Janssen Research & Development

Clinical Study Report Synopsis
[Protocol 28431754DIA3012; Phase 3]

JNJ-28431754 (Canagliflozin)

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SYNOPSIS

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

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Status: Approved

Date: 23 May 2013

Prepared by: Janssen Research & Development, LLC

Protocol No.: 28431754DIA3012

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel Group, 26 Week Multicenter Study With a 26 Week Extension to Evaluate the Efficacy, Safety, and Tolerability of JNJ 28431754 (Canagliflozin) Compared With Placebo in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin and Pioglitazone Therapy

Study Name: The CANTATA-MP Trial

EudraCT Number: 2009-018070-64

NCT No.: NCT01106690

Clinical Registry No.: CR017032

Coordinating Investigator(s): [redacted], MD, [redacted] USA

Study Center(s): Seventy-four centers in 11 countries including 48 centers in North America (34 in the United States, 12 in Canada, 2 in Mexico), 17 centers in Europe[a] (3 in Finland, 2 in France, 4 in Germany, 1 in Greece, 3 in Spain, 4 in the United Kingdom), and 9 centers in the rest of the world (5 in India, 4 in Thailand).

Publication (Reference): None

Study Period: 13 April 2010 to 10 July 2012; Week 52 database lock: 19 July 2012

Phase of Development: 3

Objectives: This study was designed to assess the efficacy, safety, and tolerability of canagliflozin in subjects with type 2 diabetes mellitus (T2DM) with inadequate glycemic control on a maximally or near-maximally effective dose of metformin and pioglitazone. The primary objectives were to assess the

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

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.

Additional objectives related to efficacy were to assess the effect of canagliflozin after 26 (relative to placebo) and 52 weeks of treatment on glycemic control (HbA_{1c} and fasting plasma glucose [FPG]), body weight, proportion of subjects with HbA1c <7.0% and <6.5%, 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 and diastolic blood pressure (SBP and DBP), time to rescue therapy and proportion of subjects receiving rescue therapy, and fasting measure of beta-cell function (ie, HOMA-B).

This Clinical Study Report (CSR) covers the results through the Week 52 Visit. In addition to data included in the 26-week core double-blind period CSR, this CSR includes data collected during the active controlled double-blind extension period (Week 26 to 52).

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

Approximately 360 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 dual combination of metformin and pioglitazone were to be randomly assigned in a 1:1:1 ratio to the addition of treatment with canagliflozin 100 mg, canagliflozin 300 mg, or matching placebo added to ongoing stable doses of metformin and pioglitazone at entry into the 26-week placebo-controlled, double-blind treatment period (core period). At entry into the extension period, subjects in the canagliflozin group (100 mg or 300 mg) continued treatment, while subjects on placebo were switched to active therapy in a blinded fashion (treatment with sitagliptin 100 mg over encapsulated to match double-blind canagliflozin and placebo capsules). No hypothesis testing was specified for the Week 52 endpoints.

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 cardiovascular (CV) (potential major adverse CV events, hospitalized unstable angina, and hospitalized congestive heart failure), and venous thromboembolism/pulmonary embolism, (2) independent assessment committees evaluated blinded data for fracture, and hepatic, and renal events, (3) an Independent Data Monitoring Committee (IDMC) reviewed unblinded serious adverse events (all) 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 360 adult subjects into the study. A total of 344 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 (All Randomized Subjects)

(Study 28431754-DIA3012: All Randomized Subjects Analysis Set)

	Pbo/Sita (N=115) n (%)	Cana 100 mg (N=115) n (%)	Cana 300 mg (N=114) n (%)	Cana Total (N=229) n (%)	Total (N=344) n (%)
Subjects who were randomized	115 (100)	115 (100)	114 (100)	229 (100)	344 (100)
Subjects who were randomized, but not dosed	0	2 (1.7)	0	2 (0.9)	2 (0.6)
Subjects in the mITT analysis set	115 (100)	113 (98.3)	114 (100)	227 (99.1)	342 (99.4)
Subjects in the mITT analysis set who discontinued before the Week 52 visit	37 (32.2)	17 (14.8)	25 (21.9)	42 (18.3)	79 (23.0)
Subjects in the mITT analysis set who received rescue therapy before the Week 52 visit	19 (16.5)	5 (4.3)	3 (2.6)	8 (3.5)	27 (7.8)
Subjects in the extension mITT analysis set[a]	77 (67.0)	102 (88.7)	96 (84.2)	198 (86.5)	275 (79.9)
Subjects in the Week 52 completers analysis set[b]	62 (53.9)	91 (79.1)	86 (75.4)	177 (77.3)	239 (69.5)
Subjects in the safety analysis set	115 (100)	113 (98.3)	114 (100)	227 (99.1)	342 (99.4)
Subjects in the extension safety analysis set[c]	90 (78.3)	103 (89.6)	96 (84.2)	199 (86.9)	289 (84.0)

[a] 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 who met 1 of the following 5 criteria:

- On dual combination metformin and pioglitazone, both agents at protocol-specified doses* (stable doses for at least 16 weeks prior to screening), with an HbA_{1c} of ≥7.0% and ≤10.5% at screening (or at Week -2, if screening measurement is more than 3 weeks prior to Week -2)

  or

- On dual combination metformin and pioglitazone (stable doses for at least 8 weeks prior to screening), with either agent at a dose *below* protocol-specified*, with an HbA_{1c} of ≥7.5 % and ≤11.0% at screening, *and* has an HbA_{1c} of ≥7.0% and ≤10.5% at Week -2, after at least 8 weeks on stable protocol-specified* doses of metformin and pioglitazone

  or

- On dual combination metformin and rosiglitazone, with an HbA_{1c} of ≥7.0% and ≤10.5% at screening (stable doses for at least 8 weeks prior to screening), *and* has an HbA_{1c} of ≥7.0% and ≤10.5% at Week -2, after at least 8 weeks on stable protocol-specified* doses of metformin and pioglitazone

  or

- On a peroxisome proliferator-activated receptor gamma (PPARγ) agent (pioglitazone or rosiglitazone) in dual combination with another oral antihyperglycemic agent (AHA), with an HbA_{1c} of ≥7.0% and ≤10.5% at screening (stable doses for at least 8 weeks prior to screening), *and* has an HbA_{1c} of ≥7.0% and ≤10.5% at Week -2, after at least 8 weeks on stable protocol-specified* doses of metformin and pioglitazone

  or

- On metformin, a PPARγ agent (pioglitazone or rosiglitazone), and a sulphonylurea (SU) (or meglitinide) or a dipeptidyl peptidase-4 (DPP-4) inhibitor in triple combination therapy with an HbA_{1c} of ≥6.5% and ≤9.5% at screening (stable doses for at least 8 weeks prior to screening), *and* has an HbA_{1c} of ≥7.0% and ≤10.5% at Week -2, after at least 8 weeks on stable protocol-specified* doses of metformin and pioglitazone

*Protocol-specified doses = metformin ≥2,000 mg per day (or ≥1,500 mg per day, if unable to tolerate a higher dose) and pioglitazone 30 mg or 45 mg per day.

Test Product, Dose and Mode of Administration, Batch No.: Canagliflozin capsules containing active 100 mg (batch/lot numbers: 09K16/G002, 09J30/G002, 30845.6, 32783.1) or 300 mg (batch/lot numbers: PD3157, PD3156, PD3307, PD3391, PD3393, PD3403, 32783.8) for oral administration.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo to match canagliflozin (batch/lot numbers: PD3220, 09J28/G001, 30845.2, 32580.4) and commercially available sitagliptin supplied by the sponsor (batch/lot nos.: 10C31/G018, 30485.2, 32783.9).

Duration of Treatment: The total duration of the study, which included the optional prescreening visit, the 52-week double blind treatment phase, and the 4-week follow-up is approximately 59 weeks (for subjects on a protocol-specified dose of metformin and pioglitazone at study entry) to 78 weeks (for subjects not on a protocol specified dose of metformin and pioglitazone at study entry).

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

Criteria for Evaluation: The key efficacy measure at Week 52 was HbA_{1c}. Additional measures of efficacy at Week 52 included FPG; body weight, body mass index (BMI) and waist circumference; SBP and DBP; fasting plasma lipids (LDL-C, HDL-C, non-HDL-C, total cholesterol, and triglycerides), use of rescue medication, and fasting measure of beta-cell function (ie, HOMA2%-B).

Safety was evaluated based on adverse events, safety laboratory tests (hematology, serum chemistry, urinalysis, and pregnancy test), hypoglycemic episodes (eg, collected from the subject diary provided to subjects), 12-lead electrocardiograms (ECGs), vital sign measurements (blood pressure and pulse rates), body weight, physical examinations, and self-monitored blood glucose (SMBG).

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. No study hypotheses were tested for evaluation at the Week 52 timepoint.

Efficacy: The primary efficacy analysis of changes from baseline in HbA_{1c} at 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 dose of pioglitazone at randomization [30 or 45 mg]) 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; and waist circumference and BMI. The least-squares means (LS means) for the change from baseline values at Week 52 and each timepoint 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.

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, serious adverse events leading to discontinuation of study drug, and serious drug-related adverse events were summarized by treatment group for the entire double-blind treatment 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 (UTI) 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 initiation of glycemic rescue medication* and *regardless of use of glycemic rescue medication*. Predefined limits of change and descriptive statistics were provided for other safety parameters for the entire 52-week double-blind treatment phase, including all data, regardless of the initiation of rescue medication.

Summaries of laboratory parameters, vital signs and ECGs (including predefined limits of change [PDLCs]) from baseline to Week 52 were provided.

RESULTS:

STUDY POPULATION:

Subject and Treatment Information and Baseline Characteristics

A total of 877 subjects were screened, and a total of 344 subjects were randomly assigned to study treatment. There were 342 mITT subjects (randomized subjects who received at least 1 dose of double-blind study medication), of whom 275 (80%) subjects entered the extension period and did not take rescue medications in the core period, comprising the extension mITT analysis set. The mITT analysis set and the safety analysis set (mITT, as treated) were identical. The 52-week completers' analysis set excludes subjects who were rescued prior to the Week 52 visit (n=27) or who discontinued double-blind study drug before the Week 52 visit (n=79); overall, 239 subjects were in the completer's population (note: some subjects were rescued and then did not complete the 52 double-blind week treatment phase). As shown in the tabular summary below, throughout the 52-week study period, a higher proportion of subjects in the placebo/sitagliptin group (32%) discontinued the study compared with the canagliflozin 100 mg (15%) or 300 mg (22%) groups. The most frequent reason for discontinuation was "Other" (nearly 12%, occurring more frequently in the placebo/sitagliptin group).

The rate of discontinuations was lower for subjects during the extension period (extension safety analysis set) relative to the entire double-blind treatment phase (mITT analysis set): 13% in the placebo/sitagliptin group, 7% in the canagliflozin combined group, and 9% over all treatments.

Reasons for Discontinuation (mITT)

(Study 28431754-DIA3012: Modified Intent-To-Treat Analysis Set)

Subject Disposition Category	Pbo/Sita (N=115) n (%)	Cana 100 mg (N=113) n (%)	Cana 300 mg (N=114) n (%)	Cana Total (N=227) n (%)	Total (N=342) n (%)
Total number of subjects discontinued	37 (32.2)	17 (15.0)	25 (21.9)	42 (18.5)	79 (23.1)
Primary reason for discontinuation[a]					
Adverse event	7 (6.1)	2 (1.8)	5 (4.4)	7 (3.1)	14 (4.1)
Creatinine or eGFR withdrawal criteria	0	3 (2.7)	2 (1.8)	5 (2.2)	5 (1.5)
Lack of efficacy on rescue therapy	1 (0.9)	0	0	0	1 (0.3)
Lost to follow-up	1 (0.9)	1 (0.9)	3 (2.6)	4 (1.8)	5 (1.5)
Noncompliance with study drug	0	1 (0.9)	1 (0.9)	2 (0.9)	2 (0.6)
Physician decision	1 (0.9)	3 (2.7)	2 (1.8)	5 (2.2)	6 (1.8)
Protocol violation	1 (0.9)	0	0	0	1 (0.3)
Withdrawal of consent	1 (0.9)	1 (0.9)	0	1 (0.4)	2 (0.6)
Unable to take protocol defined rescue therapy	2 (1.7)	1 (0.9)	0	1 (0.4)	3 (0.9)
Other	23 (20.0)	5 (4.4)	12 (10.5)	17 (7.5)	40 (11.7)

[a] As indicated by the investigator on the eCRF for mITT subjects who discontinued before the Week 52 visit.

Note: Percentages calculated with the number of subjects in each group as denominator.

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The overall mean duration of subject exposure (prior to rescue medication) for the 52-week double-blind treatment period was modestly greater in the canagliflozin groups compared with placebo, with 78% of subjects in the canagliflozin groups having at least 50 weeks of exposure, compared with 54% of subjects in the placebo/sitagliptin group. In the placebo/sitagliptin group, given the higher number of subjects who were rescued, subject exposure including exposure after initiation of rescue medication was modestly higher than when including only exposure prior to rescue therapy. For the canagliflozin groups, there was no meaningful increase in exposure when exposure after rescue therapy was included.

Baseline Characteristics

Baseline demographic characteristics were generally similar across treatment groups, with the exception of modest differences across treatment groups in the proportions of individuals in different race groups and by ethnicity, unlikely to meaningfully impact treatment responses. The median age of subjects in the study was 57 years, and a higher proportion of men than women were randomly assigned. Consistent with the regions of the world in which subjects were recruited, approximately 74% of the subjects were white, with approximately 16% of subjects Asians, and 6% of subjects black or African-American; approximately 16% of subjects were of Hispanic or Latino ethnicity.

Baseline weight and BMI were generally similar across treatment groups, with means of 94.1 kg and 32.5 kg/m^2, respectively, and with about 61% of the subjects being obese (BMI $\geq$30 kg/m^2). Subjects had mild to moderate hyperglycemia at baseline reflected by a baseline mean HbA_{1c} ranging from 7.9 to 8.0% across groups, with median HbA_{1c} values slightly lower than mean values. Subjects had a mean duration of diabetes of approximately 10 years; overall, approximately 20% of subjects were reported to have a history of a diabetic microvascular complication (1 or more of retinopathy, nephropathy, or neuropathy).

EFFICACY RESULTS:

In the extension mITT analysis set, the LS mean change from baseline in HbA_{1c} at Week 52 was -1.07% for the canagliflozin 300 mg group and -0.98% for the canagliflozin 100 mg group. In both treatment groups, decreases from baseline were most rapid through Week 12, and were more gradual through Week 34, with small changes subsequently observed. The results for the mITT analysis set were similar to

those for the extension mITT analysis set, with only slightly smaller reductions from baseline in HbA_{1c} for both canagliflozin 300 mg (-1.03%) and 100 mg (-0.92%) seen in the mITT analysis set.

Substantial glycemic improvements (in the proportion to <7.0% HbA_{1c} goal and FPG) were seen, with greater reductions seen with canagliflozin 300 mg relative to canagliflozin 100 mg. In addition to improvements in glucose control, reductions in body weight and in SBP, and increases in HDL-C were seen with canagliflozin, as well as an increase in LDL-C and the LDL-C/HDL-C ratio.

Change from Baseline to Week 52 for Efficacy Endpoints - LOCF

(Study 28431754-DIA3012: Extension mITT Analysis Set)

	-------- Cana 100 mg -------		-------- Cana 300 mg -------	
Endpoints	LS Mean	(95% CI)	LS Mean	(95% CI)
HbA_{1c} Change (%)	-0.98	(-1.120; -0.847)	-1.07	(-1.207; -0.926)
Achieving 7% HbA_{1c} target	52.94		64.58	
FPG Change (mmol/L)	-1.60	(-1.901; -1.292)	-1.85	(-2.166; -1.540)
Body Weight %Change (%)	-2.9	(-3.8; -2.0)	-4.0	(-5.0; -3.1)
Systolic BP Change (mmHg)	-3.50	(-5.635; -1.357)	-4.27	(-6.469; -2.067)
Diastolic BP Change (mmHg)	-2.26	(-3.788; -0.731)	-2.49	(-4.055; -0.917)
HDL-C %Change (%)	7.4	(4.0; 10.8)	11.8	(8.4; 15.3)
LDL-C %Change (%)	11.7	(4.9; 18.5)	13.2	(6.2; 20.2)
Ratio of LDL-C to HDL-C (%)	6.1	(-0.7; 12.9)	3.0	(-4.0; 10.0)
Total Cholesterol (%)	6.8	(3.1; 10.6)	8.6	(4.7; 12.4)
Non-HDL-C (%)	7.3	(1.9; 12.7)	8.1	(2.6; 13.7)
Triglycerides %Change (%)	4.8	(-3.6; 13.3)	0.4	(-8.3; 9.1)

Note: For continuous endpoints, the within-in group least squares mean change from baseline and CI are based on ANCOVA models with terms for treatment and stratification factor and adjusting for the baseline value as a covariate.

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SAFETY RESULTS:

Adverse Events: The overall incidence of subjects with adverse events for the safety analysis set over the 52-week treatment phase was similar in the canagliflozin 300 mg and the placebo/sitagliptin groups, and slightly lower in the canagliflozin 100 mg group. Compared with the placebo/sitagliptin group, the incidence of drug-related adverse events was higher in the canagliflozin 300 mg group and lower in the canagliflozin 100 mg group. The higher rate of drug-related adverse events in the 300 mg group was largely due to a higher incidence of several specific adverse events discussed below. The overall incidences of serious adverse events, adverse events leading to discontinuation, and adverse events related to study drug leading to discontinuation were low and not meaningfully different across treatment groups. There were no subjects with serious adverse events related to study drug or deaths reported during the 52-week treatment period. The overall incidence of adverse events that occurred in the 26-week extension period was similar in the canagliflozin 300 mg and placebo/sitagliptin groups, but slightly higher in the canagliflozin 100 mg group. Only 1 discontinuation due to an adverse event (in the placebo/sitagliptin group) was seen during the extension period, with a low incidence of serious adverse events, higher in the canagliflozin groups, none considered as related to study drug or leading to discontinuation.

Summary of Adverse Events During Entire Double-Blind Treatment Period (Safety) - Regardless of Rescue Medication
(Study 28431754-DIA3012: Safety Analysis Set)

Number (%) of subjects with at least one TEAE of following types	Pbo/Sita (N=115) n (%)	Cana 100 mg (N=113) n (%)	Cana 300 mg (N=114) n (%)	Cana Total (N=227) n (%)
Any adverse events	88 (76.5)	79 (69.9)	87 (76.3)	166 (73.1)
Adverse events leading to discontinuation	7 (6.1)	2 (1.8)	5 (4.4)	7 (3.1)
Adverse events related to study drug[a]	27 (23.5)	22 (19.5)	33 (28.9)	55 (24.2)
Adverse events related to study drug[a] and leading to discontinuation	6 (5.2)	2 (1.8)	3 (2.6)	5 (2.2)
Serious adverse events	6 (5.2)	8 (7.1)	7 (6.1)	15 (6.6)
Serious adverse events leading to discontinuation	1 (0.9)	0	2 (1.8)	2 (0.9)
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

Note: Percentages calculated with the number of subjects in each group as denominator.
[a] Related to study drug includes relationship determined by investigators: possibly related, probably related and very likely related.
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Summary of Adverse Events During Extension Period (Extension Safety) - Regardless of Rescue Medication
(Study 28431754-DIA3012: Extension Safety Analysis Set)

Number (%) of subjects with at least one TEAE of following types	Pbo/Sita (N=90) n (%)	Cana 100 mg (N=103) n (%)	Cana 300 mg (N=96) n (%)	Cana Total (N=199) n (%)
Any adverse events	41 (45.6)	53 (51.5)	46 (47.9)	99 (49.7)
Adverse events leading to discontinuation	1 (1.1)	0	0	0
Adverse events related to study drug[a]	5 (5.6)	7 (6.8)	9 (9.4)	16 (8.0)
Adverse events related to study drug[a] and leading to discontinuation	1 (1.1)	0	0	0
Serious adverse events	1 (1.1)	5 (4.9)	3 (3.1)	8 (4.0)
Serious adverse events leading to discontinuation	0	0	0	0
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

Note: Percentages calculated with the number of subjects in each group as denominator.
[a] Related to study drug includes relationship determined by investigators: possibly related, probably related and very likely related.
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Over the entire double-blind treatment phase, adverse events were most frequently reported (ie, >10% of subjects in any treatment group) in the following system organ classes (SOCs): Gastrointestinal disorders; General disorders and administration site conditions; Infections and infestations; Injury, poisoning and procedural complications; Musculoskeletal and connective tissue disorders; Nervous system disorders; Respiratory, thoracic, and mediastinal disorders; and Skin and subcutaneous tissue disorders. For the Renal and urinary disorders and Reproductive system and breast disorders SOCs, higher incidences were observed in the canagliflozin groups relative to the placebo/sitagliptin group with the 95% CI around the between-group difference (for 1 or both canagliflozin groups) from placebo/sitagliptin excluding "0". The higher incidence of events in the Renal and urinary disorders SOC was primarily related to a higher incidence of adverse events of pollakiuria. The higher incidence in the Reproductive system and breast disorders SOC was related to several adverse events occurring at a low incidence (≤2% in a canagliflozin group), but not reported in the placebo/sitagliptin group, with the most common including balanitis and several terms reflecting symptomatic vulvovaginal adverse events. The adverse events that were common (incidence ≥5% in one or the other canagliflozin groups) included the following: diarrhea, peripheral

edema, nasopharyngitis, upper respiratory tract infection, urinary tract infection, vulvovaginal mycotic infection, hypoglycemia, arthralgia, back pain, headache, pollakiuria, and hypotension. The incidence of drug-related adverse events was lower in the canagliflozin 100 mg group relative to the placebo/sitagliptin group (19.5% and 23.5%, respectively) and slightly higher in the canagliflozin 300 mg group (28.9%). The slight increase in the canagliflozin 300 mg group was related to the osmotic diuresis-related adverse events and to vulvovaginal adverse events. The overall incidence of episodes of documented hypoglycemia was generally low and similar in each treatment group (4% in the canagliflozin 100 mg group and 6% in the canagliflozin 300 mg and placebo/sitagliptin groups).

Safety Laboratory Assessments: Small increases from baseline in hemoglobin concentration were observed at Week 52 compared with baseline in the canagliflozin 100 mg and 300 mg groups (4.9% and 5.6%, respectively) compared with a slight decrease from baseline in the placebo/sitagliptin group (-1.6%). For estimated glomerular filtration rete (eGFR), small to moderate mean percent decreases were observed at Week 52 in the canagliflozin 100 mg and 300 mg groups (-1.6% and -5.3%, respectively) and in the placebo/sitagliptin group (-3.9%). No meaningful differences were observed across groups in the proportion of subjects meeting PDLC criteria for a decrease in eGFR. Small to moderate mean percent increases from baseline in serum creatinine were observed at Week 52 in the canagliflozin 100 mg and 300 mg groups (2.3% and 5.6%, respectively) and in the placebo/sitagliptin group (4.3%). The median percent changes in serum creatinine were also small across groups. Moderate mean percent increases from baseline in blood urea nitrogen (BUN) were observed at Week 52 in the canagliflozin 100 mg and 300 mg groups (13.6% and 21.3%, respectively) compared with a small decrease in the placebo/sitagliptin group (-1.5%). For alanine aminotransferase (ALT), small to moderate mean percent decreases from baseline were observed at Week 52 in the canagliflozin 100 mg and 300 mg groups (-3.1% and -7.0%, respectively) relative to a small increase in the placebo/sitagliptin group (1.9%). Aspartate aminotransferase (AST) and alkaline phosphatase showed negligible mean percent increases in the canagliflozin 100 mg group (0.1% and 0.2%, respectively) and small mean percent increases in the canagliflozin 300 mg group (1.0% and 2.0%, respectively); in the placebo/sitagliptin group, there was a moderate mean percent increase in AST (3.5%) and a moderate mean percent decrease in alkaline phosphatase (-6.7%). For gamma-glutamyl transferase (GGT), moderate mean percent decreases from baseline were observed in the canagliflozin 100 mg and 300 mg groups (-7.5% and -14.0%, respectively) relative to a smaller decrease in the placebo/sitagliptin group (-1.2%). For bilirubin, moderate mean percent increases were observed with canagliflozin 100 mg and 300 mg (13.6% and 13.2%, respectively), with a small decrease in the placebo/sitagliptin group (-2.3%); however, no increase in the median percent change from baseline in bilirubin in any treatment group was observed, indicating that the mean percent change reflects the influence of outlier values.

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 and ECG.

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

CONCLUSION(S):

- Over a 52-week double-blind treatment phase, canagliflozin provided clinically important and sustained glycemic improvements (in HbA_{1c} change from baseline, proportion to <7.0% HbA_{1c} goal, and FPG), with greater reductions seen with canagliflozin 300 mg relative to canagliflozin 100 mg. In addition to improvements in glucose control, reductions in body weight and in SBP were seen with canagliflozin. Canagliflozin treatment led to an increase in HDL-C, but also led to an increase in LDL-C, with smaller increases in non-HDL-C and no notable change in the LDL-C/HDL-C ratio.
- Canagliflozin was overall generally well tolerated, with a safety profile showing an increase in adverse events of genital mycotic infections, and in adverse events related to osmotic diuresis (eg,

polyuria, pollakiuria) or reduced intravascular volume (eg, postural dizziness), and no increase in adverse events of UTI, relative to the placebo/sitagliptin group.

- Overall, this 52-week study met the key primary and secondary hypotheses, suggesting sustained glycemic efficacy with both canagliflozin doses (with the canagliflozin 300 mg dose providing additional benefit compared with the 100 mg dose), and with an agent that was overall well-tolerated, with an adverse event profile consistent with prior observations.