Janssen Research & Development

Clinical Study Report Synopsis
[Protocol 28431754DIA3002; Phase 3]

JNJ-28431754 (Canagliflozin)

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SYNOPSIS

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Name of Sponsor/Company	Janssen Research & Development, LLC
Name of Finished Product	To be determined
Name of Active Ingredient(s)	Canagliflozin (JNJ-28431754)

Protocol No.: 28431754DIA3002

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, Multicenter Study, to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin and Sulphonylurea Therapy

Study Name: CANTATA-MSU

EudraCT Number: 2009-016366-88

NCT No.: NCT01106625

Clinical Registry No.: CR017005

Coordinating Investigator(s): [redacted], MD; [redacted], United Kingdom

Study Center(s): 85 study centers in 11 countries, including 42 centers in North America (38 in the United States, 4 in Mexico), 24 centers in Europe[a] (6 in France, 6 in the United Kingdom, 4 in Belgium, 4 in Hungary, 4 in Spain), 5 centers in Central America (5 in Guatemala), and 14 centers in the rest of world (5 in Australia, 5 in Russia, 4 in Israel)

Publication (Reference):

John Wilding, Chantal Mathieu, Frank Vercruysse, Keith Usiskin, Ling Deng, William Canovatchel Canagliflozin (CANA), a Sodium Glucose Co-Transporter 2 Inhibitor, Improves Glycemic Control and Reduces Body Weight in Subjects With Type 2 Diabetes (T2D) Inadequately Controlled With Metformin (MET) and Sulfonylurea (SU). American Diabetes Association 72nd Scientific Session, June 8-12, 2012, Philadelphia, PA, Poster Presentation date: June 9, 2012 from 11:30am-12:30pm, Number: 1022-P (corresponding abstract also submitted).

John Wilding, Chantal Mathieu, Ling Deng, Shawn Black, Frank Vercruysse, William Canovatchel, Gary Meininger. Canagliflozin, a Sodium Glucose Co-Transporter 2 Inhibitor, Improves Glycaemia in Subjects With Type 2 Diabetes Inadequately Controlled With Metformin Plus Sulphonylurea. Annual Meeting of the European Association for the Study of Diabetes (EASD), October 1-5, 2012 in Berlin, Germany. Poster Presentation Date: October 3, 2012 from 1:15pm-2:15pm, Number: 766, Session: PS 058 (corresponding abstract also submitted).

Polidori D, Vercruysse F, Ferrannini E. MOA beta-cell function Canagliflozin, a Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitor, Improves Indices of β-cell Function in Patients with Type 2 Diabetes on

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

Metformin Plus Sulphonylurea . Poster Presentation date: October 3, 2012 from 1:15pm-2:15pm, Number: 761, Session: PS 058 (corresponding abstract also submitted).

John Wilding, Chantal Mathieu, Ling Deng, Shawn Black, Frank Vercruysse, William Canovatchel, Gary Meininger. Canagliflozin Improves Glycemia in Subjects With Type 2 Diabetes on Metformin Plus Sulfonylurea. 4th Biennial World Congress on Controversies in Diabetes, Obesity and Hypertension (CODHy) November 8-11, 2012 in Barcelona, Spain. Poster Number: 73 (corresponding abstract also submitted).

Study Period: 07 April 2010 to 17 April 2012; Week 52 database lock: 21 June 2012

Phase of Development: 3

Objectives:

The study was designed to assess the efficacy, safety, and tolerability of canagliflozin compared with placebo in subjects with type 2 diabetes mellitus (T2DM) who had inadequate glycemic control on combination therapy with metformin and a sulphonylurea (SU). The primary objectives were to assess the effect of canagliflozin relative to placebo on glycosylated hemoglobin (HbA_{1c}) after 26 weeks of treatment and to assess the safety and tolerability of canagliflozin.

The secondary objectives were to assess the effect of canagliflozin relative to placebo after 26 and 52 weeks of treatment on: fasting plasma glucose (FPG), the proportion of subjects with HbA_{1c} <7.0% or <6.5%, body weight, fasting plasma lipids (ie, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], total cholesterol, LDL-C to HDL-C ratio, and triglycerides), systolic blood pressure (SBP) and diastolic blood pressure (DBP), time to rescue medication and proportion of subjects receiving rescue medication, and fasting measure of beta-cell function (ie, homeostasis model assessment [HOMA]-B).

Objectives in a subset of subjects (approximately 25% of total subjects) who underwent a frequently-sampled mixed-meal tolerance test (FS-MMTT) to assess the effect of canagliflozin relative to placebo at Week 26 are described in the 26-Week Core Double-Blind Period clinical study report (CSR) (referred to as the Week 26 CSR in the following sections).

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

Approximately 450 adult subjects (≥18 and ≤80 years of age) with T2DM who had inadequate glycemic control (ie, HbA_{1c} of ≥7.0% to ≤10.5%) on the combination of metformin and SU, were to be randomly assigned in a 1:1:1 ratio to once-daily administration of canagliflozin 100 mg, canagliflozin 300 mg, or placebo and entered the 52-week double-blind treatment phase (consisting of a 26-week core, placebo-controlled, double-blind treatment period followed by a 26-week extension period).

Several 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; 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): It was planned to enroll approximately 450 subjects into the study. A total of 469 subjects were randomized to placebo, canagliflozin 100 mg, and canagliflozin 300 mg in a 1:1:1 manner. The numbers of subjects included in the various analysis sets by treatment group are summarized below.

Summary of Analysis Sets and Disposition
(Study 28431754-DIA3002: All Randomized Subjects Analysis Set)

	Placebo (N=156) n (%)	CANA 100 mg (N=157) n (%)	CANA 300 mg (N=156) n (%)	CANA Total (N=313) n (%)	Total (N=469) n (%)
Subjects who were randomized	156 (100)	157 (100)	156 (100)	313 (100)	469 (100)
Subjects in the mITT analysis set	156 (100)	157 (100)	156 (100)	313 (100)	469 (100)
Subjects in the mITT analysis set who discontinued before the Week 52 visit	66 (42.3)	48 (30.6)	45 (28.8)	93 (29.7)	159 (33.9)
Subjects in the mITT analysis set who received rescue therapy before the Week 52 visit	38 (24.4)	14 (8.9)	8 (5.1)	22 (7.0)	60 (12.8)
Subjects in the extension mITT analysis set [a]	103 (66.0)	125 (79.6)	125 (80.1)	250 (79.9)	353 (75.3)
Subjects in the Week 52 completers' analysis set [b]	59 (37.8)	95 (60.5)	104 (66.7)	199 (63.6)	258 (55.0)
Subjects in the safety analysis set	156 (100)	157 (100)	156 (100)	313 (100)	469 (100)
Subjects in the extension safety analysis set [c]	119 (76.3)	127 (80.9)	128 (82.1)	255 (81.5)	374 (79.7)

[a] Includes MITT subjects who entered extension and didn't receive rescue medication in core period. This analysis set is used in the efficacy analysis.
[b] Includes MITT subjects who completed the Week 52 visit and had not initiated rescue medication.
[c] Includes MITT subjects who entered extension. This analysis set is used in the Week 26 - Week 52 safety analysis.
Note: Percentages calculated with the number of subjects in each group as denominator.
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Diagnosis and Main Criteria for Inclusion: Man or woman ≥18 and ≤80 years of age with T2DM and currently treated with metformin and an SU, meeting the following HbA_{1c} eligibility criteria:

	HbA_{1c}	
Subjects	Screening Visit	Week -2 Visit
On metformin and an SU at protocol-specified doses for at least 8 weeks prior to screening	≥7.0% and ≤10.5%	n/a
On metformin and an SU, either or both at doses below protocol-specified	≥7.5%	≥7.0% and ≤10.5%

Key: HbA_{1c} =hemoglobin A_{1c} (glycosylated hemoglobin), SU=sulphonylurea

Test Product, Dose and Mode of Administration, Batch No.: Canagliflozin capsules containing active 100 mg (batch/lot numbers: 09J30/G002, 09K06/G002, PD3387, PD3390) or 300 mg (batch/lot numbers: PD3157, PD3156, PD3391, PD3401, 30845.3) for oral administration.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo to match canagliflozin (batch/lot numbers: PD3221, 09L16/G001, 10B22/G001, 30845.8) for oral administration.

Duration of Treatment: The total duration of the study was approximately 59 weeks (for subjects on protocol-specified doses of metformin and an SU at the screening visit) to 72 weeks (for subjects on metformin and an SU, with 1 or both agents below protocol-specified doses who had their antihyperglycemic agent [AHA] regimen adjusted to protocol-specified doses), including a pretreatment phase, a 52-week double-blind treatment phase (26-week core double-blind period and a 26-week double-blind extension period), and a 30-day posttreatment phase for follow-up contact.

A separate report summarized the results of the 26-week core double-blind treatment period. This report summarizes the results of the entire 52-week double-blind treatment phase (including the 26-week core double-blind period and the 26-week extension double-blind period).

Evaluations: Efficacy laboratory assessment at Week 52 included HbA_{1c}, FPG, and fasting plasma lipids (LDL-C, HDL-C, non-HDL-C, ratio of LDL-C to HDL-C, total cholesterol, and triglycerides). Additional efficacy assessments at Week 52 included body weight, SBP and DBP, the proportion of subjects with HbA_{1c} <6.5% and <7%, body mass index (BMI) and waist circumference, the use of rescue medication, and time to initiation of rescue medication.

A subset of subjects who underwent the FS-MMTT during the core-double blind period; the measurements taken during the FS-MMTT are described in the Week 26 CSR.

Safety assessment was based on reported adverse events, safety laboratory tests (including hematology, chemistry, routine urinalysis), 12-lead electrocardiograms (ECGs), vital sign measurements (blood pressures and pulse rates), body weight, physical examinations and self-monitored blood glucose (SMBG) and collection of hypoglycemic episodes (eg, from the diary provided to the subjects), regardless of whether considered to be adverse events by the reporting investigator.

A blood sample was collected on Day 1 from subjects who had consented to participate in the pharmacogenomics component of the study to allow for pharmacogenomic research, as necessary.

Statistical Methods:

Sample Size Determination: Sample size determination was based on the primary endpoint (change in HbA_{1c} from baseline at Week 26, as discussed in the Week 26 CSR). There were no hypotheses tested for evaluations at Week 52.

Efficacy: The primary efficacy endpoint (the change in HbA_{1c} from baseline through Week 26) and key secondary endpoints are described in the Week 26 CSR. The last observation carried forward (LOCF) method was applied when the Week 52 values were missing. In subjects receiving rescue medication, their measurements made before rescue were used as the last observations.

An analysis of covariance (ANCOVA) model with treatment (canagliflozin 100 mg and canagliflozin 300 mg) and stratification factors (whether or not a subject entered the AHA adjustment period and participation in the FS-MMTT) as fixed effects and HbA_{1c} baseline value as covariate, based on the modified intent-to-treat (mITT) analysis set and extension mITT analysis sets was used to evaluate changes or percent changes from baseline at Week 52 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; fasting HOMA2-%B, and waist circumference and BMI. The least-squares means (LS means) for the change from baseline values at Week 52 and each time point through Week 52, 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 52 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 52. No treatment differences were calculated.

Pharmacodynamics: No pharmacodynamic studies were performed during the extension period. Please refer to the Week 26 CSR for detail regarding related statistical methodology and results of pharmacodynamic assessment of beta-cell function and urinary glucose excretion (UGE) during a frequently sampled mixed meal tolerance test (FS-MMTT)

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 52-week double-blind phase and for the extension double-blind period (ie, Week 26 to Week 52). 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 genital infections. Safety analyses for overall and specific adverse events were performed including all data, regardless of the initiation of rescue medication. Analyses and summaries of hypoglycemic episodes were provided for both *prior to the rescue medication* and *regardless of the rescue medication*. Predefined limits of change and descriptive statistics were provided for other safety parameters for the entire 52-week double-blind phase, including all data, regardless of the initiation of rescue medication.

RESULTS:

STUDY POPULATION:

Subject and Treatment Information and Baseline Characteristics

A total of 1,021 subjects were screened and a total of 469 subjects were randomized to study treatment. Overall, 66% completed the 52-week double-blind treatment phase, with the rate of discontinuation higher in the placebo than in the canagliflozin groups. The allocation of treatment assignment in the safety analysis and the efficacy analysis were the same as no subject took incorrect double-blind study drug for a predominant part of the double-blind treatment phase. Thus, the mITT analysis set and the safety analysis set were identical.

Reason for Discontinuation
(Study 28431754-DIA3002: All Randomized Subjects Analysis Set)

	Placebo (N=156) n (%)	CANA 100 mg (N=157) n (%)	CANA 300 mg (N=156) n (%)	CANA Total (N=313) n (%)	Total (N=469) n (%)
Total number of subjects discontinued	66 (42.3)	48 (30.6)	45 (28.8)	93 (29.7)	159 (33.9)
Primary reason for discontinuation [a]					
Adverse event	8 (5.1)	11 (7.0)	11 (7.1)	22 (7.0)	30 (6.4)
Creatinine or eGFR withdrawal criteria	1 (0.6)	2 (1.3)	3 (1.9)	5 (1.6)	6 (1.3)
Lost to follow-up	6 (3.8)	3 (1.9)	6 (3.8)	9 (2.9)	15 (3.2)
Noncompliance with study drug	2 (1.3)	1 (0.6)	0	1 (0.3)	3 (0.6)
Physician decision	4 (2.6)	0	1 (0.6)	1 (0.3)	5 (1.1)
Protocol violation	2 (1.3)	2 (1.3)	3 (1.9)	5 (1.6)	7 (1.5)
Withdrawal of consent	10 (6.4)	7 (4.5)	8 (5.1)	15 (4.8)	25 (5.3)
Unable to take protocol defined rescue therapy	18 (11.5)	6 (3.8)	4 (2.6)	10 (3.2)	28 (6.0)
Other	15 (9.6)	16 (10.2)	9 (5.8)	25 (8.0)	40 (8.5)

[a] As indicated by the investigator on the eCRF for randomized subjects who discontinued before the Week 52 visit.
Key: CANA=canagliflozin, eCRF=electronic case report form, eGFR=estimated glomerular filtration rate, N=total number of subjects, n=total number of subjects in subgroup
Note: Percentages calculated with the number of subjects in each group as denominator.
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The most common reason for discontinuation was in the category of other (8.5%), which included a variety of reasons, some reported in ≤5 subjects (transportation issues, moving, family- or job-related, lack of efficacy, disallowed therapy) and also included 14 subjects who withdrew from the study due to the rat carcinogenicity study results, but agreed to continued follow-up (and hence were not classified as withdrawal of consent). Other common reasons for discontinuation were adverse event, which occurred slightly more frequently in subjects in the canagliflozin groups (7.0% and 7.1% of subjects in the

canagliflozin 100 mg and 300 mg groups, respectively, and 5.1% in the placebo group); inability to take defined rescue medication (ie, insulin), which occurred more commonly in the placebo group relative to the canagliflozin groups (3.8% and 2.6% of subjects in the canagliflozin 100 mg and 300 mg groups, respectively, and 11.5% in the placebo group); and withdrawal of consent (in 5.3% of subjects), which occurred slightly more frequently in the placebo group relative to the canagliflozin groups (4.5% and 5.1% of subjects in the canagliflozin 100 mg and 300 mg groups, respectively, and 6.4% in the placebo group).

The overall mean duration of subject exposure (prior to rescue medication) for the 52-week double-blind treatment phase was greater in the canagliflozin groups compared with placebo, with 63.3% of subjects in the canagliflozin groups having at least 50 weeks of exposure, compared with 38.5% of subjects in the placebo group.

Baseline Characteristics

Baseline demographic characteristics for the mITT analysis set were generally similar across treatment groups. The median age of subjects in the study was 58 years, and nearly equal proportions of women and men were randomized. Consistent with the regions of the world in which subjects were recruited, 83% of the subjects were white, 6% were black or African-American, and 1% were Asian; 23% of subjects were of Hispanic or Latino ethnicity.

For the mITT analysis set, baseline mean weight was 92.8 kg and baseline mean BMI was 33.0 kg/m^2; these were generally similar across treatment groups, with 66% 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 8.1% and 8.0%, respectively, across all groups. Subjects had long-standing diabetes, with a mean duration of disease of nearly 10 years, reflective of a population already on dual combination AHA therapy. With this relatively long duration of disease, a moderate proportion (26%) had at least 1 microvascular complication of diabetes.

EFFICACY RESULTS:

In the mITT analysis set, the LS mean change from baseline in HbA_{1c} at Week 52 was -0.96% for the canagliflozin 300 mg group and -0.74% for the canagliflozin 100 mg group, with an LS mean change from baseline of 0.01% seen in the placebo group. These results at Week 52 are similar to the results observed at Week 26 across treatment groups, with the placebo-subtracted change from baseline in canagliflozin groups at Week 52 similar to that observed at Week 26.

Substantial and sustained glycemic improvements were seen in FPG, proportion of subjects achieving HbA_{1c} goal of <7.0%, and percent change from baseline in body weight, with greater reductions seen with canagliflozin 300 mg relative to canagliflozin 100 mg. In addition, reductions from baseline through Week 52 in systolic blood pressure and diastolic blood pressure were observed in the canagliflozin groups compared with the placebo group. Relative to the placebo group, percent increases from baseline in HDL-C at Week 52 were observed for both canagliflozin groups; relative to the placebo group, LDL-C was increased in the canagliflozin 300 mg group by approximately 8% at Week 52, with no notable change in the 100 mg group. No notable numerical differences were identified for other lipid endpoints.

Change from Baseline to Week 52 for Primary and Secondary Efficacy Endpoints (mITT LOCF)
(Study 28431754-DIA3002: Modified Intent-to-Treat Analysis Set)

Endpoints	CANA 100 mg (Placebo-Subtracted) LS Mean (95% CI)	CANA 300 mg (Placebo-Subtracted) LS Mean (95% CI)
HbA_{1c} Change (%)	-0.75 (-0.945; -0.554)	-0.97 (-1.165; -0.772)
Proportion Achieving 7% HbA_{1c} Target	20.7 (10.1; 31.2)	34.0 (23.2; 44.7)
FPG Change (mmol/L)	-1.64 (-2.143; -1.136)	-2.07 (-2.577; -1.566)
Body Weight Percent Change (%)	-1.3 (-2.1; -0.5)	-2.2 (-3.0; -1.4)
Systolic BP Change (mmHg)	-3.74 (-6.222; -1.256)	-2.99 (-5.478; -0.496)
Diastolic BP Change (mmHg)	-1.56 (-3.193; 0.064)	-1.09 (-2.718; 0.547)
HDL-C Percent Change (%)	3.2 (-0.1; 6.5)	4.9 (1.6; 8.2)
LDL-C Percent Change (%)	-0.6 (-7.7; 6.5)	7.9 (0.8; 15.0)
Ratio of LDL-C to HDL-C (%)	-4.0 (-10.8; 2.8)	1.4 (-5.4; 8.2)
Total Cholesterol (%)	-0.9 (-4.9; 3.1)	3.6 (-0.4; 7.6)
Non-HDL-C (%)	-1.5 (-6.9; 3.9)	3.7 (-1.7; 9.0)
Triglycerides Percent Change (%)	3.8 (-7.8; 15.4)	2.0 (-9.6; 13.6)

Key: ANCOVA=analysis of covariance, BP=blood pressure, CANA=canagliflozin, CI=confidence interval, HbA_{1c}=glycosylated hemoglobin, HDL-C=high-density lipoprotein cholesterol, FPG=fasting plasma glucose, 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 associated CI based on ANCOVA models with terms for treatment and stratification factors and adjusting for the baseline value as a covariate.
Note: For the proportion of patients achieving 7.0% HbA_{1c} target, CI of the difference in proportion is based on normal approximation to binomial distribution with continuity correction.

SAFETY RESULTS:

Adverse Events: The overall incidence of subjects with adverse events over the 52-week treatment phase was slightly lower in the canagliflozin 100 mg group (67.5%) than in the canagliflozin 300 mg and placebo groups (73.1% and 71.2%, respectively). A higher incidence of drug-related adverse events was observed in both of the canagliflozin groups compared with the placebo group. The overall incidence of adverse events leading to discontinuation was low in all groups and higher in the canagliflozin groups than in the placebo group. The overall incidence of serious adverse events was low across all groups, lower in the canagliflozin groups compared with the placebo group. There were no deaths reported during the entire 52-week double-blind treatment phase.

Several specific adverse events occurred at a higher incidence in the canagliflozin groups relative to placebo, including balanitis, vulvovaginitis (and related terms), urinary tract infections, adverse events consistent with osmotic diuresis (eg, polyuria, pollakiuria, thirst), diarrhea, and constipation. The incidences of these specific adverse events were generally low and few subjects discontinued due to these adverse events. Higher incidences of drug-related adverse events compared to placebo were observed in both canagliflozin groups.

Summary of Adverse Events During Entire Double-Blind Treatment Phase – Regardless of Rescue Medication
(Study 28431754-DIA3002: Safety Analysis Set)

Number (%) of subjects with at least 1 adverse event of following types	Placebo (N=156) n (%)	CANA 100 mg (N=157) n (%)	CANA 300 mg (N=156) n (%)	CANA Total (N=313) n (%)
Any adverse events	111 (71.2)	106 (67.5)	114 (73.1)	220 (70.3)
Adverse events leading to discontinuation	7 (4.5)	11 (7.0)	12 (7.7)	23 (7.3)
Adverse events related to study drug [a]	24 (15.4)	41 (26.1)	57 (36.5)	98 (31.3)
Adverse events related to study drug [a] and leading to discontinuation	2 (1.3)	5 (3.2)	12 (7.7)	17 (5.4)
Serious adverse events	13 (8.3)	7 (4.5)	8 (5.1)	15 (4.8)
Serious adverse events leading to discontinuation	3 (1.9)	4 (2.5)	0	4 (1.3)
Serious adverse events related to study drug [a]	0	0	1 (0.6)	1 (0.3)
Serious adverse events related to study drug [a] and leading to discontinuation	0	0	0	0
Deaths	0	0	0	0

[a] Related to study drug includes relationship determined by investigators: possibly related, probably related and very likely related.

Key: CANA=canagliflozin, N=total number of subjects, n=total number of subjects in subgroup.
Note: Percentages calculated with the number of subjects in each group as denominator.
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The overall incidence of subjects with adverse events that occurred in the extension period was higher in the canagliflozin 100 mg (50.4%) and 300 mg (56.3%) compared with the placebo group (44.5%), with a higher incidence of drug-related adverse events observed in both canagliflozin groups compared with the placebo group. The incidence of adverse events leading to discontinuation in the extension period was low and similar across groups. The overall incidence of serious adverse events in the extension period was low across all groups, lower in the canagliflozin groups relative to the placebo group.

Summary of Adverse Events During Extension Period - Regardless of Rescue Medication
(Study 28431754-DIA3002: Extension Safety Analysis Set)

Number (%) of subjects with at least 1 adverse event of following types	Placebo (N=119) n (%)	CANA 100 mg (N=127) n (%)	CANA 300 mg (N=128) n (%)	CANA Total (N=255) n (%)
Any adverse events	53 (44.5)	64 (50.4)	72 (56.3)	136 (53.3)
Adverse events leading to discontinuation	2 (1.7)	2 (1.6)	3 (2.3)	5 (2.0)
Adverse events related to study drug [a]	4 (3.4)	11 (8.7)	21 (16.4)	32 (12.5)
Adverse events related to study drug [a] and leading to discontinuation	0	1 (0.8)	3 (2.3)	4 (1.6)
Serious adverse events	6 (5.0)	3 (2.4)	2 (1.6)	5 (2.0)
Serious adverse events leading to discontinuation	1 (0.8)	1 (0.8)	0	1 (0.4)
Serious adverse events related to study drug [a]	0	0	0	0
Serious adverse events related to study drug [a] and leading to discontinuation	0	0	0	0
Deaths	0	0	0	0

[a] Related to study drug includes relationship determined by investigators: possibly related, probably related and very likely related.

Key: CANA=canagliflozin, N=total number of subjects, n=total number of subjects in subgroup
Note: Percentages Calculated With The Number of Subjects In Each Group As Denominator.
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Safety Laboratory Assessment: A few small changes in laboratory safety analytes were observed with canagliflozin 100 mg and 300 mg, including a small increase in hemoglobin and a moderate rise in blood urea nitrogen (BUN), and a small increase in serum creatinine; moderate decreases in serum urate and alanine aminotransferase (ALT) were observed.

Small increases from baseline in hemoglobin concentration were observed at Week 52 relative to baseline in the canagliflozin 100 mg and 300 mg groups (4.2% and 4.4%, respectively) compared with a slight decrease in placebo (-1.6%).

Moderate mean percent increases in BUN were observed at Week 52 compared with baseline in the canagliflozin 100 mg and 300 mg groups (14.5% and 17.5%, respectively), compared with a 5.5% increase in the placebo group. Small increases in mean percent change from baseline in serum creatinine were observed at Week 52 in the all treatment groups, which was relatively greater in the canagliflozin 300 mg group (7.7%) compared with the canagliflozin 100 mg and placebo groups (2.5% and 2.8%, respectively).

No meaningful mean changes from baseline were observed in serum electrolytes, including serum chloride, potassium, sodium, or phosphate. A small to moderate increase in magnesium was observed in the canagliflozin groups (7.1% and 9.7% in the canagliflozin 100 mg and 300 mg groups, respectively) with no notable change in the placebo group.

Moderate mean decreases from baseline in serum urate were observed at Week 52 in the canagliflozin 100 mg and 300 mg groups (-8.8% and -9.4%, respectively) compared with a small change in the placebo group (0.7%). For ALT, dose-related mean percent reductions from baseline were observed at Week 52 with canagliflozin 100 mg and 300 mg treatment (-3.8% and -9.7%, respectively), with a mean percent increase (6.6%) observed in the placebo group.

Other Safety Assessments: Treatment with canagliflozin 100 mg and 300 mg led to modest reductions in blood pressure (systolic reduction greater than diastolic), with no meaningful change in pulse rate.

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

CONCLUSION(S):

- Over a 52-week double-blind treatment phase, both doses of canagliflozin provided clinically important and sustained glycemic improvements (in HbA_{1c} and FPG change from baseline) and increased the proportion of subjects meeting HbA_{1c} goals, with greater reductions seen with the canagliflozin 300 mg dose compared with the canagliflozin 100 mg dose. In addition to improvements in glucose control, canagliflozin provided weight loss with an incremental benefit of the 300 mg dose relative to the 100 mg dose.
- Canagliflozin was overall well tolerated; canagliflozin treatment was associated with an increased incidence of adverse events of genital mycotic infections and adverse events related to osmotic diuresis (eg, pollakiuria, nocturia, polyuria, urine output increased, dry mouth, and thirst), but with these events generally considered mild and not generally leading to discontinuation of treatment.
- In the present study, canagliflozin, used as add-on therapy to subjects on an agent itself associated with hypoglycemia (an SU agent), was associated with an approximately two-fold increase in the incidence of hypoglycemia, but without an increase in events of severe hypoglycemia.

Overall, this 52-week study 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 adverse events associated with treatment that are manageable, and infrequently require discontinuation of canagliflozin.