Janssen Research & Development

Statistical Analysis Plan

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 JNJ-28431754DIA3018; Phase 3

JNJ-28431754 (canagliflozin)

Amendment 3

Status:	Approved
Date:	22 September 2023
Prepared by:	Janssen Research & Development, LLC
CCI	[redacted]

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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ABBREVIATIONS

ACR	albumin/creatinine ratio
AE	adverse event
AHA	antihyperglycemic agent
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
BMI	body mass index
CI	confidence interval
CSR	clinical study report
CTx	carboxy-telopeptide
DBP	diastolic blood pressure
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOT/EW	end-of-treatment/early withdrawal
FAS	Full analysis set
FOIA	Freedom of Information Act
FPG	fasting plasma glucose
GCP	Good Clinical Practice
HbA_{1c}	Hemoglobin A_{1c}
HDL-C	high-density lipoprotein-cholesterol
IDMC	Independent Data Monitoring Committee
IWRS	interactive web response system
KM	Kaplan-Meier
LDL-C	low-density lipoprotein-cholesterol
LLN	Lower Limit of Normal
LOCF	last observation carried forward
LS mean	least-squares mean
MAR	missing at random
MCMC	Monte Carlo Markov chains
MI	multiple imputation
MH	medical history
MedDRA	medical dictionary for regulatory activities
MMRM	mixed model for repeated measures
PDLC	pre-defined limit of change
PD	pharmacodynamics
PK	pharmacokinetic(s)
PMM	pattern mixture model
PP	per protocol
PT	preferred term
PTH	parathyroid hormone
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SGLT2	sodium-glucose co-transporter 2
SOC	System Organ Class
SPERT	Safety, Planning, Evaluation, and Reporting Team
TEAE	Treatment-Emergent Adverse Event
T2DM	Type 2 Diabetes Mellitus
ULN	Upper Limit of Normal
UTI	urinary tract infection
WHODD	World Health Organization Drug Dictionary

AMENDMENT HISTORY

Amendment 1 (17 July 2018)

Applicable Section(s)	Description of Change
Rationale: The reason for this amendment is to include analyses of the primary efficacy endpoint in an independently powered subset of subjects on a background of diet and exercise only. Clarifying text is added and minor typographical errors are also addressed.	
Section 1.1. Major Secondary Objectives	Major secondary objectives have been updated to reflect the change above.
Section 1.3. Statistical Hypotheses for Trial Objectives, (Secondary Hypotheses)	Secondary hypotheses have been updated to reflect the change above.
Section 1.4. Sample Size Justification	The details of the assumptions for the sample size justification have been updated based on adult data from Stenlöf (2013).
Section 3. Interim Analysis and Data Monitoring Committee Review	Section streamlined with reference to the IDMC Charter for further details.
Section 5.1.1. Level of Significance	Text and figure describing the multiplicity adjustment have been updated to accommodate the hypothesis testing for the subset of subjects on a background of diet and exercise only.
Section 5.2.3. Analysis Methods	Text to address the additional analyses of the change in HbA_{1c} in AHA subsets has been added.
References	The following reference has been added: Stenlöf K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab. 2013;15(4):372-382.

Amendment 2 (11 May 2023)

Applicable Section(s)	Description of Change
The purpose of this amendment is to make this document consistent with Protocol Amendment 4 in terms of the analysis specifications and other pertinent details including the primary efficacy analysis based on the pattern mixture model. An additional analysis of primary efficacy endpoint using informative Bayesian Prior is added due to revised estimates of the treatment effect and the standard deviation specified in the Written Request Amendment 5. This analysis will be performed in the event that the study on its own does not yield significant results based on primary efficacy analysis. Two additional sensitivity analyses of the primary efficacy endpoint are also included. Clarifying text is added as applicable and minor typographical errors are also addressed.	
Section 1.4. Sample Size Justification	This section is updated to make it consistent with Protocol Amendment 4
Section 5.1.1. Level of Significance	Text and figure describing the multiplicity adjustment have been updated to reflect the deletion of the hypothesis testing for the subset of subjects on a background of diet and exercise only and make it consistent Protocol Amendment 4.
Section 5.2.2 Estimand	Section updated to be consistent with Protocol Amendment 4
Section 5.2.3. Analysis Methods	Details of the primary and secondary efficacy analyses of the primary efficacy endpoint using pattern mixture model have been added. Text added to mention that Bayesian analysis of primary efficacy endpoint will be performed in the event the primary efficacy analysis does not yield significant results. Analysis of the primary efficacy endpoint based on copy reference multiple imputation (MI) as well as tipping point analysis have been added as sensitivity analyses. Additionally, supportive analyses have been placed together for further clarity. Other minor editorial changes have been made to provide clarity.
Section 5.3 Secondary Efficacy Endpoints	Section updated to be consistent with Protocol Amendment 4
References	The following reference has been deleted as it is no longer applicable:

	Stenlöf K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab. 2013;15(4):372-382.

Amendment 3 (22 September 2023)

Applicable Section(s)	**Description of Change**
The purpose of this amendment is to correct minor inconsistencies at few places in the description of the supportive analyses and subgroup analyses. Additionally, clarifying text is added to the description of the sensitivity analysis based on mixed model for repeated measures (MMRM).	
Section 5.2.3. Analysis Methods	<u>Changes in the description of the sensitivity analysis based on MMRM.</u> In the description of the sensitivity analysis of the primary efficacy endpoint based on mixed model for repeated measures (MMRM), the following sentence is added to consider other covariance structures in case the model does not converge using the unstructured covariance: "*In case the model does not converge using the unstructured covariance then alternative covariance structures (such as compound symmetry and AR (1)) will be considered.*" Furthermore, since MMRM is not the primary efficacy analysis, the following sentence has been deleted: "*This sensitivity analysis will constitute the primary analysis based on a specific health authority request.*" <u>Changes in the description of re-randomization test</u> Since MMRM will be utilized to perform the re-randomization test, to be consistent, the phrase "primary efficacy comparison" have been replaced with "treatment comparison" as applicable at couple of places since primary efficacy comparison is based on Pattern Mixture Model (PMM) and not MMRM. <u>Changes in the description of subgroup analyses</u> In the paragraph describing the subgroup analyses, the phrase 'primary efficacy analysis' is replaced with 'primary efficacy endpoint' to be consistent since subgroups will be analyzed based on MMRM.

1. INTRODUCTION

This statistical analysis plan (SAP) contains the definitions of analysis sets, derived variables, and statistical methods for the analyses of efficacy and safety data from the canagliflozin study 28431754DIA3018.

1.1. Trial 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 ≤10.5%), 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 on HbA_{1c} in the subset of subjects on a background of metformin (with or without insulin).
- After 26 weeks of treatment, to assess the effect of canagliflozin relative to placebo on HbA_{1c} in the subset of subjects on a background of diet and exercise only.
- 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 blood pressure (SBP) and diastolic blood pressure (DBP).
  - 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 (ACR).

1.2. Trial Design

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.

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 randomized subjects that will be ≥10 to <15 years of age, 30% to 75% of participants will be female, and at least 20% in both age subsets (10 to <15 years, and ≥15 to <18 years) will be male, and 30% of participants that will have ethnicity and life-style comparable to Europe (these include Greece, Poland, Russia, Brazil and Mexico).

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 antihyperglycemic agent (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 estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^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.

1.3. Statistical Hypotheses for Trial Objectives

In children and adolescents (≥10 to <18 years) with T2DM who have inadequate glycemic control (ie, HbA_{1c} of ≥6.5% to ≤10.5%), 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).
- After 26 weeks of treatment, canagliflozin reduces HbA_{1c} relative to placebo in the subset of subjects on a background of diet and exercise only.

1.4. Sample Size Justification

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% change in HbA_{1c}) and an associated common standard deviation (SD) 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).

1.5. Randomization and Blinding

Stratification

Dynamic randomization (ie, covariate-adjusted randomization) will be used 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

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. On Day 1, 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 randomized subjects that will be ≥10 to <15 years of age, 30% to 75% of participants will be female, and at least 20% in both age subsets (10 to <15 years, and ≥15 to <18 years) will be male, and 30% of participants that will have ethnicity and life-style comparable to Europe.

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} results and the Week 12 eGFR value, the following will occur:

- Subjects with HbA_{1c} value <7.0% or eGFR <60 mL/min/1.73 m2 will not be undergoing re-randomization and instead will be continuing 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/1.73 m2 will be re-randomized in a 1:1 ratio (in a blinded fashion via 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.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

The double-blind treatment phase will begin with the day when the first dose of double-blind study medication (either canagliflozin or placebo) is taken, which will be denoted as study Day 1. All efficacy and safety measurements at each visit will be assigned a study day relative to this date. All data collected on or after study Day 1 up to and including the End-of-treatment/Early Withdrawal (EOT/EW) visit will be considered within the double-blind treatment phase (ie, baseline through endpoint).

While the Time and Events Schedule of the protocol indicates the visit timing and procedures for each visit, the timing of a subject's actual visit may not be exactly as per the protocol indicated target day / visit window (note that the protocol does not indicate required visit windows, but rather provides clear guidance for visit timing). Consequently, for the purpose of analysis, the conventions outlined below will be used to allocate the data collected at each actual visit to a planned protocol visit by defining visit windows.

The reference day is study Day 1.

Baseline will be defined as the pre-dosing measure closest to or including Day 1 (prior to dose administration). If the pre-dosing measure on Day 1 is missing, the latest available measurement prior to Day 1 will be used.

If a subject has two or more actual visits in one analysis visit window, the visit closest to the target day will be used as the study visit for that analysis visit window. However, results from all visits will be included in the safety analyses (eg, pre-defined limits of change analysis) to assure that all on-treatment results are included. If two study visits are the same number of days from the target day within the same visit window, the later visit will be considered the study visit for that target

day. Even though all visits will be allocated an analysis visit window, only planned protocol visits for each variable will be included in the by-visit analyses.

Table 1 summarizes the analysis visit windows for laboratory, vital signs, physical examination, and other key safety variables.

Table 1: Time Intervals for Analysis Visit Windows – Double-Blind Treatment Period

Scheduled Visit Time (label on output)	Time Interval (Day)[a]	Target Time Point (Day)
Baseline	≤1[b]	1
Week 6	1[c] to 64	43
Week 12	65 to 113	85
Week 20	114 to 162	141
Week 26	163 to 211	183
Week 34	212 to 267	239
Week 42	268 to 330	295
Week 52	≥ 331	365

[a] Relative to the day of the first dose of double-blind study medication.
[b] Up to the first dose of double-blind study medication.
[c] Immediately following the first dose of double-blind medication. For variables without time or reference collected at baseline, the first window after baseline starts on Day 2 according to the protocol.

2.2. Analysis Sets

Unless otherwise specified, all analyses will use the Full Analysis set (FAS), which is defined below. If additional subjects need to be excluded from the analysis sets, the subjects will be identified before database lock, and the reasons for the exclusion will be documented in the clinical study report.

2.2.1. Efficacy Analysis Set(s)

The FAS 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 26-week per protocol (PP) analysis set consists of all FAS subjects who complete the 26-week double-blind treatment period and have no major protocol deviations that may affect the interpretation of the primary efficacy endpoint (including but not limited to initiation of glycemic rescue therapy) within the 26 weeks of core double-blind treatment period.

The subjects who complete the 26-week core double-blind treatment period are defined as those subjects who receive study drug and have non-missing HbA_{1c} measurement at Week 26. In the case that the subjects discontinue from the treatment or have drug interruption at Week 26, the HbA_{1c} measurement needs to be taken no later than the last dose of study drug at Week 26 plus 7 days and the subjects' last dose date needs to be on or after Day 163 based on the visit windows in Table 1.

The 52-week PP analysis set consists of all FAS subjects who complete the 52-week double-blind treatment period (ie, documented in the eCRF by the investigator that the subject complete treatment in the study through the Week 52 visit) and have no major protocol deviations that may

affect the interpretation of the efficacy endpoint (including but not limited to initiation of glycemic rescue therapy) within the 52 weeks of treatment.

Major protocol deviations are defined in Section 4.5.

2.2.2. Safety Analysis Set

The safety analysis set consists of the subjects who are randomized and take at least 1 dose of study drug.

2.3. Definition of Subgroups

Subgroups are defined as follows:

- AHA subgroups: diet and exercise only; metformin monotherapy; insulin monotherapy; combination of metformin and insulin.
- Age: ≥10 to <15 years of age; ≥15 to <18 years.
- Sex: female; male.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

An Independent Data Monitoring Committee (IDMC) will be established to monitor safety data on an ongoing basis. A separate IDMC Charter will include an overview of the proposed summary tables/figures/listings to be provided to the IDMC by the Statistical Support Group. No interim analysis will be performed.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

Baseline anthropometric and demographic characteristics will be summarized by treatment group and overall (all treatments pooled together) for the FAS and PP analysis sets. Descriptive statistics (N, mean, SD, median, and range) will be provided by treatment group for continuous variables such as age, body weight, and BMI at baseline.

The number and percentage of subjects in the categories of the following variables at baseline will also be summarized by treatment group:

- Age group: 10 to <15, ≥15 to <18 years old
- Sex: male, female.
- Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Multiple, Not reported.
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not reported.
- AHA background: diet and exercise only, metformin monotherapy, insulin monotherapy, combination of metformin and insulin.

Descriptive statistics (N, mean, SD, median, and range) will also be provided by treatment group for baseline disease characteristics such as:

- HbA_{1c}
- FPG
- Body weight
- 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).
- SBP and DBP.
- 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.

The number and percentage of subjects with history of medical conditions by SOC and preferred term (based upon the general medical history [MH] eCRF) will be summarized by treatment group and overall.

4.2. Disposition Information

Subject disposition for all randomized subjects will be summarized by treatment group and overall using the following:

- Subjects who are randomized;
- Subjects who are randomized but not dosed (subjects excluded from the FAS);
- Subjects in the FAS;
- Subjects who complete the 26-week core double-blind treatment period (defined in Section 2.2.1);
- Subjects in the 26-week PP analysis set;
- Subjects who receive rescue therapy during the 26-week core double-blind treatment period;
- Subjects who complete the 52-week double-blind treatment phase (ie, investigator indicates on the eCRF [treatment disposition page] that the subject completed treatment);
- Subjects who receive rescue therapy during the 52-week double-blind treatment phase;
- Subjects in the 52-week PP analysis set;
- Subjects in the FAS who discontinue from treatment before the Week 52 visit (ie, investigator indicates on the eCRF [treatment disposition page] that the subject discontinued from the treatment prior to the Week 52 visit);
- Subjects in the safety analysis set.

For subjects who discontinue after randomization, the corresponding reasons for discontinuation from the treatment and discontinuation from the study will be summarized. Listings will be

provided for subjects whose predominant treatment differs from their randomized treatment and for subjects who temporarily take the wrong study medication.

For time to early discontinuation, Kaplan-Meier (KM) curves will be plotted by treatment group for the 52-week double-blind treatment phase. Descriptive analyses for the time to early termination will be provided.

4.3. Treatment Compliance

Treatment compliance will be based on the information from drug compliance eCRF page. The number and percent of subjects who have at least 75% study drug compliance from Baseline will be presented for Week 26 and Week 52 separately.

4.4. Extent of Exposure

Treatment duration is defined as the amount of elapsed time between the first and the last day that study medication was taken (inclusive). It will be calculated (in days) in terms of the difference in relative study days between the last and first dose of study medication, plus one day. If the end date of the medication intake is not known (e.g., subject is lost to follow-up), it will be imputed as the earlier of the disposition date (i.e., date of last contact with subject) or 28 days from the date that the last medication kit was dispensed.

Descriptive statistics (N, mean, SD, median, and range) will be presented by treatment group for treatment duration. The number of subjects with duration in each of the following categories (<2 weeks, 2 to <6 weeks, 6 to <12 weeks, 12 to <18 weeks, 18 to <26 weeks, 26 to <34 weeks, 34 to <42 weeks, 42 to <52 weeks, and ≥52 weeks) will also be presented by treatment group as well as overall.

For subjects who discontinue from treatment prematurely (i.e., before Week 52), exposure will be summarized through the last day of dosing of double-blind study medication for that subject.

4.5. Protocol Deviations

The following list of protocol deviations may affect the interpretation of the primary efficacy endpoint and therefore, subjects with any of these protocol deviations will be excluded from the PP analysis set. The complete list of subjects with these protocol deviations will be identified prior to database lock and a summary of reasons for exclusion will be provided in the CSR.

- Subject has taken a prohibited medication including other SGLT2 inhibitors, or other AHAs that are not approved for use in pediatric population (including commercially available canagliflozin) for > 7 consecutive days within the last 90 days prior to the study's primary endpoint at Week 26 (excluding from 26-week PP analysis set) or at Week 52 (excluding from 52-week PP analysis set).
- Subject has had a change in his/her dose of background therapy during the double-blind period for ≥2 consecutive weeks within the last 90 days prior to the study's primary endpoint at Week 26 (excluding from 26-week PP analysis set) or at Week 52 (excluding from 52-week PP analysis set).

- Subject has taken pharmacologic (non-replacement) dose of a corticosteroid agent (oral or parenteral) for ≥2 consecutive weeks during the last 90 days prior to the study's primary endpoint at Week 26 (excluding from 26-week PP analysis set) or at Week 52 (excluding from 52-week PP analysis set).
- Subject has received study drug other than the one to which he/she was randomized for ≥2 consecutive weeks during the last 90 days prior to the study's primary endpoint at Week 26 (excluding from 26-week PP analysis set) or at Week 52 (excluding from 52-week PP analysis set).
- Subject has taken less than 75% of their double-blind study medication of either canagliflozin or placebo during the core double-blind treatment period (excluding from 26-week PP analysis set) or during the 52-week double-blind treatment phase (excluding from 52-week PP analysis set).

4.6. Prior and Concomitant Medications

Prestudy (i.e., medications taken before initiation and stopped prior to initiation of double-blind study medication) and concomitant medications (i.e., medications taken after initiation of double-blind study medication that were either started prior or after initiation of double-blind study medication) including antihyperglycemic agents (AHAs) and all other medications are collected (prestudy AHAs taken in the 6 months prior to study enrollment and other medications taken 30 days prior to enrollment).

All prestudy and concomitant medications are coded using World Health Organization Drug Dictionary (WHODD) and Anatomical Therapeutic Chemical (ATC) codes (Attachment 1).

Prestudy and concomitant medications will be summarized by the number of subjects taking pre-specified categories of medications by treatment group and overall.

5. EFFICACY

The efficacy analysis of the primary and secondary efficacy endpoints will be performed based on the FAS (Section 2.2.1). Assessment of the primary efficacy endpoint (i.e., change from baseline in HbA_{1c}) on the 26-week PP analysis set will be conducted as supportive analyses.

Regardless of the actual treatments the subjects receive, efficacy data will be analyzed according to the randomization assignment.

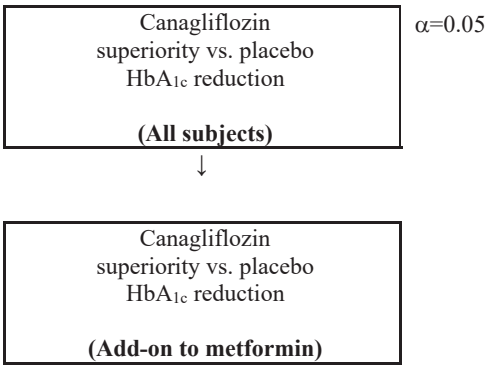
5.1. Analysis Specifications

5.1.1. Level of Significance

Unless otherwise specified, all statistical tests will be interpreted at a 2-sided significance level of 5% and all confidence intervals at a 2-sided confidence level of 95%.

To strongly control the family-wise error rate at the 5% significance level, a sequential testing procedure as illustrated in Figure 1 below will be applied. The primary endpoint will be first tested in all subjects (i.e., 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 1: Testing Sequence



As the secondary efficacy endpoints listed in Section 5.3 are supportive in nature, no corresponding hypothesis testing will be performed and therefore they are not included in the testing sequence above.

5.1.2. Data Handling Rules

For the endpoints at Week 12 and Week 26, data collected after Week 26 will be excluded from the statistical model. For the endpoints at Week 52, data collected up to Week 52 will be included in the statistical model.

For subjects who will be undergoing re-randomization, data collected during the Week 12 window will be considered in the statistical analysis only if the measurements are taken prior to the re-randomization date.

Unlike other assessments which were scheduled to be collected once at each visit, three consecutive readings of the SBP and DBP were taken (at intervals of at least 1 minute apart) and recorded. The average of the multiple measurements will be computed at each visit for all subjects and this averaged value will be used in all the analyses and summaries of blood pressure.

Unless otherwise stated, all efficacy analyses and summaries will be performed using the treatment groups assigned by Interactive Web Response System (IWRS).

5.2. Primary Efficacy Endpoint(s)

5.2.1. Definition

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

5.2.2. Estimand

The clinical scientific question of interest is:

What is the mean treatment difference at Week 26 on change from baseline in HbA_{1c} expected from treatment assignment to either canagliflozin or placebo in children and adolescents with T2DM who have inadequate glycemic control, regardless of treatment discontinuation or initiation of rescue medication?

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.
- Treatment: canagliflozin (100 mg or 300 mg) vs placebo.
- Intercurrent events (ICEs) (events that preclude observation of the variable or affect its interpretation): treatment discontinuation or initiation of rescue medication; ICEs are addressed with the treatment policy strategy, targeting the effect of treatment assignment, regardless of the occurrence of ICE.
- Population-level summary: difference in means versus placebo.

5.2.3. Analysis Methods

Primary Analysis

The primary analysis is based on the FAS dataset, including all HbA1c measurements collected from randomization to Week 26, including the measurements collected after treatment discontinuation or initiation of rescue medication.

The primary analysis will be based on pattern mixture model (PMM), as described below:

- Any intermediate missing data will be multiply imputed using Monte Carlo Markov Chains (MCMC), under a Missing at Random (MAR) assumption.
- Then the participants with ICEs and missing Week 26 HbA1c values will be multiply imputed using a multiple imputation (MI) model based on the participants with ICEs and non-missing Week 26 HbA1c values. An MI regression will be applied to impute all monotone missing values, using treatment group, stratification factors, baseline HbA_{1c} and the change from baseline in HbA_{1c} at Weeks 6, 12 and 20. If this MI model does not converge then a Copy Reference MI model will be used instead, as described in the sensitivity analysis section.
- Any Week 26 missing values for change from baseline in HbA_{1c} in participants without ICEs will be imputed based on the MI regression (see description above) applied to all participants.
- A total of 1000 multiple imputations will be performed. A seed equal to 345 will be used in all MI models.
- After MI, each of the multiply imputed datasets will be analyzed using analysis of covariance (ANCOVA) with terms for treatment, stratification factors, and baseline HbA_{1c}.
- Rubin's rules will be applied to combine the ANCOVA results across the imputed datasets, including the Week 26 LS Means for each treatment group and the difference vs placebo in LS Means.

Secondary analysis of the primary efficacy endpoint

The secondary analysis is based on a subset of subjects on background metformin (with or without insulin) from the FAS dataset, including all HbA1c measurements collected from randomization to Week 26, including the measurements collected after treatment discontinuation or initiation of

rescue medication. The attributes of estimand for this analysis is the same as the primary efficacy estimand except the population is a subset of subjects with background metformin (with or without insulin). The same analysis based on PMM will be performed as described above.

Bayesian analysis of the primary efficacy endpoint

Bayesian Analysis of the Primary Efficacy Endpoint for overall study and subset of subjects with metformin (with or without insulin) will be performed in the event that the study on its own yields non-significant result based on primary efficacy analysis. Full details of the Bayesian analysis will be included in a separate supplemental SAP.

Sensitivity and supportive Analyses

The following sensitivity analyses will also be performed, all aligned with the primary estimand:

- A Copy Reference MI model will be performed (Ratitch 2013). After any intermediate missing data will be imputed based on MCMC, monotone missing data will be imputed as following:
  - For the canagliflozin group, imputation will be performed using an imputation model based on the placebo/reference group, conditional on the stratification factors, baseline HbA_{1c} and the observed change from baseline values at previous time points relative to the mean of the model for the placebo group. Participants in the canagliflozin group will be imputed as if they had always been members of the placebo group.
  - For the placebo group, imputation will assume Missing at Random.
  - A total of 1000 multiple imputations will be performed. A seed equal to 345 will be used in all MI models.
  - After MI, each of the multiple imputed datasets will be analyzed using ANCOVA with terms for treatment, stratification factors, and baseline HbA_{1c}.
  - Rubin's rules will be applied to combine the ANCOVA results across the imputed datasets.
- A tipping point analysis will also be performed. This analysis starts with a MAR MI model (intermediate missing imputed with MCMC and monotone missing imputed with a MI regression model, using treatment group, stratification factors, baseline HbA_{1c} and the change from baseline in HbA_{1c} at Weeks 6, 12 and 20). Then each imputed value for monotone missing in the canagliflozin group will be made worse by a difference Delta. Each imputed dataset will be analyzed using ANCOVA and Rubin's rules will be applied to combine the ANCOVA results across the imputed datasets. A sequence of Delta worsening adjustments will be applied, starting with zero with increments of 0.1 until the results reach statistical non-significance. The results corresponding to all applied Delta adjustments will be plotted together with the results from the primary analysis, Copy Reference MI analysis and the other sensitivity analyses.
- 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. In case the model does not converge using the unstructured covariance then alternative covariance structures (such as compound symmetry and AR(1)) will be considered.

- 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.

In addition, based on the FAS with the data collected up to Week 26, the following supportive analysis will be performed:

- A re-randomization test (Proschan 2011) (utilizing the MMRM) will be used to determine the p-value for the treatment comparison of the primary efficacy endpoint (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 treatment comparison. This process will be repeated at least 1,000 times. The p-value for the treatment 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.
- A supportive analysis of the primary endpoint will be conducted based on the 26-week PP analysis set using the same mixed model with repeated measures as in the sensitivity analysis.

Subgroup Analyses

Additional analyses of the primary efficacy endpoint in the FAS will be performed to examine if the treatment effect is different for the subgroups defined in Section 2.3. The interaction of treatment with each of the subgroups will be analyzed based on the MMRM model for the primary efficacy endpoint with the addition of the interaction term. If an interaction is observed (significance<0.10), then further evaluations will be performed to assess and explain the nature of the interaction [quantitative or qualitative interaction]. The LS mean change from baseline and the 95% CI for the LS means differences between canagliflozin compared to placebo will be presented for the subgroups.

In the event of small subgroups, descriptive statistics may be provided in lieu of model-based estimates.

5.3. Secondary Efficacy Endpoints

5.3.1. Definition

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

- Change from baseline in FPG.
- The proportion of subjects with HbA_{1c} <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 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).
- Change from baseline in SBP and DBP.

The secondary efficacy endpoint at Week 12 and Week 52:

- Change from baseline in HbA_{1c}.

The analysis of the above endpoints will use the same attributes of the primary estimand except that the population level summary for the categorical endpoints will be difference in proportions.

5.3.2. Analysis Methods

The estimands for the secondary endpoints are the same as for the primary efficacy endpoint except for the variable.

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.

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. It is possible that the generalized linear mixed model may fail to converge for the binary secondary efficacy endpoint of the proportion of subjects with HbA_{1c} <7.0% (and HbA_{1c} <6.5% and HbA_{1c} <7.5%) due to few subjects meeting the threshold. In this case, a logistic regression model will be used. The model will include treatment and stratification factor as fixed effects, and baseline HbA_{1c} value as a covariate. This alternative approach will be applied on the LOCF data at Week 26/Week 52 and the observed data by visit. Odds ratios and the 2-sided 95% CIs for the treatment comparisons will be derived from the model.

The time to event data (e.g., time to receiving rescue therapy or discontinuing due to need for rescue therapy) will be plotted using the KM method. The difference in proportion of subjects receiving rescue therapy or discontinuing due to need for rescue therapy between canagliflozin and placebo with 95% confidence intervals will be provided.

5.4. Other Efficacy Variable(s)

5.4.1. Definition

Additional endpoints of interest include the following:

- Change from baseline in HbA_{1c} at Week 26 between canagliflozin 100 mg and placebo.
- Change from baseline in HbA_{1c} at Week 26 between canagliflozin 100 mg followed by a dose increase to 300 mg and placebo.
- Percent change from baseline in lipids at Week 26 and at Week 52 between canagliflozin and placebo.
- Change from baseline in SBP and DBP at Week 26 and at Week 52 between canagliflozin and placebo.

5.4.2. Analysis Methods

The comparisons by dose (canagliflozin 100 mg without up-titration after Week 12 and canagliflozin 100 mg up-titrate to 300 mg after Week 12) to placebo will be tested for reference purpose by 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 ≥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.

Given that lipids are only collected at baseline, Week 26 and Week 52, the percent change in lipid parameters (except for triglycerides) will be analyzed using an analysis of covariance at Week 26 and at Week 52 with LOCF applied when the Week 26 or Week 52 values are missing. The model will be similar to the supportive approach listed in Section 5.2.3. The percent change in triglycerides will be analyzed using nonparametric methods as outlined below given its skewed nature. A Wilcoxon rank sum test will be performed to compare canagliflozin to placebo. Additionally, the Hodges-Lehman estimator for the difference in the medians and the distribution-free confidence intervals based on the Wilcoxon rank sum test (Hollander 2013) will also be provided.

The change from baseline in SBP and DBP will be analyzed using an MMRM model similar to the one used to analyze the primary efficacy endpoint.

6. SAFETY

All safety analyses and summaries will be based on the safety analysis set (Section 2.2.2). Safety data will be analyzed according to the predominant treatment received, in the event that a subject

received a treatment other than that to which they were randomly assigned to receive. The predominant treatment is defined as the treatment to which the subject was exposed for the greatest duration during the double-blind treatment phase.

There will be no imputation of missing values for clinical laboratory test results, vital signs measurements in the safety analyses and there will be no hypothesis testing for results from safety analyses.

6.1. Adverse Events

Adverse events will be summarized for the 26-week core double-blind treatment period and for the 52-week double-blind treatment phase separately. AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock. Therefore, the preferred terms presented in Attachment 2 may be updated to reflect such updates. A treatment-emergent AE (TEAE) is defined as an adverse event with an onset after the initiation of double-blind study medication and before the last study medication date + 30 days. AEs with a start date prior to initiation of double-blind study medication which are subsequently reported to have either an increase in intensity or change in attribution in relationship to study medication (ie, no attribution to possible, probably, very likely) after the initiation of double-blind study medication will also be considered as TEAEs. Treatment-emergent AEs before the initiation of rescue therapy and TEAEs regardless of rescue therapy will be summarized separately for the 26-week core double-blind treatment period and for the 52-week double-blind treatment phase.

The overall incidence (ie, number and percent of subjects with one or more AE in each category) of AEs, AEs leading to discontinuation of study medication, drug-related AEs, drug-related AEs leading to discontinuation of study medication, serious AEs, serious AEs leading to discontinuation of study medication, serious drug-related AEs, serious drug-related AEs leading to discontinuation of study medication and deaths, will be summarized by treatment group.

AEs by SOC (ie, number and proportion of subjects with one or more AEs within a SOC) will be summarized by treatment group.

For each AE, the percentage of subjects who experienced at least one occurrence of the given event will be provided by preferred term, grouped by SOC, and presented by treatment group. In addition, the incidence of AEs (by preferred term, grouped by SOC, and presented by treatment group) will also be summarized by severity (by each designation, and pooling mild or moderate), by the relationship to study medication, by the action taken regarding the study medication, as well as by the outcome. The relationship to study medication will be presented by 2 categories: related (which includes possibly related, probably related and very likely related, as reported by the investigator) and not related (which includes not related and doubtfully related, as reported by the investigator), as well as by individual designation.

Listings will also be generated for deaths, SAEs, and AEs leading to discontinuation.

As a screening tool, the 95% CIs for percentage difference between canagliflozin and placebo will be provided for the AEs which are reported in at least four or more subjects in any treatment group.

Four (rule-of-4) was chosen based on the recommendation from the Safety, Planning, Evaluation, and Reporting Team (SPERT) (Crowe 2009) for studies with less than 400 subjects in each treatment group. No multiplicity adjustment will be applied. The exclusion of "0" in the 95% CI around the difference in incidence (canagliflozin compared to placebo) for a particular AE does not necessarily imply that the higher incidence is related to drug. The intent of providing the 95% CIs is as a filter to identify AEs that require additional assessment.

Adverse events that are identified by the above screening procedure will be subject to further evaluation. The additional assessment may include some or all of the following:

1. Investigator assessed relationship of AE to study drug, investigator assessed intensity of AE.

2. Time to AE relative to start of double-blind study medication, duration of AE, action taken on study drug/occurrence of AEs leading to discontinuation.

3. Other relevant safety information such as observations in other canagliflozin trials, observations in trials of other members of the SGLT2 inhibitor class, biological plausibility of the AE as related to SGLT2 inhibition or to canagliflozin.

All hypoglycemic events will be reported on an eCRF page specific for hypoglycemia. If the hypoglycemia event is considered to be an AE/SAE in the opinion of the investigator, the event was also to be recorded on the AE/SAE eCRF page. Hypoglycemia as AEs/SAEs will be presented in the tabulation of AEs described above. All additional analysis of hypoglycemia events (Section 6.1.2) will be based on results collected using the hypoglycemia eCRF. Reconciliation will be conducted to assure that all hypoglycemia events reported as AEs are also recorded on the hypoglycemia eCRF form; however, hypoglycemia events reported on the hypoglycemia eCRF do not have to be reported as an AE of hypoglycemia as this determination is left to the investigator's clinical judgement.

6.1.1. Selected Adverse Events for Additional Analysis

To support the additional assessment of particular categories of AEs, such as vulvovaginal candidiasis, balanitis or balanoposthitis, urinary tract infections (UTIs), volume depletion, hepatic injury, renal impairment/renal failure, hypersensitivity, venous thromboembolic event, photosensitivity, and malignancy, groupings of selected preferred terms will be created. A blinded review prior to database lock will be performed to assure that no reported term suggestive of the AE of interest is omitted. The list of preferred terms that are to be combined for assessment of each of the pre-specified AEs is provided in Attachment 2. Given the planned sample size of the study (ie, 146 subjects overall), listings may be provided instead of summary tables for any selected AEs below that are reported with low incidence (ie, <5%).

Fracture events identified by the investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to an independent fracture adjudication committee to confirm that events were fractures, to determine fracture location (anatomic region) and type (low trauma or not). Summary of the fracture events will be based on the adjudicated events of fracture.

Diabetic ketoacidosis (DKA) identified by investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to an independent DKA adjudication committee. Summary of the DKA events will be based on the adjudicated events of DKA.

Pancreatitis identified by investigator or the sponsor for meeting the criteria pre-specified in the charter will be sent to an independent pancreatitis adjudication committee. Summary of the pancreatitis events will be based on the adjudicated events of pancreatitis.

Lower extremity amputation will be recorded on a dedicated amputation case report form page. Summary of the lower extremity amputation will be based on the case report form page.

6.1.2. Hypoglycemia

Hypoglycemia episodes are collected by a specific, dedicated eCRF. Investigators are also asked to report episodes of hypoglycemia as an adverse event if they evaluate the episode as such. Analyses discussed below are based upon events reported through the hypoglycemia eCRF. Note that reconciliation will be performed to assure that all events reported as AEs are also recorded on the hypoglycemia eCRF.

A subject will be counted as having a documented hypoglycemia episode when there is either a biochemically confirmed hypoglycemic episode (ie, concurrent fingerstick glucose or plasma glucose ≤70 mg/dL [3.9 mmol/L]), and/or a severe hypoglycemic episode, as reported on the hypoglycemia eCRF, as follows:

- Biochemically documented hypoglycemia episode: a hypoglycemia episode with a concurrent reported glucose value of ≤70 mg/dL (3.9 mmol/L), regardless of whether the episode is associated with symptoms (symptomatic hypoglycemia) or not (asymptomatic hypoglycemia)
- Severe hypoglycemia episode: a hypoglycemia episode that has
  - the answer "Yes" for "Convulsions/Seizure" or "Loss of consciousness/Coma" to the question "Any signs/symptoms present?", or
  - check "Subject was not Capable of Treating Self and Required Assistance" to the question "If treatment given indicate assistance needed."

Only treatment-emergent hypoglycemia episodes, reported on the eCRF for hypoglycemia, will be summarized. Treatment-emergent is defined the same way as treatment-emergent AEs (defined in Section 6.1). Given the potential confounding of rescue medication to the treatment effect, treatment-emergent hypoglycemia episodes before the initiation of rescue therapy will also be summarized.

Because the background AHA may affect the risk of hypoglycemia, treatment-emergent hypoglycemia episodes will be summarized for both 26-week core double-blind treatment period and 52-week double-blind treatment phase by the following background AHA groups at randomization before the initiation of rescue therapy and regardless of rescue therapy.

- Diet and exercise only; or metformin monotherapy.
- On insulin (with or without metformin).

The percentage of subjects with documented hypoglycemia episodes (ie, biochemically documented and/or severe) and subjects with biochemically documented, and with severe hypoglycemia episodes separately, will be summarized by treatment group. For subjects with biochemically documented hypoglycemia episodes, the percentage of subjects will be summarized for each of the following glucose levels (≤70 mg/dL [3.9 mmol/L], <56 mg/dL [3.1 mmol/L], and <36 mg/dL [2.0 mmol/L], "Low" results will be included in all three categories) by treatment group. For subjects with severe hypoglycemia episodes, the percentage of subjects by each answer of the 2 questions for severe hypoglycemia on the eCRF will be summarized by treatment group. Event rate by person-year (total number of episodes/total exposure) will be calculated by treatment group separately for documented and for severe hypoglycemia.

Subjects who had 0, 1, 2, or ≥3 documented episodes and subjects who had 0, 1, 2, or ≥3 severe hypoglycemic episodes will be summarized by treatment group.

In addition, the incidence of all episodes of hypoglycemia reported on the eCRF for hypoglycemia will be summarized (this includes events without concurrent fingerstick glucose reported and events with fingerstick glucose >70 mg/dL [3.9 mmol/L]) by treatment group.

6.2. Clinical Laboratory Tests

Laboratory data will be summarized for each type of laboratory test listed in Attachment 3. Normal reference ranges for each test will be provided. Descriptive statistics (N, mean, SD, median, and range, as well as the 95% CI for the change from baseline) will be reported for each laboratory analyte at baseline and at each scheduled time point for absolute value and for change from baseline. The descriptive statistics will be presented based on measurements on study medication, including up to a maximum of 2 days after the last dose of study medication, as well as all measurements regardless of the time of the last dose of double-blind study drug. Summaries based on both standard units (SI) and conventional units will be provided.

The percentage of subjects with specific treatment-emergent laboratory values meeting pre-defined limit of change (PDLC) criteria will be summarized for these laboratory analytes. The 95% CI for the percentage difference between canagliflozin compared to placebo will be provided for each PDLC criterion which have at least 4 or more subjects in any treatment group; a corresponding listing will also be provided. The criteria for PDLC values are listed in Attachment 4.

6.3. Vital Signs and Physical Examination Findings

Descriptive statistics (N, mean, SD, median, and range) will be reported for SBP and DBP and pulse at each scheduled time point for absolute value and for change from baseline, including the 95% CI for the change from baseline. The descriptive statistics will be presented based on measurements on study medication, including up to a maximum of 2 days after the last dose of study medication, as well as all measurements regardless of the time of the last dose. The blood pressure measurements will be based on the average of the consecutive sitting blood pressure readings that were to be collected at each visit.

A treatment-emergent vital sign abnormality is defined as a change from baseline and subsequent post-baseline value that satisfies the criteria listed in the PDLC list (Attachment 4). For each vital sign parameter, the proportion of subjects with a treatment-emergent abnormality will be tabulated by treatment group.

7. PHARMACOKINETICS/PHARMACODYNAMICS

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. No population-based PK modeling is planned for this study.

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ATTACHMENTS

Attachment 1: Prestudy and Concomitant Medications Classified by ATC Code and/or Other Conditions

Antihyperglycemic Agents (AHA)

ATC Code starts with 'A10' (Drugs used in diabetes)

Insulin

ATC Code starts with 'A10A' (Insulins and analogues)

Biguanides

ATC Codes start with 'A10BA' (Biguanides); and/or 'A10BD' (combinations of oral blood glucose lowering drugs)

Antimicrobial Therapies

Antifungals: ATC Codes start with 'D01' (Antifungals for dermatological use), 'J02' (Antimycotics for systemic use), 'G01AF' (Imidazole derivatives), and 'G01AG' (Triazole derivatives).
Antibacterials: ATC Codes start with 'D06' (Antibiotics and chemotherapeutics for dermatological use), 'J01' (Antibacterials for systemic use), 'G01AA' (Antibiotics), 'G01AB' (Arsenic compounds), 'G01AC' (Quinoline derivatives), 'G01AD' (Organic acids), and 'G01AE (Sulfonamides)'

Lipid-Altering Medications

ATC Codes start with 'C10'

Lipid modifying agents, plain
ATC Codes start with 'C10A'

Lipid modifying agents, combinations
ATC Codes start with 'C10B'

Attachment 2: List of Preferred Terms for Selected AEs of Interest

Vulvovaginal Candidiasis

Genital candidiasis; Genital infection; Genital infection female; Genital infection fungal; Urogenital infection fungal; Vaginal infection; Vaginal Inflammation; Vulvitis; Vulvovaginal candidiasis; Vulvovaginal mycotic infection; Vulvovaginitis.

Balanitis or Balanoposthitis

Acquired phimosis; Balanitis; Balanitis candida; Balanoposthitis; Balanoposthitis infective; Erosive balanitis; Gangrenous balanitis; Genital candidiasis; Genital infection; Genital infection fungal; Genital infection male; Penile infection; Phimosis; Posthitis.

Urinary Tract Infections

Bacterial pyelonephritis; Bacterial ureteritis; Bacterial urethritis; Bladder candidiasis; Cystitis; Cystitis bacterial; Cystitis escherichia; Cystitis gonococcal; Cystitis haemorrhagic; Cystitis interstitial; Cystitis klebsiella; Cystitis pseudomonal; Emphysematous cystitis; Emphysematous pyelonephritis; Escherichia urinary tract infection; Fungal cystitis; Funguria; Genitourinary tract infection; Kidney infection; Perinephric abscess; Pyelocystitis; Pyelitis; Pyelonephritis; Pyelonephritis acute; Pyelonephritis chronic; Pyelonephritis fungal; Pyelonephritis mycoplasmal; Pyelonephritis viral; Pyonephrosis; Renal abscess; Renal cyst infection; Streptococcal urinary tract infection; Ureter abscess; Ureteritis; Uretheritis; Urethral abscess; Urethral carbuncle; Urethral stricture post infection; Urinary bladder abscess; Urinary tract abscess; Urinary tract infection; Urinary tract infection bacterial; Urinary tract infection enterococcal; Urinary tract infection fungal; Urinary tract infection pseudomonal; Urinary tract infection staphylococcal; Urosepsis; Urethritis; Urethritis noninfective.

Volume Depletion

Blood pressure decreased; Blood pressure orthostatic decreased; Dehydration; Diastolic hypotension; Dizziness postural; Hypotension; Hypovolaemia; Hypovolemic shock; Orthostatic hypotension; Orthostatic intolerance; Postural orthostatic tachycardia syndrome; Presyncope; Shock; Shock symptom; Syncope; Urine output decreased.

Renal Impairment/Renal Failure

Acute kidney injury; Acute phosphate nephropathy; Acute prerenal failure; Anuria; Azotaemia; Blood creatinine increased; Blood urea increased; Continuous haemodiafiltration; Dialysis; Glomerular filtration rate decreased; Haemodialysis; Haemofiltration; Hypercreatinaemia; Neonatal anuria; Nephritis; Nephropathy toxic; Oliguria; Peritoneal dialysis; Prerenal failure; Renal failure; Renal failure acute; Renal failure neonatal; Renal impairment; Renal impairment neonatal.

Hypersensitivity

Anaphylactic reaction; Anaphylactic shock; Anaphylactoid reaction; Anaphylactoid shock; Angioedema; Laryngeal oedema; Laryngotracheal oedema; Oropharyngeal swelling; Pharyngeal oedema; Rash; Rash erythematous; Rash generalized; Rash generalized; Rash macular; Rash maculopapular; Rash maculo-papular; Rash papular; Rash pruritic; Rash pustular; Rash vesicular; Small bowel angioedema; Swollen tongue; Tongue oedema; Urticaria.

Venous Thromboembolic Event

Deep vein thrombosis; Deep vein thrombosis postoperative; Embolism venous; Iliac vein occlusion; Inferior vena cava syndrome; Inferior vena caval occlusion; Jugular vein occlusion; Mesenteric vein thrombosis; Mesenteric venous occlusion; Obstructive shock; Portosplenomesenteric venous thrombosis; Post procedural pulmonary embolism; Postpartum venous thrombosis; Pulmonary embolism; Pulmonary infarction; Pulmonary microemboli; Pulmonary oil microembolism; Pulmonary thrombosis; Renal vein embolism; Renal vein occlusion; Subclavian vein thrombosis; Vascular occlusion; Venous thrombosis; Venous thrombosis in pregnancy; Venous thrombosis limb; Visceral venous thrombosis.

Photosensitivity

Actinic elastosis; Actinic prurigo; Administration site photosensitivity reaction; Application site photosensitivity reaction; Chronic actinic dermatitis; Hartnup disease; Implant site photosensitivity; Infusion site photosensitivity reaction; Injection site photosensitivity reaction; Juvenile spring eruption; Medical device site photosensitivity reaction; Photodermatosis; Photokeratitis; Photoonycholysis; Photosensitivity reaction; Polymorphic light eruption; Solar dermatitis; Solar urticaria; Sunburn; Vaccination site photosensitivity.

Hepatic Injury

Acute graft versus host disease in liver; Acute hepatic failure; Acute yellow liver atrophy; Allergic hepatitis; Ammonia increased; Ascites; Asterixis; Autoimmune hepatitis; Bacterascites; Biliary ascites; Biliary cirrhosis; Biliary cirrhosis primary; Biliary fibrosis; Bilirubin excretion disorder; Biopsy liver abnormal; Child-Pugh-Turcotte score increased; Cholaemia; Cholestasis; Cholestatic liver injury; Cholestatic pruritus; Chronic graft versus host disease in liver; Chronic hepatic failure; Chronic hepatitis; Coma hepatic; Cryptogenic cirrhosis; Diabetic hepatopathy; Drug-induced liver injury; Duodenal varices; Focal nodular hyperplasia; Gallbladder varices; Gastric varices; Gastric varices haemorrhage; Graft versus host disease in liver; Haemangioma of liver; Haemorrhagic ascites; Haemorrhagic hepatic cyst; Hepatectomy; Hepatic adenoma; Hepatic atrophy; Hepatic calcification; Hepatic cirrhosis; Hepatic cyst; Hepatic cyst ruptured; Hepatic encephalopathy; Hepatic encephalopathy prophylaxis; Hepatic failure; Hepatic fibrosis; Hepatic fibrosis marker abnormal; Hepatic haemangioma rupture; Hepatic hydrothorax; Hepatic infiltration eosinophilic; Hepatic lesion; Hepatic necrosis; Hepatic steatosis; Hepatitis; Hepatitis acute; Hepatitis cholestatic; Hepatitis chronic active; Hepatitis chronic persistent; Hepatitis fulminant; Hepatitis toxic; Hepatobiliary disease; Hepatocellular foamy cell syndrome; Hepatocellular injury; Hepatopulmonary syndrome; Hepatorenal failure; Hepatorenal syndrome; Hepatotoxicity; Hyperbilirubinaemia; Icterus index increased; Intestinal varices; Ischaemic hepatitis; Jaundice;

Jaundice cholestatic; Jaundice hepatocellular; Liver and small intestine transplant; Liver disorder; Liver injury; Lupoid hepatic cirrhosis; Lupus hepatitis; Mixed liver injury; Nodular regenerative hyperplasia; Non-alcoholic steatohepatitis; Non-cirrhotic portal hypertension; Ocular icterus; Oedema due to hepatic disease; Oesophageal varices haemorrhage; Parenteral nutrition associated liver disease; Peripancreatic varices; Periportal oedema; Portal hypertension; Portal hypertensive enteropathy; Portal hypertensive gastropathy; Portal triaditis; Portal vein cavernous; transformation; Portal vein dilatation; Portopulmonary hypertension; Radiation hepatitis; Renal and liver transplant; Retrograde portal vein flow; Reye's syndrome; Reynold's syndrome; Splenic varices; Splenic varices haemorrhage; Subacute hepatic failure; Varices oesophageal; Varicose veins of abdominal wall.

Malignancy Renal Cell Cancer

Clear cell renal cell carcinoma, Clear cell sarcoma of the kidney, Denys-Drash syndrome, Hereditary leiomyomatosis renal cell carcinoma, Hereditary papillary renal carcinoma, Metastatic renal cell carcinoma, Nephroblastoma, Non-renal cell carcinoma of kidney, Papillary renal cell carcinoma, Renal cancer, Renal cancer metastatic, Renal cancer recurrent, Renal cancer stage I, Renal cancer stage II, Renal cancer stage III, Renal cancer stage IV, Renal cell carcinoma, Renal cell carcinoma recurrent, Renal cell carcinoma stage I, Renal cell carcinoma stage II, Renal cell carcinoma stage III, Renal cell carcinoma stage IV, Rhabdoid tumour of the kidney.

Malignancy Bladder Cancer

Bladder adenocarcinoma recurrent, Bladder adenocarcinoma stage 0, Bladder adenocarcinoma stage I, Bladder adenocarcinoma stage II, Bladder adenocarcinoma stage III, Bladder adenocarcinoma stage IV, Bladder adenocarcinoma stage unspecified, Bladder cancer, Bladder cancer recurrent, Bladder cancer stage 0, with cancer in situ, Bladder cancer stage 0, without cancer in situ, Bladder cancer stage I, with cancer in situ, Bladder cancer stage I, without cancer in situ, Bladder cancer stage II, Bladder cancer stage III, Bladder cancer stage IV, Bladder squamous cell carcinoma recurrent, Bladder squamous cell carcinoma stage 0, Bladder squamous cell carcinoma stage I, Bladder squamous cell carcinoma stage II, Bladder squamous cell carcinoma stage III, Bladder squamous cell carcinoma stage IV, Bladder squamous cell carcinoma stage unspecified, Bladder transitional cell carcinoma, Bladder transitional cell carcinoma metastatic, Bladder transitional cell carcinoma recurrent, Bladder transitional cell carcinoma stage 0, Bladder transitional cell carcinoma stage I, Bladder transitional cell carcinoma stage II, Bladder transitional cell carcinoma stage III, Bladder transitional cell carcinoma stage IV, Metastases to bladder, Metastatic carcinoma of the bladder, Neuroendocrine carcinoma of the bladder, Transitional cell carcinoma.

Malignancy Phaeochromocytoma

Phaeochromocytoma, Phaeochromocytoma crisis, Phaeochromocytoma excision, Phaeochromocytoma malignant.

Malignancy Breast Cancer

Apocrine breast carcinoma, Breast angiosarcoma, Breast angiosarcoma metastatic, Breast cancer, Breast cancer female, Breast cancer in situ, Breast cancer male, Breast cancer metastatic, Breast

cancer recurrent, Breast cancer stage I, Breast cancer stage II, Breast cancer stage III, Breast cancer stage IV, Breast neoplasm, Breast sarcoma, Breast sarcoma metastatic, Breast sarcoma recurrent, Contralateral breast cancer, HER-2 positive breast cancer, Hormone refractory breast cancer, Inflammatory carcinoma of breast recurrent, Inflammatory carcinoma of breast stage III, Inflammatory carcinoma of breast stage IV, Inflammatory carcinoma of the breast, Intraductal papillary breast neoplasm, Intraductal proliferative breast lesion, Invasive breast carcinoma, Invasive ductal breast carcinoma, Invasive lobular breast carcinoma, Invasive papillary breast carcinoma, Lobular breast carcinoma in situ, Malignant nipple neoplasm, Malignant nipple neoplasm female, Malignant nipple neoplasm male, Medullary carcinoma of breast, Metaplastic breast carcinoma, Metastases to breast, Mucinous breast carcinoma, Neuroendocrine breast tumour, Nipple neoplasm, Oestrogen receptor positive breast cancer, Paget's disease of nipple, Phyllodes tumour, Triple negative breast cancer, Tubular breast carcinoma.

Malignancy Testicular

Benign neoplasm of testis, Leydig cell tumour of the testis, Sertoli cell testicular tumour, Spermatocytic seminoma, Testicle adenoma, Testicular cancer metastatic, Testicular neoplasm, Testicular papilloma, Testis cancer.

Attachment 3: Clinical Laboratory Tests

The clinical laboratory tests include following panels and assessments:

- Hematology panel
  - hemoglobin
  - platelet count
  - hematocrit
  - red blood cell (RBC) count
  - white blood cell (WBC) count with differential
- 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/1.73 m^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/1.73 m^2) = (0.70 × height in cm) / serum creatinine in mg/dL for boys from 13 to <18 years of age

Attachment 4: Criteria for Pre-defined Limit of Change (PDLC) and Abnormal Values

Laboratory Test	Parameter for ANY value and LAST value
Chemistry	
ALT	Absolute Value: >3X ULN
	Absolute Value: >5X ULN
	Absolute Value: >8X ULN
AST	Absolute Value: >3X ULN
	Absolute Value: >5X ULN
	Absolute Value: >8X ULN
ALT >3X ULN and Tbili >2X ULN	Composite: ALT >3X ULN and Tbili >2X ULN [with the Tbili elevation >2 X ULN within 30 days of the ALT elevation >3x ULN]
AST >3X ULN and Tbili >2X ULN	Composite: AST >3X ULN and Tbili >2X ULN [with the Tbili elevation >2 X ULN within 30 days of the AST elevation >3x ULN]
Bilirubin	Composite: >ULN and >25% increase from BL
	Absolute Value: >2X ULN
Bicarbonate	Absolute Value: <16 mEq/L
Calcium	Composite: >ULN and >10% increase from BL
Magnesium	Composite: >ULN and >25% increase from BL
Phosphorus	Composite: >ULN and >25% increase from BL
Potassium	Composite: <LLN and >15% decrease from BL
	Composite: >ULN and >15% increase from BL
	Absolute Value: ≥6.5 mEq/L
Sodium	Composite: <LLN and decrease >5 mEq/L or more from BL
	Composite: >ULN and increase>5 mEq/L or more from BL
Urate	Composite: <LLN and >25% decrease from BL
Hematology	
Hemoglobin	Change: ≥ 2 g/dL decrease from BL
	Change: ≥ 2 g/dL increase from BL
Vital signs	
Pulse	Absolute Value: ≤50 beats per minute
	Absolute Value: ≥100 beats per minute
Systolic Blood Pressure	Composite: ≥20 mm Hg decrease from BL and ≤90 mm Hg
	Composite: ≥20 mm Hg increase from BL and ≥160 mm Hg
Diastolic Blood Pressure	Composite: ≥15 mm Hg decrease from BL and ≤50 mm Hg
	Composite: ≥15 mm Hg increase from BL and ≥100 mm Hg

ULN = Upper Limit of Normal; LLN = Lower Limit of Normal; BL = Baseline