Janssen Research & Development

Clinical Study Report Synopsis
[Protocol 28431754DIA3006; 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.: 28431754DIA3006

Title of Study: A Randomized, Double-Blind, Placebo- and Active-Controlled, 4-Arm, Parallel Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-28431754 (Canagliflozin) Compared with Sitagliptin and Placebo in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Monotherapy

Study Name: CANTATA-D

EudraCT Number: 2009-016525-34

NCT No.: NCT01106677

Clinical Registry No.: CR017023

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

Study Center(s): 169 study centers in 22 countries, including 55 centers in North America (50 in the United States [US], 5 in Mexico), 40 centers in Europe[a][1] (3 in Bulgaria, 5 in Czech Republic, 4 in Estonia, 3 in Greece, 3 in Italy, 5 in Latvia, 5 in Poland, 2 in Portugal, 8 in Slovakia, and 2 in Sweden), 23 centers in Central/South America (7 in Argentina, 8 in Colombia and 8 in Peru), and 51 centers in the rest of world (10 in India, 5 in Malaysia, 11 in Russia, 2 in Singapore, 6 in Thailand, 5 in Turkey and 12 in Ukraine).

Publication (Reference): None.

Study Period: 07 April 2010 to Week 52 database lock on 17 August 2012

Phase of Development: 3

Objectives: This study was designed to assess the efficacy, safety, and tolerability of canagliflozin in subjects with T2DM with inadequate glycemic control on a maximally effective dose of metformin in monotherapy. The primary objectives were to assess the effect of canagliflozin relative to placebo on HbA_{1c} after 26 weeks of treatment and to assess the safety and tolerability of canagliflozin.

The secondary objectives after 52 weeks of treatment were to assess the effect of canagliflozin relative to sitagliptin on: fasting plasma glucose (FPG), body weight, proportion of subjects with HbA_{1c} <7.0% or <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 blood pressure (SBP) and diastolic blood pressure (DBP), time to rescue therapy and proportion of

[a][1] Includes the European Union, European Economic Area, European Free Trade Association countries

subjects receiving rescue therapy, and fasting measure of beta-cell function (ie, homeostasis model assessment [HOMA-B]).

This CSR presents the results through Week 52 and other information relevant to both Period I (Day 1 to Week 26) and Period II (Week 26 to 52); detailed data relating to the Period I is presented in a separate CSR (referred to as the Period I CSR in the following sections).

Methodology: This study was a randomized, double-blind, 4-arm, parallel-group, global multicenter study, conducted to evaluate the efficacy, safety, and tolerability of canagliflozin in subjects with T2DM who were inadequately controlled with metformin immediate release (IR) monotherapy.

It was planned that approximately 1,260 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 metformin IR monotherapy (on a dose of ≥2,000 mg/day, or ≥1,500 mg/day, if unable to tolerate a higher dose) would be randomly assigned in a 2:2:2:1 ratio to once daily administration of canagliflozin 100 mg, canagliflozin 300 mg, sitagliptin 100 mg, or matching placebo added to stable doses of metformin IR in monotherapy and entered into the 52-week treatment period, composed of a 26-week, placebo- and active-controlled, double-blind treatment period (Period I) followed by a 26-week active-controlled, double-blind period (Period II).

Several safety 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 and also cardiovascular (CV) events (major adverse cardiovascular events plus events of hospitalized unstable angina [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 event and CV events, (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 1,260 subjects into the study. A total of 1,284 subjects were randomly assigned to placebo, canagliflozin 100 mg, canagliflozin 300 mg, sitagliptin 100 mg, and placebo in a 2:2:2:1 ratio. 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-DIA3006: All Randomized Subjects Analysis Set)

	Pbo/Sita (N=183) n (%)	CANA 100 mg (N=368) n (%)	CANA 300 mg (N=367) n (%)	CANA Total (N=735) n (%)	Sita 100 mg (N=366) n (%)	Total (N=1284) n (%)
Subjects who were randomized	183 (100)	368 (100)	367 (100)	735 (100)	366 (100)	1284 (100)
Subjects in the mITT analysis set	183 (100)	368 (100)	367 (100)	735 (100)	366 (100)	1284 (100)
Subjects in the mITT analysis set who discontinued before the Week 52 visit	45 (24.6)	70 (19.0)	68 (18.5)	138 (18.8)	81 (22.1)	264 (20.6)
Subjects in the mITT analysis set who received rescue therapy before the Week 52 visit	46 (25.1)	54 (14.7)	34 (9.3)	88 (12.0)	66 (18.0)	200 (15.6)
Subjects in the extension mITT analysis set [a]	128 (69.9)	311 (84.5)	320 (87.2)	631 (85.9)	295 (80.6)	1054 (82.1)
Subjects in the Week 52 completers analysis set [b]	98 (53.6)	246 (66.8)	268 (73.0)	514 (69.9)	238 (65.0)	850 (66.2)
Subjects in the PP analysis set	98 (53.6)	244 (66.3)	265 (72.2)	509 (69.3)	237 (64.8)	844 (65.7)
Subjects in the safety analysis set	183 (100)	368 (100)	367 (100)	735 (100)	366 (100)	1284 (100)
Subjects in the extension safety analysis set [c]	153 (83.6)	316 (85.9)	321 (87.5)	637 (86.7)	313 (85.5)	1103 (85.9)

Key: CANA=canagliflozin, Pbo/Sita=placebo/sitagliptin, Sita=sitagliptin

[a] Includes mITT subjects who entered Period II and didn't receive rescue medication in Period I.

[b] Includes mITT subjects who completed the Week 52 visit and had not initiated rescue medication.

[c] Includes mITT subjects who entered Period II. 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.

Diagnosis and Main Criteria for Inclusion: Man or woman ≥18 and ≤80 years of age with T2DM who met 1 of the following 4 criteria:

- on metformin IR monotherapy at a stable protocol-specified dose* for at least 8 weeks before screening and had an HbA_{1c} of ≥7.0% and ≤10.5% at screening (or at Week -2, if screening measurement was more than 3 weeks before Week -2)

  or

- on metformin XR monotherapy at a protocol-specified dose* with an HbA_{1c} of ≥7.0% and ≤10.5% at screening and had a Week -2 visit HbA_{1c} of ≥7.0% and ≤10.5%, after at least 8 weeks on a stable protocol-specified dose* of metformin IR

  or

- on metformin monotherapy (IR or XR) at a dose <2,000 mg/day with an HbA_{1c} of ≥7.5% and ≤11.0% at screening and had a Week -2 visit HbA_{1c} of ≥7.0% and ≤10.5%, after at least 8 weeks on a stable protocol-specified dose* of metformin IR

  or

- on metformin (IR or XR) in combination with an sulphonylurea (SU) with an HbA_{1c} of ≥6.5% and ≤9.5% at screening and had a Week -2 visit HbA_{1c} of ≥7.0% and ≤10.5%, after at least 8 weeks on a stable protocol-specified dose* of metformin IR

*Protocol-specified dose of metformin: ≥2,000 mg/day (or ≥1,500 mg/day, if unable to tolerate a higher dose)

Test Product, Dose and Mode of Administration, Batch No.: Canagliflozin capsules containing active 100 mg (batch/lot numbers: 32783.1, 09J30/G002, 09K06/G002, PD3092, PD3387, PD3390) and 300 mg (batch/lot numbers: 30845.14, 32783.8, 09K06/G003, 09L02/G003, PD3154, PD3155, PD3156, PD3304, PD3305, PD3393, PD3397) for oral administration.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo to match canagliflozin (batch/lot numbers: 30845.2, 32580.4, 09J28/G001, 09L16/G001, PD3220, PD3221) and sitagliptin 100 mg (batch/lot numbers: 30009.1, 30485.2, 10C31/G018, PD3234, PD3280).

Duration of Treatment: The total duration of the study, which included the optional prescreening visit, the 2-week run-in period, the 52-week double-blind treatment phase, and the 4-week follow-up is approximately 59 (for subjects on a protocol-specified dose of metformin at study entry) to 71 weeks (for subjects not on a protocol-specified dose of metformin IR at study entry).

Evaluations: The primary efficacy measure at Week 52 was $HbA_{1c.}$ Secondary measures of efficacy at Week 52 included FPG, body weight, BMI and waist circumference, use of glycemic rescue therapy, fasting lipid profile, and systolic and diastolic blood pressure.

Safety was evaluated based on the following measures: adverse events, safety laboratory tests (hematology, serum chemistry, urinalysis, and pregnancy tests), hypoglycemic episodes, 12-lead electrocardiograms (ECGs), vital sign measurements (blood pressure and pulse rate), 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 (optional) pharmacogenomics component of the study to allow for pharmacogenomic research, as necessary.

Statistical Methods:

Sample Size Determination: The primary hypothesis of this study was that canagliflozin is superior to placebo in reducing HbA_{1c} from baseline at Week 26. Assuming a group difference of 0.5% between canagliflozin and placebo group, and a common standard deviation of 1.0% with respect to the change in HbA_{1c}, and using a 2-sample, 2-sided t-test with type I error rate of 0.05, it was estimated that 86 subjects per treatment group would be required to achieve 90% power to demonstrate the superiority of canagliflozin over placebo.

Efficacy: The primary efficacy endpoint was the change in HbA_{1c}, from baseline through Week 26. The key secondary efficacy endpoint was the change in HbA_{1c}, from baseline through Week 52. The LOCF method was applied when the Week 52 values were missing. In subjects receiving rescue therapy, their measurements made before rescue were used as the last observations.

An analysis of covariance (ANCOVA) model with treatments (canagliflozin, placebo, and sitagliptin) and the stratification factor (whether the subject was on metformin monotherapy or metformin and an SU agent at screening) as fixed effects and HbA_{1c} baseline value as covariate, based on the mITT analysis set, was used for the primary efficacy analysis in the study. The treatment difference (canagliflozin minus placebo) in the least-squares (LS) means and the 2-sided 95% confidence interval (CI) were estimated based on this model. The p-values for the testing of superiority in terms of HbA_{1c} were calculated by comparing the LS means.

The analysis of major secondary efficacy endpoints was performed using the mITT analysis set; analyses based on the PP analysis set were performed as supportive analyses. The continuous secondary endpoints (change from baseline in FPG, SBP, percent change from baseline in fasting HDL-C, fasting triglycerides, and body weight at Week 52) were analyzed with an ANCOVA model similar to the primary efficacy endpoint (ie, treatment and stratification factor as fixed effects, and the corresponding baseline value as a covariate).

Two families of hypotheses were defined relative to the comparisons with placebo at Week 26 and the comparisons with sitagliptin at Week 52, respectively. In Family 1, the testing of the first 2 hypotheses between canagliflozin and placebo on the reduction of HbA_{1c} constituted the primary comparisons. The comparison with sitagliptin in Family 2 was initiated after the superiority of canagliflozin to placebo in the primary comparisons was established.

Safety: The overall incidence (ie, number and percent of subjects with 1 or more adverse event in each category) of adverse events, serious adverse events, 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. Adverse events which were defined in the protocol as requiring the collection of additional information and additional analysis included: urinary tract infections, vulvovaginitis and genital infections in men. Descriptive statistics for the additional information collected for fracture adverse events, cardiovascular adverse events, and skin (photosensitivity) adverse events were provided. 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.

RESULTS:

Subject and Treatment Information

A total of 2,883 subjects were screened and a total of 1,284 subjects were randomly assigned to study treatment. Overall, more than 79% of the randomly assigned subjects completed 52 weeks of treatment, with a modestly higher proportion in both canagliflozin groups completing relative to the sitagliptin and placebo/sitagliptin groups. A modest proportion of subjects in the canagliflozin groups (12% in the 2 groups combined) received rescue therapy, compared with a moderate proportion of subjects in the sitagliptin and placebo/sitagliptin groups (18% and 25%, respectively). The all randomized subjects analysis set, mITT analysis set (randomized subjects who received at least 1 dose of double-blind study medication), and the safety analysis set (mITT, as treated) were all identical. Among subjects who completed the 52-week double-blind treatment period without rescue therapy initiated (ie, the completers' analysis set), 6 (0.7%) subjects (2 in the canagliflozin 100 mg group, 3 in the canagliflozin 300 mg group, and 1 in the sitagliptin 100 mg group were identified prior to database lock with pre-specified protocol deviations that could affect the interpretation of the key secondary efficacy endpoint and, hence, were excluded from the PP analysis set (pre-specified in the SAP). There were no notable differences between treatment groups with respect to the percentage of subjects with protocol deviations.

Reasons for Discontinuation (mITT)
(Study 28431754-DIA3006: Modified Intent-To-Treat Analysis Set)

	Pbo/Sita (N=183) n (%)	CANA 100 mg (N=368) n (%)	CANA 300 mg (N=367) n (%)	CANA Total (N=735) n (%)	Sita 100 mg (N=366) n (%)	Total (N=1284) n (%)
Primary Reason for Discontinuation [a]	45 (24.6)	70 (19.0)	68 (18.5)	138 (18.8)	81 (22.1)	264 (20.6)
Adverse Event	8 (4.4)	20 (5.4)	12 (3.3)	32 (4.4)	17 (4.6)	57 (4.4)
Creatinine or eGFR Withdrawal Criteria	3 (1.6)	5 (1.4)	5 (1.4)	10 (1.4)	5 (1.4)	18 (1.4)
Death	0	0	1 (0.3)	1 (0.1)	1 (0.3)	2 (0.2)
Lack of Efficacy on Rescue Therapy	3 (1.6)	1 (0.3)	0	1 (0.1)	4 (1.1)	8 (0.6)
Lost to Follow-Up	3 (1.6)	3 (0.8)	7 (1.9)	10 (1.4)	6 (1.6)	19 (1.5)
Noncompliance with Study Drug	0	3 (0.8)	0	3 (0.4)	0	3 (0.2)
Physician Decision	5 (2.7)	4 (1.1)	4 (1.1)	8 (1.1)	6 (1.6)	19 (1.5)
Pregnancy	0	1 (0.3)	0	1 (0.1)	0	1 (0.1)
Protocol Violation	2 (1.1)	1 (0.3)	0	1 (0.1)	3 (0.8)	6 (0.5)
Study Terminated by Sponsor	0	1 (0.3)	1 (0.3)	2 (0.3)	0	2 (0.2)
Withdrawal of Consent	6 (3.3)	7 (1.9)	16 (4.4)	23 (3.1)	7 (1.9)	36 (2.8)
Unable to Take Protocol Defined Rescue Therapy	0	0	0	0	1 (0.3)	1 (0.1)
Other	15 (8.2)	24 (6.5)	22 (6.0)	46 (6.3)	31 (8.5)	92 (7.2)

Key: CANA=canagliflozin, eGFR=estimated glomerular filtration rate, Pbo/Sita=placebo/sitagliptin, Sita=sitagliptin
[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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Reasons for Discontinuation for Subjects Who Entered Period II (Extension Safety)
(Study 28431754-DIA3006: Extension Safety Analysis Set)

	Pbo/Sita (N=153) n (%)	CANA 100 mg (N=316) n (%)	CANA 300 mg (N=321) n (%)	CANA Total (N=637) n (%)	Sita 100 mg (N=313) n (%)	Total (N=1103) n (%)
Primary Reason for Discontinuation [a]	15 (9.8)	18 (5.7)	22 (6.9)	40 (6.3)	28 (8.9)	83 (7.5)
Adverse Event	1 (0.7)	1 (0.3)	5 (1.6)	6 (0.9)	9 (2.9)	16 (1.5)
Creatinine or eGFR Withdrawal Criteria	2 (1.3)	4 (1.3)	3 (0.9)	7 (1.1)	2 (0.6)	11 (1.0)
Death	0	0	0	0	1 (0.3)	1 (0.1)
Lack of Efficacy on Rescue Therapy	2 (1.3)	0	0	0	4 (1.3)	6 (0.5)
Lost to Follow-Up	0	2 (0.6)	2 (0.6)	4 (0.6)	2 (0.6)	6 (0.5)
Physician Decision	2 (1.3)	3 (0.9)	2 (0.6)	5 (0.8)	3 (1.0)	10 (0.9)
Protocol Violation	1 (0.7)	0	0	0	0	1 (0.1)
Withdrawal of Consent	1 (0.7)	3 (0.9)	2 (0.6)	5 (0.8)	1 (0.3)	7 (0.6)
Unable to Take Protocol Defined Rescue Therapy	0	0	0	0	1 (0.3)	1 (0.1)
Other	6 (3.9)	5 (1.6)	8 (2.5)	13 (2.0)	5 (1.6)	24 (2.2)

Key: CANA=canagliflozin, eGFR=estimated glomerular filtration rate, Pbo/Sita=placebo/sitagliptin, Sita=sitagliptin
[a] As indicated by the investigator on the eCRF for extension safety 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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For the mITT analysis set, the most common reason for withdrawal from the study was in the category of "Other" leading to 7.2% of subjects discontinuing. If subjects decided to discontinue from the study, but agreed to post-study follow-up, this was classified as “Other”. The most common specific reasons in the category of "Other" were (1) withdrawal of study drug/agreed to have follow-up: withdrawal of study drug 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 a rat carcinogenicity study results [see sample consent form]), (2) an error with the drug supply packing list that led to unblinding (specifically, centers were inadvertently supplied with unblinding information on packing lists [in boxes supplying study drug]) ─ the sponsor required that the affected subjects be discontinued, and (3) subjects who moved away from the investigational site. The second most common reason for discontinuation from the study was in the category of “Adverse Event” leading to 4.4% of subjects discontinuing. The third most common reason for discontinuation was “Withdrawal of consent” (3.8%), which was also related to the re-consenting for the rat carcinogenicity findings (subjects withdrew consent for continuing on study drug and for post-study follow-up contacts).

For the extension safety analysis set, discontinuations in the sitagliptin and placebo/sitagliptin group were more common than in the canagliflozin groups. This difference was mainly driven by a higher proportion of subjects in the sitagliptin group (2.9%) discontinuing due to “Adverse Event”, and in the sitagliptin and placebo/sitagliptin group (1.3% in both groups) discontinuing due to “lack of efficacy on rescue therapy,” relative to either canagliflozin group.

The overall mean duration of subject exposure (prior to rescue medication) for subjects in the mITT analysis set over the 52-week double-blind treatment phase was greater in the canagliflozin groups compared with sitagliptin and placebo/sitagliptin, with 70.2% of subjects in the combined canagliflozin group having at least 50 weeks of exposure, compared with 65.0% in the sitagliptin group and 55.2% of subjects in the placebo/sitagliptin group. The overall mean duration of subject exposure (regardless of rescue medication) for subjects in the extension safety analysis set was similar across all treatment groups.

Baseline Characteristics

Baseline demographic characteristics for the mITT analysis set were generally similar across treatment groups. The median age of subjects was approximately 56 years, and a higher proportion of women than men were randomly assigned to double-blind study drug treatment. Consistent with the regions of the world in which subjects were recruited, 70.2% of the subjects were white, with approximately 14.2% of subjects Asian, and 3.5% of subjects black or African-American; approximately 29% of subjects were of Hispanic or Latino ethnicity.

The baseline mean body weight for the mITT analysis set was 87.2 kg, and the baseline mean BMI was 31.8 kg/m^2 in the randomized population, with the baseline weight and BMI generally similar across treatment groups. More than half of the subjects were obese (BMI $\geq$30 kg/m^2).

Subjects had mild to moderate hyperglycemia at baseline reflected by a baseline mean HbA_{1c} of 7.9% for the overall study population, with values that were comparable across treatment arms and approximately 85% of subjects having a baseline HbA_{1c} <9.0%. The mean duration of diabetes in randomized subjects was 6.9 years (median 5.7 years), as expected since patients were already on monotherapy or dual combination AHA therapy at screening. Approximately 20% of subjects had a history of at least 1 diabetic microvascular complication, consistent with the antecedent duration of disease.

The baseline demographic and anthropometric characteristics of subjects in Ext mITT analysis set and in extension safety analysis set were consistent with those of subjects in the mITT analysis set.

Baseline diabetic characteristics for subjects in the Ext mITT analysis set and extension safety analysis set were consistent with those of subjects in the mITT analysis set.

EFFICACY RESULTS:

Primary Endpoint: The primary efficacy analysis was the change from baseline in HbA_{1c} to Week 26, which was previously met and described in the Period I CSR.

Key Secondary Endpoint: Reductions in HbA_{1c} at Week 52 were observed with both doses of canagliflozin: LS mean changes from baseline of -0.88% and -0.73% in the canagliflozin 300 mg and 100 mg groups, respectively. In the sitagliptin group, the LS mean change from baseline was -0.72% at Week 52.

Secondary Endpoints: The other glycemic endpoints tested (body weight percent change, FPG change, systolic BP change, and HDL-C percent change) reached statistical significance for both doses. Statistical significance for lowering triglycerides was not met in the present study. See summary table below for details.

Change from Baseline to Week 52 LOCF for Primary and Secondary Efficacy Endpoints in Order of Predefined Hierarchical Testing Sequence (mITT)

(Study 28431754-DIA3006: Modified Intent-to-Treat Analysis Set)

Endpoints	CANA 100 mg (Sita-Subtracted) Mean (95% CI)	p-value [a]	CANA 300 mg (Sita-Subtracted) Mean (95% CI)	p-value [a]
HbA_{1c} Change (%)	0.00 (-0.119; 0.122)		-0.15 (-0.273; -0.031)	
Body Weight %Change (%)	-2.4 (-3.0; -1.8)	<0.001	-2.9 (-3.4; -2.3)	<0.001
FPG Change (mmol/L)	-0.48 (-0.738; -0.218)	<0.001	-0.98 (-1.241; -0.718)	<0.001
Systolic BP Change (mmHg)	-2.87 (-4.464; -1.276)	<0.001	-3.99 (-5.589; -2.389)	<0.001
Triglycerides %Change (%)	2.3 (-3.9; 8.5)	0.466	3.2 (-3.1; 9.5)	0.319
HDL-C %Change (%)	5.2 (2.5; 7.9)	<0.001	7.2 (4.4; 10.0)	<0.001

Key: BP=blood pressure, CANA=canagliflozin, CI=confidence interval, FPG=fasting plasma glucose, HbA_{1c}=glycosylated hemoglobin, HDL-C=high-density lipoprotein cholesterol, PPG=postprandial glucose.

[a] Nominal p-value.

Note: For continuous endpoints, the least squares mean is presented with associated p-values and CI based on ANCOVA models with terms for treatment and stratification factors and adjusting for the baseline value as a covariate.

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SAFETY RESULTS:

Adverse Events: The overall incidence of adverse events over the 52-week treatment period was generally similar across all the treatment groups, with a higher incidence in the canagliflozin 100 mg group (72.3%), compared to the canagliflozin 300 mg, sitagliptin, and placebo/sitagliptin groups (62.7%, 64.5% and 66.7%, respectively). The incidence of adverse events leading to discontinuation was low in all groups, but higher in the canagliflozin 100 mg group. The incidences of adverse events related to study drug were higher in the canagliflozin groups and sitagliptin group, relative to the placebo/sitagliptin group. The incidence of serious adverse events and serious adverse events leading to discontinuation was low and similar across groups. One death occurred each in the canagliflozin 300 mg, sitagliptin, and placebo/sitagliptin groups. None were considered related to study drug.

The overall incidence of adverse events that occurred in Period II was similar across all the treatment groups, with adverse events leading to discontinuation higher in sitagliptin group relative to the canagliflozin or placebo/sitagliptin groups, and adverse events related to study drug higher in canagliflozin groups and sitagliptin group, relative to the placebo/sitagliptin group. Higher incidences of serious adverse events and serious adverse events leading to discontinuation were observed in sitagliptin group relative to the canagliflozin or placebo/sitagliptin groups.

The adverse events that were common (incidence ≥5% in any treatment group) included the following: diarrhea, nasopharyngitis, upper respiratory tract infection, urinary tract infection, arthralgia, back pain, headache, and pollakiuria. The incidence of pollakiuria and urinary tract infection was higher in the canagliflozin groups, relative to the sitagliptin or placebo/sitagliptin groups. For the other common adverse events, the incidences were higher in the sitagliptin and/or placebo/sitagliptin groups relative to the canagliflozin groups.. The overall incidence of adverse events that occurred in Period II (Week 26 to 52) was low. Similar low incidence of adverse events related to osmotic diuresis and reduced intravascular volume depletion, and renal-related adverse events were seen across all treatment groups.

There was a higher incidence of drug-related adverse events with canagliflozin treatment, with an incidence of 26.4% and 19.9% and in the canagliflozin 100 mg and 300 mg groups, respectively, and an incidence in sitagliptin and placebo/sitagliptin groups of 19.7% and 12.6%, respectively. This higher incidence in the canagliflozin groups was mainly due to a higher incidence of drug-related adverse events in the Infections and infestations SOC (such as urinary tract infection, vulvovaginitis and related terms), the Renal and urinary disorders SOC (such as pollakiuria and polydipsia), and the Reproductive system and breast disorders SOC (such as balanitis and vulvovaginal pruritus).

The incidence of drug related adverse events reported during Period II was lower across treatment groups than observed in Period I, and higher in the canagliflozin 100 mg (9.2%) and sitagliptin (8.9%) groups relative to canagliflozin 300 mg (5.0%) and placebo/sitagliptin (4.6%) groups.

Adverse Events During Entire Double-Blind Treatment Period (Safety) - Regardless of Rescue Medication

(Study 28431754-DIA3006: Safety Analysis Set)

Number (%) of Subjects with at least one TEAE of following Types	Pbo/Sita (N=183) n (%)	CANA 100 mg (N=368) n (%)	CANA 300 mg (N=367) n (%)	CANA Total (N=735) n (%)	Sita 100 mg (N=366) n (%)	Non-CANA (Pbo/Sita; Sita) (N=549) n (%)
Any adverse events	122 (66.7)	266 (72.3)	230 (62.7)	496 (67.5)	236 (64.5)	358 (65.2)
Adverse events leading to discontinuation	8 (4.4)	19 (5.2)	12 (3.3)	31 (4.2)	16 (4.4)	24 (4.4)
Adverse events related to study drug [a]	23 (12.6)	97 (26.4)	73 (19.9)	170 (23.1)	72 (19.7)	95 (17.3)
Adverse events related to study drug [a] and leading to discontinuation	3 (1.6)	12 (3.3)	5 (1.4)	17 (2.3)	6 (1.6)	9 (1.6)
Serious adverse events	7 (3.8)	15 (4.1)	12 (3.3)	27 (3.7)	18 (4.9)	25 (4.6)
Serious adverse events leading to discontinuation	2 (1.1)	4 (1.1)	5 (1.4)	9 (1.2)	6 (1.6)	8 (1.5)
Serious adverse events related to study drug [a]	0	1 (0.3)	1 (0.3)	2 (0.3)	0	0
Serious adverse events related to study drug [a] and leading to discontinuation	0	0	1 (0.3)	1 (0.1)	0	0
Deaths	1 (0.5)	0	1 (0.3)	1 (0.1)	1 (0.3)	2 (0.4)

Key: CANA=canagliflozin, Pbo/Sita=placebo/sitagliptin, SD=standard deviation, Sita=sitagliptin

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

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

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Adverse Events During Period II (Extension Safety) - Regardless of Rescue Medication

(Study 28431754-DIA3006: Extension Safety Analysis Set)

Number (%) of Subjects with at least one TEAE of following Types	Pbo/Sita (N=153) n (%)	CANA 100 mg (N=316) n (%)	CANA 300 mg (N=321) n (%)	CANA Total (N=637) n (%)	Sita 100 mg (N=313) n (%)	Non-CANA (Pbo/Sita; Sita) (N=466) n (%)
Any adverse events	63 (41.2)	138 (43.7)	119 (37.1)	257 (40.3)	134 (42.8)	197 (42.3)
Adverse events leading to discontinuation	1 (0.7)	0	1 (0.3)	1 (0.2)	8 (2.6)	9 (1.9)
Adverse events related to study drug [a]	7 (4.6)	29 (9.2)	16 (5.0)	45 (7.1)	28 (8.9)	35 (7.5)
Adverse events related to study drug [a] and leading to discontinuation	0	0	1 (0.3)	1 (0.2)	3 (1.0)	3 (0.6)
Serious adverse events	3 (2.0)	3 (0.9)	4 (1.2)	7 (1.1)	10 (3.2)	13 (2.8)
Serious adverse events leading to discontinuation	0	0	1 (0.3)	1 (0.2)	4 (1.3)	4 (0.9)
Serious adverse events related to study drug*	0	0	1 (0.3)	1 (0.2)	0	0
Serious adverse events related to study drug [a] and leading to discontinuation	0	0	1 (0.3)	1 (0.2)	0	0
Deaths	0	0	0	0	1 (0.3)	1 (0.2)

Key: CANA=canagliflozin, Pbo/Sita=placebo/sitagliptin, Sita=sitagliptin

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

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

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Safety Laboratory Assessment: Generally, only small differences in the canagliflozin groups relative to sitagliptin or placebo/sitagliptin were observed in mean changes from baseline over time for safety laboratory parameters. For ALT, dose-related small to moderate mean reductions from baseline were observed at Week 52 with canagliflozin treatment. Smaller mean decreases from baseline in the canagliflozin groups were seen for AST. Modest mean increases were observed in serum bilirubin in the canagliflozin groups. Small percent increases in mean percent change from baseline in serum creatinine levels were observed across treatment groups, with less increase in the canagliflozin 100 mg and 300 mg groups relative to the sitagliptin and placebo/sitagliptin groups. Similarly, reductions in eGFR were observed across the treatment groups, with smaller mean percent changes in the canagliflozin 100 mg and 300 mg groups and placebo/sitagliptin group relative to sitagliptin group. Moderate mean percent increases from baseline in BUN were observed at Week 52 in the canagliflozin 100 mg and 300 mg groups, relative to smaller increases in the sitagliptin and placebo/sitagliptin groups. Small increases in mean percent change from baseline in serum magnesium were seen at Week 52 in the canagliflozin 100 mg and 300 mg groups relative to minimum changes in the sitagliptin and placebo/sitagliptin groups. No notable mean changes from baseline were observed in serum electrolytes, including serum chloride, potassium, or sodium. Moderate mean percent decreases from baseline in serum urate were observed at Week 52 in the canagliflozin 100 mg and 300 mg groups relative to sitagliptin and placebo/sitagliptin groups, for which a small mean percent increase from baseline was observed.

Small increases from baseline in hemoglobin concentration were observed at Week 52 in the canagliflozin 100 mg and 300 mg groups compared with a decrease from baseline in the sitagliptin and placebo/sitagliptin groups. In the canagliflozin groups, the increases in hemoglobin were evident at Week 12 and remained generally stable through Week 52. Commensurate increases in blood erythrocytes and hematocrit were observed.

There was a mean percent reduction in urine pH in the canagliflozin 100 mg and 300 mg groups, respectively, and a mean percent increase in the sitagliptin and placebo/sitagliptin groups. These changes were seen at Week 26 and remained at the Week 52 assessment. No clinically meaningful differences in other parameters assessed by urine dipstick or in the urine sediment were observed at Week 52 in the canagliflozin relative to the placebo/sitagliptin group

Other Safety Assessments: In the canagliflozin 100 mg and 300 mg groups, reductions from baseline in SBP and lesser reductions from baseline in DBP were observed at Week 52, relative to changes observed in sitagliptin and placebo/sitagliptin groups. No notable change in pulse rate was observed across treatment groups.

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

CONCLUSIONS:

- Canagliflozin provide sustained and clinically important glycemic efficacy on a background of metformin over 52 weeks, with both doses of canagliflozin demonstrating non-inferiority on HbA_{1c}-lowering relative to sitagliptin, and with canagliflozin 300 mg providing statistically superior HbA_{1c}-lowering efficacy relative to sitagliptin.
- Statistically significant decreases in body weight for both doses of canagliflozin relative to sitagliptin over 52 weeks, as well as improvements in FPG and systolic BP for canagliflozin relative to sitagliptin were demonstrated in this study. A greater increase was observed for HDL-C for both canagliflozin doses, relative to the sitagliptin group. A small increase in LDL-C was observed with canagliflozin relative to sitagliptin, with a smaller increase in non-HDL-C, and with no change in the LDL-C/HDL-C ratio.
- Canagliflozin was overall well tolerated, with an increase in adverse events of genital mycotic infections, and in adverse events related to osmotic diuresis, and with a low incidence of hypoglycemia.

Overall, this study met the key primary and secondary hypotheses, suggesting a favorable efficacy profile with canagliflozin on a background of maximally effective doses of metformin, and a well characterized safety and tolerability profile with adverse events associated with treatment that are manageable and do not generally require discontinuation of treatment.