

SYNOPSIS

<u>Name of Sponsor/Company</u>	Janssen Research & Development*
<u>Name of Investigational Product</u>	JNJ-28431754 (canagliflozin)

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Status: Approved
Date: 14 September 2017
Prepared by: Janssen Research & Development, LLC

Protocol No.: 28431754DIA4003

Title of Study: A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects With Type 2 Diabetes Mellitus

Study Name: The “CANVAS-R” Trial (CANagliflozin cardioVascular Assessment Study-Renal)

EudraCT Number: 2013-003050-25

NCT No.: NCT01989754

Clinical Registry No.: CR102647

Coordinating Investigator: Melanie Davies, MD - PPD

Study Center(s): Subjects were enrolled at 419 sites in 24 countries, including 87 centers in North America (58 in the US, 15 in Canada, 14 in Mexico), 234 centers in Europe (12 in Belgium, 8 in Czech Republic, 11 in France, 11 in Germany, 11 in Hungary, 14 in Italy, 21 in Netherlands, 21 in Poland, 30 in Russian Federation, 30 in Spain, 14 in Sweden, 32 in Ukraine, and 19 in the United Kingdom), 32 centers in Central/South America (12 in Argentina and 20 in Brazil) and 66 centers in the rest of the world (12 in Australia, 7 in China, 9 in Malaysia, 8 in New Zealand, 22 in South Korea, and 8 in Taiwan).

Publication (Reference): Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondou N, Shaw W, Law G, Desai M, Matthews DR. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *New England Journal of Medicine*. 2017 Jun 12. DOI: 10.1056/NEJMoa1611925

Neal B, Perkovic V, Matthews DR, et. al. Rationale, design and baseline characteristics of the CANagliflozin cardioVascular Assessment Study-Renal (CANVAS-R): A randomized, placebo-controlled trial. *Diabetes, Obesity and Metabolism*. 2017;19(3):387-393.

Neal B, Perkovic V, Mahaffey KW, et. al. Optimizing the analysis strategy for the CANVAS Program: A prespecified plan for the integrated analyses of the CANVAS and CANVAS-R trials. *Diabetes, Obesity and Metabolism*. 2017 ePub <http://onlinelibrary.wiley.com/doi/10.1111/dom.12924/full> Last accessed on 11 August 2017.

Study Period: The first subject was enrolled on 17 January 2014. The last visit for the last subject was on 23 February 2017. Final database lock was 28 March 2017.

Phase of Development: Phase 4**Objectives:****Primary Objective**

In subjects with T2DM receiving standard care, but had inadequate glycemic control and were at elevated risk of cardiovascular (CV) events, to assess the effect of canagliflozin compared to placebo on progression of albuminuria.

Secondary Objectives

In subjects with type 2 diabetes mellitus (T2DM) receiving standard care, but had inadequate glycemic control and were at elevated risk of CV events, to assess the effect of canagliflozin compared to placebo on:

the composite endpoint of death from CV causes or hospitalization for heart failure

death from CV causes

Methodology: This was a randomized, double-blind, placebo-controlled, parallel group, multicenter, Phase 4 study to evaluate the effects of canagliflozin compared to placebo on progression of albuminuria, an important intermediate marker of renal injury and progression of diabetic nephropathy. The study was conducted in subjects with T2DM, receiving standard of care for hyperglycemia and CV risk factors, who had either a history of or were at high risk of CV events. The planned total sample size was approximately 5,700 subjects. The effects of canagliflozin were evaluated against a background of standard of care for the treatment of hyperglycemia and CV risk factors, with study investigators counseled to assure appropriate management according to applicable national guidelines for the care of patients with T2DM, with treatment individualized as clinically appropriate.

Subjects meeting all inclusion and none of the exclusion criteria, and successfully completing the 2-week run-in period, were randomly allocated to initial treatment with canagliflozin 100 mg or matching placebo administered once daily (in a 1:1 ratio). After 13 weeks, the dose of canagliflozin (or matching placebo) was to be increased from 100 mg to 300 mg if the subject required additional glycemic control, provided the 100-mg dose was well tolerated.

Subjects were expected to be followed for a maximum of about 3.5 years. The DIA3008 and DIA4003 studies were scheduled for joint close-out and analysis when at least 688 cardiovascular events had been observed and the last participant who had undergone randomization had approximately 78 weeks of follow-up. The global trial end date (GTED) was the stopping date of the study (ie, targeted date when the last subject completed the last study visit) and all visits (including the 30-day off-drug follow-up visit) were to be completed prior to the GTED.

Several monitoring and adjudication committees were commissioned for this study, including an Academic Research Organization (ARO) which provided scientific and academic oversight and site monitoring for some sites; a Steering Committee of external scientific experts; an Independent Data Monitoring Committee (IDMC); an independent Endpoint Adjudication Committee (EAC), which reviewed blinded data for selected specific events; separate adjudication committees, which were employed to review cases of diabetic ketoacidosis (DKA), fracture, renal events, and pancreatitis; and a company internal Medical Safety Review Committee (MSRC).

Number of Subjects (planned and analyzed): It was planned to enroll 5,700 subjects in this study in order to accrue sufficient major adverse cardiovascular events (MACE) to meet the Food and Drug Administration (FDA) post-marketing requirement for combined enrollment across the CANVAS program and to have statistical power to demonstrate the superiority of canagliflozin over placebo for albuminuria progression.

A total of 5,813 subjects were randomized; however, 1 subject was randomized twice (ie, assigned 2 different subject IDs at 2 different sites). The subject is included only once in the Intent-to-treat (ITT), On-study and On-treatment analysis sets using the first subject ID assigned. Thus, 2,905 and 2,907 subjects were randomly assigned to the placebo and canagliflozin groups in the ITT analysis set, respectively. Two subjects randomly assigned to placebo and 3 subjects randomly assigned to canagliflozin were not dosed with study drug and hence were not included in the On-study and On-treatment analysis sets.

Analysis Sets

Analysis Set	Analysis Population	Data Period	Placebo (N)	Cana (N)
Randomized subjects	All randomized subjects	N/A	2906*	2907
Intent-to-treat (ITT)	Randomized subjects	Day 1 to the last trial contact date up to the GTED	2905	2907
On-study	Treated subjects	Day 1 to the last trial contact date up to the GTED	2903	2904
On-treatment	Treated subjects	Day 1 to the last dose date plus X ^a days or the last trial contact date, whichever was earlier.	2903	2904

* One subject was randomized at 2 different sites; only the first randomization was included in the analysis sets

Key: GTED = global trial end date (ie, the stopping date of the study and end of all visits, including the 30-day off-treatment follow-up visit); ITT= intent-to-treat

^a X is 2 days for laboratory (except ACR) and vital sign measurements, and 30 days for CV and mortality endpoints, and adverse events.

Diagnosis and Main Criteria for Inclusion:

Men and women with a diagnosis of T2DM with glycated hemoglobin (HbA_{1c}) level $\geq 7.0\%$ to $\leq 10.5\%$ at screening and either (1) not on antihyperglycemic agent (AHA) therapy at screening or (2) on AHA monotherapy or combination therapy with any approved agent: eg, sulfonylurea, metformin, pioglitazone, alpha-glucosidase inhibitor, glucagon-like peptide-1 (GLP-1) analog, dipeptidyl peptidase-4 (DPP-4) inhibitor, or insulin, who also had a history or high risk of CV events defined on the basis of either:

- age ≥ 30 years with documented symptomatic atherosclerotic CV events: including stroke; myocardial infarction (MI); hospital admission for unstable angina; coronary artery bypass graft; percutaneous coronary intervention (with or without stenting); peripheral revascularization (angioplasty or surgery); symptomatic with documented hemodynamically-significant carotid or peripheral vascular disease; or amputation secondary to vascular disease, or
- age ≤ 50 years with 2 or more of the following risk factors determined at the screening visit: duration of T2DM of 10 years or more, systolic blood pressure (SBP) > 140 mmHg (average of 3 readings) recorded at the screening visit, while the subject was on at least 1 blood pressure-lowering treatment, current daily cigarette smoker, documented micro- or macro-albuminuria (as defined in the study protocol) within 1 year of screening, or documented high-density lipoprotein cholesterol (HDL-C) of < 1 mmol/L (< 39 mg/dL) within 1 year of screening, were eligible for this study.

Test Product, Dose and Mode of Administration, Batch No.: Canagliflozin was supplied for this study as over-encapsulated 100- or 300-mg tablets in a gray-colored, hard, gelatin capsule. The over-encapsulated tablet was backfilled with microcrystalline cellulose to prevent the tablet from rattling in the capsule shell.

The bulk batch numbers for canagliflozin 100 mg were: 46567.10, 46567.4, 46567.5, 46567.8, 53061.4, HG-13F031, HG-13F032, HG-13F033, HG-13L048, HG-14G034, HG-14G038, HG-14I059, HG-14J063, and HG-15D024. The bulk batch numbers for canagliflozin 300 mg were: 46567.11, 46567.6, 46567.7,

EJTS9, HG-13F029, HG-13F030, HG-13H037, HG-14A004, HG-14G035, HG-14G036, HG-14G042, HG-14I054, HG-14I055, HG-14I058, HG-15E031, and HG-15E032.

Reference Therapy, Dose and Mode of Administration, Batch No.: Matching placebo capsules consisted of microcrystalline cellulose within a gray-colored, hard, gelatin capsule.

The bulk batch numbers for placebo were: 46567.2, 46567.3, HG-13E017, HG-13E018, HG-13F025, HG-14E022, HG-14G037, HG-14H053, 14F17/G001, 46567.12, 53061.3, HG-13E018, HG-13F025, HG-13K045, HG-14E022, HG-15C016, 14F17/G001, 46567.1, 46567.12, 46567.3, 53061.3, EHTSB, HG-13E018, HG-13F025, HG-13K045, HG-14D021, HG-14G037, HG-14H052, HG-14H053, and HG-15C017.

Duration of Treatment: The study consisted of a 2-week, single-blind placebo run-in period, followed by a double-blind treatment phase, and a 30-day post-treatment follow-up period. At Week 13, the dose of canagliflozin (or matching placebo) was to be increased from 100 mg to 300 mg if the subject required additional glycemic control, provided the 100-mg dose was well-tolerated. Subjects were expected to be followed for a maximum of about 3.5 years. The CANVAS (DIA3008) and CANVAS-R (DIA4003) studies were scheduled for joint close-out and analysis when at least 688 cardiovascular events had been observed and the last participant who had undergone randomization had approximately 78 weeks of follow-up. The GTED was the stopping date of the study (ie, targeted date when the last subject completed the last study visit) and all visits (including the 30-day off-drug follow-up visit) were to be completed prior to the GTED.

Criteria for Evaluation:

Efficacy: Efficacy was based on the following variables: urinary albumin/creatinine ratio (ACR), adjudicated CV death, hospitalization for heart failure, serum creatinine, HbA_{1c}, newly initiated anti-hyperglycemic therapy, renal death, and requirement for renal replacement therapy. The primary efficacy outcome was progression of albuminuria, defined as the development of micro-albuminuria or macro-albuminuria in a subject with baseline normo-albuminuria or the development of macro-albuminuria in a subject with baseline micro-albuminuria, accompanied by an ACR value increase of greater than or equal to 30% from baseline. Secondary efficacy endpoints were 1) the composite endpoint of death from CV causes (CV Death) or hospitalization for heart failure and, 2) death from CV causes (CV Death).

Safety: Safety was based on MACE events, incidence of serious adverse events and adverse events that led to study drug discontinuation, serious and nonserious selected adverse events of interest, clinical laboratory tests (hematology, serum chemistry, urinalysis, HbA_{1c}, and fasting lipid profile), vital sign measurements (blood pressure and pulse rate), and body weight.

Statistical Methods:

Study Hypotheses: The primary hypothesis of the study was: in subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk of CV events, canagliflozin compared to placebo reduces the rate of progression of albuminuria. The secondary hypothesis of the study was: in subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk of CV events, canagliflozin compared to placebo 1) reduces the composite endpoint of death from CV causes or hospitalization for heart failure, and 2) reduces death from CV causes.

Sample Size Determination: As per the FDA Guidance, analysis of a postmarketing safety trial alone, or together with a similar premarketing trial should demonstrate that the upper bound of the 2-sided 95% confidence interval (CI) of the CV risk ratio of test drug to comparator be less than 1.3. In the communications with the United States (US) FDA and the sponsor, the FDA indicated that the sponsor needed to rule out 1.3 as the upper bound of the CI using MACE (CV death, non-fatal MI, or non-fatal stroke). To accrue sufficient MACE within an appropriate time-period post-approval, the FDA requested initiation of a new dedicated study or expansion of the DIA3008 enrollment, in order to randomize a total

of 10,000 subjects. As a result of these discussions, the sponsor proposed to conduct a second CANVAS-like study (now referenced as CANVAS-R) with approximately 5,700 randomized subjects.

Based on the interim data from DIA3008, where ACR was measured periodically at scheduled visits, it was projected that the annual progression rate for the DIA4003 study would be approximately 7.4%. Assuming a 22% relative risk reduction for albuminuria progression, an annual progression rate in the placebo arm of 7.4%, an 18-month enrollment period, a maximum treatment period of 36 months, and an annual discontinuation (from treatment) rate of 10%, it was estimated that 693 events would be reported. With 5,700 subjects enrolled, the power to demonstrate the superiority of canagliflozin over placebo for albuminuria progression would be 90.5%, with type I error rate of 0.05 (two-sided).

Efficacy:

Primary Efficacy Endpoint: The primary efficacy endpoint was the time to the first occurrence of progression of albuminuria. The primary analysis was based on the ITT analysis set. Subjects without baseline and/or post-baseline ACR measurements were excluded from the primary efficacy analysis. Furthermore, subjects with macro-albuminuria at baseline (ACR >300 mg/g) were also excluded from the analysis. The primary efficacy analysis was based on results of ACR measurements from a single visit. The date of the progression/regression event was defined as the visit date of the first urine sample for the potential progression/regression findings.

For the ITT analysis, the time from Day 1 to first visit date observing progression (ie, using the visit date of the original sample collection) of albuminuria was analyzed. Endpoint events that occurred during the data period were considered as eligible events and the event dates were the first dates observing progression; otherwise, subjects were censored at the date of the last ACR measurement up to GTED.

The hazard ratio (HR) of canagliflozin compared to placebo and its 95% CI were estimated using a Cox proportional hazards regression model. The response variable in the model was time to progression and the model included treatment and baseline albuminuria status as the explanatory variables. Canagliflozin was considered superior to placebo in the reduction of progression if the p-value of the test of significance, ie, the Wald test from the Cox model specified above, was ≤ 0.05 in the context of the multiplicity adjustment. Subgroup analyses of the primary efficacy endpoint based on baseline demographic and disease characteristics were also performed, as well as additional supportive analyses.

Secondary Efficacy Endpoints: Analyses of the secondary endpoints used the ITT analysis set and were done using adjudicated events. Adjudication of these outcomes by the EAC was done in a blinded fashion. Subgroup analyses of the secondary efficacy endpoints based on baseline demographic variables and baseline disease characteristics were also performed.

The analysis of the composite of CV death or hospitalization for heart failure was based on time to the first occurrence of the composite event. The HR of canagliflozin compared to placebo and its 95% CI were estimated using a stratified Cox proportional hazards regression model with treatment as the explanatory variable and history of CV disease (secondary and primary prevention) as the stratification factor. The p-value from the stratified log-rank test for the treatment effect was also reported.

The analysis of CV death was based on time to the first occurrence of CV death. The HR of canagliflozin compared to placebo and its 95% CI were estimated using a stratified Cox proportional hazards regression model with treatment as the explanatory variable and history of CV disease (secondary and primary prevention) as the stratification factor. The p-value from the stratified log-rank test for the treatment effect was also reported.

Adjudicated MACE Events: Time to the first occurrence of MACE was analyzed using the ITT analysis set. The HR of all canagliflozin compared to placebo and its 95% CI was estimated using a stratified Cox proportional hazards model with treatment (all canagliflozin and placebo) as the explanatory variable and prior CV disease subgroup (secondary prevention and primary prevention) as the stratification factors. The p-value of the stratified log-rank test for treatment effect was also reported for the primary analysis. To assess the potential association between MACE events and volume depletion adverse events and fulfill a health authority postmarketing request, the HR was estimated using the same stratified Cox model as in the main analysis for events occurring within the first 30 days, and within the first 90 days post-randomization. In addition, Kaplan-Meier plots including data within the first 30 days and first 90 days are presented. Additionally, time to the first occurrence of each component of MACE as well as fatal/non-fatal MI and fatal/non-fatal stroke were analyzed using the same Cox model described above.

Multiplicity Adjustment: Per the statistical analysis plan (SAP) for the integrated analysis of the DIA3008 and DIA4003 studies, only one alpha family was proposed for the testing of the multiple hypotheses based on the integrated data and the DIA4003 data. The Type I error for these tests was strictly controlled via a gatekeeping procedure. If the MACE and the mortality endpoints in the integrated analysis succeeded in rejecting the null hypotheses, all of the alpha for testing (ie, 5%) was to pass to the testing of the primary and the secondary hypotheses in the DIA4003 study. The tests for the DIA4003 hypotheses were to proceed sequentially, conditional on the statistical significance of the hypothesis tests in the integrated analysis at the 5% significant level.

Safety: The safety analysis was based primarily on the On-Treatment analysis set; the analyses of malignancy, amputation, fracture and DKA were based primarily on the On-Study analysis set. Summaries, listings, and subject narratives were provided, as appropriate, for those subjects who died, who discontinued treatment due to an adverse event, who experienced a serious adverse event, or who experienced an adverse event of interest. Further analyses were conducted on the prespecified adverse events for which additional information was collected from the investigators, including male mycotic genital infections, hypoglycemia, selected malignancies, photosensitivity, venous thromboembolic events, fracture, amputation, and DKA. Predefined limit of change (PDLC) criteria for laboratory values and vital signs were prespecified in the SAP.

RESULTS:

STUDY POPULATION:

Subject Disposition and Study Completion/Withdrawal Information: A total of 7,801 subjects were screened and a total of 5,813 subjects were randomized; however, 1 subject was randomized twice (ie, assigned 2 different subject IDs at 2 different sites). The subject is included only once in the ITT and On-treatment analysis sets using the first subject ID assigned. Thus, 2,905 and 2,907 subjects were randomly assigned to the placebo and canagliflozin groups in the ITT analysis set, respectively. Two subjects randomly assigned to placebo and 3 subjects randomly assigned to canagliflozin were not dosed with study drug and hence were not included in the On-treatment analysis set.

Study completion information and vital status are summarized in the table below. The proportion of subjects who completed the study ($\geq 98.6\%$) and the proportion with known final vital status ($\geq 99.7\%$) was comparable in both treatment groups.

Study Completion and Vital Status (Study 28431754-DIA4003: All Randomized Subjects Analysis Set)

	Placebo (N=2906) n (%)	Cana (N=2907) n (%)	Total (N=5813) n (%)
Subjects in ITT analysis set	2905 (>99.9)	2907 (100)	5812 (>99.9)
Completed Study*	2866 (98.6)	2872 (98.8)	5738 (98.7)
Final vital status known**	2898 (99.7)	2901 (99.8)	5799 (99.8)
Alive	2792 (96.1)	2802 (96.4)	5594 (96.2)
Died	106 (3.6)	99 (3.4)	205 (3.5)
Final Vital Status Unknown	7 (0.2)	6 (0.2)	13 (0.2)

Note: *A subject is considered as having completed the study, regardless of whether the subject is on or off study drug, if the subject is followed until a time point between the notification of the GTED and the GTED, or until the time of death for subjects who died prior to the GTED.

Note: **Including results from the search of public records.

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

Note: One subject was randomized at 2 different sites and only the first randomization was included in the ITT analysis set.

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The annualized rate of study drug discontinuation was 9.5, and 11.4 per 100 subject-years in the canagliflozin and placebo group, respectively. The 2 most common reasons for discontinuation of study drug were subjects who decided to withdraw from study drug for personal reasons (ie, “withdrawn from study medication,” 7.4%) and adverse events leading to discontinuation (6.1%). Other specific reasons for discontinuation of study drug were less common.

Demographic and Baseline Characteristics: Baseline demographic, anthropometric, and disease history characteristics were generally similar between treatment groups. The median age of subjects was 64 years and 62.8% of subjects were men. Approximately 82% of the subjects were white, 8.4% of subjects identified as Asians, and 4.0% identified as Black or African-American; approximately 20% of subjects in each treatment group were Hispanic or Latino ethnicity. At sites in the US, 13.8% of subjects identified as African-American. Approximately 59% of subjects in each treatment group were obese (ie, body mass index [BMI] ≥ 30 kg/m²) based upon National Institutes of Health criteria, with a median BMI of 31.2 kg/m² for the total population.

Subjects had mild to moderate hyperglycemia at baseline, reflected by a mean baseline HbA_{1c} of 8.3%; approximately 25% of subjects had a baseline HbA_{1c} $\geq 9.0\%$. Subjects had a mean duration of diabetes of 13.7 years. Approximately 47% of the population had a history of 1 or more microvascular complications of diabetes and the distribution of microvascular diabetic complications was similar between treatment groups. The microvascular complications of diabetes included, in order of frequency, “Other diabetic neuropathy” (ie, diabetic neuropathy other than autonomic neuropathy), diabetic retinopathy, diabetic nephropathy, and autonomic neuropathy. With respect to baseline renal function, the mean estimated glomerular filtration rate (eGFR) was 75.9 mL/min/1.73m², and approximately 23% of subjects had a baseline eGFR < 60 mL/min/1.73m², with no notable difference between treatment groups. At baseline, 68.4% of subjects had normo-albuminuria, 22.7% of subjects had micro-albuminuria, 8.2% had non-nephrotic range macro-albuminuria, and 0.8% had nephrotic range macro-albuminuria. The proportion of subjects with a history of amputation was slightly higher in the placebo group (3.0%) than in the canagliflozin group (2.5%).

The treatment groups were also similar with respect to baseline cardiovascular disease characteristics. Although $>90\%$ of subjects had a history of hypertension, most subjects were normotensive at baseline. The treatment groups were well-controlled and well-balanced with respect to subjects with hyperlipidemia. Mean high-density lipoprotein cholesterol (HDL-C) was 1.17 mmol/L, mean low-density lipoprotein cholesterol (LDL-C) was 2.29 mmol/L, and median triglycerides were 1.70 mmol/L. Similar

proportions of subjects in both treatment groups had values above and below thresholds for HDL-C (ie, ≥ 1.01 mmol/L) and low-density lipoprotein cholesterol (LDL-C) (ie, > 1.81 mmol/L) at baseline.

Duration of Exposure to Study Drug: The overall mean duration of exposure to study drug was 94.44 weeks, with 43.2% exposed to study drug for ≥ 104 weeks, and 6.7% of subjects with ≥ 130 weeks of exposure. The total exposure to canagliflozin was 5,310.7 subject-years in the canagliflozin group and 5,199.9 subject years in the placebo group. A total of 1,972 (68.0%) subjects and 2,279 (78.5%) subjects in the canagliflozin and placebo groups, respectively, were up-titrated to the 300-mg dose of study drug during the study, while 929 (32.0%) subjects and 623 (21.5%) subjects in the canagliflozin and placebo groups, respectively, remained on 100 mg throughout the study. Most subjects in both the canagliflozin and placebo groups were up-titrated to 300 mg of study drug (or matching placebo) by Week 26; few additional subjects were up-titrated after Week 26.

Duration of Study: The mean and median duration of the study, including on-treatment and off-treatment follow-up, was 107.95 and 108.29 weeks, respectively, with comparable durations in both treatment groups.

EFFICACY RESULTS: As part of the testing sequence to control the type I error rate across the CANVAS program, all the p-values presented for the efficacy endpoints are nominal due to the statistically insignificant results of the hypothesis test for all-cause mortality in the integrated analysis of the pooled studies.

Primary Efficacy Analysis - Progression of Albuminuria: Progression of albuminuria occurred in fewer subjects randomized to canagliflozin compared to placebo (99.80 versus 153.01 per 1,000 subject-years, respectively) corresponding to a HR of 0.64 (95% CI: 0.57, 0.73; $p < 0.0001$).

Progression of Albuminuria (Study 28431754-DIA4003: Intent-To-Treat Analysis Set)

	----- Placebo -----		----- Cana -----		HR[b] (95% CI)	P-value[b][c]
	n/N(%)	EVRT[a]	n/N(%)	EVRT[a]		
Progression of Albuminuria[d]	635/2518 (25.2)	153.01	446/2541 (17.6)	99.80	0.64 (0.57, 0.73)	<.0001

Note: [a] Event rate per 1000 patient-years.

Note: [b] Hazard ratio (all canagliflozin compared to placebo) and its 95% CI are estimated using a Cox proportional hazard model including the effect of treatment and baseline albuminuria status.

Note: [c] P-values correspond to test of superiority at a two-sided significance level at 0.05.

Note: [d] Progression from baseline normoalbuminuria (ACR < 30 mg/g) to microalbuminuria (ACR ≥ 30 mg/g and ≤ 300 mg/g)/macroalbuminuria (ACR of > 300 mg/g) or from baseline microalbuminuria to macroalbuminuria with an ACR increase $\geq 30\%$ from baseline. Subjects with macroalbuminuria at baseline (ACR > 300 mg/g) are excluded from the analysis.

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The results of the primary analysis of progression of albuminuria were confirmed in several supportive analyses, including the On-Treatment analysis set, as well as a sensitivity analysis of confirmed progression of albuminuria in the ITT analysis set (ie, progression of albuminuria based only on results of urinary ACR measurements from a urine sample that was confirmed from a second sample collected approximately 1 to 2 months later or progression observed at the last urinary ACR measurement where no confirmatory samples could be obtained) and in a sensitivity analysis in which only subjects with a baseline nephrotic range macro-albuminuria (urinary ACR $> 3,000$ mg/g) were excluded from the analysis set.

Progression of Albuminuria (Study 28431754-DIA4003: Intent-To-Treat Analysis Set)

Analysis Set Endpoint	----- Placebo -----		----- Cana -----		
	n/N(%)	EVRT[a]	n/N(%)	EVRT[a]	HR[b] (95% CI)
ITT					
Progression[c]	635/2518 (25.2)	153.01	446/2541 (17.6)	99.80	0.64 (0.57, 0.73)
Confirmed Progression[c][d]	440/2518 (17.5)	100.21	298/2541 (11.7)	64.36	0.63 (0.54, 0.72)
Progression Excluding Baseline ACR>3000 mg/g[e]	660/2742 (24.1)	145.85	466/2765 (16.9)	95.95	0.65 (0.57, 0.73)
On-Treatment					
Progression[c]	615/2518 (24.4)	149.49	425/2541 (16.7)	96.06	0.63 (0.56, 0.72)

Note: [a] Event rate per 1000 patient-years.

Note: [b] Hazard ratio (all canagliflozin compared to placebo) and its 95% CI are estimated using a Cox proportional hazard model including the effect of treatment and baseline albuminuria status.

Note: [c] Progression from baseline normoalbuminuria (ACR<30 mg/g) to microalbuminuria (ACR ≥ 30 mg/g and ≤ 300 mg/g)/macroalbuminuria

(ACR of>300 mg/g) or from baseline microalbuminuria to macroalbuminuria with an ACR increase ≥ 30% from baseline.

Subjects with macroalbuminuria at baseline (ACR>300 mg/g) are excluded from the analysis.

Note: [d] Repeatedly and consecutively confirmed progression plus the last progression without confirmation.

Note: [e] It summarises ≥ 1 step progression in the following categories: baseline normoalbuminuria, baseline microalbuminuria, and baseline non-nephrotic range macroalbuminuria.

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Subgroup analyses of progression of albuminuria revealed greater reduction in progression of albuminuria in European subjects, subjects with higher blood pressure at baseline, micro-albuminuria at baseline, and in those subjects taking a renin-angiotensin-aldosterone system (RAAS) inhibitor; however, no qualitative differences were observed.

Secondary Efficacy Endpoints: Secondary efficacy endpoints included CV death and the composite of CV death or hospitalization for heart failure in the ITT analysis set. Canagliflozin reduced the risk of the composite of CV death or hospitalization for heart failure compared with placebo, with an HR for canagliflozin versus placebo of 0.72 (95% CI: 0.55, 0.94). The HR for CV death comparing canagliflozin to placebo was 0.86 (95% CI: 0.61, 1.22).

Exploratory Cardiovascular Endpoints: The HR for all-cause mortality comparing canagliflozin with placebo was 0.92 (95% CI: 0.70, 1.21).

The incidence rates of time to first occurrence of MACE were 27.05 per 1,000 subject-years in the canagliflozin group and 32.95 per 1,000 subject-years in the placebo group, with a HR of canagliflozin versus placebo of 0.82 (95% CI: 0.66, 1.01). The point estimates for the HRs for each of the individual MACE components comparing canagliflozin to placebo were similar to the HR for the MACE composite.

Time to the First Occurrence of MACE (Including Components) (Study 28431754-DIA4003: Intent-To-Treat Analysis Set)

Endpoint	----- Placebo -----		----- Cana -----		HR[b] (95% CI)
	n/N(%)	EVRT[a]	n/N(%)	EVRT[a]	
MACE[c]	193/2905 (6.6)	32.95	160/2907 (5.5)	27.05	0.82 (0.66, 1.01)
CV Death	70/2905 (2.4)	11.60	61/2907 (2.1)	10.06	0.86 (0.61, 1.22)
Non-Fatal MI	73/2905 (2.5)	12.34	63/2907 (2.2)	10.55	0.85 (0.61, 1.19)
Non-Fatal Stroke	63/2905 (2.2)	10.62	52/2907 (1.8)	8.71	0.82 (0.57, 1.18)

Note: [a] Event rate per 1000 patient-years.

Note: [b] P-value corresponds to a test of superiority at a two-sided significance level at 0.05. Hazard ratio (canagliflozin compared to placebo), 95% CI and p-value are estimated using a stratified Cox proportional hazard model including treatment as the explanatory variable, and stratified by prior CV disease subgroup.

Note: [c] MACE is the abbreviation for major adverse cardiovascular event and is the composite of cardiovascular death, non-fatal myocardial

infarction (MI), and non-fatal stroke.

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SAFETY RESULTS:**Adverse Events:**

The incidence rate of serious adverse events was lower in the canagliflozin group compared to placebo (129.11 vs 142.99 per 1,000 subject years, respectively); the incidence rate difference was -13.88 per 1,000 subject-years and the 95% CI excluded 0 (95% CI: -27.7, -0.05). The incidence rates of adverse events leading to study drug discontinuation were similar in the canagliflozin and placebo groups (38.15 vs 35.98 per 1,000 subject years, respectively; IRD: 2.17; 95% CI: -5.06, 9.40). The adjusted incidence rate difference for overall fatal adverse events between the canagliflozin and placebo groups was -1.24 (95% CI: -5.93, 3.45) With the exception of the preferred term of ‘myocardial infarction,’ all adverse events with a fatal outcome had a 95% CI for the adjusted incidence rate differences between the canagliflozin and placebo groups that included 0. The adjusted incidence rate difference for myocardial infarction between the canagliflozin and placebo groups was 1.16 (95% CI: 0.07, 2.25).

Safety Laboratory Assessments:

Protocol-specified safety laboratory analyte parameters were evaluated based on review of summary statistics for mean changes over time and by assessing the incidence of safety laboratory analyte measurements meeting the PDLC criteria.

Based upon “any” post-baseline double-blind treatment period measurement, more canagliflozin-treated subjects compared with placebo-treated subjects had decreases in eGFR (<80 mL/min/1.73m² and >30% decrease from baseline) and increases in magnesium (greater than upper limit of normal [>ULN] and >25% increase from baseline) that met the PDLC criteria. Also, fewer canagliflozin-treated subjects compared with placebo-treated subjects had decreases in magnesium (less than lower limit of normal [<LLN] and >25% decrease from baseline), in phosphate (<LLN and >25% decrease from baseline), and in sodium (<LLN and a decrease of >5 mmol/L from baseline) that met the PDLC criteria. There were no significant differences between treatment groups in the 3 PDLC criteria related to serum potassium.

The incidence rates for any post-baseline value elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) were similar in both treatment groups at each threshold. The incidences of last post-baseline value elevations in ALT or AST were generally similar for each threshold in both treatment groups.

Based upon any post-baseline double-blind treatment period measurement, more canagliflozin-treated subjects compared with placebo-treated subjects had increases in hemoglobin (≥20 g/L from baseline) and decreases in platelets (<LLN and >25% decrease from baseline) that met the PDLC criteria. For both

hemoglobin and platelets, the incidence of the last post-baseline value was also higher in the canagliflozin group compared to placebo. The incidence rates of either a decrease (ie, <LLN and >25% decrease from baseline) or increase (ie, >ULN and >50% increase from baseline) from baseline in leukocytes for 'any' and the 'last' post-baseline value were similar between the treatment groups.

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

CONCLUSIONS:

- In subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk for CV events, canagliflozin reduced the rate of progression of albuminuria and the risk of the composite of CV death or hospitalization for heart failure; canagliflozin did not reduce the risk of CV death
- Safety findings were consistent with the known safety profile of canagliflozin, except that an increase in fracture risk was not observed
- Upon cessation of canagliflozin, eGFR increased suggesting that the initial eGFR decline with canagliflozin is reversible and not due to a deleterious effect on renal function