketone levels in the presence of these possible precipitants, regardless of the presence of symptoms of DKA (such as nausea, abdominal pain, dehydration, polyuria), as these are nonspecific and might be interpreted as gastroenteritis, or signs and symptoms of osmotic-diuresis related to the use of study drug. In addition, it is paramount to instruct subjects and parents/legal guardians to test ketones in such occasions regardless of the concomitant glucose level, as blood glucose might be incongruously low (<250 mg/dL [<13.9 mmol/L]) and not as high as one would expect to observe during ketosis and DKA.

Ketone measurements performed during illness or periods of increased risk of ketone elevation, should preferably be done ***prior*** to dosing of study drug to allow prompt interruption of study drug, if required.

During sick days, subjects must refer to the algorithm (see Attachment 2, Suggested Algorithm for Ketone Monitoring and Findings of Elevated Ketones) to determine, based on severity of illness, degree of ketosis, and ability to increase insulin dose and food intake, the appropriate frequency of retesting of ketones and glucose, action with blinded study drug, need to seek immediate medical attention, or to contact the study site.

Subjects are required to enter pertinent information related to elevated ketones during illness (eg, concomitant [or closest in time] glucose levels, insulin dose and changes in insulin dose [if applicable], precipitating factors) on a subject diary and the information will be captured on a specific eCRF. Upon review of the subject's ketone measurements, the site will be required to report only the episodes of elevated ketone levels (ie, ≥0.6 mmol/L) and the pertinent information onto the specific eCRF. The concomitant illness should be reported as a separate adverse event and study drug treatment interruptions will be documented on the eCRF.

Note: If subjects cannot obtain capillary blood ketone measurement, a urine ketone measurement should be obtained. Deviations from this process should be documented on the subject's diary.

9.2.2. Management of Blinded Study Drug During Ketonemia

Subjects will be instructed to interrupt blinded study drug for the following reasons:

- **Surgery and invasive procedures**
  - Subjects undergoing pre-planned major surgery (eg, requiring general anesthesia), will be instructed to interrupt blinded study drug at least 3 days prior to the surgery. Study drug may be resumed after recovery from surgery and after consultation with the investigational site.
  - Subjects undergoing minor surgical and non-surgical procedures will be instructed to interrupt study drug on the day of the procedure (or starting the day prior to the procedure if deemed appropriate, such as in preparation for a colonoscopy) and resume dosing on the following day if their non-fasting blood ketone level on the day following the procedure is <0.6 mmol/L and the subject has completely recovered from the procedure.
- **Persistent elevated ketonemia ≥0.6 mmol/L** (with or without symptoms of ketosis, regardless of concomitant glucose levels)
  - Persistent elevated ketonemia is defined as blood ketone levels ≥0.6 mmol/L and confirmed by a repeat assessment (eg, within 1 hour or sooner, if in the presence of symptoms). If urine ketone is being used to assess ketone status, then a value of "moderate/large" urine ketone will be used.

- In the presence of illness/symptoms, or presence of potential risk factors for ketosis (eg, insulin dose reduction, etc), subjects should assess ketone levels ***prior*** to dosing blinded study drug to allow timely interruption of study drug should ketone levels be elevated.

Subjects should be advised to contact the study site immediately for further instructions regarding management of blinded study drug, insulin dose-adjustment, and possible need to seek immediate medical attention.

Cause of dose interruption of blinded study drug and duration of study drug interruption will be captured on a specific adverse event eCRF and study drug administration eCRF, respectively.

9.3. Self-Monitoring of Blood Glucose

Run-in Period Management

Subjects will receive diet/exercise counseling at the single-blind placebo run-in visit (Week -2) for their glycemic control. During this visit, subjects should also be counseled to perform fasting SMBG determinations, and to enter results into the protocol-specified study diary that will be provided to each subject, as described in Section 9.1.1.4, Subject Diary: Collection of Self-Monitoring of Blood Glucose (SMBG), Ketones, and Possible Hypoglycemic Event Information.

Note: During the pretreatment phase, subjects will be counseled to perform fasting SMBG measurements a minimum of 3 days during the 2-week run-in period. The measurements do not have to be made on 3 consecutive days. Additional SMBG measurements may be performed by the subjects at the discretion of the investigator and per local guidelines.

Double-blind Treatment Phase Glycemic Management

During the double-blind treatment phase, investigators will counsel subjects to perform regular fasting SMBG determinations a minimum of 3 days per week with additional measurements made as considered clinically appropriate by the investigator and per local guidelines.

9.4. Study Management: Committees

9.4.1. Medical Safety Review Committee

An internal MSRC will be established to ensure that the safety of subjects participating in the study is not compromised. The MSRC will include, but will not be limited to, at least one medical expert and at least one statistician. The MSRC will include members from the sponsor. The MSRC will monitor the progress of the study by reviewing blinded data on a regular basis and will refer safety concerns to an IDMC.

Details of the composition, roles, and responsibilities are documented in the MSRC charter.

9.4.2. Independent Data Monitoring Committee

An IDMC will be commissioned for this study to review accumulated, unblinded safety information during the study. Details of the composition, roles, and responsibilities will be documented in the IDMC charter.

The IDMC will have responsibility for safety review during the study, including serious adverse events, adverse events of interest, and events resulting in study drug discontinuation.

9.5. Efficacy Evaluations

9.5.1. Measures of Efficacy/Efficacy Endpoints

The primary measure of efficacy is HbA_{1c}. Secondary measures of efficacy include FPG, body weight, proportion of subjects with an HbA_{1c} <7.5%, <7.0%, and <6.5%, time to rescue, and proportion of subjects receiving rescue therapy.

Efficacy endpoints (ie, criteria for evaluation of efficacy measures) include the following:

The primary efficacy endpoint will be the change in HbA_{1c} from baseline to Week 26; only subjects who have both baseline and at least one post-baseline measurement will be included.

Key secondary endpoints include the change from baseline to Week 26 and change from baseline to Week 52 in FPG, body weight, proportion of subjects with an HbA_{1c} <7.5%, <7.0%, and <6.5%, time to rescue, and proportion of subjects receiving rescue therapy.

Additional secondary endpoints are BMI, fasting lipid profile, systolic and diastolic blood pressure, and change in HbA_{1c} from baseline to Week 12.

9.6. Pharmacokinetic Evaluations

9.6.1. Sample Collection and Handling

Venous blood samples of 4 mL will be collected at Week 12, Week 26, EOT (Week 52), and at early withdrawal visit for determination of plasma trough concentrations of canagliflozin in all subjects. On the days when PK blood samples are collected, subjects will be instructed to refrain from taking the study drug before the clinic visit and to bring the study drug to the clinic visit. The subject will be instructed to take the dose of study drug immediately before the subject's next meal. Subjects will record the time that the study drug was taken on the day preceding the clinic visit in the subject diary. The exact dates and times of blood sampling must be recorded in the eCRF or laboratory requisition form. Refer to laboratory manual for further information regarding the collection, handling, shipment and labeling of biological samples.

9.6.2. Analytical Procedures

Plasma samples will be analyzed to determine concentrations of canagliflozin using a validated, specific, and sensitive liquid chromatography-dual mass spectrophotometry (LC-MS/MS) method under the supervision of the sponsor's bioanalytical facility.

9.6.3. Pharmacokinetic Parameters

For each treatment, trough concentrations at each visit will be summarized by descriptive statistics, including arithmetic mean, standard deviation, minimum, maximum, and median. Population based PK modeling may be applied to the available plasma concentrations as needed.

9.7. Biomarker Evaluations

Markers of Bone Turnover and Markers of Calcium and Phosphate Homeostasis

Bone turnover markers (serum osteocalcin and serum collagen type 1 CTx) and markers of calcium and phosphate homeostasis (calcium, magnesium, phosphate, PTH, 25-hydroxy Vitamin D, calcitonin; urinary excretion of calcium and phosphate) will be measured in this study. These markers will be collected on Day 1, Week 26, EOT (Week 52), and at early withdrawal visit.

9.8. Safety Evaluations

Safety and tolerability evaluations, according to the time points provided in the Time and Events Schedule will include:

- Collection/monitoring of adverse events
- Collection of potential hypoglycemic episodes (eg, from the subject diary provided to subjects)
- Ketone monitoring
- Physical examinations
- Body weight
- Vital signs (blood pressures and pulse rates)
- Safety laboratory tests (including chemistry, hematology, urinalysis) (see Attachment 7, Clinical Laboratory Tests)
- SMBG
- Bone turnover markers (serum osteocalcin and serum collagen type 1 CTx)
- Markers of calcium and phosphate homeostasis (calcium, magnesium, phosphate, PTH 25-hydroxy Vitamin D, calcitonin, urinary excretion of calcium and phosphate)
- Urinary ACR
- Assessment of growth velocity and Tanner Staging (Refer to Attachment 6, Tanner Staging)

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study, beginning from when informed consent is provided. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting. Information about all adverse events (serious

or not) should be recorded in source documents (eg, progress notes) according to Good Clinical Practice (GCP) and retained at the study sites. All adverse events will be recorded on an eCRF.

Adverse Events of Interest and Special Interest and Collection of Additional Information

For adverse events of interest and of special interest (see Section 12, Adverse Event Reporting), investigators will be asked to provide additional information and documentation to support a detailed assessment. Investigators may also be asked to provide additional information on other adverse events, based upon review by the MSRC, and the IDMC (refer to Section 9.4.1, Medical Safety Review Committee, and Section 9.4.2, Independent Data Monitoring Committee, respectively).

Information pertaining to adverse events of interest will be recorded on supplemental case report forms.

Follow-Up Collection of Safety Information

Any clinically significant abnormalities persisting at the time treatment is discontinued (either prematurely or at completion of the study) will be followed by the investigator until resolution or until a clinically stable endpoint is reached, or until further follow-up is no longer considered by the investigator to provide clinically meaningful information. (See Section 9.1.5, Post-Treatment Phase [Follow-up], for details of follow-up required).

Management of Hyperglycemia

Subjects will be asked to monitor their fasting blood glucose during the study. The number of SMBG measurements to be performed by the subjects will be at the discretion of the investigator and per local guidelines. The subjects will be asked to contact the study site in the presence of sustained hyperglycemia (see Section 6.2.2, Glycemic Rescue Therapy: Criteria and Implementation). If glycemic control does not improve despite reinforcement of background AHA therapy, diet and exercise counseling and after correction of potential cause leading to the hyperglycemia, then glycemic rescue may be initiated as outlined in Section 6.2.2, Glycemic Rescue Therapy: Criteria and Implementation.

Collection of Information on Possible Hypoglycemic Episodes

Subjects will be asked to collect fingerstick glucose determinations at the time of possible hypoglycemic episodes, and to document information on these events, including the fingerstick glucose results, in a subject diary. This diary will be reviewed by study-site personnel at each scheduled visit (see Attachment 4, Hypoglycemia: Definitions, Symptoms and Treatment). Information on possible hypoglycemic episodes will be collected on a separate hypoglycemia eCRF, and hypoglycemic episodes that are considered by the investigator to be adverse events of hypoglycemia should also be recorded on the adverse event eCRF.

Collection of Information on Possible Ketone-Related Events

Information on serious and non-serious ketosis-related adverse events and related terms such as diabetic ketoacidotic hyperglycaemic coma, ketonuria, ketonaemia, ketosis, urine ketone body

present, acidosis, metabolic acidosis, blood ketone body present, blood ketone body increased will be collected on a separate eCRF and also recorded on the adverse event eCRF. If a ketosis-related adverse event meets the criteria used to define a serious adverse event (SAE), the event must be captured as an SAE on the Adverse Event eCRF.

Subjects will be asked to collect capillary blood ketones during periods of increased risk of ketonemia and to document these in a subject diary. Detailed information of episodes of elevated ketone levels requiring corrective actions (eg, increase in insulin dose, study drug interruption, etc) will be collected on the subject diary which will be reviewed by study site personnel at each scheduled visit. Information on episodes of elevated ketones will be collected on a separate eCRF, and adverse events of elevated ketone levels requiring corrective actions that are considered by the investigator to be adverse events of elevated ketones should also be recorded on the adverse event eCRF.

Clinical Laboratory Tests

Subjects will be monitored with safety laboratory measurements as described in Attachment 7, Clinical Laboratory Tests.

In addition to the laboratory reports, alerts will be provided to investigators by the central laboratory identifying important laboratory changes or key out-of-range values, so the investigator can follow-up as necessary.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. The laboratory reports must be filed with the source documents.

Urine samples from first morning void on day of designated visits will be collected for urine albumin and creatinine determinations. This urine sample should not be collected if the subject is menstruating, has exercised vigorously in the past 24 hours, or had a fever or an active infection within the past 2 days of the clinic visit. In such cases the subject may bring a first morning void specimen (or the 24-hour urine collection) to the investigational site during the subsequent week. For subjects who have atypical sleep patterns, the collection should be made at the end of the subject's usual sleep period. **Note**: if the subject cannot provide the morning void collection on the Week -2 visit, it must be provided **prior** to the Day 1 visit to assess whether the specimen is positive for protein. If the Week -2 urine sample from the first morning void shows a presence of proteinuria (ie, proteinuria +1 and above) based on the central laboratory urine dipstick, a 24-hour urine collection will be required to assess albumin and creatinine. The pre-randomization 24-hour urine sample can be collected over the 24 hours preceding the Day 1 visit (ie, start on the morning of Day -1 and complete on the morning of Day 1. Subjects who require a 24-hour urine collection prior to randomization, will be required to provide a 24-hour urine sample also on Week 26 and Week 52. Subjects who had a Week -2 first morning void negative for protein and develop a positive first morning void after randomization are not required to obtain 24-hour urine samples. Instead, in these subjects a first morning urine sample to assess albumin and creatinine will be collected for the remainder of the study.

Fasting plasma, serum, and urine archive samples will be collected (where local regulations permit) to allow for biomarker analyses and exploratory research related to canagliflozin or T2DM and obesity. The urine collections for exploratory analysis, as well as the routine urinalyses, should be obtained from a spot urine specimen in the clinic.

For SMBG monitoring during the study, refer to Section 9.3, Self-Monitoring of Blood Glucose.

Pregnancy Testing

Serum (β-hCG) pregnancy testing will be conducted for all female subjects of childbearing potential during the screening visit (refer to the Time and Events Schedule). Additionally, urine (or serum) pregnancy tests will be performed at Week 26 and Week 52 visits, or more frequently as determined necessary by the investigator, or required by local regulation, to establish the absence of pregnancy at any time during the study. Pregnancy testing will be performed for all female subjects according to local procedures unless they are premenarchal or surgically sterile. If a post-screening urine pregnancy test is positive, study drug should be immediately interrupted and then permanently discontinued if the urine test is confirmed by a serum pregnancy test (see Section 10.3, Withdrawal from the Study and Section 12.2.3, Pregnancy).

Vital Signs (Pulse, Blood Pressure)

Vital signs will consist of pulse and blood pressure measurements and will be obtained after the subject has been in a seated position for 5 minutes and before blood sample collection for laboratory tests. Pulse rate will be measured once at each clinic visit. For the blood pressure methodology, refer to Attachment 3, Method of Blood Pressure Measurement.

Body Weight

Body weight will be measured using the same calibrated scale at each visit (whenever possible). Subjects will be weighed at approximately the same time of day on the same scale, wearing underwear and a gown and without shoes; they will be instructed to empty their bladders before being weighed.

Note: If disrobing for weighing is logistically impossible, the subject must be dressed as lightly as possible, with consistency from visit to visit. The study site will be responsible for maintaining the scale during the study. Maintenance of the scale must be documented.

Physical Examination

A physical examination, including a review of body systems (head and neck, eyes, chest and lungs, cardiovascular, extremities and back, and abdomen examination), will be performed to assure that a subject meets entry criteria. Clinically relevant findings in physical examination must be documented in the source document and in the Medical History section of the eCRF.

Growth Velocity and Tanner Staging

Growth velocity will be assessed in all subjects during the study.

Tanner staging will be performed in order to assess the physical measurements of sexual development. If at any of the evaluations the subject's sexual maturation is assessed as being Tanner Stage 5, no further evaluations are needed during the study (Attachment 6, Tanner Staging).

9.9. Exploratory Biomarker Evaluations

Fasting plasma, serum, and urine archive samples will be collected (where local regulations permit) at the time points specified in the Time and Event Schedule to allow for biomarker analyses and exploratory research related to canagliflozin or T2DM and obesity. Refer to the laboratory manual for further information regarding the collection and handling of exploratory blood and urine samples.

10. SUBJECT COMPLETION, PREMATURE DISCONTINUATION OF TREATMENT, OR WITHDRAWAL FROM THE STUDY

10.1. Subject Completion

A subject will be considered to have completed the treatment phase if he or she has completed assessments at Week 52 of the double-blind treatment phase.

Subjects who prematurely discontinue study drug for any reason before completion of the double-blind phase at Week 52 will not be considered to have completed the study.

End-of-treatment evaluations will be performed when the subject completes the double-blind treatment phase at Week 52. The EOT evaluation should be followed by a 30-day off-drug follow-up visit or telephone contact to collect any serious adverse events and adverse events of interest.

If a subject discontinues from study drug prior to Week 52, he or she will be followed as per the assessments included in the Time and Events Schedule up to the Week 52 visit, without the requirement for the post-Week 52 follow-up (see Section 10.2.4, Comprehensive Follow-up at Scheduled Study Visits Following Premature Discontinuation of Study Drug, for more detail).

For details regarding the procedures performed at the EOT evaluation, refer to the Time and Events Schedule.

10.2. Study Drug Treatment Premature Discontinuation, Reinstitution, and Follow-up

10.2.1. Study Drug Treatment Premature Discontinuation

A subject should discontinue study drug for any of the following reasons:

- Subject is persistently in poor compliance with study drug or procedures.
- The investigator believes that for safety or tolerability reasons it is essential for the subject to discontinue study drug.

- The subject experiences a serious adverse event of biochemically-confirmed DKA (eg, low pH in presence of elevated serum ketones or urine ketones, etc).
- The investigator formally unblinds the subject's study treatment allocation.
- The subject becomes pregnant (study therapy should be immediately interrupted based upon a positive urinary human chorionic gonadotropin [hCG], and permanently discontinued if confirmed by a serum β-hCG test).
- Subject requires disallowed therapy (see Section 8, Prestudy and Concomitant Therapy).
- Subject has an eGFR of <45 mL/min/1.73m^2, confirmed by repeat (no sooner than 7 days and no later than 14 days from the initial report) by the central laboratory.

  Note: For subjects meeting this eGFR discontinuation criterion, a repeat determination should be performed between 7 and 14 days and study drug discontinued if the repeat determination confirms that the value still meets the criteria (unless a reversible acute cause is identified [eg, short-term illness or transient volume depletion] in which case an additional repeat determination can be performed after resolution of the illness). If the value is improving on repeat determination, but still meets the discontinuation criteria, an additional repeat measurement may be performed within 2 weeks, and the subject continued if they no longer meet the criterion or if improvement continues (in which case an additional repeat within 2 weeks may be obtained, and be used to determine subject discontinuation from the study).
- The subject meets the rescue therapy criteria, but the AHA to be initiated as rescue medication is not approved for use in the country of the investigational site, or the subject has a contraindication to the use of any approved AHA to be used as rescue medication, based upon the local label.

All subjects who prematurely discontinue study drug should continue subsequent study visits and post-treatment follow-up evaluations (see Section 10.2.4, Comprehensive Follow-up at Scheduled Study Visits Following Premature Discontinuation of Study Drug and Section 9.1.5, Post-treatment Phase [Follow-up]). Treatment should be recommenced wherever possible and routinely considered at every visit following discontinuation (see Section 10.2.3, Reinstitution of Treatment with Study Drug That Has Been Interrupted).

Subjects and/or parents[s]/legal guardian[s] who decide to discontinue double-blind study drug must be interviewed by the investigator so as to determine if a specific reason for discontinuing study drug can be identified. Subjects should be explicitly asked about the contribution of possible adverse events to their decision to discontinue study drug, and investigators should confirm that any adverse event information elicited has been documented. If a subject elects to discontinue study drug due to an adverse event, the event should be recorded as the reason for study drug discontinuation, even if the investigator's assessment is that the adverse event would not require study drug discontinuation. The reason for study drug discontinuation is to be documented in the eCRF and in the source documentation. Study drug assigned to the subject who discontinued the study may not be assigned to another subject. Subjects who discontinue study drug will not be replaced.

10.2.2. EOT and 30-Day Follow-up Assessments for Subjects Who Prematurely Discontinue Study Drug

If a subject discontinues study drug for any reason before the end of the 52-week double-blind phase, EOT and 30-day post-treatment follow-up assessments should be obtained and scheduled assessments should be continued.

Subjects who prematurely discontinue study drug will require an immediate EOT assessment (either on the day of study drug discontinuation or as soon as possible following study drug discontinuation) as well as an off-drug follow-up assessment (ie, clinic visit or telephone contact) approximately 30 days after their last dose of study drug. The Time and Events Schedule describes the evaluation required. If for some reason the subject is unable to be seen within 30 days after discontinuing study drug, the EOT visit may be omitted, but a 30-day off-drug follow-up assessment should be performed.

If a subject discontinues from study drug prior to Week 52, he or she will be followed as per the assessments included in the Time and Events Schedule (see Section 10.2.4, Comprehensive Follow-up at Scheduled Study Visits Following Premature Discontinuation of Study Drug, for more detail).

10.2.3. Reinstitution of Treatment with Study Drug that has Been Interrupted

Subjects for whom study drug is interrupted as a result of an adverse event, a life event, or other unforeseen circumstance should be encouraged to restart study drug unless there is a clear contraindication at the discretion of the investigator with concurrence from the sponsor's medical monitor.

Study drug interruption, occurring for any reason, will be documented on the appropriate eCRF.

10.2.4. Comprehensive Follow-up at Scheduled Study Visits Following Premature Discontinuation of Study Drug

It is important to note that subjects who discontinue study drug early will be required, wherever possible, to continue with scheduled visits for the duration of the study. Data collection required for subjects who discontinue study drug early will be comprehensive (as described in the Time and Events Schedule) and will be essential for every randomized subject. Subjects will continue to be followed up for specific data collection, including, vital signs, body weight, laboratory assessments, serious adverse events, adverse events of interest, and adverse events of special interest for the duration of the study. For subjects who prematurely discontinue study drug, sites will be required to make a final contact (eg, schedule the last follow-up visit) at what would have been their final scheduled visit.

Alternate Follow-up Methods

If a subject who discontinued study drug prior to Week 52 refuses or is unable to return for their regularly scheduled visits, he/she will be asked to return at a reduced visit schedule including key visits (ie, Weeks 12, 26, 42, and 52). If the subject refuses or is unable to return to the clinic for follow-up visits, the subject can be contacted at Weeks 12, 26, 42, and 52 to obtain adverse

events, and prior/concomitant medications. At the very minimum, attempts should be made at Week 52 to obtain adverse events and prior/concomitant medications. These alternate follow-up methods should be planned to coincide with the visit times outlined in the Time and Events Schedule. Details regarding discussions via telephone, email, or other such contacts must be properly documented in source records, including responses by the subject.

10.3. Withdrawal from the Study

A subject will be withdrawn from the study for any of the following reasons:

- Death
- Lost to follow-up
- Withdrawal of consent or assent (either by the subject and/or the parents[s]/legal guardian[s])

For subjects (and/or parents[s]/legal guardian[s]) withdrawing from the study before study completion, an early withdrawal evaluation should be performed as soon as possible after the last dose of study drug is taken. Refer to the Time and Events Schedule for procedures to be conducted at the EOT/early withdrawal evaluation.

10.3.1. Lost to Follow-up

If a subject is lost to follow-up, all reasonable efforts must be made by the study-site personnel to contact the subject and/or parent(s)/legal guardian(s) and to determine the subject's status and the reason for discontinuation/withdrawal. This should include repeated telephone calls, certified letters, email requests, etc. To ensure access to follow-up subjects, the study sites should attempt to obtain both primary and secondary telephone contact numbers (eg, home, work, and mobile phone numbers), as well as other contact information (eg, email addresses) from subjects before randomization. In addition, the study site should emphasize the importance of follow-up information to the subject before randomization. The measures taken to obtain follow-up information must be documented. Third-party vendors may be used to locate subjects lost to follow-up where permitted by local laws and regulations.

Subject and/or parent(s)/legal guardian(s) will be asked as a condition of entry into the study to agree to grant permission for the investigator to consult family members, the subject's physicians and medical records, or public records, to determine the subject's status during the study, in the event the subject is not reachable by conventional means (eg, office visit, telephone, email, or certified mail). The subject and/or parent(s)/legal guardian(s) are also to be advised that if the study site of the study doctor closes, and the study doctor cannot reach the subject to inform him/her, the contact information may be transferred to another study site where a new study doctor will consult with family members, the subject's physicians and medical records, or public records to determine the subject's status during the study.

10.3.2. Withdrawal of Consent

Withdrawal of consent (either by the subject or the parents[s]/legal guardian[s]) should be a very unusual occurrence in a clinical trial. The investigator should make every effort to maintain a

good relationship with subjects and their parents[s]/legal guardian[s] to avoid this occurrence. Unless consent is specifically withdrawn, subjects are expected to be followed up through the end of the study.

Subjects and/or parents[s]/legal guardian[s] who request to withdraw consent from the study should be asked if they are agreeable to be contacted to obtain post-treatment follow-up information, including the Week 52 post-treatment follow-up visit. Subjects and/or parents[s]/legal guardian[s] who are not agreeable to follow-up will be withdrawn from the study as "withdrawal of consent" and will not be scheduled for the Week 52 post-treatment follow-up visit. Subjects and/or parents[s]/legal guardian[s] who wish to discontinue study drug but agree to further follow-up have, by definition, not withdrawn consent to the trial and will be scheduled to return to the clinic for the Week 52 post-treatment follow-up visit (see Section 10.2, Study Drug Treatment Premature Discontinuation, Reinstitution, and Follow-up). The recording of withdrawal of consent in the eCRF for this study will occur after a discussion between the investigator and the subject along with the parents[s]/legal guardian[s] has taken place.

For subjects and/or parents[s]/legal guardian[s] requesting to withdraw consent, it is recommended that the withdrawal is in writing. If the subject and/or parents[s]/legal guardian[s] refuses or is physically unavailable, the study site should document and sign the reason for the subject's and/or parents[s]/legal guardian[s] failure to provide a request to withdraw and maintain this documentation in the subject's source records.

When a subject and/or parents[s]/legal guardian[s] withdraws consent before completing the study, the reason for withdrawal of consent is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw consent (either per their own decision and/or by the parents[s]/legal guardian[s]) will not be replaced.

If a subject and/or parents[s]/legal guardian[s] had previously withdrawn consent but decides to retract that withdrawal, the subject and/or parents[s]/legal guardian[s] will be re-consented. The investigator will be responsible for making all required notifications to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

10.4. Withdrawal from the Use of Samples in Future Research

A subject who withdraws consent from the study will have the following options regarding the optional research samples:

- The collected samples will be retained and used in accordance with the subject's original separate informed consent for optional research samples.
- The subject may withdraw consent for optional research samples, in which case the samples will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If

requested, the investigator will receive written confirmation from the sponsor that the samples [has] [have] been destroyed.

Withdrawal from the Optional Research Samples While Remaining in the Main Study

The subject may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research samples will be destroyed. The sample destruction process will proceed as described above.

Withdrawal from the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research samples.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

11.1. Analysis Sets

The full analysis set (FAS) population includes all subjects who are randomly assigned to a treatment group, have received at least 1 dose of study drug and have a baseline HbA_{1c} measurement.

The safety analysis set will include randomized subjects who take at least 1 dose of study drug.

The per protocol (PP) analysis set consists of all FAS subjects who complete the 26-week double-blind treatment phase and have no major protocol deviations that may affect the interpretation of the primary efficacy endpoint. Major protocol deviations will be defined in the SAP.

The primary efficacy analyses, to demonstrate the superiority of canagliflozin compared with placebo, will be based on the FAS population. Supportive analyses in the PP analysis set will also be performed for the primary endpoint of HbA_{1c}.

Efficacy data will be analyzed according to the initial randomization assignment, regardless of the actual treatment received. Safety data will be analyzed according to the predominant treatment received, in the event that subjects received a treatment other than that to which they were randomly assigned to receive. The approaches used to handle study deviations will be detailed in the SAP.

11.2. Sample Size Determination

The primary hypothesis of the study is that canagliflozin is superior to placebo in glycemic control, as measured by the change from baseline to Week 26 in HbA_{1c}.

The sample size calculation is based on the 2-stage randomization design using a 2-sample, 2-sided t-test with Type 1 error rate of 0.05. Based on the following assumptions on treatment effect (0.4% to 0.5%) and an associated common standard deviation of 0.9% and assuming 50% of the subjects will meet the re-randomization criteria at Week 12, it is estimated that at least 66 subjects per group will be required to achieve approximately 85% power. To account for attrition due to study discontinuation in a longitudinal analysis (to be described below), a 10% sample size inflation factor is employed (Lu 2008), and a total of at least 146 subjects (73 per arm) will be randomized in this study.

Treatment group	Meeting re-randomization criteria at Week 12	Placebo-subtracted group difference in change in HbA_{1c} from baseline to Week 26
canagliflozin 100 mg to canagliflozin 100 mg	No	0.5%
canagliflozin 100 mg to canagliflozin 100 mg	Yes	0.4%
canagliflozin 100 mg to canagliflozin 300 mg	Yes	0.5%

For subjects who are on background metformin (with or without insulin), it is estimated that at least 33 subjects per group (after accounting for attrition due to study discontinuation) will be required to achieve approximately 85% power to assess the efficacy of canagliflozin on a background of metformin.

Treatment group (add-on to metformin)	Meeting re-randomization criteria at Week 12	Placebo-subtracted group difference in change in HbA_{1c} from baseline to Week 26
canagliflozin 100 mg to canagliflozin 100 mg	No	0.75%
canagliflozin 100 mg to canagliflozin 100 mg	Yes	0.65%
canagliflozin 100 mg to canagliflozin 300 mg	Yes	0.75%

The assumed treatment effect above is based on a subgroup analysis of subjects with baseline eGFR of ≥90 mL/min/1.73m^2 from the add-on to metformin study of canagliflozin in adults (ie, Study DIA3006).

11.3. Efficacy Analyses

11.3.1. Primary Efficacy Endpoint

11.3.1.1. Definition

The primary efficacy endpoint will be the change in HbA_{1c} from baseline at Week 26.

Estimand

The primary efficacy estimand is described according to the following attributes:

- Population: children and adolescents (≥10 to <18 years) with T2DM who have an HbA_{1c} ≥6.5% to ≤11.0%

- Variable: change in HbA_{1c} from baseline to Week 26
- Treatments: canagliflozin vs placebo
- Intercurrent event (events that preclude observation of the variable or affects its interpretation): treatment discontinuation or initiation of rescue medication, variable is used regardless of early treatment discontinues or initiation of rescue medication
- Treatment policy strategy: the measurements of the variable of interest are used regardless of the occurrence of the intercurrent event
- Population-level summary for the variable: the placebo-subtracted difference (ie, canagliflozin versus placebo) in least-squares mean change of HbA_{1c} from baseline at Week 26 along with the 2-sided 95% CI

This estimand targets the effect of canagliflozin on the variable measured and follows an "ITT principle" strategy.

The main analysis of the primary efficacy outcome will be based on all HbA_{1c} measurements (regardless of the occurrence of treatment discontinuation or initiation of rescue medication) and will employ pattern mixture modelling using multiple imputation methods. The imputed datasets will be analyzed using analysis of covariance (ANCOVA) with terms for treatment, stratification factors, and baseline HbA_{1c}. Additional details will be specified in the SAP.

The following sensitivity analyses will also be performed using the primary estimand:

- The primary efficacy endpoint will be analyzed using a mixed model for repeated measures (MMRM) based on restricted maximum likelihood. The analysis will use the observed data and will include the fixed, categorical effects of treatment, stratification factors (ie, background AHA and age group), visit, and treatment-by-visit interaction, as well as the fixed, continuous covariates of baseline and baseline-by-visit interaction. An unstructured covariance will be used to model the within-patient errors. This sensitivity analysis will constitute the primary analysis based on a specific health authority request.
- The change from baseline in HbA_{1c} will be analyzed using an ANCOVA model with treatment and the stratification factors as fixed effects and baseline HbA_{1c} value as a covariate. The treatment differences in the least-squares means and the 2-sided 95% CI will be estimated based on this model. The last observation carried forward (LOCF) method will be applied when the Week 26 values are missing.

The following supplementary analysis will be performed using the primary estimand:

- A re-randomization test (Proschan 2011) (utilizing the MMRM as described above) will be used to determine the p-value for the primary efficacy comparison (ie, comparing all subjects who are randomized to canagliflozin to all subjects who are randomized to placebo). The re-randomization test will fix the observed HbA_{1c} data, regenerate treatment assignments for the entire study using the same minimization algorithm employed in the study and compute the test statistics corresponding to the primary efficacy comparison. This process will be repeated at least 1,000 times. The p-value for the primary efficacy comparison will be defined as the proportion of re-randomized studies whose test statistic for that comparison is at least as extreme as that of the original treatment assignment.

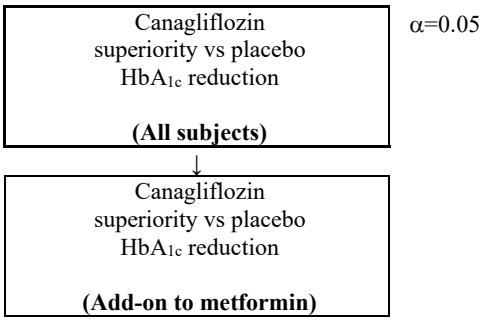
The primary efficacy endpoint will also be performed in the subset of FAS subjects on a background of metformin (with or without insulin) using the main analysis methods described above. Analyses for the other AHA subgroups in the FAS may also be performed.

Additional details on the data handling rules (including the definition of data windows used for analysis) will be described in the SAP.

11.3.2. Multiplicity Adjustment

To strongly control the family-wise error rate at the 5% significance level, a sequential testing procedure as illustrated in Figure 2 below will be applied. The primary endpoint will be first tested in all subjects (ie, FAS), and if the results are significant (2-sided alpha level of 0.05), it will then proceed to test the subset of subjects on a background of metformin (with or without insulin).

Figure 2: Testing Sequence



The formal hypothesis testing above will be based on all randomized subjects in the FAS.

The comparisons by canagliflozin dose to placebo will also be presented and analyzed using the weights in the analyses described below.

- When comparing subjects who initially receive canagliflozin 100 mg with no dose increase to 300 mg to placebo: All subjects start with a weight of 1. After Week 12, subjects with an HbA_{1c} ≥7.0% and eGFR ≥60 mL/min/1.73m^2 who are re-randomized to continue canagliflozin 100 mg will have a weight of 2. The subjects who are re-randomized to up-titrate to canagliflozin 300 mg will have a weight of 0.
- When comparing subjects who initially receive canagliflozin 100 mg followed by a dose increase to 300 mg to placebo: All subjects start with a weight of 1. After Week 12, subjects with an HbA_{1c} ≥7.0% and eGFR ≥60 mL/min/1.73m^2 who are re-randomized to continue canagliflozin 100 mg will have a weight of 0 and those who are re-randomized to up-titrate to canagliflozin 300 mg will have a weight of 2.

As the secondary efficacy endpoints listed in Section 11.3.3, Secondary Efficacy Endpoints, are supportive in nature, no corresponding hypothesis testing will be performed, and therefore they are not included in the testing sequence above.

11.3.3. Secondary Efficacy Endpoints

The secondary efficacy endpoints at Week 26 and Week 52 include:

- Change from baseline in FPG
- The proportion of subjects with HbA1c <7.5%, <7.0%, and <6.5%
- Time to rescue and proportion of subjects receiving rescue therapy
- Percent change from baseline in body weight
- Change from baseline in BMI
- Percent change from baseline in lipids
- Change from baseline in systolic and diastolic blood pressure

The secondary efficacy endpoint at Week 12 and Week 52:

- Change from baseline in HbA_{1c}

The estimands for the analysis of the secondary endpoints are the same as for the primary efficacy endpoint.

The categorical secondary efficacy endpoint of maintaining HbA_{1c} <7.0% (and HbA_{1c} <6.5% and HbA_{1c} <7.5%) will be analyzed longitudinally using a generalized linear mixed model in the FAS population. The model will include the fixed, categorical effects of treatment, stratification factors (ie, background AHA and age group), visit, and treatment-by-visit interaction, as well as the fixed, continuous covariates of baseline and baseline-by-visit interaction. An unstructured covariance will be used to model the within-subject errors. The odds ratio and 2-sided 95% CI for the treatment comparisons at Week 26 (canagliflozin compared to placebo) will be estimated based on this model.

Continuous endpoints (except for triglycerides) will be analyzed with an MMRM model as described before in the FAS population. For the endpoints with post-baseline assessments taken only at Week 26 and Week 52, an analysis of covariance (ANCOVA) model similar to the primary efficacy endpoint will be used at Week 26. The least-squares means for the treatment comparisons and their 2-sided 95% confidence intervals will be estimated based on this model. The analysis of percent change in triglycerides may be based on nonparametric methods (given the anticipated skewed nature of this parameter) or alternative methods, to be further described in the SAP.

11.4. Pharmacokinetic Analyses

Concentrations will be reported for all subjects at all visits. Concentrations below the lower limit of quantification or missing will be labeled as such in the concentration database. Descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, and maximum will be calculated and provided by treatment arm, and by treatment and background treatment. Population based PK modeling may be applied to the available plasma concentrations as needed.

11.5. Biomarker Analyses

Changes in serum osteocalcin and serum collagen type 1 CTx over time will be summarized by treatment group. Associations between baseline levels and changes from baseline in select markers and clinical response at 26 and 52 weeks of treatment will be explored. Biomarker analyses will be summarized in separate technical reports.

Biomarker results will be presented in a separate report.

11.6. Safety Analyses

Subjects in the safety analysis set (defined as subjects who are randomized and take at least 1 dose of study drug) will be included in the denominators for the summaries of adverse event, exposure, and concomitant medication data. There will be no imputation of missing values for clinical safety laboratory test results and vital sign measurements, in the safety analyses. Descriptive statistics for clinical laboratory test results and vital sign measurements will be presented based on measurements on study drug, including up to a maximum of 2 days after the last dose of study drug, as well as all measurements regardless of the time of the last dose of double-blind study drug. All safety analyses (except hypoglycemia) will be summarized regardless of the use of rescue medication; given the potential confounding due to rescue medication, analyses related to hypoglycemia will only be presented prior to rescue medication.

Adverse Events

The terms used in the eCRFs by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the treatment phase (ie, treatment-emergent adverse events) will be included in the analysis. Additionally, a summary of all reported adverse events (regardless of whether treatment-emergent) will also be provided.

For each adverse event, the percentage of subjects who experienced at least 1 occurrence of the given event will be summarized by treatment group. The percentage of subjects with specific treatment-emergent adverse events will be summarized by severity and relationship to study drug, as classified by the investigator, by treatment group.

Special attention will be given to those subjects who died, or who discontinued treatment due to an adverse event, or who experienced a severe or a serious adverse event (eg, summaries, listings, and narrative preparation may be provided, as appropriate).

Further analyses, to be described in the SAP for this study, will be conducted on the pre-specified adverse events for which additional information is collected from the investigators (refer to Section 9.8, Safety Evaluations), and on other adverse events.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (to be specified in the SAP) will be referred to in the summary. Descriptive

statistics will be reported for each laboratory analyte at baseline and at each scheduled time point and for change from baseline.

Laboratory analyses will include percent change in lipids (ie, LDL-C, non-HDL-C and total cholesterol) from baseline at Week 26, and percent change in the ratio of LDL-C to HDL-C and non-HDL to LDL-C from baseline at Week 26, and change from baseline in bone turnover markers (serum osteocalcin and serum collagen type 1 CTx) and markers of calcium and phosphate homeostasis (calcium, magnesium, phosphate, PTH, 25-hydroxy Vitamin D, calcitonin; urinary excretion of calcium and phosphate). Additional laboratory parameters (listed in Attachment 7, Clinical Laboratory Tests) will also be analyzed.

Hypoglycemic Episodes

Hypoglycemic episodes are collected on a separate eCRF and are also collected on the adverse event eCRF (for all such events considered as adverse events by the investigator). The primary analysis of hypoglycemia will be based upon data from the hypoglycemia eCRF (and not from the adverse event database). No reconciliation of hypoglycemia data from the adverse event eCRF and the hypoglycemic eCRF will be performed (except to assure that all adverse events of hypoglycemia are also recorded on the hypoglycemia eCRF).

Hypoglycemic episodes will be classified as *either* biochemically documented (ie, a hypoglycemia episode with a concurrent reported glucose value of ≤70 mg/dL [≤3.9 mmol/L]) and/or severe. The primary hypoglycemic analysis of interest will be all biochemically documented hypoglycemic episodes regardless of the presence of symptoms plus all severe hypoglycemic episodes. For each type of hypoglycemia, the percentage of subjects with at least one event will be summarized by treatment group. The hypoglycemic episode rate per subject year exposure, based on the number of episodes adjusted by exposure duration, will be reported by treatment group for each classification of hypoglycemia. (See Attachment 4, Hypoglycemia: Definitions, Symptoms, and Treatment).

Vital Signs

Descriptive statistics for pulse and sitting blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

Physical Examination

Physical examination findings will not be summarized except when reported as an adverse event.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

For adverse events of interest, investigators will be asked to provide additional information. Adverse events of interest include all malignancies, severe hypersensitivity reactions (eg, angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, and pregnancy.

The following adverse events have been designated as adverse events of special interest and need to be reported to Janssen within 24 hours of becoming aware of the event, which is the same timeframe for reporting of serious adverse events. These adverse events must be reported using a supplemental reporting form, to complement standard information collected on the Adverse Event/SAE eCRF, together with the SAE report for serious events.

- Diabetic ketoacidosis and adverse events related to DKA, ketoacidosis, metabolic acidosis or acidosis
- Amputations
- Pancreatitis
- Serious adverse events of UTIs including urosepsis and pyelonephritis

Additional information and documentation will be requested from investigators to support a detailed assessment of all deaths. Investigators may also be asked to provide additional information on other adverse events, based upon review by the MSRC. If adverse events of interest are identified in the future, guidance concerning the reporting of those events may be provided to investigators via appropriately-documented study communications.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH].)

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.2.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

A serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For canagliflozin, the expectedness of an adverse event will be determined by whether or not it is listed in the IB.

12.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the study drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the study drug. An alternative explanation, eg, concomitant drug(s) or disease(s), is inconclusive. The relationship in time is reasonable; thus, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the study drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Procedures

12.2.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the study (including subjects who discontinue study drug treatment).

Data will be collected in source documents and on the eCRF for all adverse events.

All deaths will also be recorded.

For adverse events of interest (see Section 9.8, Safety Evaluations) a supplemental eCRF will be used to collect additional information. Investigators may be asked to provide additional information on adverse events, based upon review by the MSRC or the IDMC.

Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form, which must be completed and signed by a member of the study-site personnel, and transmitted to the sponsor within 24 hours. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

Study research staff should make study subjects aware of potential signs and symptoms of DKA such as difficulty breathing, nausea, vomiting, abdominal pain, feeling confused, fruity-smelling breath, and unusual fatigue or sleepiness. Study subjects should be instructed to contact the site if they experience such symptoms. If the investigator suspects these symptoms may be related to DKA (even if the subject's blood glucose levels are <250 mg/dL (<13.9 mmol/L), testing for urine or blood ketones should be considered.

Consistent with standard diabetes treatment guidelines, all study subjects should be provided with routine preventative foot care and early intervention for foot problems. Specifically:

- Provide or ensure that all subjects have had general foot self-care education.
- Perform a comprehensive foot evaluation (at Day 1, Week 26, and Week 52 visits) to identify risk factors for ulcers and amputations. The examination should include inspection of the skin, assessment of foot deformities, neurological assessment including pinprick or vibration testing or assessment of ankle reflexes, and vascular assessment including pulses in the legs and feet.
- Subjects who have a history of prior lower-extremity complications, loss of protective sensation, structural abnormalities, or peripheral arterial disease should be referred to foot care specialists for ongoing preventative care.

For all study subjects, there should be a clinical evaluation at every visit to assess the presence of any sign or symptom suggestive of volume depletion (eg, hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), which if present should be adequately treated either by decreasing dose or eliminating use of diuretics or other antihypertensive medications or interrupting study drug until the condition resolves.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

Subjects (or their designees, if appropriate) will be provided with a "study card" indicating the name of the investigational study drug, the study number, the investigator's name, a 24-hour emergency contact number, and, if applicable, excluded concomitant medications.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local Sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.2.2. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct

- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)
- Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:
  - Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
  - Surgery or procedure planned before entry into the study (must be documented in the eCRF).

The cause of death of a subject in a study within 30 days of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

12.2.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further treatment with study drug.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequel in the infant will be required.

12.3. Hypoglycemia

In accordance with the ADA Workshop on Hypoglycemia and as outlined in the February 2008 FDA draft guidance on developing drugs for the treatment of diabetes, hypoglycemic episodes will be classified as: severe, documented symptomatic (symptoms consistent with hypoglycemia with concurrent biochemical hypoglycemia), probable symptomatic (symptoms consistent with hypoglycemia with no concurrent glucose measurement), or asymptomatic (low measured glucose [ie, ≤70 mg/dL (≤3.9 mmol/L)], without symptoms). Refer to Attachment 4, Hypoglycemia: Definitions, Symptoms, and Treatment for additional information.

Information on events of possible hypoglycemia will be collected on a separate hypoglycemia eCRF and will also be recorded on the adverse event eCRF if considered an adverse event by the investigator. If a hypoglycemic episode meets the criteria used to define a serious adverse event, the event must be captured on the serious adverse event eCRF page.

12.4. Diabetic Ketoacidosis

Diabetic ketoacidosis, ketoacidosis, metabolic acidosis and acidosis events have occurred at a low and relatively stable frequency over time in subjects participating in canagliflozin T2DM

clinical trials. The incidence and incidence rates of these events are within the range expected based on comparisons to existing observational data. While more cases have occurred with canagliflozin, relative to comparator, the majority of the cases are confounded by co-existing medical conditions (eg, T1DM, LADA) known to cause DKA or ketoacidosis. Given the potential in routine clinical practice for misdiagnosis of T2DM for more ketosis-prone types of diabetes (eg, T1DM and LADA) and the possibility of low pancreatic beta-cell reserve and associated insulinopenia in some patients with T2DM, an increased risk of DKA with canagliflozin in patients diagnosed with T2DM cannot be excluded. If present, this increased risk is small and would not change the overall benefit/risk profile of canagliflozin. Information on events of possible DKA will be collected on a separate DKA eCRF and will also be recorded on the adverse event eCRF if considered an adverse event by the investigator. If a DKA meets the criteria used to define a serious adverse event, the event must be captured on the serious adverse event eCRF. Test for ketones in any subject who presents with signs and symptoms of ketoacidosis, such as difficulty breathing, nausea, vomiting, abdominal pain, feeling confused, fruity-smelling breath, and unusual fatigue or sleepiness even if blood glucose levels are <250 mg/dL (<13.9 mmol/L).

12.5. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.2.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

Canagliflozin 100 mg and 300 mg tablets with matching placebo tablets for each dose strength will be supplied for this study.

Study drug will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients. (IB JNJ-28431754 2020)

14.2. Packaging

The study drug will be packaged as individual bottles. The study drug will be packaged according to good manufacturing practices and local regulations. The study supplies will be packaged according to the randomization code and each unit will be labeled with a medication ID number.

Study drug will be dispensed in child-resistant packaging.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

All study drug must be stored at controlled temperatures ranging from 59°F to 86°F (15°C to 30°C) and kept out of reach of children.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study drug. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and partially used study drug returned by the subject (if applicable), must be available for verification by the sponsor's or sponsor-delegated study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or partially used study drug returned for destruction, will be documented on the drug return

form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Recruitment and retention tools
- Study binder with all other necessary documentation (Investigator Brochure, Protocol, Clinical Trial Agreement)
- The IWRS Manual and worksheets
- Template ICF
- eCRF completion guidelines
- Home blood glucose and ketone monitoring system, glucose strips, ketone strips (blood and urine), alcohol wipes, lancets, and calibration solution (optional by country/region)
- Materials to promote healthy dietary and exercise habits
- Subject diaries
- Laboratory operations manual, requisition forms, sampling supplies, and equipment, if necessary
- Computer, if the study site is assessed to require a laptop computer to enter eCRF data for the study.

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

The primary ethical consideration in the study is the investigational use of canagliflozin in children and adolescents in a non-approved indication for pediatric population.

Potential subjects and their parents/legal guardians will be fully informed of the risks and requirements of the study and, during the study, subjects and/or their parents[s]/legal guardian[s] will be given any new information that may affect their decision to continue participation. They will be told that their consent or their child's assent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects and/or their parents[s]/legal guardian[s]

who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent/assent voluntarily will be enrolled.

Hypoglycemia is a common adverse event in patients with T2DM. Treatment with canagliflozin may lead to an increase risk of hypoglycemia when administered with insulin or insulin secretagogues (eg, SU). During this study, subjects will be instructed on how to recognize and treat hypoglycemia, and subjects will be routinely monitored with fingerstick glucose levels, and reports of potential events of hypoglycemia will be carefully collected and evaluated. Subjects will be provided with a glucose meter and will provide fasting SMBG assessments. Furthermore, in the presence of recent history of recurrent episodes of hypoglycemia investigators are instructed to consider down-titration of insulin prior to up-titration of blinded study drug, and clinical judgment should be applied in managing background AHAs in the presence of increased risk of hypoglycemia.

This study design includes the use of a placebo group, which is of key importance in helping to characterize both the safety and efficacy of canagliflozin. A study without a placebo arm cannot properly determine the glucose-lowering efficacy of an AHA, given the impact of co-interventions, and the natural history of the disease, on the course of glucose over time. Similarly, given background occurrence of adverse events in this population are relatively common, without a placebo, it is not possible to precisely define the safety and tolerability profile of a new AHA. Given the continuing need for new medications to improve the care of patients with T2DM, providing a thorough evaluation of a medication such as canagliflozin that may provide good efficacy and other useful benefits, is important. However, the importance of the placebo group must be balanced with the increased risk that subjects allocated to placebo will not achieve glycemic control consistent with current diabetes guidances during their participation in this study. As described above, all subjects will receive diet and exercise counseling, and will have regular fingerstick glucose monitoring, glycemic rescue therapy will be implemented with progressively lower glucose cutpoints for the first 6 months, and HbA_{1c} goal thereafter.

When referring to the signing of the ICF, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each subject, his or her parent(s) (preferably both parents, if available) or a legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be obtained from all subjects. For the purposes of this study, all references to subjects who have provided consent (and assent as applicable) refers to the subjects and his or her parent(s) or the subject's legal guardian(s) or legally acceptable representative(s) who have provided consent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parents still want them to participate.

For a subject who completes the study (including all procedures outlined in the pretreatment and double-blind treatment phases) the total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from this pediatric population

based upon the standard of the World Health Organization.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation.

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent/Pediatric Assent

Subject’s parent(s) or legally accepted representative(s) must give written consent, granting permission for his/her child to participate in the study according to local requirements after the nature of the study has been fully explained. Children (minors) or subjects who are unable to comprehend the information provided for this study can be enrolled only after obtaining consent of a parent(s) or legally accepted representative(s). Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on institutional policies. Written assent should be obtained from subjects who

are able to write. A separate assent form written in language that the subject can understand should be developed based on the age of the treated population.

Parental permission must be given by signing the consent document. Minors will be asked to provide assent and sign an informed assent document. During the assent process, an explanation of the study, its purposes and requirements will be given to the child, verbally, in language appropriate to the child's developmental and functional status.

The requirement of reconsenting pediatric subjects who become adults is determined by the applicable local regulations and the IRB/IEC requirements.

The ICF(s)/pediatric assent must be signed before performance of any study-related activity. The ICF(s) and assent form that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent/assent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects and their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects and parents/legally acceptable representatives will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject ID register for the purposes of long-term follow-up if needed and that their records may be accessed by Health Authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF/pediatric assent the subject and parent or legally acceptable representative are authorizing such access, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatment, or to obtain information about his or her survival status.

The subject and parent or legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's or his or her legally acceptable representative's personally dated signature. After having obtained the consent and assent, a copy both must be given to the subject and parent or legally acceptable representative.

If the subject and parent or legally acceptable representative are unable to read or write, an impartial witness should be present for the entire informed consent/pediatric assent process

(which includes reading and explaining all written information) and should personally date and sign the ICF/assent after the oral consent of the subject and parent or legally acceptable representative is obtained.

When prior consent of the subject is not possible and the subject's parent or legally acceptable representative is not available, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject and parent or legally acceptable representative must be informed about the study as soon as possible and give consent/assent to continue.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory biomarker and PK research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand canagliflozin, to understand T2DM in the pediatric population, and to understand differential drug responders. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.4, Withdrawal from the Use of Samples in Future Research).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information page(s) provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator.
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, informed assent/consent forms, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable.
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable.
- Documentation of investigator qualifications (eg, curriculum vitae).
- Completed investigator financial disclosure form from the principal investigator, where required.
- Signed and dated Clinical Trial Agreement, which includes the financial agreement.
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all sub-investigators.
- Documentation of sub-investigator qualifications (eg, curriculum vitae).
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable.
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject ID and enrollment log to permit easy ID of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject ID and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject ID and date of birth. In

cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: subject ID, eligibility, and study ID; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an eCRF and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the eCRF. Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in eCRFs prepared by the sponsor. Data must be entered into eCRFs in English. Study-site personnel must complete the eCRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

The investigator must verify that all data entries in the eCRFs are accurate and correct.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or study-site personnel must adjust the eCRF (if applicable) and complete the query.

If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- Study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto-query (generated by the eDC tool).
- Study-site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare data entered into the eCRFs with the hospital or clinic records (source documents); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed with the last visit/follow-up contact for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject visit at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor 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 IEC/IRB or local Health Authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the investigator.
- Discontinuation of further study drug development.

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the eCRFs. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding canagliflozin or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of canagliflozin, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain eCRF data from all study sites that participated in the study, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate

report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

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Attachment 1: Instructions on Ketone Monitoring and Sick Day Management

The guidelines for ketone measurement during illness or in the presence of other possible risk factors for DKA and the interventions presented here are aimed at early identification of elevated ketone levels and timely intervention in order to prevent or reduce the risk of progression to ketoacidosis and:

- limit risk of emergency room visits/hospitalization
- allow outpatient management, either by subject alone or with healthcare provider over the phone
- allow prompt study drug interruption

It is paramount that subjects receive detailed counseling on various aspects of sick day management and ketone monitoring with particular focus on the following aspects:

Importance of monitoring ketones any time the subject is ill or does not feel well, or has any potential precipitating factors for DKA

During illness or stress, or any time a possible cause for ketonemia (eg, skipping an insulin dose, increased alcohol consumption, strenuous physical exercise, etc), has occurred regardless of symptoms (subjects are requested to assess blood ketones (or urine ketones) to determine the absence or presence of ketones, degree of ketonemia (or ketonuria), and response to treatment (ie, interrupting study drug, increasing insulin, carbohydrate and fluid intake and monitoring blood glucose). As DKA can occur with blood glucose levels <250 mg/dL (<13.9 mmol/L), it is extremely important that the subject does NOT rely on blood glucose levels as a trigger to measure ketone levels.

Recognition of signs and symptoms of DKA

The study site personnel must ensure that the subject and parents/guardians are educated on recognizing signs and symptoms of DKA (ie, nausea, vomiting, abdominal pain, increased urination and thirst, fruity-smelling breath, rapid, deep respirations, headache, somnolence, etc). It is fundamental that in the presence of these signs/symptoms concomitant ketone levels are obtained to determine the proper actions and course of treatment, given that many of the signs/symptoms of DKA are nonspecific (eg, gastrointestinal symptoms) and may vary with degree of ketone elevation.

Generally,

- thirst, frequent urination, and sweet breath may occur with blood ketones <1.0 mmol/L (small/moderate urine ketones),
- dry mouth, nausea, stomach cramps, and/or vomiting may occur with blood ketones from 1.0 to 3.0 mmol/L (moderate/large urine ketones),
- labored deep breathing, extreme weakness, confusion, and eventually unconsciousness (coma) may occur with blood ketones >3.0 mmol/L (large urine ketones)

The study site personnel must also educate the subject on the importance of measuring capillary blood ketone (or urine ketones) ***regardless*** of the concomitant glucose levels, as these may be not as elevated (ie, >250 mg/dL [>13.9 mmol/L]) as usually observed during DKA.

Also, the subject must be instructed when to call the study site and what action to take while awaiting further instructions and when to seek immediate medical attention. In particular, in the presence of blood ketones ≥0.6 mmol/L (repeated and confirmed), subjects are required to:

- contact the study site to receive further instructions based on the clinical assessment of the investigator or delegate
- interrupt study drug

- increase insulin if subject is on insulin (without increasing risk of hypoglycemia)
- increase carbohydrate and fluid intake
- seek immediate medical attention if appropriate increases in insulin and fluid intake cannot be managed by the subject (due to hypoglycemia, vomiting etc) and/or the subject shows signs/symptoms of DKA such as nausea, vomiting, abdominal pain, dehydration, or rapid breathing

Management of insulin and food intake during illness and/or in presence of elevated ketone levels

Subjects who are on insulin must be instructed to NOT reduce or interrupt insulin treatment during sick days and/or in the presence of ketone elevations, even if they are vomiting and unable to eat. Subjects should be educated on the importance of increasing insulin and carbohydrates in the presence of elevated ketones, unless there is increased risk of hypoglycemia (eg, reduced glucose levels in subject who is vomiting). If the subject is unable to increase insulin in the presence of elevated ketones due to fear of hypoglycemia, the subject should seek immediate medical attention.

Subjects should be instructed to eat small meals and to eat more frequently when they are ill. Soft foods or liquids are often tolerated best. Fluid intake is essential during illness. If vomiting, diarrhea, or fever is present, the subject should be instructed to take small quantities of liquids every 15 to 30 minutes. Clear broth, tea, or other fluids can supplement liquids containing carbohydrate. Eating about 10 to 15 g carbohydrate every 1 to 2 hours is usually sufficient. Foods and beverages containing about 15 g carbohydrate that can be considered for subjects include:

½ cup (~ 125 mL) regular gelatin
½ cup (~ 125 mL) ice cream
½ cup (~ 125 mL) custard
1 regular double Popsicle
¾ cup (~ 200 mL) regular ginger ale
½ cup (~ 125 mL) regular soft drink
½ cup (~ 125 mL) orange or apple juice
1 cup (~ 250 mL) Gatorade
1 cup (~ 250 mL) creamed soup

Attachment 2: Suggested Algorithm for Ketone Monitoring and Findings of Elevated Ketones

Subjects will be instructed to measure capillary blood ketone levels:

- any time the subject is ill or does not feel well
- subject has undergone a minor procedure (eg, dental extraction)
- anytime a possible cause for ketonemia has occurred that would predispose the subject to DKA (eg, skipping insulin dose, strenuous physical exercise, reduced carbohydrate intake)

Ketone measurements during periods of increased risk of ketonemia/ketonuria must be obtained ***regardless*** of the concomitant blood glucose values; ketone measurements should preferably be done prior to dosing to allow prompt interruption of study drug, if required. Ketone should be measured until the etiology for measuring ketones has abated (eg, illness has subsided).

Instructions for Elevated Ketone Findings

- If **blood ketone ≥0.6 mmol/L** (with or without symptoms, regardless of concomitant glucose levels) confirmed by repeat assessment (suggested repeat measurement one hour later or sooner if in presence of symptoms), the subject should be instructed to:
  - contact the investigator or qualified assigned designee immediately (if possible)
  - if dose of study drug has not yet been taken, skip that dose and resume, with the permission of the investigator or qualified site personnel, once blood ketone levels are <0.6 mmol/L and precipitating cause (if identified) has resolved
  - if subject is on prandial insulin, increase insulin every 2 to 3 hours until the blood ketones have decreased to <0.6 mmol/L
  - continue monitoring blood glucose
  - increase carbohydrate and fluid intake to allow increased insulin dosing if on insulin treatment
  - continue monitoring blood ketones at least every 4 to 6 hours until ketone levels reach levels ≤0.2 mmol/L

The investigator or qualified assigned designee should review the potential precipitating factors with the subject, and correct if necessary

- Illness/infection
- Reduction or missed insulin dose
- Reduction in carbohydrate intake or fasting
- Alcohol consumption
- Strenuous exercise
- Significant stress
- In female subjects, phase of menstrual cycle

Subjects are to be instructed to *SEEK IMMEDIATE MEDICAL ATTENTION* in the presence of blood ketones ≥0.6 mmol/L, regardless of blood glucose levels, IF:

- **appropriate increases in insulin and/or fluid intake cannot be managed by subject (due to hypoglycemia, vomiting etc)**

- **the subject shows signs/symptoms of DKA such as nausea, vomiting, abdominal pain, dehydration, or rapid breathing**

It should be noted that these recommendations are provided as guidance to subjects and investigators. Investigators are expected to use their clinical judgment and knowledge of the subject's medical history and assessment of present condition.

Whenever possible, the management should be based on capillary blood ketone levels. Only in those rare instances in which capillary blood ketones cannot be obtained, a urine ketone levels may be used. A urine ketone level of moderate/large may be considered an approximation of blood ketone level of 0.6 mmol/L. It should be noted however, that in the presence of dehydration, urinary ketone measurements may be difficult to obtain and may not provide reliable readings.

For any confirmed ketone level ≥0.6 mmol/L that triggers the above actions, the subject will be requested to enter detailed information in the subject diary, including (but not limited to) ketone and glucose values, precipitating factors (eg, changes in insulin dose regimen, illness), and treatment received.

Attachment 3: Method of Blood Pressure Measurement

Subject Preparation

The subject should remove all clothing that covers the location of cuff placement. (The sleeve should not be rolled up so that it has a tourniquet effect.)

The subject should be comfortably seated with legs uncrossed, and back and arm supported, so that the upper arm is at the level of the right atrium (midpoint of the sternum).

The subject should be instructed to relax and not talk; approximately 5 minutes should pass before the first reading is taken.

Blood Pressure Measurement Device

Blood pressure readings should be taken manually with a mercury sphygmomanometer or an automated blood pressure monitor.

Cuff Size

Correct blood pressure measurement in children requires the use of a cuff that is appropriate for the size of the child's upper arm A technique that can be used to select a blood pressure cuff size of appropriate size is to select a cuff that has a bladder width that is at least 40% of the arm circumference midway between the olecranon and the acromion. This will usually be a cuff bladder that will cover 80% to 100% of the circumference of the arm.

Arm Circumference (cm)	Size
<22	Older Child (9 x 18 cm)
22-26	Small Adult (12 x 22 cm)
27-34	Adult (16 x 30 cm)

Cuff Placement

Palpate the brachial artery in the antecubital fossa.

Place the midline of the bladder of the cuff so that it is over the arterial pulse on the subject's bare upper arm. The lower end of the cuff should be 2 to 3 cm above the antecubital fossa to allow space for the stethoscope.

Pull the cuff snugly around the bare upper arm.

Neither the observer nor the subject should talk.

Inflation/Deflation

Inflate the cuff to at least 30 mmHg above the point at which the radial pulse disappears.

Deflate the mercury column at 2 to 3 mmHg per second.

The first and last audible sounds should be taken as systolic and diastolic pressure.

Number of Measurements

Three readings should be taken at intervals of at least 1 minute apart, and the results recorded.

Blood pressure should be measured at the screening visit in both arms. If there is an inter-arm difference of more than 10 mmHg in either the systolic or diastolic pressure, *it is recommended to use the arm with the higher pressure for all subsequent blood pressure measurement during the study.*

If possible, if the blood pressure is measured manually, it should be taken by the same individual, using the same equipment, at each visit so as to reduce inter-observer variability. (AHA 2005)

Attachment 4: Hypoglycemia: Definitions, Symptoms, and Treatment

Hypoglycemia is defined and classified as follows:

Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose (PG) concentration ≤70 mg/dL (≤3.9 mmol/L)

Asymptomatic hypoglycemia is defined as an event not accompanied by typical symptoms of hypoglycemia but with a measured PG concentration ≤70 mg/dL (≤3.9 mmol/L)

Probable symptomatic hypoglycemia is defined as an event during which symptoms of hypoglycemia are not accompanied by a PG determination.

Severe hypoglycemia is defined as an event requiring the assistance of another person to actively administer a carbohydrate, glucagon, or other resuscitative actions. A subject is considered to "require assistance" if he/she is unable to help himself/herself. An act of kindness to assist a subject when it is not necessary does not qualify as "requiring assistance". These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurologic recovery attributable to the restoration of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration.

The classification of hypoglycemic episodes will determine how the event is captured in the eCRF. Refer to Section 12.3, Hypoglycemia, for further details.

Symptoms

Subjects will receive counseling regarding the symptoms of and treatment for hypoglycemia. Signs and symptoms of hypoglycemia and other specific details will be captured in the subject diary, which will be returned to the study center for review by study-site personnel at each visit. The following list of symptoms is not meant to be exhaustive but represents the more common symptoms associated with hypoglycemia:

- Seizure
- Loss of consciousness
- Headache
- Tremor
- Hunger
- Sweating
- Nervousness
- Palpitations
- Light headedness
- Blurred vision
- Disorientation
- Dizziness
- Feeling faint

Treatment

The treatment of hypoglycemia requires the ingestion of glucose- or carbohydrate-containing foods. The acute glycemic response correlates better with the glucose content than with the carbohydrate content of the food. Therefore, glucose (15 to 20 g) is the preferred treatment for hypoglycemia. Although pure glucose may be the preferred treatment, any form of carbohydrate that contains glucose will raise blood glucose (BG) and may be used. Adding protein to a carbohydrate does not affect the glycemic response and does not prevent subsequent hypoglycemia. However, adding fat may retard and then prolong the acute hypoglycemic response. Treatment effects should be apparent within 15 minutes although the effects may only be temporary. Therefore, PG should be retested in approximately 15 minutes, as additional treatment may be necessary.

Attachment 5: Guideline for Collecting Height Measurements (CDC 2015)

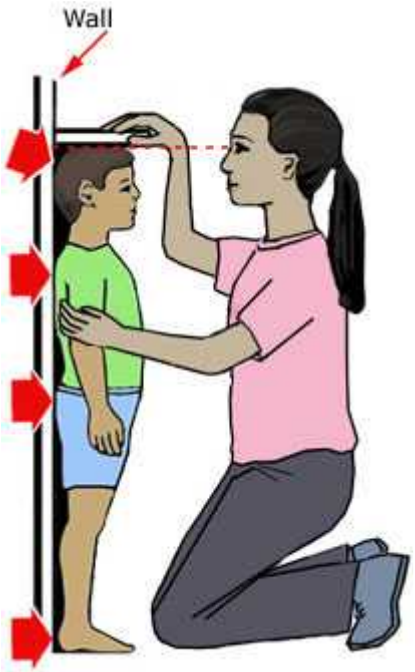
Height

Standing height will be measured without shoes using a stadiometer. The stadiometer must be calibrated when mounting it to the wall, and according to the manufacturer's instructions thereafter.

To measure height accurately:

1. Remove the subject's shoes, bulky clothing, and hair ornaments, and unbraid hair that interferes with the measurement.
2. Take the height measurement on flooring that is not carpeted and against a flat surface such as a wall with no molding.
3. Have the subject stand with feet flat, together, and against the wall. Make sure legs are straight, arms are at sides, and shoulders are level.
4. Make sure the subject is looking straight ahead and that the line of sight is parallel with the floor.
5. Take the measurement while the subject stands with head, shoulders, buttocks, and heels touching the flat surface (wall). (See Figure 2.) Depending on the overall body shape of the child or teen, all points may not touch the wall.
6. Use a flat headpiece to form a right angle with the wall and lower the headpiece until it firmly touches the crown of the head.
7. Make sure the measurer's eyes are at the same level as the headpiece.
8. Lightly mark where the bottom of the headpiece meets the wall.
9. Accurately record the height to the nearest 1/8th inch or 0.1 centimeter.

Figure 2



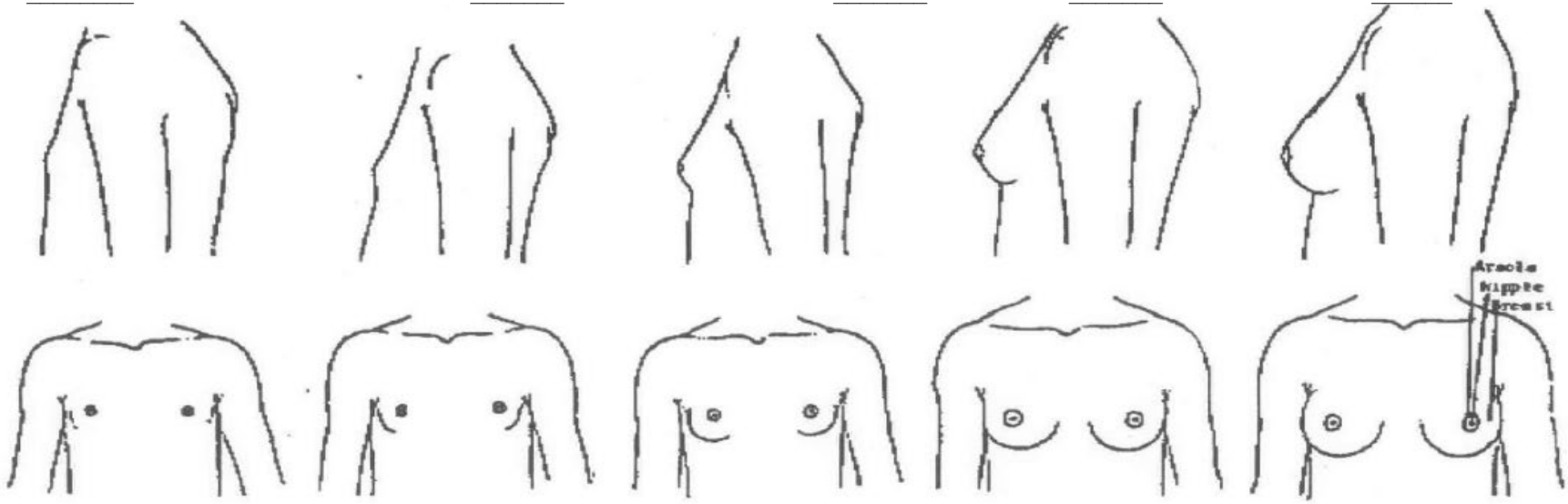
Attachment 6: Tanner Staging

Tanner Staging must be performed by the investigator or site staff and not by the subject and parent or legally acceptable representative.

Female – Breast development

The drawings on this page show different stages of development of the breasts. A female passes through each of the 5 stages shown by these sets of drawings. Please look at each set of drawings and read the sentences under the drawing. Then choose the set of drawings closest to the subject's stage of breast development and mark it as "1" on the line above that drawing. Then choose the drawing that is the next closest to the subject's stage of breast development and mark it as "2".

1. Drawing A
2. Drawing B
3. Drawing C
4. Drawing D
5. Drawing E



The nipple is raised a little in this stage. The rest of the breast is still flat.

This is the breast bud stage. In this stage, the nipple is raised more than in Stage 1. The breast is small and round. The areola is larger than in Stage 1.

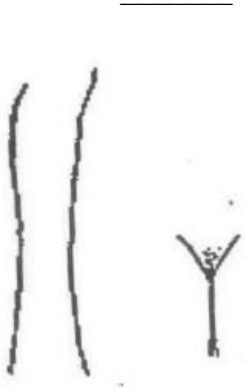
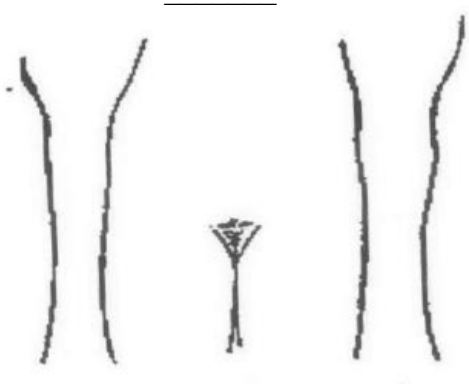
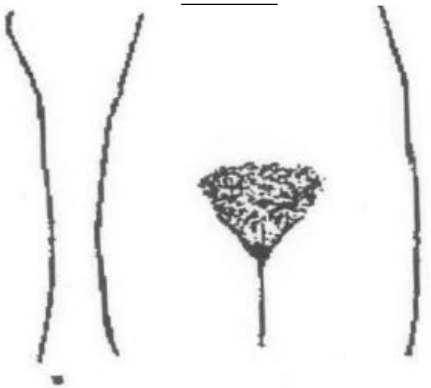
The areola and the breast are both larger than in Stage 2. The areola does not stick out away from the breast.

The areola and the nipple make up a mound that sticks up above the shape of the breast. (**Note**: This stage may not happen at all for some female. Some female develop from Stage 3 to Stage 4).

This is the mature adult stage. The breasts are fully developed. Only the nipple sticks out in this stage. The areola has moved back to the general shape of the breast.

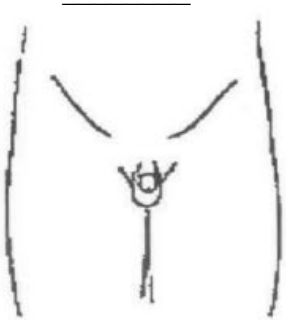
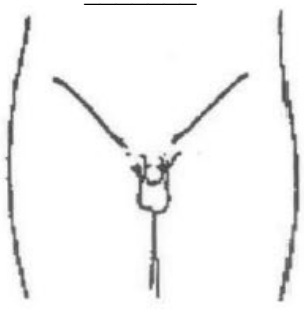
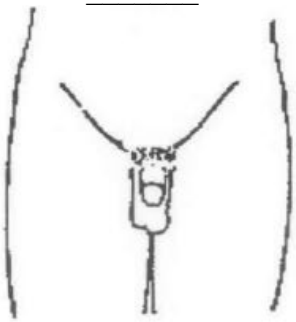
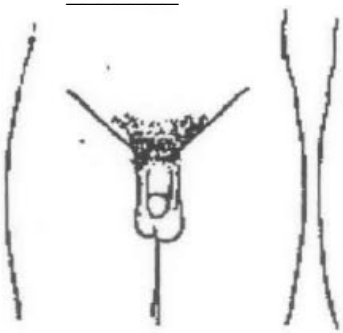
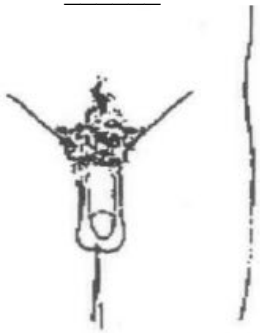
Female – Pubic hair

The drawings on this page show different amounts of female pubic hair. A female passes through each of the 5 stages shown by these drawings. Please look at each drawing and read the sentences under the drawing. Then choose the drawing closest to the subject's stage of hair development and mark it as "1" on the line above that drawing. Then choose the drawing that is next closest to the subject's stage of hair development and mark it as "2".

1. Drawing A	2. Drawing B	3. Drawing C	4. Drawing D	5. Drawing E
_____	_____	_____	_____	_____
				
There is no pubic hair.	There is a little long, lightly, colored hair. This hair might be straight or a little curly.	The hair is darker in this stage. It is coarser and more curled. It has spread out and thinly covers a larger area.	The hair is now as dark, curly, and coarse as that of an adult female. However, the area that the hair covers is not as large as that of an adult female. The hair has not spread out to the thighs.	The hair now is like that of an adult female. It also covers the same area as that of the adult female. The hair usually forms a triangle (Δ) pattern as it spreads out to the thighs.

Male – Pubic hair

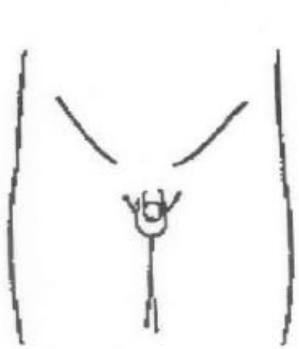
The drawings on this page show different amounts of male pubic hair. A male passes through each of the 5 stages shown by these drawings. Please look at each drawing and read the sentences under the drawing. Then choose the drawing closest to the subject's stage of hair development, mark it as "1" on the line above that drawing. Then choose the drawing that is next closest to the subject's stage of hair development and mark it as "2". In choosing the right picture, look only at the pubic hair and not at the size of the testes, scrotum, and penis.

1. Drawing A	2. Drawing B	3. Drawing C	4. Drawing D	5. Drawing E
_____	_____	_____	_____	_____
				
There is no pubic hair at all.	There is a little soft, long, lightly curled hair. Most of the hair is at the base of the penis. This hair may be straight or a little curly.	The hair is darker in this stage. It is coarser and more curled. It has spread out and thinly covers a somewhat larger area.	The hair is now as dark, curly, and coarse as that of an adult male. However, the area that the hair covers is not as large as that of an adult male. The hair has not spread out to the thighs.	The hair has spread out to the thighs. The hair is now like that of an adult male. It covers the same area as that of an adult male.

Male – Development of external genitalia

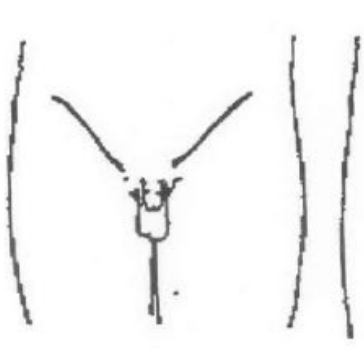
The drawings on this page show different stages of development of the testes, scrotum, and penis. A male passes through each of the 5 stages shown by these drawings. Please look at the drawings and read the sentences under the drawing. Then choose the drawing closest to the subject's stage of development and mark it as "1" on the line above that drawing. Then choose the drawing that is next closest to the subject's stage of development and mark it as "2". In choosing the right picture, look only at the stage of development, not at pubic hair.

1. Drawing A _____



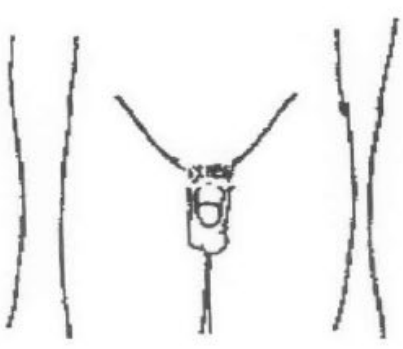
The testes, scrotum, and penis are about the same size and shape as they were when you were a child.

2. Drawing B _____



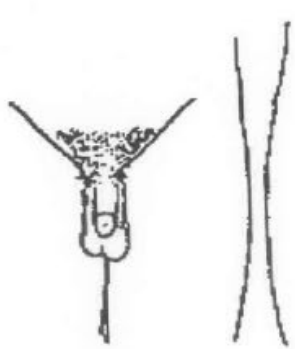
The testes and scrotum have gotten a little larger. The skin of the scrotum has changed. The scrotum, the sack holding the testes, has lowered a bit. The penis has gotten only a little larger.

3. Drawing C _____



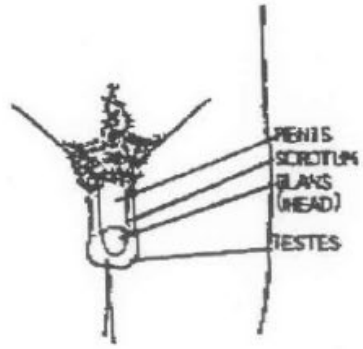
The penis has grown mainly in length. The testes and scrotum have grown and dropped lower than in Stage 2.

4. Drawing D _____



The penis has grown even larger. It is wider. The glans (the head of the penis) is bigger. The scrotum is darker than before. It is bigger because the testes have gotten bigger.

5. Drawing E _____



The penis, scrotum, and testes are the size and shape of that of an adult male.

Attachment 7: Clinical Laboratory Tests

Blood samples for serum chemistry and hematology, and a urine sample for urinalysis will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF and take appropriate action (eg, repeating abnormal laboratory result or further evaluation as considered clinically appropriate). The following tests will be performed by the central laboratory.

- Hematology Panel

  -hemoglobin
  -hematocrit
  -red blood cell (RBC) count
  -white blood cell (WBC) count with differential
  -platelet count

- Serum Chemistry Panel

  -sodium
  -potassium
  -chloride
  -bicarbonate
  -blood urea nitrogen (BUN)
  -creatinine
  -aspartate aminotransferase (AST)
  -alanine aminotransferase (ALT)
  -gamma-glutamyltransferase (GGT)
  -total bilirubin
  -alkaline phosphatase
  -creatine phosphokinase (CPK)
  -lactic acid dehydrogenase (LDH)
  -uric acid
  -calcium
  -phosphate
  -albumin
  -total protein
  -magnesium

- Fasting serum lipid profile (low-density lipoprotein-cholesterol [LDL-C], high-density lipoprotein-cholesterol [HDL-C], total cholesterol, non-HDL-C, LDL-C to HDL-C ratio, non-HDL-C to LDL-C ratio, and triglycerides).
- HbA_{1c}
- FPG
- C-peptide (random and fasting)
- Blood ketones
- Bone turnover markers (serum osteocalcin and serum collagen type 1 carboxy-telopeptide [CTx])
- Markers of calcium and phosphate homeostasis (calcium, magnesium, phosphate, PTH, 25-hydroxy Vitamin D, calcitonin; urinary excretion of calcium and phosphate)
- Urinalysis

  Dipstick done at central laboratory
  -specific gravity
  -pH
  -glucose
  -protein
  -blood
  -ketones
  -bilirubin
  -urobilinogen
  -nitrite

-leukocyte esterase

If dipstick result is abnormal, microscopic examination will be performed.

- First morning void urine for Urinary ACR
- Subject who have a Week -2 first morning void showing a presence with proteinuria (ie, proteinuria +1 and above) based on the central laboratory urine dipstick, will require a 24-hour urine collection prior to randomization and thereafter.
- Serum (β-human chorionic gonadotropin [β-hCG] pregnancy testing will be conducted for all female subjects of childbearing potential at screening visit. Additional urine (or serum) pregnancy tests may be performed, as determined necessary by the investigator, or required by local regulation, to establish the absence of pregnancy at any time during the study.
- Testing for pancreatic autoimmunity (GAD and islet cell antigen 2 [IA2] antibody) will be conducted in subjects with no available documentation at time of screening.
- Subjects must be fasting for at least 8 hours before collection of blood samples that require fasting (eg, glucose, lipid panel, etc).

Central laboratory will report the estimated glomerular filtration rate (eGFR) at study visits when serum creatinine is measured as specified below:

- Estimated Glomerular Filtration Rate (eGFR)
  - eGFR will be calculated using Schwartz formula:
    - eGFR (mL/min/1.73m^2) = (0. 55 × height in cm) / serum creatinine in mg/dL for girls from 10 to <18 years of age and boys from 10 to 12 years of age
    - eGFR (mL/min/1.73m^2) = (0.70 × height in cm) / serum creatinine in mg/dL for boys from 13 to <18 years of age

Attachment 8: Maturity-Onset Diabetes of the Young (MODY)

SOURCE: National Diabetes Information Clearinghouse (NDIC) https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes/9.

Maturity-Onset Diabetes of the Young (MODY) is a monogenic form of diabetes that usually first occurs during adolescence or early adulthood and it accounts for 1% to 5% of all cases of diabetes in the United States. Many different gene mutations have been shown to cause MODY, all of which limit the ability of the pancreas to produce insulin (see Table below). This process leads to the high BG levels characteristic of diabetes. Patients with MODY may have only mild or no symptoms of diabetes and their hyperglycemia may only be discovered during routine blood tests. Patients with MODY are generally not overweight and do not have other risk factors for type 2 diabetes, such as hypertension or hyperlipidemia. While both T2DM and MODY can run in families, patients with MODY typically have a family history of diabetes in multiple successive generations. MODY can be diagnosed by genetic testing.

Type	Affected gene	Affected protein	Incidence	Age at diagnosis	Inheritance pattern	Overweight/ Obesity	Transient/ Permanent	Treatment
MODY 1	*HNF4A*	hepatocyte nuclear factor 4α (alpha)	Rare	Adolescence or early adulthood	Autosomal dominant	No	Permanent	For most, oral sulfonylureas; some patients may need insulin
MODY 2	*GCK*	glucokinase	MODY 2 and MODY 3 account for about two-thirds of all cases of MODY MODY 2 is the second-most common form of MODY	Mild hyperglycemia may be present at birth; otherwise, early childhood	Autosomal dominant	Lower than normal birth-weight can occur	Permanent	Diet modification and physical activity; medications usually not required; some patients do not require any treatment during childhood
MODY 3	*TCF1*	hepatic nuclear factor 1α(alpha) or HNF1α (alpha) or *HNF1A*	MODY 3 is the most common form of MODY	Adolescence or early adulthood	Autosomal dominant	No	Permanent	Initially, treat with diet modification; can be treated with oral sulfonylureas; some patients may need insulin
MODY 4	*IPF1*; also known as *PDX1*	insulin promoter factor 1	Rare	Early adulthood; can present later	Autosomal dominant	No	Permanent	Oral sulfonylureas; some patients may need insulin
MODY 5	*TCF2*	hepatic nuclear factor 1β (beta) or *HNF1B*	Rare	Adolescence or early adulthood	Autosomal dominant	No	Permanent	Insulin; patients also may need treatment for related conditions such as kidney failure or cysts
MODY 6	*NeuroD1,* or *BETA2*	neurogenic differentiation factor 1	Rare	In the fourth decade of life	Autosomal dominant	No	Permanent	Insulin

Patients who are suspected to have MODY should first undergo genetic testing and only after exclusion of MODY can be considered for enrollment into the study.

INVESTIGATOR AGREEMENT

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I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: [electronic signature appended at the end of the protocol] Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	14-Aug-2020 17:21:22 (GMT)	Document Approval

Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

A Randomized, Multicenter, Double-Blind, Parallel-Group, Placebo-Controlled Study to Investigate the Efficacy and Safety of Canagliflozin in Children and Adolescents (≥10 to <18 years) with Type 2 Diabetes Mellitus

Protocol 28431754DIA3018; Phase 3
AMENDMENT 3

JNJ-28431754 (canagliflozin)

CCI [redacted]

United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

Status: Approved
Date: 26 May 2020
Prepared by: Janssen Research & Development, LLC
CCI [redacted]

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If at any time a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted after consultation takes place between the participant and investigator, and with the agreement of the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the electronic case report form (eCRF).

The sponsor will continue to monitor the conduct and progress of the clinical study and any changes (eg, delay or discontinuation in recruitment, site monitoring and audits) will be communicated to the sites and health authorities according to local guidance. If a participant has tested positive for COVID-19, the adverse event (AE) should be reported on the Adverse Event eCRF and the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL:

Study Visits and Assessments:

Pre-Randomization:

- For sites located in areas under travel restrictions due to the COVID-19 outbreak, screening visits for new subjects should be temporarily discontinued and Site Managers should be notified. If subjects are actively in Screening and/or Run-In period, the Site Manager should be contacted to determine the best course of action for each subject. As a reminder, the visit window for single-blind Run-In Period is +/- 4 days.
- Once in the Run-In period, if a subject is not able to return to the site for their next scheduled visit (ie, Randomization Visit) within the allowable visit window, the Site Manager must be contacted, and the subject should be registered as a Screen-failure. The subject should be re-screened when conditions permit after consultation with the Study Responsible Physician (see Protocol Section 4.4 for further guidance).

Post-Randomization:

- All subjects should return for scheduled in-clinic visits when possible. As a reminder, the double-blind treatment phase provides a +/-7 day window around each visit for scheduling.
- For subjects who are unable to return to complete a scheduled in-clinic visit, the scheduled in-clinic visit should be changed to a virtual contact (eg, via telephone, video-conferencing, or other channels) to collect information on the subject's current health status, medication compliance, and any new or ongoing AEs as well as changes in concomitant medications. The virtual method used for contacting the subject must be allowable per local regulations and documented in the subject's source record as well as entered in the Comments eCRF clearly designating the contact as "COVID-19-related". Additional virtual contacts may be conducted in between scheduled visits if deemed clinically appropriate by the Investigator and all virtual contacts must be recorded as outlined above.
- All subjects should continue to have protocol-specified central laboratory assessments when possible. If central laboratory tests cannot be performed or ambient samples cannot be collected by courier due to local restrictions and regulations relating to the COVID-19 outbreak, the use of an accredited local laboratory is permitted for all visits and all protocol-specified laboratory assessments, especially those outlined for Weeks 12, 26, and 52 and for essential laboratory measurements related to safety/efficacy (eg, HbA_{1c}, eGFR, etc) as outlined in the Protocol's Time and Events Schedule. Additional guidance on the recording of local laboratory assessments in the clinical database can be found in the eCRF Completion Guidelines. Site Managers must be informed of all local laboratory assessments performed.
- Every effort should be made to keep subjects on treatment as deemed clinically appropriate. For subjects who cannot attend scheduled in-clinic visits and run out of study drug as a result, a direct-to-subject shipment program may be available as local regulations allow (see **Study Drug Resupply** section below). If it is not possible to resupply subjects with study drug, the protocol allows for study drug to be temporarily interrupted. Any changes in study drug administration must be documented in the subject's source record and the Study Drug Administration eCRF using the "COVID-19-related" prefix. When conditions improve, travel restrictions are lifted, and the subjects are willing and able to come to the clinic, subjects

should be evaluated and encouraged to restart study drug unless there is a clear contraindication at the discretion of the Investigator and with concurrence from the Study Responsible Physician (see Protocol Section 10.2.3 for further guidance).

- All subjects and parents/legal guardians should be reminded of the instructions pertaining to sick day management, glucose/ketone monitoring, timely intervention of diabetic ketoacidosis (DKA), and when to seek medical attention for any urgent conditions that were provided to each subject and parent/legal guardian at the time of study enrollment.
- All protocol deviations (eg, missed, delayed or modified visits/laboratory assessments, adjustments to study procedures, missed doses of study drug, etc) occurring as a result of restrictions relating to the COVID-19 outbreak must be documented in detail within the subject's source records and on the Comments eCRF using the "COVID-19-related" prefix.

Study Drug and Clinical Supplies:

- Continue to check that all clinical supplies, such as study drug kits, laboratory kits, and ancillary supplies (eg, glucometers, glucose strips, ketone strips and control solution, etc) are available (and within expiry) in sufficient quantities to accommodate the next 2 study visit for each subject enrolled. Site Managers should be contacted with any questions or concerns relating to clinical supplies.

Study Drug Resupply

- For subjects who are not able to return to the site for their next scheduled visit, a caregiver or family member may be permitted to receive study drug on behalf of the subject if first discussed and agreed to by the subject or parents/legal guardians. Identification of the individual who is granted permission to receive the study drug on behalf of the subject must be confirmed and documented in the subject's source records and on the study drug accountability forms. The site staff must confirm that the study drug is provided to the appropriate individual while ensuring the proper chain of custody for the study drug and maintaining subject privacy.
- The site staff may deliver study drug directly to subject's home with approval from the IRB/EC overseeing the trial and in accordance with site approved procedures. The chain of custody for the study drug and transit conditions must be documented within the subject's source records.
- If no other alternative is feasible, the Site Manager should be contacted to confirm if local regulations allow for direct-to-subject study drug shipments. Permission from the subject or parents/legal guardians and the Sponsor is required prior to implementing a direct-to-subject study drug shipment and all permissions must be recorded in the subject's source record and on the Comments eCRF using the "COVID-19-related" prefix.

Data Entry and Site Monitoring:

- The regular assessment and reporting of adverse events and changes in concomitant medications should continue as outlined in the eCRF Completion Guidelines.
- If on-site monitoring is not possible as a result of the COVID-19 outbreak, site monitoring will be performed remotely. Site Managers will schedule on-site or remote monitoring visits as conditions dictate.

To ensure the safety of subjects and their families as well as site staff, the guidance offered in this Appendix is to be followed on a temporary basis at those sites impacted by the COVID-19 outbreak in order to enable continuity of treatment and the continuation of protocol-specified assessments outlined in the Protocol's Time and Events Schedule. Every effort should be made to complete all protocol-required assessments when possible.

INVESTIGATOR AGREEMENT

COVID-19 Appendix
JNJ-28431754 (canagliflozin) Clinical Protocol 28431754DIA3018

INVESTIGATOR AGREEMENT

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Institution and Address: _____

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(Day Month Year)

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Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Ins PPD

Sig _____ Date: PPD
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Status: Approved, Date: 26 May 2020