Janssen Research & Development

Clinical Study Report Synopsis
[Protocol 28431754DIA3004; Phase 3]

JNJ-28431754 (Canagliflozin)

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

SYNOPSIS

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

Status: Approved

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Prepared by: Janssen Research & Development, LLC

Protocol No.: 28431754DIA3004, Amendment INT-2

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 Canagliflozin Compared in the Treatment of Subjects With Type 2 Diabetes Mellitus Who Have Moderate Renal Impairment

Study Name: not applicable

EudraCT Number: 2009-017136-40

NCT No.: NCT01064414

Clinical Registry No.: CR017008

Coordinating/Principal Investigator(s): [redacted] Canada

Study Center(s): 89 study centers in 19 countries, including 28 centers in North America (19 in the United States, 8 in Canada, 1 in Mexico), 30 centers in Europe[a] (6 in Belgium, 6 in France, 5 in Germany, 1 in Italy, 3 in Latvia, 3 in Poland, 3 in Romania, 3 in Spain), 3 centers in Central/South America (3 in Brazil), and 28 centers in the rest of world (3 in Australia, 3 in India, 5 in Malaysia, 8 in Russia, 4 in New Zealand, 3 in South Africa, 2 in South Korea)

Publication (Reference): none

Study Period: 02 March 2010 to 02 August 2012; Week 52 database lock: 20 August 2012

Phase of Development: 3

Objectives: The primary objectives were (1) to assess the effect of the addition of canagliflozin relative to the addition of placebo on glycosylated hemoglobin (HbA_{1c}) after 26 weeks of treatment in adult subjects (≥25 years of age) with type 2 diabetes mellitus (T2DM) with inadequate glycemic control on their current diabetes treatment regimen and with moderate renal insufficiency and (2) to assess the safety and tolerability of canagliflozin relative to placebo. This Clinical Study Report (CSR) covers the results of the study through the Week 52 Visit. In addition to data included in the 26-week double-blind core period CSR (Week 26 CSR), this CSR includes data collected during the 26-week active controlled double-blind extension period (Week 26 to 52).

The secondary objectives were to assess the effect of the addition of canagliflozin relative to the addition of placebo after 26 and 52 weeks of treatment on: (1) fasting plasma glucose (FPG), (2) proportion of subjects achieving HbA_{1c} <7.0%, (3) systolic (SBP) and diastolic blood pressure (DBP), (4) proportion of

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

subjects receiving rescue medication and time to rescue medication, (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), (6) body weight, (7) renal function (estimated glomerular filtration rate [eGFR] and albumin to creatinine ratio [ACR]), and (8) over 26-weeks of treatment, assess exposure-response relationships of canagliflozin using a population pharmacokinetic (PK) modelling approach. An exploratory objective was to explore the relationship between responses to canagliflozin, as measured by the change in HbA_{1c} at Week 26 with genetic variations associated with T2DM and obesity.

Objectives in a subset of 125 subjects who underwent a 24-hour urine collection were to assess the effect of canagliflozin relative to placebo at Week 26 on: urinary glucose, urinary albumin, and urinary creatinine are described in the Week 26 CSR.

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 on their current diabetes treatment regimen.

Approximately 272 adult subjects (≥25 years of age) with T2DM who were inadequately controlled on their current diabetes treatment regimen (ie, HbA_{1c} of ≥7.0% and ≤10.5%) and had moderate renal impairment (eGFR ≥30 and <50 mL/min/1.73m^2) were randomized in a 1:1:1 ratio to addition of once-daily administration of canagliflozin 100 mg, canagliflozin 300 mg, or matching placebo added to their ongoing stable diabetes treatment regimen (eg, diet, exercise, and antihyperglycemic agent [AHA] therapy) 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).

A 24-hour urine collection substudy was to be performed in a subset of 125 subjects (from centers in countries that elected to participate) to measure urinary creatinine, albumin, and glucose.

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, and hepatic, and renal events, (3) an Independent Data Monitoring Committee (IDMC) reviewed unblinded serious adverse events and CV events, and (4) a company internal Medical Safety Review Committee (MSRC) monitored the safety of subjects participating in the study by reviewing blinded data on a regular basis.

Number of Subjects (planned and analyzed): Planned: Approximately 240 adult subjects were planned with 80 subjects per treatment group. Analyzed: A total of 272 subjects were randomized to placebo, canagliflozin 100 mg, and canagliflozin 300 mg in a 1:1:1 manner. With the permuted block randomization design of the study, the total number of subjects between treatment groups remained balanced despite the higher than anticipated enrollment. Therefore the global over enrollment had minimal impact on the planned statistical analysis for this study. 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-DIA3004: All Randomized Subjects Analysis Set)

	Placebo (N=91) n (%)	CANA 100 mg (N=90) n (%)	CANA 300 mg (N=91) n (%)	CANA Total (N=181) n (%)	Total (N=272) n (%)
Subjects who were randomized	91 (100)	90 (100)	91 (100)	181 (100)	272 (100)
Subjects who were randomized, but not dosed	1 (1.1)	0	2 (2.2)	2 (1.1)	3 (1.1)
Subjects in the mITT analysis set	90 (98.9)	90 (100)	89 (97.8)	179 (98.9)	269 (98.9)
Subjects in the mITT analysis set who discontinued before the Week 52 visit	26 (28.6)	23 (25.6)	13 (14.3)	36 (19.9)	62 (22.8)
Subjects in the mITT analysis set who received rescue therapy before the Week 52 visit	32 (35.2)	17 (18.9)	18 (19.8)	35 (19.3)	67 (24.6)
Subjects in the extension mITT analysis set [a]	63 (69.2)	67 (74.4)	77 (84.6)	144 (79.6)	207 (76.1)
Subjects in the Week 52 completer's analysis set [b]	40 (44.0)	50 (55.6)	59 (64.8)	109 (60.2)	149 (54.8)
Subjects in the safety analysis set	90 (98.9)	90 (100)	89 (97.8)	179 (98.9)	269 (98.9)
Subjects in the extension safety analysis set [c]	76 (83.5)	72 (80.0)	81 (89.0)	153 (84.5)	229 (84.2)

[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.
Key: CANA=canagliflozin, mITT=modified intent-to-treat, N=total number of subjects, n=total number of subjects in subgroup
Note: Percentages were calculated with the number of subjects in each group as denominator.
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Diagnosis and Main Criteria for Inclusion: Subjects enrolled in this study were required to meet all of the following key acceptance criteria at screening or at the indicated visit: (1) adult man or woman ≥25 years of age with T2DM (ie, women must be postmenopausal, surgically sterile, heterosexually active and practicing a highly effective method of birth control, or not heterosexually active); (2) have a HbA_{1c} ≥7.0% to ≤10.5% at (pre)screening and Week -2 visits; (3) have moderate renal impairment defined as eGFR values ≥30 and <50 mL/min/1.73m^2 at the Week -2 visit, together with generally stable renal function (ie, ≤25% decline in eGFR at Week-2 relative to the (pre)screening visit value); (4) either not on AHA therapy at screening (off for at least 12 weeks) or on a stable regimen of AHA in monotherapy or combination therapy (for at least 8 weeks prior to Week -2 and 12 weeks for pioglitazone) being used in accordance with local prescribing information (ie, local label[s]) for patients with T2DM and moderate renal impairment; and (5) have a FPG ≤270 mg/dL (15 mmol/L) at Week -2 visit. Subjects were required to adhere to the prohibitions and restrictions specified in the protocol and must have signed all required informed consent documents indicating an understanding of the purpose of and the procedures required to participate in the study.

Test Product, Dose and Mode of Administration, Batch No.: Canagliflozin capsules containing active 100 mg tablets (Lot nos: PD3092, 09K06/G002, PD3387, 32783.1) or 300 mg tablets (Lot nos: PD3307, PD3158, PD3395, 32783.3) for oral administration.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo capsules to match canagliflozin capsules in appearance (size and color) (batch/lot nos: PD3221, PD3220, 09L16/G001, 10I08/G001); oral administration as described above.

Duration of Treatment: The total duration of treatment was approximately 63 to 72 weeks for each subject, depending on the length of the pretreatment phase (included the optional prescreening visit, screening visit approximately 4-weeks before the Week -2 visit, an AHA adjustment period if needed, and the 2-week single-blind placebo run-in period [ie, Week -2 visit to baseline Day 1 visit]), the 26-week double-blind placebo-controlled core period, the 26-week double-blind, placebo-controlled extension phase, and a 30-day posttreatment phase for follow-up contact.

A separate CSR (Week 26 CSR) 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: 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%, BMI and waist circumference, the use of rescue medication, and time to initiation of rescue medication.

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

Renal safety assessments included eGFR, based upon serum creatinine, and ACR measured in the first morning urine collection (for both measures, used the mean of 2 determinations: 1 performed on the day prior to the visit and 1 on the visit day). The eGFR was calculated based on the 4-variable formula according to the Modification of Diet in Renal Disease (MDRD) study (Levey 2006), with the correction for the standardized creatinine method (Myers 2006; Stevens 2006). Additional measures of renal safety included urinalysis, and creatinine clearance (CrCl) calculated using the Cockroft-Gault formula (Cockcroft 1976). In addition, blood urea nitrogen (BUN), ACR, and CrCl were directly measured in a subset of 125 subjects undergoing 24-hour urine collections.

Pharmacokinetics: Venous blood samples were collected for determination of plasma trough concentrations of canagliflozin at specified time points to document the steady-state PK exposure of canagliflozin in subjects with moderate renal impairment.

Pharmacodynamics: Urine glucose and creatinine concentrations were measured from the first morning void at the time points specified in the Time and Events Schedule located in the protocol. Urinary glucose excretion (UGE) was calculated as the ratio of urine glucose and creatinine concentrations reported as glucose (mg)/creatinine (mg). Also 24-hour urine samples for glucose and creatinine measurements were collected in a subset of subjects.

Pharmacogenomics: A blood sample (10 mL) was collected on Day 1 from subjects who consented to participate in the pharmacogenomics component of the study to allow for pharmacogenomics research, as necessary.

Exploratory: Two blood samples (a 10-mL for plasma and a 8.5-mL for serum) and a 9-mL urine sample were collected at specified time points and archived to allow for exploratory research and biomarker assessment related to canagliflozin, T2DM, or obesity.

Statistical Methods:

Sample Size Determination: Sample size determination was based on the primary endpoint (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 treatments and stratification factors as fixed effects and adjustment for HbA_{1c} and eGFR baseline covariates, 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 time point through Week 52, and their 2-sided 95% 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 percentages of subjects with HbA_{1c} <7.0% and <6.5%, and subjects with at least 5% of body weight reduction were summarized by treatment group at Week 52. In addition, the percentages of subjects with HbA_{1c} <7.0% and <6.5% were analyzed with a logistic model with treatment and the stratification factors as fixed effects, and baseline HbA_{1c} and baseline eGFR as covariate using the LOCF approach. The odds ratios and their 2-sided 95% CIs for each canagliflozin group compared to placebo were derived from the model for descriptive purposes only, and no p-values were estimated.

Safety Analyses: 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.

Renal Safety Analyses

For renal safety endpoints including the changes in eGFR and ACR from baseline to Weeks 26 and to Week 52, an ANCOVA model was used with treatment and stratification factors as fixed effects and adjusting for the baseline covariate. Additional covariates explored and were prespecified in the study SAP. The treatment difference (ie, each canagliflozin dose minus placebo) in the LS means and their 2-sided 95% confidence interval (CI) were estimated based on this model.

Additionally, eGFR and the progression of albuminuria based on ACR were analyzed categorically at Week 26 and Week 52 as follows. Subjects were classified as having normoalbuminuria (ACR of <3.5 mg/mmol [<30 mg/g]), microalbuminuria (ACR ≥3.5 mg/mmol [≥30 mg/g] and ≤35 mg/mmol [≤300mg/g]), or macroalbuminuria (ACR of >35 mg/mmol [>300 mg/g]). Progression in albuminuria was defined as a change from (1) normoalbuminuria to either microalbuminuria or macroalbuminuria or

(2) microalbuminuria to macroalbuminuria. The proportion of subjects who experienced progression in albuminuria from baseline to the endpoint visit (ie, Week 26 and Week 52) was analyzed using logistic regression with terms for treatment and stratification factors, and baseline ACR as a covariate. Additionally, the proportion of subjects with ≥30% and ≥50% decline in eGFR were analyzed using a similar logistic regression model.

Other renal safety parameters, such as the change from baseline in CrCl (measured directly in a subset of subjects who have 24-hour urine collections and calculated by the Cockcroft-Gault formula), serum creatinine, and BUN, were summarized descriptively by visit.

Pharmacokinetic Analyses: The PK data from this study was to be integrated with plasma concentration-time data collected across other clinical development studies and subjected to population PK analysis for the investigation of the potential effects of demographic characteristics and other subject covariants on the PK of canagliflozin.

Pharmacodynamic Analyses: The change in the urinary glucose to creatinine ratio from baseline through Week 52 was summarized using descriptive statistics.

RESULTS:

STUDY POPULATION:

Subject and Treatment Information and Baseline Characteristics

A total of 1,910 subjects were screened and a total of 272 subjects were randomized to study treatment. Overall, 77.2% 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 was 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.

Reasons for Discontinuation During the Entire Double-Blind Phase
(Study 28431754-DIA3004: Modified Intent-To-Treat Analysis Set)

Subject Disposition Category	Placebo (N=90) n (%)	CANA 100 mg (N=90) n (%)	CANA 300 mg (N=89) n (%)	CANA Total (N=179) n (%)	Total (N=269) n (%)
Primary reason for discontinuation [a]	26 (28.9)	23 (25.6)	13 (14.6)	36 (20.1)	62 (23.0)
Adverse event	6 (6.7)	5 (5.6)	4 (4.5)	9 (5.0)	15 (5.6)
Death	0	2 (2.2)	0	2 (1.1)	2 (0.7)
Lost to follow-up	1 (1.1)	0	0	0	1 (0.4)
Noncompliance with study drug	1 (1.1)	1 (1.1)	0	1 (0.6)	2 (0.7)
Physician decision	1 (1.1)	0	0	0	1 (0.4)
Protocol violation	2 (2.2)	1 (1.1)	2 (2.2)	3 (1.7)	5 (1.9)
Withdrawal of consent	5 (5.6)	3 (3.3)	3 (3.4)	6 (3.4)	11 (4.1)
Other	10 (11.1)	11 (12.2)	4 (4.5)	15 (8.4)	25 (9.3)

[a] As indicated by the investigator on the eCRF for mITT subjects who discontinued before the Week 52 visit.
Key: CANA=canagliflozin, eCRF=electronic case report form, mITT=modified intent-to-treat, N=total number of subjects, n=total number of subjects in subgroup
Note: Percentages were calculated with the number of subjects in each group as denominator.

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The most common reason for discontinuation was the category of "Other" (9.3% of subjects), followed by adverse events (5.6%), and withdrawal of consent (4.1%). Withdrawal of consent was generally due to the requirement to re-sign a revised informed consent form (implemented during the ongoing study conduct) that included updated information on preclinical safety findings (specifically, updated information on rat carcinogenicity study results). The category of "Other" reasons for discontinuation included a variety of reasons, with the most common related to a site closed by an ethics committee due to the preclinical carcinogenicity findings (Site [redacted] with 6 subjects); no other discernible pattern was evident (other reasons, generally involving 2 or 3 subjects included transportation issues getting to the study site, subject moving from the area, family- or job-related issues, lack of time to continue to participate in study visits, subject perceived lack of efficacy, use of disallowed therapy) and also included several subjects who did not want to continue on study drug (related to the preclinical carcinogenicity findings) but agreed to continued follow-up (and hence were not classified as withdrawal of consent).

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 54.4% of subjects in the canagliflozin 100 mg group and 68.5% of subjects in the canagliflozin 300 mg group having at least 50 weeks of exposure, compared with approximately 45.6% of subjects in the placebo group.

Baseline Characteristics

Baseline demographic characteristics in the mITT population were generally similar across treatment groups. The median age of subjects in the study was 69 years, and approximately 61% of subjects were men. Consistent with the regions of the world in which subjects were recruited, approximately 80% of the subjects were white, 10% of subjects were Asian, and 1.9% of subjects black or African American; approximately 8% of subjects were of Hispanic or Latino ethnicity.

Baseline mean weight for the mITT analysis set was 91.2 kg and baseline mean body mass index (BMI) was 33.0 kg/m^2; these were generally similar across treatment groups, with approximately 68% 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} of 7.9% to 8.0% across all groups, with similar median values. Subjects had a mean duration of diabetes of slightly more than 16 years, as would be anticipated in subjects who have already developed moderate renal insufficiency. Approximately 80% of subjects had a reported history of 1 or more diabetic microvascular complications, consistent with the long duration of diabetes prior to study entry and presence of renal disease.

EFFICACY RESULTS:

In the mITT analysis set, the LS mean reductions in HbA_{1c} relative to placebo of -0.41% and -0.27% in the canagliflozin 300 mg and 100 mg groups, respectively (with the 95% CI for the between-group difference for the canagliflozin 300 mg dose and placebo excluding "0" and the difference for the canagliflozin 100 mg and placebo including "0"), at Week 52 were similar to those observed at Week 26.

With regard to other endpoints, canagliflozin also provided moderate numerical improvements in FPG over the 52-week double-blind treatment phase, with maximal efficacy already achieved by Week 6, and a modest progressive increase in FPG. At Week 52, the reduction in the canagliflozin 300 mg group was slightly greater than in the canagliflozin 100 mg group, however throughout the entire 52 week period, FPG decreases in both canagliflozin groups were of similar magnitude without a clear dose response.

In addition to the substantial glycemic improvements observed, body weight was meaningfully reduced over the 52-week study with canagliflozin at both doses studied (placebo-subtracted change from baseline difference of -1.5% and -1.1% for the 100 mg and 300 mg doses, respectively).

The results of additional efficacy endpoint at Week 52 are summarized in the table below.

Change from Baseline to Week 52 for Primary and Secondary Efficacy Endpoints (LOCF)
(Study 28431754-DIA3004: Modified Intent-to-Treat Analysis Set)

	CANA 100 mg (Placebo-Subtracted)		CANA 300 mg (Placebo-Subtracted)	
Endpoints	LS Mean[a]	(95% CI)	LS Mean[a]	(95% CI)
HbA_{1c} Change (%)	-0.27	(-0.532;0.001)	-0.41	(-0.676;-0.142)
FPG Change (mmol/L)	-0.65	(-1.536;0.236)	-0.80	(-1.695;0.089)
Achieving 7.0% HbA_{1c} target[b]	1.21	(0.54; 2.72)	1.75	(0.79; 3.89)
Body Weight Percent Change (%)	-1.5	(-2.6;-0.4)	-1.1	(-2.2;-0.0)
Systolic BP Change (mmHg)	-5.49	(-9.301;-1.676)	-6.69	(-10.53;-2.858)
HDL-C Percent Change (%)	1.9	(-2.9;6.8)	2.8	(-1.9;7.6)
Triglycerides Percent Change (%)	2.5	(-9.9;14.9)	-0.8	(-13.0;11.4)

Key: AHA=antihyperglycemic agent, ANCOVA=analysis of covariance, BP=blood pressure, CANA=canagliflozin, CI=confidence interval, CV=cardiovascular, eGFR=estimated glomerular filtration rate, HbA_{1c}=glycosylated hemoglobin, HDL-C=high-density lipoprotein cholesterol, FPG=fasting plasma glucose, LOCF=last observation carried forward

[a] For continuous endpoints, the pairwise comparison and CIs were based on an ANCOVA model with treatment, AHA washout, and atherosclerotic CV disease history as factors, and baseline eGFR and baseline vlue as covariates.

[b] For achieving 7.0% HbA_{1c} target, value presented is the odds ratio and the CI based on the logistic regression model with treatment, AHA washout, atherosclerotic CV disease history, and baseline eGFR as factors and baseline HbA1cas covariate.

SAFETY RESULTS:

Adverse Events: The overall incidence of adverse events during the 52-week treatment phase was slightly higher in the placebo group as compared to the canagliflozin groups. The incidence of drug-related adverse events was slightly higher in the canagliflozin 100 mg group, and moderately higher in the canagliflozin 300 mg group, as compared to the placebo group. Most specific adverse events that were reported as drug related were reported only once with only a few terms reported in 2 or more subjects (eg, hypoglycemia, pollakiuria). The overall incidence of adverse events leading to discontinuation was low across treatment groups, and similar in the canagliflozin 100 mg and placebo groups, with a slightly lower incidence in the canagliflozin 300 mg group. The incidence of serious adverse events was slightly lower for the canagliflozin 100 mg and 300 mg groups than for placebo. Few serious adverse events leading to discontinuation or serious adverse events related to study drug occurred, with the incidence not meaningfully different across groups.

There were 6 deaths reported during the 52-week double-blind treatment phase (including the 30-day follow-up period), with 2 deaths reported in the placebo group and 4 deaths in the canagliflozin 100 mg group. Additionally, 3 subjects died more than 30 days after discontinuation from the study, including 2 subjects in the canagliflozin 100 mg dose group and 1 subject in the placebo group. There were no deaths reported in the canagliflozin 300 mg group. None of the deaths or adverse events with an outcome of death were considered as drug-related by the investigator.

Summary of Adverse Events During the Entire Double-Blind Treatment Phase – Regardless of Rescue Medication
(Study 28431754-DIA3004: Safety Analysis Set)

Number (%) of subjects with at least 1 adverse event of following types	Placebo (N=90) n (%)	CANA 100 mg (N=90) n (%)	CANA 300 mg (N=89) n (%)	CANA Total (N=179) n (%)
Any adverse events	78 (86.7)	77 (85.6)	72 (80.9)	149 (83.2)
Adverse events leading to discontinuation	6 (6.7)	6 (6.7)	4 (4.5)	10 (5.6)
Adverse events related to study drug [a]	23 (25.6)	24 (26.7)	31 (34.8)	55 (30.7)
Adverse events related to study drug [a] and leading to discontinuation	2 (2.2)	1 (1.1)	1 (1.1)	2 (1.1)
Serious adverse events	24 (26.7)	18 (20.0)	21 (23.6)	39 (21.8)
Serious adverse events leading to discontinuation	4 (4.4)	4 (4.4)	3 (3.4)	7 (3.9)
Serious adverse events related to study drug [a]	2 (2.2)	1 (1.1)	3 (3.4)	4 (2.2)
Serious adverse events related to study drug [a] and leading to discontinuation	1 (1.1)	0	1 (1.1)	1 (0.6)
Deaths	2 (2.2)	4 (4.4)	0	4 (2.2)

[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 adverse events that occurred in the 26-week extension period (Week 26 to Week 52) was similar in the canagliflozin and placebo groups. The incidence of adverse events leading to discontinuation and adverse events related to the study drug was low in all the groups. A modestly higher incidence of drug-related adverse events was seen in the canagliflozin groups, relative to the placebo group; no substantive differences in other categories of adverse events were noted. The incidence of serious adverse events was similar across groups. The incidence of serious adverse events leading to discontinuation, as well as serious adverse events related to study drug, was low in all treatment groups. There were 3 deaths reported during the Extension Period and none of them were considered to be drug-related by the investigator.

Summary of Adverse Events During the Extension Period – Regardless of Rescue Medication

(Study 28431754-DIA3004: Extension Safety Analysis Set)

Number (%) of subjects with at least 1 adverse event of following types	Placebo (N=76) n (%)	CANA 100 mg (N=72) n (%)	CANA 300 mg (N=81) n (%)	CANA Total (N=153) n (%)
Any adverse events	52 (68.4)	49 (68.1)	53 (65.4)	102 (66.7)
Adverse events leading to discontinuation	1 (1.3)	2 (2.8)	2 (2.5)	4 (2.6)
Adverse events related to study drug [a]	8 (10.5)	10 (13.9)	11 (13.6)	21 (13.7)
Adverse events related to study drug [a] and leading to discontinuation	0	1 (1.4)	0	1 (0.7)
Serious adverse events	11 (14.5)	8 (11.1)	12 (14.8)	20 (13.1)
Serious adverse events leading to discontinuation	1 (1.3)	1 (1.4)	2 (2.5)	3 (2.0)
Serious adverse events related to study drug [a]	1 (1.3)	0	1 (1.2)	1 (0.7)
Serious adverse events related to study drug [a] and leading to discontinuation	0	0	0	0
Deaths	1 (1.3)	2 (2.8)	0	2 (1.3)

[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 mean percent increase in hemoglobin, a moderate rise in BUN, a moderate increase in serum creatinine, and small to moderate decreases in serum urate. A moderate mean percent increase in alanine aminotransferase (ALT) was observed in the canagliflozin 100 mg group, with a small decrease in the canagliflozin 300 mg group. No meaningful mean changes from baseline were observed in serum electrolytes, including serum sodium, chloride, bicarbonate, or potassium; a moderate increase in magnesium was observed in the canagliflozin groups with no notable change in the placebo group. Small increases in serum phosphate were observed with canagliflozin.

Other Safety Assessments: Treatment with canagliflozin 100 mg and 300 mg led to 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):

In subjects who have T2DM with moderate renal insufficiency, with a high incidence of comorbidities and diabetic complications:

- Over a 52-week double-blind treatment phase, 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 similar benefit at both canagliflozin doses.
- Over a 52-week double-blind treatment phase, both doses of canagliflozin provided clinically useful and statistically significant reductions in HbA_{1c}.
- Dose-dependent, numerical percent reductions in systolic blood pressure were observed with both doses of canagliflozin relative to placebo.
- In this population of subjects with moderate renal insufficiency who had substantial comorbidities and a high incidence of diabetic complications, canagliflozin was overall well tolerated.

- There was no increase in the incidence of female or male mycotic genital infections observed over the 52-week treatment period in the canagliflozin groups relative to placebo. There was an increase in the incidence of urinary tract infection adverse events with a higher canagliflozin dose, without an increase in upper tract infections or serious adverse events.
- There was an increase in adverse events related to osmotic diuresis (eg, thirst, pollakiuria), and in adverse events related to a reduction in intravascular volume (eg, hypotension, postural dizziness) with canagliflozin treatment; these generally occurred early after initiation of treatment, and were mild or moderate in intensity without requiring interruption or discontinuation of canagliflozin.
- Transient reductions in renal function were seen with canagliflozin treatment; these were generally reversible with continuing treatment— or, less frequently, reversible shortly after discontinuing canagliflozin, consistent with reductions in intravascular volume. There were no events that led to the requirement for renal replacement therapy.

Overall, this study in subjects with moderate renal insufficiency met the key primary and key secondary hypotheses, suggesting a favorable efficacy profile, and a safety and tolerability profile consistent with expectations.