Janssen Research & Development

Clinical Study Report Synopsis
[28431754DIA3010 (104-Week Double-blind Phase)]

JNJ-28431754 (Canagliflozin)

Redaction and Removal of Information in This Document

- Information (including individual data listings, where applicable) has been removed or redacted to protect the privacy of patients, study subjects, and all named persons associated with the study. Names of companies other than Janssen Research & Development or Johnson & Johnson affiliates have been redacted, unless a contractual agreement is in place with those companies to disclose their names.
- Information has been removed or redacted to protect commercially confidential information.
- Aggregate data have been included, with any direct reference to an individual patient or study subject excluded.
- To disclose as much scientifically useful data as possible, no information other than that outlined above has been removed or redacted.

SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development LLC*
Name of Finished Product	Invokana
Name of Active Ingredient(s)	Canagliflozin (JNJ-28431754)

* Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Infectious Diseases BVBA; Janssen R&D Ireland; or Janssen Research & Development, LLC. The term "sponsor" is used to represent these various legal entities as identified on the Sponsor List.

Status: Approved

Date: 4 November 2013

Prepared by: Janssen Research & Development, LLC

Protocol No.: 28431754DIA3010 (104-Week Double-blind Phase)

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Compared With Placebo in the Treatment of Older Subjects With Type 2 Diabetes Mellitus Inadequately Controlled on Glucose Lowering Therapy

Study Name: Not applicable

EudraCT Number: 2010-018411-15

NCT No.: NCT01106651

Clinical Registry No.: CR017014

Principal Investigator: [redacted] MD, [redacted] United States

Study Centers: A total of 90 study centers in 17 countries participated, including 46 centers in North America (38 in the United States, 8 in Canada), 23 centers in Europe[a] (2 in France, 6 in the United Kingdom, 6 in Poland, 2 in Romania, 4 in Spain, 1 in Switzerland, 1 in Greece, 1 in Sweden), 5 centers in Central/South America (5 in Colombia), and 16 centers in the rest of the world (3 in Australia, 4 in New Zealand, 3 in India, 1 in South Africa, 1 in Hong Kong, 4 in Ukraine).

Publication (Reference): None

Study Period: 12 April 2010 to Week 104 database lock (DBL) on 28 June 2013

Phase of Development: 3

Objectives: Study objectives were to assess the efficacy, safety, and tolerability of canagliflozin compared with placebo in older subjects (ie, ≥55 to ≤80 years of age) with type 2 diabetes mellitus (T2DM) with inadequate glycemic control on their current diabetes treatment regimen. There were 3 separate and independent database locks for this study: (1) the first occurred after all subjects had either completed the Week 26 visit or discontinued prior to this visit (referred to as the Core Study Period), (2) a second preplanned database lock occurred after all subjects had completed the Week 52 visit or

[a] Includes the European Union, European Economic Area, European Free Trade Association countries

discontinued prior to this visit (for interim assessment of bone safety), and (3) a third database lock was to occur after all subjects had completed the Week 104 visit or discontinued prior to this visit (referred to as the Extension Phase of the study from Week 26 to Week 104). The study objectives and results obtained after 26 weeks of treatment are described in the 26-Week Core clinical study report (CSR) (referred to as the Week 26 CSR). An interim assessment of bone density was performed at Week 52 and the objectives and results are summarized in the Week 52 Bone Safety CSR. This final CSR (referred to as the Week 104 Final CSR) covers results from Day 1 through the Week 104 Visit. In addition to data included in the Week 26 Core CSR, this CSR (ie, Week 104 Final CSR) includes data collected during the 78-week double-blind extension period (ie, Week 26 to Week 104). In addition, this Week 104 final CSR summarizes the effects on bone safety following 104 weeks of double-blind treatment with canagliflozin. A separate Statistical Analysis Plan (SAP) describes the analysis sets, derived variables, and statistical methods for the analysis of efficacy and safety data for Week 52 (for analyses not already described in the previous Week 52 Bone Safety CSR) and for the full 104-week study period (ie, Day 1 through the Week 104 endpoint).

The objectives at Week 52 and Week 104 were to:

Primary Objective:

- to assess the safety and tolerability of canagliflozin.

Secondary Objectives:

After 52 weeks of treatment, assess the effect of canagliflozin relative to placebo on:

- glycemic control (ie, glycosylated hemoglobin [HbA_{1c}] and fasting plasma glucose [FPG])
- proportion of subjects achieving HbA_{1c} <7.0% and <6.5%
- body weight
- fasting plasma lipids (ie, low density lipoprotein cholesterol [LDL-C], high density lipoprotein cholesterol [HDL-C], non-HDL-C, total cholesterol, LDL-C to HDL-C ratio, and triglycerides)
- systolic blood pressure (SBP) and diastolic blood pressure (DBP)

After 104 weeks of treatment, assess the effect of canagliflozin relative to placebo on:

- bone mineral density (BMD) at the lumbar spine, hip, and distal forearm as measured by Dual energy X-ray absorptiometry (DXA)
- glycemic control (ie, HbA_{1c} and FPG)
- proportion of subjects achieving HbA_{1c} <7.0% and <6.5%
- body weight
- fasting plasma lipids (ie, LDL-C, HDL-C, non-HDL-C, total cholesterol, LDL-C to HDL-C ratio, and triglycerides)
- SBP and DBP

Additional Objective:

After 104 weeks of treatment, to assess the effect of canagliflozin relative to placebo on time to rescue therapy and proportion of subjects receiving rescue therapy.

Methodology: This study was a Phase 3 randomized, double-blind, placebo-controlled, parallel-group, 3-arm, global multicenter study conducted to evaluate the efficacy, safety and tolerability of the addition of canagliflozin (100 mg daily and 300 mg daily) relative to placebo in older subjects with T2DM who

were inadequately controlled on their current diabetes treatment regimen. Allowed antihyperglycemic (AHA) therapies for subjects entering the study were specified in the protocol.

Seven hundred sixteen adult subjects (≥55 to ≤80 years of age) with T2DM who had inadequate glycemic control (ie, HbA_{1c} of ≥7.0% to ≤10.0%) on their current diabetes treatment regimen, were randomly assigned in a 1:1:1 ratio to once daily administration of canagliflozin 100 mg, canagliflozin 300 mg, or placebo at entry into the 26-week core, placebo-controlled, double-blind treatment period. At entry into the 78-week double-blind extension period, subjects in the canagliflozin treatment groups (100 mg or 300 mg) and placebo group continued their respective treatment. No hypothesis testing was specified for the Week 52 or Week 104 endpoints.

Several safety and data monitoring committees were commissioned for the canagliflozin development program, as follows: (1) an independent Endpoint Adjudication Committee (EAC) reviewed blinded data for selected adverse events, including major adverse cardiovascular (CV) events and events of hospitalized unstable angina (collectively referred to as MACE-plus), hospitalized congestive heart failure, and venous thromboembolism/pulmonary embolism, and all deaths; (2) independent assessment committees reviewed blinded data for assessment of fracture, hepatic, and renal events, (3) an Independent Data Monitoring Committee (IDMC) reviewed unblinded serious adverse events and CV events, and (4) a company internal Medical Safety Review Committee (MSRC) monitored the safety of subjects participating in the study by reviewing blinded data on a regular basis.

Number of Subjects (planned and analyzed): Planned: Approximately 720 subjects were planned. Analyzed: A total of 716 subjects were randomized to placebo, canagliflozin 100 mg, and canagliflozin 300 mg in a 1:1:1 manner. Two randomized subjects were not dosed with double-blind study drug and were discontinued prior to administration of double-blind drug, therefore the modified intent-to-treat (mITT) analysis set included 714 subjects.

Diagnosis and Main Criteria for Inclusion: Subjects enrolled were required to meet all of the following key acceptance criteria at screening or at the indicated visit: (1) man or woman ≥55 and ≤80 years of age with T2DM (women must be at least 3 years postmenopausal), (2) have a HbA_{1c} ≥7.0% to ≤10.0% at (pre)screening (or at Week -2, if HbA_{1c} obtained more than 3 weeks prior to Week -2 visit), and either not on AHA therapy at screening (off for at least 12 weeks) or on a stable regimen of AHA with any approved agents (including metformin, sulphonylurea [SU], dipeptidylpeptidase-4 (DPP-4) inhibitor, alpha-glucosidase inhibitor (AGI), glucagon-like peptide-1 (GLP-1) analogue, or insulin for a minimum of 12 weeks prior to screening visit, or pioglitazone for at least 6 months before screening visit) used in accordance with local prescribing information, (3) have a body mass index (BMI) of ≥20 to ≤40 kg/m^2, inclusive, at screening.

Test Product, Dose and Mode of Administration, Batch No.: Canagliflozin capsules containing active 100 mg (Lot nos: PD3093, 09K06/G002, PD3387, PD3388, PD3389, 30845.6, 32783.1, 32783.4) or 300 mg (Lot nos: PD3304, PD3305, PD3393, PD3395, 30845.3, 30845.4, 30845.15, 32783.3, 32783.6) for oral administration.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo capsules to match canagliflozin capsules (batch/lot nos: PD3221, 09L16/G001, 09J28/G001, 30845.2, 10I08/G001, 32580.4) for oral administration.

Duration of Study: The total duration of the full study was to be approximately 110 weeks for each subject, depending on the length of the pretreatment phase (including the optional prescreening visit 1 week prior to the screening visit), the 2-week single-blind placebo run-in period (Week -2 visit to the baseline visit on Day 1), the 26-week placebo-controlled, double-blind core period, the 78-week placebo-controlled, double-blind extension period, and the 30-day post-treatment phase for follow-up contact (ie, after the last dose of study drug). This report summarizes the results of the entire 104-week double-blind treatment period (including the 26-week core double-blind treatment period and the 78-week

extension double-blind treatment period). Bone safety was assessed at Week 52 and these results are summarized in the Week 52 Bone Safety Report. A separate report summarized the results of the 26-week core double-blind treatment period.

Criteria for Evaluation: Efficacy laboratory assessments at Week 104 included HbA_{1c}, FPG, fasting plasma lipids (LDL-C, HDL-C, non-HDL-C, total cholesterol, the ratio of LDL-C to HDL-C, and triglycerides. Additional efficacy measurements at Week 104 included body weight, SBP and DBP, the proportion of subjects with HbA_{1c} <6.5% and <7.0%, the use of rescue medication, and the time to initiation of rescue medication.

Safety assessment at Week 104 was based on reported adverse events, safety laboratory tests (including chemistry, hematology, routine urinalysis), 12-lead electrocardiograms (ECGs), vital sign measurements (blood pressure and pulse rate), predefined limits of change (PDLC) for laboratory measures, vital signs and ECGs, body weight, physical examinations, self-monitored blood glucose (SMBG), and collection of hypoglycemia episodes (eg, from the diary provided to the subjects), regardless of whether considered to be adverse events by the reporting investigator.

Bone safety assessments at baseline, Week 26, Week 52, and Week 104 included measurements of bone turnover biomarkers (ie, prespecified measurement of serum collagen type-1 carboxytelopeptide [CTx] and propeptide amino terminal of type I procollagen [P1NP] at baseline, Week 12, and Week 26). Osteocalcin and estradiol (females only) (not prespecified in SAP) were measured on archived specimens at baseline and Week 52. Serum CTx and P1NP were measured at Week 52 using archived specimens. An assessment of bone turnover markers was not preplanned at Week 104. Bone mineral density was measured at the lumbar spine, hip (including femoral neck and total hip), and distal forearm using DXA technology (prespecified at Week 26, Week 52, and Week 104). A central vendor was employed for instrument calibration across the study and for central reading of the data. Refer to the Week 26 core CSR for a description of the results of the bone safety assessments performed during the 26-week core double-blind period. An interim assessment of bone safety was performed at 52-weeks and the results are summarized in the Week 52 Bone Safety Report. Bone mineral density was measured at Week 104 and these results are reported in this CSR.

A blood sample was collected on Day 1 from subjects who consented to participate in the pharmacogenomics component of the study to allow for pharmacogenomic research, as necessary. Refer to the Week 26 CSR for a description of the sample collection for pharmacogenomics testing for the 26-week core double-blind period.

Two fasting blood samples (plasma and serum) and urine samples were collected at specified time points and archived to allow for exploratory research and biomarker assessment related to canagliflozin, T2DM, or obesity.

Statistical Methods:

Sample Size Determination:

Sample size determination was based on the primary endpoint (ie change in HbA_{1c} from baseline) at Week 26 and the key secondary objective to assess the effect of canagliflozin on bone density (ie, percent change in lumbar spine BMD from baseline) at Week 26, as described in detail in the Week 26 CSR, Week 52, and Week 104. There were no hypotheses tested for evaluations at Week 104.

Efficacy: The primary efficacy endpoint was the change in HbA_{1c} from baseline at Week 26 and key secondary endpoints are described in the Week 26 CSR. The last observation carried forward (LOCF) method was applied when Week 104 values were missing. In subjects that received rescue medication, measurements made prior to rescue were used as the last observations.

An analysis of covariance (ANCOVA) model with treatments (canagliflozin 100 mg and canagliflozin 300 mg) and stratification factors as fixed effects and the corresponding baseline value as covariate, based

on the mITT analysis set and the Extension mITTanalysis set, was used to evaluate changes or percent changes from baseline at Week 104 in the following continuous efficacy variables: HbA_{1c}, FPG, body weight, SBP, DBP, fasting plasma lipids, including LDL-C, HDL-C, non-HDL-C, total cholesterol, ratio of LDL-C to HDL-C, and triglycerides, waist circumference and BMI. The least-squares means (LS means) for the change or percent change from baseline values at Week 104 and each time point through Week 104, and their 2-sided 95% confidence interval (CI) were estimated based on the ANCOVA model for the canagliflozin 300 mg and 100 mg groups. No treatment differences (and the associated CIs and p-values) were calculated for the Week 104 analysis.

The categorical secondary efficacy endpoints (proportion of subjects with HbA_{1c} <6.5% and <7.0% and subjects with at least 5% body weight reduction) were summarized by treatment group at Week 104. No treatment differences were calculated.

Safety: The incidence (ie, number and percent of subjects with 1 or more adverse event in each category) of adverse events, serious adverse events, deaths, adverse events leading to discontinuation, drug-related adverse events, serious drug-related adverse events, drug-related adverse events leading to discontinuation of study drug, and serious adverse events leading to discontinuation of study drug were summarized by treatment group for the entire 104-week double-blind phase and for the 78-week double-blind extension period (ie, Week 26 to Week 104). Specific adverse events that were predefined in the protocol as requiring the collection of additional information, to support additional analysis (eg, time to first event), included urinary tract infection adverse events and male and female superficial genital infections. The primary safety analyses for overall and specific adverse events excluded data after the initiation of rescue therapy. Secondary safety analyses for overall and specific adverse events were performed including all data, regardless of the initiation of rescue therapy. Predefined limits of change and descriptive statistics were provided for other safety parameters for the entire 104-week double-blind phase, including all data, regardless of the initiation of rescue medication. The rescue medication(s) used in the study were summarized by treatment group. The summaries of all adverse events, exposure, and concomitant medications including data after initiation of rescue therapy were provided. There was no imputation of missing values for clinical laboratory test results, vital sign measurements, and ECG evaluations in the analyses. Summaries of laboratory parameters, vital signs, and ECGs (including PDLCs) from baseline to Week 104 were provided.

Bone Safety Analyses: The percent changes in lumbar spine BMD from baseline to Week 26, Week 52, and Week 104 was the primary bone site for BMD assessment of canagliflozin relative to placebo. Percent changes in lumbar spine BMD were calculated using assessments from the central reader. An ANCOVA model with treatments, center, and other baseline characteristics (defined in the SAP) as fixed effects and baseline BMD as a covariate were used for the analysis. The treatment difference (ie, canagliflozin dose groups minus placebo, respectively) in the LS means and their 2-sided 95% CIs were estimated based on this model. The primary treatment comparisons were the canagliflozin 300 mg dose group against placebo and the canagliflozin 100 mg dose group against placebo at Week 26, Week 52, and at Week 104. Refer to the Week 26 CSR for a description of the bone safety analyses performed for the 26-week core double-blind period; refer to the 52-Week Bone Safety Report for a discussion of bone safety analyses at Week 52.

Other measurements that were used to assess bone safety included BMD at other bone sites (hip, femoral neck, and distal forearm), bone turnover markers (preplanned at Week 26 and from archived samples for Week 52), and quantitative computed tomography (QCT) of spine and hip (only at 52-weeks) analyzed in a similar ANCOVA model at each time point. The treatment differences between canagliflozin (100 mg once daily and 300 mg once daily) and placebo in the LS mean and their 2-sided 95% CIs were provided.

RESULTS:

STUDY POPULATION:

A total of 1,902 subjects were screened and a total of 716 subjects were randomized to study treatment (2 randomized subjects were discontinued prior to administration of double-blind drug, therefore the mITT analysis set included 714 subjects). Overall, 72.9% of subjects completed the 104-week treatment phase, with a moderately greater proportion of subjects in both canagliflozin groups (76.3% and 75.4% in the canagliflozin 100 mg and 300 mg groups, respectively) completing the study relative to the placebo group (66.9%). A smaller proportion of subjects in each of the canagliflozin groups (20.3% and 16.5% in the canagliflozin 100 and 300 mg groups, respectively) received rescue medication before the Week 104 visit compared with a moderate proportion (37.2%) of subjects in the placebo group. Of the 716 randomized subjects, 362 (50.6%) subjects completed the 104-week study and did not initiate rescue therapy (ie, Completers analysis set). No subject met the criteria for removal from the mITT analysis set in forming the safety analysis set (ie, having taken the incorrect double-blind study drug for a predominant part of the double-blind treatment period); hence, these analysis sets were identical.

Summary of Analysis Sets and Disposition (All Randomized Subjects)
(Study 28431754-DIA3010: All Randomized Subjects Analysis Set)

	Placebo (N=239) n (%)	Cana 100 mg (N=241) n (%)	Cana 300 mg (N=236) n (%)	Cana Total (N=477) n (%)	Total (N=716) n (%)
Subjects who were randomized	239 (100)	241 (100)	236 (100)	477 (100)	716 (100)
Subjects in the mITT analysis set	237 (99.2)	241 (100)	236 (100)	477 (100)	714 (99.7)
Subjects in the mITT analysis set who discontinued before the Week 104 visit	79 (33.1)	57 (23.7)	58 (24.6)	115 (24.1)	194 (27.1)
Subjects in the mITT analysis set who received rescue therapy before the Week 104 visit	89 (37.2)	49 (20.3)	39 (16.5)	88 (18.4)	177 (24.7)
Subjects in the Extension mITT analysis set[a]	170 (71.1)	220 (91.3)	205 (86.9)	425 (89.1)	595 (83.1)
Subjects in the Week 104 Completers analysis set[b]	78 (32.6)	142 (58.9)	142 (60.2)	284 (59.5)	362 (50.6)
Subjects in the PP analysis set	172 (72.0)	220 (91.3)	205 (86.9)	425 (89.1)	597 (83.4)
Subjects in the Safety analysis set	237 (99.2)	241 (100)	236 (100)	477 (100)	714 (99.7)
Subjects in the Extension Safety analysis set[c]	193 (80.8)	224 (92.9)	207 (87.7)	431 (90.4)	624 (87.2)

[a] Includes mITT subjects who entered extension and didn't receive rescue medication in core period I. This analysis set was used in the efficacy analysis.
[b] Includes mITT subjects who completed the Week 104 visit and had not initiated rescue medication.
[c] Includes mITT subjects who entered extension. This analysis set is used in the Week 52 - Week 104 safety analysis.
Key: CANA=canagliflozin; mITT=modified intent-to-treat; PP=per protocol
Note: Percentages calculated with the number of subjects in each group as denominator.

Overall, 27.2% of subjects discontinued during the 104-week double-blind treatment phase, with a larger proportion of subjects who discontinued in the placebo group (33.3%) than in the canagliflozin 100 mg (23.7%) and 300 mg (24.6%) groups. The most common reasons for discontinuation were in the category of 'other' (11.9% of subjects overall), which included a variety of reasons, including transportation issues, moving, family- or job-related, lack of efficacy, disallowed therapy, and also subjects who withdrew from the study due to the rat carcinogenicity study results, but agreed to continued follow-up. Other common reasons for discontinuation included adverse events (6.9% overall), which occurred slightly more frequently in subjects in the canagliflozin 300 mg group (9.7%) compared to 3.7% of subjects in the canagliflozin 100 mg group and 7.2% in the placebo group, withdrawal of consent (3.5% of subjects overall), which occurred slightly more frequently in the placebo group (5.9%) relative to the canagliflozin groups (2.9% and 1.7% of subjects in the canagliflozin 100 mg and 300 mg groups, respectively), and lost to follow-up (2.2% of subjects overall). Withdrawal of consent was generally due to the requirement to re-sign a revised informed consent form (implemented during the ongoing study conduct) that included updated information on preclinical safety findings (specifically, updated information on rat carcinogenicity study results).

Reasons for Discontinuation During the Entire Double-blind Period (mITT)
(Study 28431754-DIA3010: Modified Intent-To-Treat Analysis Set)

Subject Disposition Category	Placebo (N=237) n (%)	Cana 100 mg (N=241) n (%)	Cana 300 mg (N=236) n (%)	Cana Total (N=477) n (%)	Total (N=714) n (%)
Total number of subjects discontinued	79 (33.3)	57 (23.7)	58 (24.6)	115 (24.1)	194 (27.2)
Primary reason for discontinuation[a]					
Adverse event	17 (7.2)	9 (3.7)	23 (9.7)	32 (6.7)	49 (6.9)
Death[b]	0	3 (1.2)	0	3 (0.6)	3 (0.4)
Lost to follow-up	8 (3.4)	2 (0.8)	6 (2.5)	8 (1.7)	16 (2.2)
Noncompliance with study drug	1 (0.4)	0	2 (0.8)	2 (0.4)	3 (0.4)
Physician decision	4 (1.7)	3 (1.2)	1 (0.4)	4 (0.8)	8 (1.1)
Protocol violation	1 (0.4)	2 (0.8)	1 (0.4)	3 (0.6)	4 (0.6)
Withdrawal of consent	14 (5.9)	7 (2.9)	4 (1.7)	11 (2.3)	25 (3.5)
Product quality complaint	0	1 (0.4)	0	1 (0.2)	1 (0.1)
Other	34 (14.3)	30 (12.4)	21 (8.9)	51 (10.7)	85 (11.9)

[a] As indicated by the investigator on the eCRF for mITT subjects who discontinued before the Week 104 visit.
[b] Three subjects discontinued the study during the 104-week double-blind period due to death. Six deaths were reported during the double-blind study: all occurred during the extension phase of the study. Two of the 6 deaths were treatment-emergent and 4 deaths were non-treatment-emergent based on the pre-specified algorithm described in the SAP which defines treatment-emergent.

Key: Cana=canagliflozin; eCRF=electronic case report form; mITT=modified intent-to-treat; N=total number of subjects, n=total number of subjects in subgroup; SAP=statistical analysis plan.
Note: Percentages calculated with the number of subjects in each group as denominator.

The overall mean duration of subject exposure (prior to rescue medication) for subjects in the mITT analysis set over the entire 104-week double-blind treatment period was modestly greater in the canagliflozin groups compared with placebo, with 59.1% of subjects in the canagliflozin groups having ≥102 weeks of exposure, compared with 32.1% of subjects in the placebo group. The mean exposure to study medication (prior to rescue) was greater in the canagliflozin groups (81.3 weeks) compared to placebo (58 weeks).

Baseline Characteristics: Baseline demographic characteristics for the mITT analysis set were generally similar across treatment groups, except for a slightly higher percentage of males in the placebo group, (60.3%) relative to the pooled canagliflozin population (53%). The median age of subjects in the study was 63 years (range: 55 to 80 years). Consistent with the regions of the world in which subjects were recruited, 77% of the subjects were white, 9% were Asians, 8% were black or African-American; 15% of subjects were of Hispanic or Latino ethnicity.

Mean baseline body weight was 89.5 kg and mean baseline BMI was 31.6 kg/m^2; these were generally similar across treatment groups, with 62.2% of the subjects being obese (BMI ≥30 kg/m^2). Subjects had mild to moderate hyperglycemia at baseline reflected by a baseline mean and median HbA_{1c} of 7.7%. Subjects had long-standing diabetes, with a median duration of disease of nearly 10 years (range 0.3 to 50.2 years), reflective of a population (75.7% of subjects) already on a background of 2 or more AHA therapies. With this relatively long duration of disease, a moderate proportion (approximately 30% [213/714 subjects]) had at least 1 microvascular complication of diabetes, with neuropathy present in approximately 22% of subjects at baseline. The mean estimated glomerular filtration rate (eGFR) at baseline in the overall population was 77.5 mL/min/1.73 m^2.

There were 695 (97%) subjects on AHA therapy, including 529 (approximately 74%) subjects on an AHA therapy associated with hypoglycemia (ie, insulin and sulphonylureas) and 166 (approximately 24%) subjects on an AHA therapy not associated with hypoglycemia.

EFFICACY RESULTS:

Primary Endpoint: At Week 104, the LS mean changes from baseline in HbA_{1c} in the mITT analysis set were -0.43% and -0.32% for the canagliflozin 300 mg and 100 mg groups, respectively, and 0.17% for the placebo group. The placebo-subtracted differences were -0.60% and -0.49% for the canagliflozin 300 mg and 100 mg groups, respectively. For both canagliflozin groups, the nadir in HbA_{1c} was reached at Week 12, with a subsequent stable reduction through Week 34, then small progressive increases through Week 104; for the placebo group, the nadir was reached at Week 6 with a subsequent continual rise in HbA_{1c}. The changes from baseline in HbA_{1c} at Week 26 were -0.73%, -0.60%, and -0.03% for canagliflozin 300 mg, canagliflozin 100 mg, and placebo, respectively (presented in the Week 26 core CSR). Results in the Completers analysis set were consistent with the results for the mITT analysis. Additional sensitivity analyses (ie, mixed model repeated measures) were also consistent with the results for the mITT analysis.

Secondary Endpoints: In the mITT analysis set, the proportions of subjects who achieved a HbA_{1c} value <7.0% at Week 104 were 41.9% and 35.8% in the canagliflozin 300 mg and 100 mg groups, respectively, and 20.3% in the placebo group. The placebo-subtracted mean changes from baseline in FPG at Week 104 were -1.30 mmol/L and -1.18 mmol/L in the canagliflozin 300 mg and 100 mg groups, respectively and the 95% CIs of difference from placebo excluded "0" for both canagliflozin dose groups. The nadir in FPG reduction was reached at Week 26 for both canagliflozin groups with small increases thereafter; for the placebo group, a noticeable increase was observed through Week 18, with a subsequent stable change in FPG through Week 104. The placebo-subtracted mean percent changes from baseline in body weight at Week 104 in the mITT analysis were -3.2% and -2.3% for canagliflozin 300 mg and 100 mg groups, respectively, with the 95% CIs of difference from placebo excluding "0" for both canagliflozin dose groups. For both canagliflozin groups, body weight reductions were observed through Week 104; for the placebo group, a small gradual reduction in body weight was observed through Week 104. Decreases in SBP were observed with both doses of canagliflozin in the mITT analysis: the mean placebo-subtracted changes from baseline at Week 104 were -7.49 mmHg and -5.75 mmHg for the canagliflozin 300 mg and 100 mg groups, respectively, with the 95% CIs of difference from placebo excluding "0" for both canagliflozin dose groups. For the canagliflozin groups, the nadirs in change from baseline in SBP reduction were observed at Week 34, with small increases through Week 52 and subsequent stable change through Week 104; for the placebo group, a steady increase in SBP was observed through Week 104. Decreases in DBP were observed with both doses of canagliflozin in the mITT analysis: the mean placebo-subtracted changes from baseline at Week 104 were -2.61 mmHg and -1.54 mmHg for the canagliflozin 300 mg and 100 mg groups, respectively, with the 95% CIs of difference from placebo excluding "0" for both canagliflozin dose groups. Increases in HDL-C were observed with both canagliflozin groups in the mITT analysis: the placebo-subtracted mean percent changes from baseline to Week 104 were 4.8% and 3.6% for the canagliflozin 300 mg and 100 mg groups, respectively. The 95% CIs for the between-group difference from placebo excluded "0" for both canagliflozin dose groups. In the mITT analysis, the placebo-subtracted mean percent changes from baseline in triglycerides at Week 104 were 3.9% and -4.4% for the canagliflozin 300 mg and 100 mg groups, respectively. In the mITT analysis, the placebo-subtracted mean percent changes from baseline in LDL-C at Week 104 were 2.5% and 2.8% in the canagliflozin 300 mg and 100 mg groups, respectively. The 95% CIs of difference from placebo included "0" for both canagliflozin dose groups. Median increases in LDL-C from baseline were 5.6% and 1.1% in the canagliflozin 300 mg and 100 mg groups, respectively, with a median increase of 0.4% in the placebo group. For both canagliflozin groups, the maximal increases in LDL-C were observed by Week 26, with smaller increases from baseline after Week 26 through Week 104.

Change from Baseline to Week 104 LOCF for Efficacy Endpoints (mITT)
(Study 28431754-DIA3010: Modified Intent-to-Treat Analysis Set)

Endpoints	----------Cana 100 mg --------- ------- (Placebo-Subtracted)----- Mean (95% CI)	--------------Cana 300 mg ---------- ------- (Placebo-Subtracted) ------ Mean (95% CI)
HbA_{1c} Change (%)	-0.49 (-0.648; -0.324)	-0.60 (-0.765; -0.437)
Achieving 7.0% HbA_{1c} target	15.6 (7.2; 24.0)	21.7 (13.0; 30.3)
FPG Change (mmol/L)	-1.18 (-1.578; -0.785)	-1.30 (-1.696; -0.894)
Body Weight % Change (%)	-2.3 (-3.1; -1.6)	-3.2 (-4.0; -2.4)
Systolic BP Change (mmHg)	-5.75 (-8.016; -3.486)	-7.49 (-9.778; -5.195)
Diastolic BP Change (mmHg)	-1.54 (-2.841; -0.235)	-2.61 (-3.931; -1.293)
HDL-C % Change (%)	3.6 (0.4; 6.9)	4.8 (1.5; 8.1)
LDL-C % Change (%)	2.8 (-3.7; 9.2)	2.5 (-4.0; 9.0)
Triglycerides % Change (%)	-4.4 (-13.5; 4.8)	3.9 (-5.4; 13.1)

Key: ANCOVA=analysis of covariance; BP=blood pressure; Cana=canagliflozin; CI=confidence interval; FPG=fasting plasma glucose; HbA_{1c}=glycosylated hemoglobin; HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol; LOCF=last observation carried forward; mITT=modified intent-to-treat.

Note: For continuous endpoints, the least squares mean is presented with CI based on ANCOVA models with terms for treatment and stratification factors, and adjusting for the baseline value as a covariate. For the dichotomous endpoint: Achieving 7.0% HbA_{1c} target, differences in % are presented; the CIs are based on the normal approximation to binomial distribution with continuity correction.

PHARMACOGENOMIC RESULTS:

No DNA samples from subjects in this study were analyzed.

SAFETY RESULTS:

Adverse Events: Over the 104-week treatment period. the overall incidence of treatment-emergent adverse events in the canagliflozin 100 mg and 300 mg groups (88.0 % and 89.8%, respectively) was similar to the placebo group (86.1%), with a low incidence of adverse events leading to discontinuation. More subjects in the canagliflozin 300 mg (10.2%) had an adverse event that led to discontinuation then subjects in the placebo group (6.8%) or canagliflozin 100 mg (4.6%). Serious adverse events were low and balanced across treatment groups with the incidences in the canagliflozin 100 mg group (16.6%) compared to the canagliflozin 300 mg group (18.2%) and the placebo group (17.3%). During the 104-week treatment period, the incidence of serious adverse events that led to discontinuation from the study was low; higher in the placebo group (3.0%) compared to the canagliflozin groups (0.8%). The incidence of serious adverse events that were considered drug-related by the investigator was low across treatment groups (0.8% and 3.0% in the canagliflozin 100 and 300 mg groups, respectively and 2.5% in the placebo group).

There was a dose-related higher incidence of drug-related adverse events in the canagliflozin groups relative to the placebo group, with an incidence of 42.7% and 50.4% in the canagliflozin 100 mg and 300 mg groups, respectively, and 39.7% in the placebo group. The higher incidence with canagliflozin was due to a higher incidence of several specific adverse events (or groupings of similar adverse event terms) in the canagliflozin groups relative to the placebo group in a number of system organ classes (SOCs): in the Infections and infestations SOC with a higher incidence of adverse events of genital mycoytic infections (vulvovaginitis and related terms) and adverse events of urinary tract infection (with no increase in incidence of upper urinary tract infections); Gastrointestinal disorders SOC (with a higher incidence of upper abdominal pain, constipation, and dry mouth); Renal and urinary disorders SOC (with a higher incidence of dysuria, pollakiuria, and polyuria); and Reproductive system and breast disorders SOC (with a higher incidence of vulvovaginal adverse events and balanitis/balanoposthitis). Most drug-related adverse events were mild or moderate in intensity, and had resolved or were resolving at the end of the 104-week double-blind treatment phase. Drug-related adverse events that led to discontinuation were low across treatment groups, with a slightly higher incidence in the canagliflozin 300 mg group (6.4%) compared to placebo (3.8%). The incidence of drug-related adverse events that were considered

serious by the investigator was low across treatment groups (0.8% and 3.0% in the canagliflozin 100 and 300 mg groups, respectively and 2.5% in the placebo group).

Six subjects died during the 104-week treatment period; all 6 deaths occurred during the extension phase of the study. Four of the 6 subjects that died were in the canagliflozin 100 mg group and 2 deaths were in the placebo group. Two of the 6 deaths were treatment-emergent and 4 deaths were non-treatment-emergent based on the pre-specified algorithm in the SAP which defines treatment-emergent. Among the 2 subjects with treatment-emergent deaths, both were in the canagliflozin 100 mg group; among the 4 non-treatment-emergent deaths, 2 subjects were in the canagliflozin 100 mg group and 2 were in the placebo group. There were no deaths in the canagliflozin 300 mg group.

Treatment-Emergent Adverse Events During Entire 104-Week Double-Blind Treatment Period (Safety) - Regardless of Rescue Medication
(Study 28431754-DIA3010: Safety Analysis Set)

Number (%) of Subjects with at least 1 treatment-emergent adverse event of following types	Placebo (N=237) n (%)	Cana 100 mg (N=241) n (%)	Cana 300 mg (N=236) n (%)	Cana Total (N=477) n (%)
Any adverse events	204 (86.1)	212 (88.0)	212 (89.8)	424 (88.9)
Adverse events leading to discontinuation	16 (6.8)	11 (4.6)	24 (10.2)	35 (7.3)
Adverse events related to study drug[a]	94 (39.7)	103 (42.7)	119 (50.4)	222 (46.5)
Adverse events related to study drug[a] and leading to discontinuation	9 (3.8)	8 (3.3)	15 (6.4)	23 (4.8)
Serious adverse events	41 (17.3)	40 (16.6)	43 (18.2)	83 (17.4)
Serious adverse events leading to discontinuation	7 (3.0)	1 (0.4)	3 (1.3)	4 (0.8)
Serious adverse events related to study drug[a]	6 (2.5)	2 (0.8)	7 (3.0)	9 (1.9)
Serious adverse events related to study drug[a] and leading to discontinuation	3 (1.3)	1 (0.4)	1 (0.4)	2 (0.4)
Deaths[b]	0	2 (0.8)	0	2 (0.4)

[a] Related to study drug includes relationship determined by investigators: possibly related, probably related and very likely related.
[b] Six deaths were reported during the study; all occurred during the extension period. Two of the 6 deaths were treatment-emergent and 4 deaths were non-treatment-emergent based on the pre-specified algorithm described in the SAP which defines treatment-emergent.
Key: Cana=canagliflozin; N=number of subjects per group; n=number of subjects per subgroup; SAP=statistical analysis plan.
Note: Percentages calculated with the number of subjects in each group as denominator.

Hypoglycemia:

During the entire study, in subjects (N=529) on an AHA therapy associated with hypoglycemia (ie, insulin or insulin secretagogue), the overall incidence of subjects who experienced at least 1 episode of biochemically documented hypoglycemia (ie, a hypoglycemia episode with a concurrent fingerstick or plasma glucose ≤70 mg/dL (≤3.9 mmol/L), or a severe hypoglycemia episode) was higher in the canagliflozin 100 mg and 300 mg groups (53.6% and 61.0%, respectively) compared to the placebo group (48.9%). In these subjects, the number of severe hypoglycemic episodes across treatment groups was low, with a lower occurrence in the canagliflozin groups relative to the placebo group

During the entire study, in subjects (N=185) not on an AHA therapy associated with hypoglycemia (ie, not on insulin or insulin secretagogue), the overall incidence of subjects who experienced at least 1 episode of biochemically documented hypoglycemia (ie, a hypoglycemia episode with a concurrent fingerstick or plasma glucose ≤70 mg/dL (≤3.9 mmol/L), or a severe hypoglycemia episode) was higher in the canagliflozin 100 and 300 mg groups (18.3% and 10.9 %, respectively) compared with the placebo group (6.6%). The majority of subjects with these hypoglycemic events had only 1 or 2 events during the 2-year study, and only 1 subject (placebo group) had a serious hypoglycemic episode (occurred during the 26-week core period).

Bone safety results: Bone density measured by DXA showed minimal changes from baseline to Week 104 in the lumbar spine (a cancellous bone region), femoral neck (a mixed cancellous and cortical

bone region) and the distal forearm (a cortical bone region), with the 95% CIs for all 3 regions including "0" for both canagliflozin treatment groups. In the total hip (a mixed cortical and cancellous region like the femoral neck), the placebo-subtracted LS mean percent change from baseline to Week 104 were -0.9% and -1.2% for the canagliflozin 100 and 300 mg groups, respectively, with the 95% CIs for the between-group difference from placebo excluding "0" for both canagliflozin groups. Greater changes in BMD in the total hip, relative to placebo, were noted in female subjects in the canagliflozin 300 mg dose group. The time course of BMD changes in the total hip region showed a relatively consistent decline in bone density over the 104-week period in both the placebo and canagliflozin groups; the loss was greater with canagliflozin relative to placebo at all measured timepoints with most of the separation between placebo and canagliflozin groups manifested by Week 52. The time course of BMD changes in the lumbar spine, distal radius, and femoral neck showed no increased separation in BMD changes from baseline over time between the canagliflozin and placebo groups.

Bone Mineral Density: Percent Change from Baseline to Week 104 - Regardless of Rescue Medication
(Study 28431754-DIA3010: Safety Analysis Set)

Endpoints – corrected BMD measurement % change	Cana 100 mg (Placebo-Subtracted) LS Mean (95% CI)	Cana 300 mg (Placebo-Subtracted) LS Mean (95% CI)
Lumbar spine	-0.3 (-1.1;0.5)	-0.7 (-1.5;0.1)
Total hip	-0.9 (-1.5;-0.2)	-1.2 (-1.9;-0.6)
Femur neck	-0.1 (-1.0;0.8)	-0.1 (-0.9;0.8)
Distal forearm	0.0 (-0.8;0.9)	-0.4 (-1.3;0.4)

Key: ANCOVA=analysis of covariance; Cana=canagliflozin; BMD=bone mineral density; CI=confidence interval; LS=least-squares; PPARγ= peroxisome proliferator-activated receptor

Note: The least squares mean is presented with associated CI based on ANCOVA models with terms for treatment, sex, T-score of lumbar spine (<-1.5 or ≥-1.5) based on central reading, and on or not on a PPARγ agent based on concomitant medication history, and adjusting for the baseline value as a covariate.

Bone turnover markers were not prespecified for analysis at Week 104. Bone biomarker results at Week 26 and Week 52 are provided in the Week 26 Core CSR and Week 52 Bone Safety Report, respectively. Briefly, serum CTx (marker of bone resorption) and P1NP (marker of bone formation) were measured at baseline, Week 26, and Week 52 (using archived specimens). Osteocalcin and estradiol (in women only) (measurements not prespecified in SAP) were measured on archived specimens at baseline and Week 52. Interim analyses of bone turnover marker results at Week 52 were reported in the Week 52 Bone Safety Report. Increases in serum CTx were seen after 26 weeks of treatment with canagliflozin, which slightly decreased after 52 weeks of treatment. Osteocalcin, a marker of bone formation, increased after 26 weeks, and further increased after 52 weeks of treatment with canagliflozin. Small decreases relative to placebo in P1NP were seen after 26 weeks; however, the changes were variable and the 95% CI for the LS mean placebo-subtracted difference for P1NP included "0" for both doses of canagliflozin. The gradual rise in osteocalcin over the 52-week treatment period is consistent with expectations of coupled bone remodeling as increases in bone formation followed the prior increase in bone resorption, as evidenced by the serum beta-CTx increase.

Safety Laboratory Assessment: Changes from baseline in laboratory analytes that were observed at Week 104 with canagliflozin 100 mg and 300 mg relative to placebo, included: increases in hemoglobin, alkaline phosphatase, magnesium, and blood urea nitrogen (BUN) and decreases in serum urate levels and gamma glutamyl transferase (GGT). No meaningful changes from baseline to Week 104 were observed relative to placebo in eGFR, alanine aminotransferase, aspartate aminotransferase, or in serum electrolytes, including serum calcium, sodium, chloride, potassium or phosphate. The mean percent changes from baseline for selected safety laboratory parameters are summarized in the table below.

Mean Percent Changes from Baseline at Week 104 for Selected Safety Laboratory Parameters – Regardless of Rescue - Within 2 Days of the Last Dose of Study Drug[a]
(Study 28431754-DIA3010: Safety Analysis Set)

	Mean % Change from Baseline at Week 104		
Parameter	Placebo	Cana 100 mg	Cana 300 mg
Hemoglobin	-1.8	3.8	4.1
ALT	7.4	2.9	0.7
AST	6.5	4.4	2.7
ALP	1.9	2.3	3.0
GGT	0.7	-1.8	-5.9
Serum bilirubin	7.5	10.2	7.4
BUN	5.2	15.0	17.0
Serum creatinine	4.5	4.3	4.4
eGFR	-2.8	-3.5	-3.5
Magnesium	-1.3	6.8	9.8
Serum urate	-0.5	-7.1	-8.9

[a] This summary includes data collected up to a maximum of 2 days after a subject's last dose of study drug in the core-double-blind period (data collected beyond 2 days after the subject's last dose of study drug are excluded from this summary).

Key: ALT=alanine aminotransferase; AST=aspartate aminotransferase; ALP=alkaline phosphatase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; GGT=gamma glutamyl transferase

Other Safety Assessments: Treatment with canagliflozin 100 mg and 300 mg led to reductions in blood pressure (systolic reductions greater than diastolic), with no concomitant change in heart rate. There were no clinically important changes in ECG observed.

STUDY LIMITATIONS: No notable study limitations were identified by the sponsor.

CONCLUSION(S):

- Over a 104-week double-blind treatment period, in this population of older subjects with T2DM with mild to moderate hyperglycemia, both doses of canagliflozin (with add-on to existing background glucose-lowering treatments) provide clinically important and sustained glycemic improvements (in HbA_{1c} and FPG change from baseline, and the proportion of subjects achieving HbA_{1c} goals) relative to placebo, with greater reductions seen with the 300 mg canagliflozin dose compared with the 100 mg canagliflozin dose.
- Canagliflozin provides clinically important, sustained improvements in other secondary non-glycemic endpoints including body weight, reductions in SBP, and increase in HDL-C, with an incremental benefit of the 300 mg dose relative to the 100 mg dose.
- Over a 104-week double-blind treatment period, canagliflozin shows inconsistent effects on bone density, with small changes from baseline in lumbar spine (cancellous bone region), femoral neck (mixed cancellous and cortical bone region), and the distal forearm (cortical bone region). Small placebo-subtracted decreases from baseline in bone density are observed in the total hip (mixed cancellous and cortical bone) and are correlated, in part, with weight loss.
- Canagliflozin is overall well-tolerated over the 104 week double-blind treatment period; the overall incidence of treatment-emergent adverse events in both canagliflozin dose groups is similar to the placebo group. Canagliflozin treatment is associated with an increased incidence of adverse events, relative to placebo, of genital mycotic infections (vulvovaginitis and related terms in females and balanitis in males), urinary tract infections, and of adverse events related to osmotic diuresis and volume-depletion (eg, thirst, polyuria, pollakiuria, nocturia) and the modest reduction in blood volume.
- Overall, most adverse events are generally considered mild to moderate in severity and not generally leading to discontinuation of treatment. The incidence of serious adverse events is low, balanced across treatment groups, with a low incidence of discontinuations.

- Canagliflozin treatment over the 104-week period shows minimal changes from baseline in laboratory safety analytes (ie, increases in hemoglobin, magnesium, BUN and moderate decrease in serum urate). No clinically meaningful changes in eGFR, calcium, or phosphate are noted. There are no clinically important changes in ECG parameters.
- In subjects on background AHA therapy associated with hypoglycemia, the proportion of subjects who experienced a hypoglycemia episode is modestly higher in the canagliflozin groups compared to placebo. A low rate of severe hypoglycemia is observed across treatment groups, with the incidence of severe hypoglycemia lower in the canagliflozin groups compared to placebo.

Overall, this 104-week study in older subjects with T2DM met the key primary and secondary hypotheses, suggesting a favorable efficacy profile (with the canagliflozin 300 mg dose providing additional benefit), and a well-characterized safety and tolerability profile with treatment-associated adverse events that are manageable, not unexpected, and infrequently require discontinuation of canagliflozin.