SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Investigational Product	JNJ-28431754 (Canagliflozin)

* Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Infectious Diseases BVBA; Janssen Sciences Ireland UC; or Janssen Research & Development, LLC. The term "sponsor" is used to represent these various legal entities as identified on the Sponsor List.

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Date: 14 September 2017

Prepared by: Janssen Research & Development, LLC

Protocol No.: 28431754DIA3008

Title of Study: A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects with Type 2 Diabetes Mellitus

Study Name: CANVAS (CANagliflozin cardioVascular Assessment Study)

EudraCT Number: 2009-012140-16

NCT No.: NCT01032629

Clinical Registry No.: CR016627

Coordinating Investigator(s): Professor Melanie J Davies, CBE, MD, [Contact]

Study Center(s): 359 centers in 24 countries (89 centers in North America [17 in Canada, 7 in Mexico, and 65 in the United States], 17 centers in Central/South America [15 in Argentina and 2 in Colombia], 118 centers in Europe [6 in Belgium, 10 in Czech Republic, 7 in Estonia, 10 in Germany, 7 in Hungary, 1 in Luxembourg, 20 in Netherlands, 9 in Norway, 14 in Poland, 16 in Spain, 7 in Sweden, and 11 in United Kingdom], and 135 centers in the rest of world [15 in Australia, 44 in India, 4 in Israel, 8 in Malaysia, 5 in New Zealand, 46 in Russia, and 13 in Ukraine]).

Publications (References):

Fulcher G, Matthews DR, Perkovic V, et al. Efficacy and Safety of Canagliflozin Used in Conjunction with Sulfonylurea in Patients with Type 2 Diabetes Mellitus: A Randomized, Controlled Trial. Diabetes Ther. 2015 Sep;6(3):289-302. doi: 10.1007/s13300-015-0117-z. Epub 2015 Jun 17.

Fulcher G, Matthews DR, Perkovic V, et al. Efficacy and safety of canagliflozin when used in conjunction with incretin-mimetic therapy in patients with type 2 diabetes. Diabetes Obes Metab. 2016 Jan;18(1):82-91. doi: 10.1111/dom.12589. Epub 2015 Dec 8.

Neal B, Perkovic V, de Zeeuw D, et al. Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS)--a randomized placebo-controlled trial. Am Heart J. 2013 Aug;166(2):217-223.e11. doi: 10.1016/j.ahj.2013.05.007. Epub 2013 Jun 24.

Neal B, Perkovic V, de Zeeuw D, et al. Efficacy and safety of canagliflozin, an inhibitor of sodium-glucose cotransporter 2, when used in conjunction with insulin therapy in patients with type 2 diabetes. Diabetes Care. 2015 Mar;38(3):403-11. doi: 10.2337/dc14-1237. Epub 2014 Dec 2.

Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. New England Journal of Medicine. 2017 Jun 12. DOI: 10.1056/NEJMoa1611925

Watts NB, Bilezikian JP, Usiskin K, et al. Effects of Canagliflozin on Fracture Risk in Patients with Type 2 Diabetes Mellitus. J Clin Endocrinol Metab. 2016 Jan;101(1):157-66. doi: 10.1210/jc.2015-3167. Epub 2015 Nov 18.

Yamout H, Perkovic V, Davies M, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes and stage 3 nephropathy. Am J Nephrol. 2014;40(1):64-74. doi: 10.1159/000364909. Epub 2014 Jul 17.

Study Period: 17 November 2009 to 22 February 2017; database lock 28 March 2017

Phase of Development: 3

Objectives:

Primary Objectives

In subjects with T2DM, with inadequate glycemic control, who had a history of or were at high risk of cardiovascular (CV) disease, to assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care on CV risk as measured by the hazard ratio (HR) for a composite endpoint (major adverse cardiovascular events [MACE] including CV death, nonfatal myocardial infarction (MI), or nonfatal stroke) and to assess the safety and tolerability of canagliflozin plus standard of care relative to placebo plus standard of care.

Note, an additional objective was to combine the data from this study with the data from DIA4003 (collectively called "the CANVAS program") in a prespecified integrated analysis of CV safety outcomes to satisfy postmarketing requirements for canagliflozin (the combined data are reported separately).

Secondary Objectives

In subjects with T2DM, with inadequate glycemic control, who had a history of or were at high risk of CV disease, to assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care at the end of the treatment period on:

- fasting measures of beta-cell function (homeostatic model assessment [HOMA]-B and the proinsulin/insulin ratio) (note: this assessment was conducted in a subset of subjects at sites that elected to participate, including only subjects who did not receive insulin at randomization)

- the proportion of subjects with progression of albuminuria (progression 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)

- urinary albumin/creatinine ratio (ACR)

- renal function (as measured by the change from baseline in estimated glomerular filtration rate [eGFR])

- glycemic efficacy (hemoglobin A_{1c} [HbA_{1c}] and fasting plasma glucose [FPG])

- body weight

- blood pressure (systolic blood pressure [SBP] and diastolic blood pressure [DBP])

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- fasting plasma lipids (triglycerides, high-density lipoprotein cholesterol [HDL-C], low density lipoprotein cholesterol [LDL-C], total cholesterol, and the ratio of LDL-C to HDL-C)

Methodology: This was a randomized, double-blind, placebo-controlled, 3 parallel-group, multicenter study to evaluate the safety, tolerability, and CV risk with canagliflozin plus standard of care compared with placebo plus standard of care in subjects with T2DM, on a wide range of background AHA therapies, who either had a history of or were at high risk of CV disease. The study was intended to assess if treatment of subjects with T2DM with canagliflozin reduces CV risk for MACE (including CV death, nonfatal MI, and nonfatal stroke) and to achieve a number of other important goals. These include the assessment of overall safety, tolerability, glycemic efficacy, and long-term effects on renal function with canagliflozin treatment. This study also provides key support for a CANVAS program assessment of CV safety, examining the composite endpoint of MACE.

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, canagliflozin 300 mg, or matching placebo administered once daily (in a 1:1:1 ratio). After randomization, subjects entered an 18-week AHA regimen stable period; after which, and for the remainder of double-blind treatment, investigators could adjust the subject's AHA regimen with the goal of achieving individualized, target glycemic control. This design of the study allowed for inclusion of 18-week substudies to examine the efficacy and safety of canagliflozin compared with placebo in combination with specific add-on AHAs (add-on to sulphonylurea monotherapy and add-on to insulin) through the first 18-weeks of the study. The substudies are completed and have been previously reported.

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): The planned recruitment of the initial cohort of this study was 4,500 subjects. This was based upon having a sufficient number of participants to support, in concert with the other controlled clinical trials in the canagliflozin development program, a detailed preapproval assessment of the safety and tolerability of canagliflozin. A second cohort was originally planned but not recruited, due to a change in the study design.

A total of 4,330 subjects were randomized, with 1,442, 1,445, and 1,443 subjects assigned to placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. Two subjects from the canagliflozin 300 mg group and 1 subject from the placebo group were randomized to the study, but were not dosed with study drug (and hence 4,327 subjects were included in the safety analyses.)

Summary of Analysis Sets

Analysis Set	Analysis Population	Data Period
Intent-to-treat (ITT)	Randomized subjects	Day 1 to the last trial contact date up to GTED
On-study (OS)	Treated subjects	Day 1 to the last trial contact date up to GTED
On-treatment (OT)	Treated subjects	Day 1 to the last dose date plus X[a] days or the last trial contact date, whichever is earlier
On-treatment Pre-INT-6 (OT INT6)	Treated subjects	Day 1 to the last dose date plus X[a] days or the last trial contact date, whichever is earlier, up to 07 January 2014

GTED=the stopping date of the study and end of all visits, including the 30-day off-drug follow-up visit

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

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Data Sets Analyzed: All Randomized Subjects

Analysis Set	Placebo (N=1442) n (%)	Cana 100 mg (N=1445) n (%)	Cana 300 mg (N=1443) n (%)	Cana Total (N=2888) n (%)	Total (N=4330) n (%)
Intent-to-treat	1442 (100)	1445 (100)	1443 (100)	2888 (100)	4330 (100)
On-study	1441 (99.9)	1445 (100)	1441 (99.9)	2886 (99.9)	4327 (99.9)
On-treatment	1441 (99.9)	1445 (100)	1441 (99.9)	2886 (99.9)	4327 (99.9)
On-treatment Pre-INT-6	1441 (99.9)	1445 (100)	1441 (99.9)	2886 (99.9)	4327 (99.9)

Diagnosis and Main Criteria for Inclusion:

Men and women with a diagnosis of T2DM with HbA$_{1c}$ level ≥7.0% to ≤10.5% at screening and either (1) not currently on AHA therapy 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) analogue, dipeptidyl peptidase 4 (DPP-4) inhibitor, or insulin were eligible for this study. Subjects had history or high risk of CV disease defined on the basis of either:

- age ≥30 years with documented symptomatic atherosclerotic CV disease: including stroke, 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 (PVD), or amputation secondary to vascular disease

- 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, 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, or documented HDL-C of <1 mmol/L (<39 mg/dL)

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 included: 30845.1, 30845.12, 30845.6, 32783.1, 32783.1, 32783.11, 32783.4, 32783.5, 33977.5, 09K16/G002, 09K16/G002, AITS6, HG-13L048, PD3092, PD3092, PD3093, PD3388, PD3389, PD3389, 37236.3, 46567.1, 46567.5, 46567.8, 53061.4, 12L04/G002, HG-13F031, HG-13F032, HG-13F033, HG-14A001, HG-14A007, HG-14A010, HG-14I059, HG-14I062, HG-15D025.

The bulk batch numbers for canagliflozin 300 mg included: 30845.11, 30845.16, 30845.16, 30845.4, 32783.12, 32783.13, 32783.15, 32783.2, 32783.3, 32783.7, 33977.7, 09K26G003, 09L02/G003, AKTS8, HG-14A003, PD3153, PD3153, PD3154, PD3155, PD3157, PD3306, PD3307, PD3396, PD3398, PD3399, PD3403, 37236.1, 37236.2, 46567.11, 46567.9, 46567.9, 54372.2, 12L06/G003, HG-13F027, HG-13F029, HG-13F030, HG-13H037, HG-13H038, HG-14A002, HG-14A003, HG-14A008, HG-14A009, HG-14I054, HG-15A004, 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 included: 30845.13, 30845.13, 30845.2, 30845.2, 30845.8, 32580.4, 32580.4, 32580.4, 32580.4, 32580.4, 46567.1, 09J28/G001, 09J28/G001, 09L16/G001, 10B22/G001, PD3091, PD3220, PD3220, 46567.1, 46567.1, 46567.12, 46567.2, 53061.1, 53061.1, 11H24/G001, 11H24/G001, 12I10/G001, HG-13E017, HG-13E017, HG-13F025, HG-14B011, HG-14B012, HG-14B012, HG-15A002.

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Duration of Treatment: As an event-driven study, the duration of DIA3008 was dependent upon the number of accumulated CV events (ie, at least 688 events from DIA3008 and DIA4003 combined, as specified in the protocol, and when the last subject randomized 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. The duration for individual subjects was expected to be up to approximately 8 years. Subjects who discontinued study drug but agreed to be contacted, were followed through the end of the study.

Criteria for Evaluation:

Efficacy: The primary measure of efficacy was the HR of the composite endpoint of MACE (CV death, nonfatal MI, nonfatal stroke). Secondary measures of efficacy include beta cell function (HOMA-B; in subjects who were not receiving insulin), progression of albuminuria (based upon categories determined by urinary ACR), proinsulin/insulin ratio (in subjects who were not receiving insulin), urinary ACR, eGFR, HbA_{1c}, FPG, body weight, blood pressure (SBP and DBP), and fasting plasma lipids (triglycerides, HDL-C, LDL-C, total cholesterol, and the ratio of LDL-C to HDL-C).

Safety: Safety was evaluated based on the following variables: adverse events, safety laboratory tests (hematology, serum chemistry, urinalysis), hypoglycemic episodes (as collected in a specific eCRF), vital sign measurements (blood pressure and pulse rate), and 12-lead electrocardiograms (ECGs).

Statistical Methods: Note, the hypotheses in DIA3008 were specified in the study protocol; however, they are considered to be exploratory in the canagliflozin CV outcome analyses. The hypotheses in this study were not included as part of the testing sequence of the CANVAS program. Accordingly, any p-values reported were considered as nominal and 95% CIs for the treatment effect were presented for descriptive purposes.

Study Hypotheses: In subjects with T2DM with inadequate glycemic control, who had a history of or were at high risk of CV disease, relative to placebo plus standard of care, canagliflozin plus standard of care:

- reduces CV risk (as measured by the HR for MACE including CV death, nonfatal MI, and nonfatal stroke)

- improves beta-cell function (change from baseline in HOMA-B) at the end of the treatment period

- reduces progression of albuminuria (ie, proportion of subjects with a ≥1-step progression of albuminuria measured by the urine ACR) at the end of the treatment period

Sample Size Determination: The sample size for the recruitment of the initial 4,500 subjects was based upon having a sufficient number of participants to support, in concert with the other controlled clinical trials in the canagliflozin development program, a detailed pre-approval assessment of the safety and tolerability of canagliflozin. Data from this initial cohort were exported and integrated with data from other Phase 3 well-controlled studies to support a planned pre-approval meta-analysis to demonstrate that the upper bound of the 2-sided 95% CI for the CV HR of canagliflozin relative to control in composite endpoint events (MACE and hospitalized unstable angina) was <1.8; the current United States (US) regulatory requirements for filing.

The assumed per annum event rate was 2.25% and the per annum study drug discontinuation rate was 5%. With an enrollment period of 1.5 years, 4,500 randomized subjects were projected to contribute sufficient CV events to support the pre-approval CV meta-analysis.

Efficacy:

Primary Efficacy Endpoint: The primary efficacy endpoint for CV benefit was time to MACE, which was calculated as the time from Day 1 to the first occurrence of MACE. Adjudication of these events by the

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Endpoint Adjudication Committee (EAC) was performed in a blinded fashion. The primary analysis was based on the intent-to-treat (ITT) analysis set for adjudicated MACE. The HR of canagliflozin (all canagliflozin group as well as each canagliflozin dose) compared with placebo and its 95% CI was estimated using a stratified Cox proportional hazards model with a term for treatment as the explanatory variable and history of CV disease (secondary and primary prevention) as a stratification factor.

Secondary Efficacy Endpoints: The continuous secondary efficacy endpoints of change from baseline at the end-of-treatment in HOMA-B, proinsulin/insulin ratio, eGFR, HbA_{1c}, FPG, blood pressure (SBP and DBP), percent change in body weight and fasting lipids (HDL-C, LDL-C, triglycerides, total cholesterol, and LDL-C/HDL-C) were analyzed using an analysis of covariance (ANCOVA) model with treatment (canagliflozin 100 mg, canagliflozin 300 mg, or placebo) as the explanatory variable and corresponding baseline value as a covariate. The treatment difference in the least squares (LS) means and the 2-sided 95% CI was estimated based on this model.

The categorical secondary efficacy endpoint was the proportion of subjects with progression of albuminuria (defined as ≥1 step increase, ie, no albuminuria to micro- or macro-albuminuria or from micro-albuminuria to macro-albuminuria). The proportion of subjects with progression of albuminuria at the end-of-treatment was analyzed using the logistic model with treatment (canagliflozin 100 mg, canagliflozin 300 mg, or placebo) as the explanatory variable and baseline albuminuria status as a covariate.

Multiplicity Adjustment: As the results of the DIA3008 study were intended to be integrated with another similar study (DIA4003), no alpha was preserved for evaluating hypotheses in DIA3008 on its own and all tests for DIA3008 were considered nominal with 2-sided 95% CIs provided for descriptive purposes.

Safety: Note, adverse event collection on electronic case report forms (eCRFs) was streamlined following the approval of the global protocol Amendment INT-6 to include only serious adverse events and adverse events that led to study drug discontinuation, with the exception of specific adverse events of interest (male mycotic genital infection, malignancy [renal cell cancer, bladder cancer, pheochromocytoma, Leydig cell tumors, breast cancer], photosensitivity, venous thromboembolic events (VTE), amputation, fracture, diabetic ketoacidosis [DKA]), which were collected regardless of whether they were serious and/or led to study drug discontinuation.

Unless otherwise specified, 2 sets of summaries of adverse events were provided. The first set was based on the data collected up to 07 January 2014 when the global Amendment INT-6 was first approved. The second set of summaries focused on the serious adverse events and adverse events leading to study drug discontinuation throughout the entire study period.

All other safety analyses and summaries (laboratory tests and vital signs) were based on data collected throughout the entire study period using either the On-treatment analysis set or the On-study analysis set, unless otherwise specified.

There was no imputation of missing values for clinical laboratory test results or vital sign measurements in the safety analyses and there was no hypothesis testing for results from the safety analyses.

RESULTS:

STUDY POPULATION:

Subject Disposition and Study Completion/Withdrawal Information: A total of 7,693 subjects were screened, and a total of 4,330 subjects were randomized, with 1,442, 1,445, and 1,443 subjects assigned to placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. Two subjects from the canagliflozin 300 mg group and 1 subject from the placebo group were randomized to the study, but were not dosed with study drug (and hence were not included in the On-treatment analysis set).

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Study completion information and vital status are summarized in the table below. The proportion of subjects who completed the study (92.3%) and the proportion with known final vital status (99.3%) was comparable in all treatment groups.

Study Completion and Vital Status (Study 28431754-DIA3008: All Randomized Subjects Analysis Set)

	Placebo (N=1442) n (%)	Cana 100 mg (N=1445) n (%)	Cana 300 mg (N=1443) n (%)	Cana Total (N=2888) n (%)	Total (N=4330) n (%)
Subjects in ITT analysis set	1442 (100)	1445 (100)	1443 (100)	2888 (100)	4330 (100)
Completed Study*	1297 (89.9)	1344 (93.0)	1355 (93.9)	2699 (93.5)	3996 (92.3)
Final vital status known**	1429 (99.1)	1437 (99.4)	1435 (99.4)	2872 (99.4)	4301 (99.3)
Alive	1254 (87.0)	1280 (88.6)	1289 (89.3)	2569 (89.0)	3823 (88.3)
Died	175 (12.1)	157 (10.9)	146 (10.1)	303 (10.5)	478 (11.0)
Final Vital Status Unknown	13 (0.9)	8 (0.6)	8 (0.6)	16 (0.6)	29 (0.7)

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 denominator.
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The proportion of subjects completing study on the study drug was 51.0%, 58.1%, and 59.6% in the placebo, canagliflozin 100 mg, and canagliflozin 300 mg respectively. The 2 most common reasons across all treatment groups for discontinuation from study drug were subjects who decided to discontinue early for personal reasons but agreed to continue to be followed (ie, "withdrawn from study medication," 18.7%), and adverse events leading to discontinuation (11.7%).

Demographic and Baseline Characteristics: Baseline demographic, anthropometric, and disease history characteristics were generally similar between treatment groups. The median age of subjects was 63 years and 66.1% of subjects were men. Overall, 73.4% of the subjects were white, 18.4% of subjects identified as Asians, and 2.4% identified as black or African-American; 9.6% were Hispanic or Latino ethnicity. At sites in the US, 13.3% of subjects identified as African-American. Approximately 60% of subjects were obese (ie, BMI $\geq$30 kg/m^2) based upon National Institutes of Health criteria, with a median BMI of 31.5 kg/m^2 for the total population.

Subjects had mild to moderate hyperglycemia at baseline, reflected by a mean baseline HbA$_{1c}$ of 8.2%; approximately 21% of subjects had a baseline HbA$_{1c}$ $\geq$9.0%. Subjects had a mean duration of diabetes of 13.4 years. Approximately 45% 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 77.2 mL/min/1.73m^2, and approximately 16% of subjects had a baseline eGFR <60 mL/min/1.73m^2, with no notable difference between treatment groups. At baseline, 71.7% of subjects had normo-albuminuria, 22.5% of subjects had micro-albuminuria, 5.5% had non-nephrotic range macro-albuminuria, and 0.3% had nephrotic range macro-albuminuria. The proportion of subjects with a history of amputation was higher in the combined canagliflozin group (2.1%) than in the placebo group (1.1%).

With respect to cardiovascular history, the proportion of subjects with prior CV disease was 58.9% overall and was balanced across treatment groups with approximately half having a history of coronary artery disease, 16% had PVD and approximately 16% had cerebrovascular disease. Most subjects (87.6%) had a history of hypertension; however, the baseline blood pressures and widespread use of

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antihypertensive agents as prior and concomitant therapy suggest that the hypertension was being controlled with treatment. Approximately 12% of all subjects had a prior history of heart failure.

Duration of Exposure to Study Drug: The overall mean duration of exposure to study drug was 222.78 weeks, with 35% exposed to study drug for ≥312 weeks. The total exposure to study drug was 12,678.8 subject-years in the combined canagliflozin group and 5,795.3 subject-years in the placebo group.

Duration of Study: The total mean and median duration of the study, including on-treatment and off-treatment follow-up, was 295.88 and 316.57 weeks, respectively, with comparable durations across all treatment groups.

<u>EFFICACY RESULTS</u>: Based on the overall testing strategy of the CANVAS program, formal hypothesis testing was not performed in the DIA3008 study, therefore the 95% CIs for the treatment effect are presented solely for descriptive purposes.

Primary Efficacy Analysis – MACE: The event rate for MACE was 26.89 per 1,000 subject-years in the combined canagliflozin group and 30.36 per 1,000 subject-years in the placebo group, with a HR of canagliflozin versus placebo of 0.88 (95% CI: 0.75, 1.03). The HRs versus placebo were 0.93 and 0.83 in the canagliflozin 100 mg and 300 mg groups, respectively.

MACE Components: The HRs of the combined canagliflozin group compared with placebo for each individual MACE component (CV death, nonfatal MI, nonfatal stroke) were less than 1. The HR point estimates for each individual MACE component were lower in the canagliflozin 300 mg group, relative to the canagliflozin 100 mg group. The CV death HR for the combined canagliflozin group versus placebo was 0.88 (95% CI: 0.70, 1.10).

Other Cardiovascular Endpoints: Canagliflozin reduced the risk of the composite of CV death or hospitalization for heart failure compared with placebo, with an HR of canagliflozin versus placebo of 0.82 (95% CI: 0.67, 0.99). The HRs were similar in the canagliflozin 300 mg and 100 mg groups.

The HR for hospitalization for heart failure in the combined canagliflozin group versus placebo was 0.77 (95% CI: 0.55, 1.08), with similar effects results seen in the canagliflozin 100 mg and 300 mg groups.

The HR for the combined canagliflozin group versus placebo for fatal/nonfatal MI and fatal/nonfatal stroke was 0.88 (95% CI: 0.68, 1.12), with a lower HR in the canagliflozin 300 mg group, relative to the canagliflozin 100 mg group.

The HR comparing for all-cause mortality in the combined canagliflozin group versus placebo was 0.84 (95% CI: 0.70, 1.01), with a lower HR in the canagliflozin 300 mg group, relative to the canagliflozin 100 mg group.

Secondary Efficacy Analyses: Glycemic Endpoints (including HOMA2-%B)

HOMA2-%B: Beta-cell function was assessed via HOMA2-%B (based upon fasting C-peptide and glucose concentrations) in a subset of subjects who were not receiving insulin at baseline. The placebo-subtracted LS mean changes from baseline were 2.79 and 4.07 in the canagliflozin 100 mg and 300 groups, respectively. Over time, the differences between the canagliflozin groups and placebo diminished such that by Weeks 104 and 208 the canagliflozin 100 mg and canagliflozin 300 mg groups, respectively, were similar to placebo.

HbA$_{1c}$: Reductions in HbA$_{1c}$ at the end of treatment compared with placebo were observed in both doses of canagliflozin, with placebo-subtracted LS mean changes from baseline of -0.27% and -0.32% for canagliflozin 100 mg and 300 mg, respectively. The 95% CI for both comparisons excluded 0. There was relatively little change in HbA$_{1c}$ seen in the placebo group, whereas both canagliflozin doses reduced the

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HbA$_{1c}$, starting approximately Week 12 through Week 52. After Week 52, the HbA$_{1c}$ levels in both canagliflozin groups gradually rose, but the reduction in HbA$_{1c}$ compared with placebo remained significant through Week 338, as the 95% CI of both comparisons at all time points excluded 0.

Fasting Plasma Glucose: Dose-related reductions in FPG from baseline to the end of the treatment were seen in the canagliflozin groups, with placebo-subtracted LS mean changes from baseline of -0.58 mmol/L and -0.73 mmol/L for canagliflozin 100 mg and 300 mg, respectively, with the 95% CI for both comparisons that excluded 0. There was relatively little change in FPG seen in the placebo group through the end of the study, whereas both canagliflozin doses reduced FPG, as seen starting Week 6 through Week 52. After Week 52, the FPG levels in both canagliflozin groups gradually rose, but the reduction in FPG compared with placebo remained significant through Week 312, as the 95% CI of both comparisons at all time points excluded 0.

Secondary Efficacy Analyses: Renal Endpoints

Progression of Albuminuria: Progression of albuminuria occurred in fewer subjects randomized to the combined canagliflozin group compared to placebo (84.96 vs 106.32 per 1,000 subject-years) corresponding to a HR of 0.80 (95% CI: 0.72, 0.90) and fewer subjects randomized to each dose progressed compared with placebo (89.76 and 80.17 vs 106.32 per 1,000 subject-years, respectively) corresponding to HRs of 0.85 (95% CI: 0.75, 0.97) for canagliflozin 100 mg and 0.76 (95% CI: 0.66, 0.86) for canagliflozin 300 mg.

Urinary Albumin/Creatinine Ratio: Relative to placebo, urinary ACR was lower by Week 12 after initiation of both doses of canagliflozin. The early and persistent reduction in urinary ACR observed in subjects treated with both doses of canagliflozin in all 3 subgroups of albuminuria, albeit to a much lesser degree in the normo-albuminuria subgroup. Although urinary ACR increased over time in the normo- and micro-albuminuric subjects at baseline in all treatment groups, separation between the canagliflozin and placebo groups was maintained throughout the duration of the study, without an apparent dose response.

Regression of albuminuria: Regression of albuminuria was more frequent among those subjects assigned canagliflozin than placebo (233.87 vs 147.40 per 1,000 subject-years, respectively; HR: 1.56; 95% CI: 1.30, 1.87) without any evidence for a dose relationship.

Change in eGFR Slope: There was a mean daily decrease (±SE) in eGFR in the placebo group of 0.0019±0.0002 mL/min/1.73m^2/day and a mean daily increase (±SE) in the canagliflozin group of 0.0011±0.0001 mL/min/1.73m^2/day. The mean between group difference was 0.0030±0.0003 mL/min/1.73m^2/day which translates to ~1.1±0.1 mL/min/1.73 m^2/year.

Composite Endpoints: Compared with placebo, subjects in the canagliflozin group showed more frequently regression of albuminuria, and showed a 36% reduction in the risk for a composite endpoint of sustained 40% reduction in eGFR, new onset macro-albuminuria, renal replacement therapy or renal death.

Other Secondary Efficacy Analyses

Body Weight: Dose-related reductions in body weight at the end of treatment were seen in the canagliflozin groups, with placebo-subtracted LS mean changes from baseline of -2.96% and -3.61% for canagliflozin 100 mg and 300 mg, respectively, with 95% CI for both comparisons that excluded 0.

Blood pressure: There were dose-related reductions in SBP and DBP at the end of treatment in both canagliflozin groups, with placebo-subtracted LS mean changes from baseline in SBP of -2.96 mmHg and -4.53 mmHg in the canagliflozin 100 mg and 300 mg groups, respectively, and in DBP of -0.82 mmHg and -1.63 mmHg, respectively, with 95% CIs for all comparisons that excluded 0.

Fasting plasma lipids: There were dose-related increases in lipid parameters at the end of treatment in the canagliflozin 100 mg and 300 mg groups, with placebo-subtracted LS mean changes from baseline in total cholesterol of 0.18 mmol/L and 0.23 mmol/L; HDL-C of 0.05 mmol/L and 0.06 mmol/L; LDL-C of 0.11 mmol/L and 0.16 mmol/L; and non-HDL-C of 0.13 mmol/L and 0.18 mmol/L, respectively, with 95% CIs for all comparisons that excluded 0.

Proinsulin/insulin ratio: The proinsulin/insulin ratio was assessed in a subset of subjects who were not receiving insulin at baseline. At the end of treatment, no between-group differences were noted.

SAFETY RESULTS:

Adverse Events

All Adverse Events up to INT-6: The incidence rate of all adverse events up until the implementation of INT-6 was comparable across treatment groups. The incidence rate of adverse events leading to discontinuation was higher in the canagliflozin 300 mg group versus placebo but not in the canagliflozin 100 mg group versus the placebo group. No differences were seen between treatment groups in the incidence rates of serious adverse events.

Summary of Any Adverse Events - Exposure-adjusted through 07JAN2014 (INT-6)
(Study 28431754-DIA3008: On-Treatment Analysis Set)

	------- Placebo ------- ------- (N=1441) ------		----- Cana 100 mg ----- ------- (N=1445) ------		----- Cana 300 mg ----- ------- (N=1441) ------		------ Cana Total ----- ------- (N=2886) ------	
	n(%)	Rate/1000 pt-yrs**	n(%)	Rate/1000 pt-yrs**	n(%)	Rate/1000 pt-yrs**	n(%)	Rate/1000 pt-yrs**
Any Adverse Events	1264 (87.7)	349.48	1278 (88.4)	331.51	1286 (89.2)	338.53	2564 (88.8)	334.99
Adverse Events Leading to Discontinuation	122 (8.5)	33.73	131 (9.1)	33.98	173 (12.0)	45.54	304 (10.5)	39.72
Adverse Events Related to Study Drug*	355 (24.6)	98.15	511 (35.4)	132.55	579 (40.2)	152.42	1090 (37.8)	142.41
Adverse Events Related to Study Drug* and Leading to Discontinuation	38 (2.6)	10.51	71 (4.9)	18.42	92 (6.4)	24.22	163 (5.6)	21.30
Serious Adverse Events	446 (31.0)	123.31	432 (29.9)	112.06	442 (30.7)	116.35	874 (30.3)	114.19
Serious Adverse Events Leading to Discontinuation	79 (5.5)	21.84	66 (4.6)	17.12	70 (4.9)	18.43	136 (4.7)	17.77
Serious Adverse Events Related to Study Drug*	27 (1.9)	7.47	35 (2.4)	9.08	30 (2.1)	7.90	65 (2.3)	8.49
Serious Adverse Events Related to Study Drug* and Leading to Discontinuation	12 (0.8)	3.32	17 (1.2)	4.41	14 (1.0)	3.69	31 (1.1)	4.05
Death	63 (4.4)	17.42	40 (2.8)	10.38	45 (3.1)	11.85	85 (2.9)	11.11

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: * Related to study drug includes relationship determined by investigators: possibly related, probably related and very likely related.
Note: **The Denominator is the total of each subject's exposure of the study medication plus 30 days up to 07Jan2014
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Death is based on the number of subjects who have AE with fatal outcome.
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Serious Adverse Events and Adverse Events Leading to Discontinuation Throughout the Study: A higher incidence rate of adverse events leading to discontinuation was seen in the canagliflozin 300 mg group versus placebo but not in the canagliflozin 100 mg group versus placebo. No notable differences were seen between treatment groups in the incidence rates of serious adverse events.

Status: Approved, Date: 14 September 2017

Summary of Serious Adverse Events or Adverse Events Leading to Discontinuation of Study Medication - Exposure - adjusted (Study 28431754-DIA3008: On-Treatment Analysis Set)

	------- Placebo ------- ------- (N=1441) ------		----- Cana 100 mg ----- ------- (N=1445) ------		---- Cana 300 mg ----- ------- (N=1441) ------		------ Cana Total ----- ------- (N=2886) ------	
	n(%)	Rate/1000 pt-yrs**	n(%)	Rate/1000 pt-yrs**	n(%)	Rate/1000 pt-yrs**	n(%)	Rate/1000 pt-yrs**
Adverse Events Leading to Discontinuation	176 (12.2)	29.81	199 (13.8)	30.75	244 (16.9)	37.99	443 (15.3)	34.35
Adverse Events Related to Study Drug* and Leading to Discontinuation	53 (3.7)	8.98	86 (6.0)	13.29	114 (7.9)	17.75	200 (6.9)	15.51
Serious Adverse Events	584 (40.5)	98.93	601 (41.6)	92.86	606 (42.1)	94.34	1207 (41.8)	93.60
Serious Adverse Events Leading to Discontinuation	111 (7.7)	18.80	120 (8.3)	18.54	115 (8.0)	17.90	235 (8.1)	18.22
Serious Adverse Events Related to Study Drug*	40 (2.8)	6.78	51 (3.5)	7.88	42 (2.9)	6.54	93 (3.2)	7.21
Serious Adverse Events Related to Study Drug* and Leading to Discontinuation	14 (1.0)	2.37	25 (1.7)	3.86	19 (1.3)	2.96	44 (1.5)	3.41
Death	91 (6.3)	15.42	87 (6.0)	13.44	78 (5.4)	12.14	165 (5.7)	12.79

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: *Related to study drug includes relationship determined by investigators: possibly related, probably related and very likely related.
Note: **The Denominator is the total of each subject's exposure of the study medication plus 30 days.
Note: Table includes only serious adverse events or adverse events leading to discontinuation.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Death is based on the number of subjects who have AE with fatal outcome.
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Adverse events observed in DIA3008 were generally consistent with the known profile of canagliflozin, except for an increased risk for amputations. Treatment with canagliflozin was associated with an approximately 2-fold non-dose-dependent increased risk for lower extremities amputations (most commonly of the toes); the incidence rate of atraumatic lower limb amputations was 5.85 vs 2.76 per 1,000 subject-years in the canagliflozin and placebo groups, respectively, and the HR was 2.12 (95% CI: 1.34 to 3.38).

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 predefined limits of change (PDLC) criteria.

Based upon "any" postbaseline measurement, higher incidence rates of canagliflozin-treated subjects compared with placebo-treated subjects (where the incidence rate difference excluded 0) were observed for increases in calcium (>upper limit of normal [ULN] and >10% increase), increases in magnesium (>ULN and >25% increase), increases in phosphate (>ULN and >25% increase), increases in sodium (>ULN and an increase of >5 mmol/L), and decreases in urate (<LLN and >25% decrease).

Based on any postbaseline values of ALT >3x ULN, a difference from placebo was observed in the canagliflozin 300 mg and combined canagliflozin groups, but not the canagliflozin 100 mg group. There were no differences observed between any canagliflozin group and placebo for ALT >5x ULN. For AST, no differences were observed for both canagliflozin doses and for the combined canagliflozin group relative to placebo for all elevation thresholds (>3x, >5x, and >10x ULN) except for the AST >8x ULN in the combined canagliflozin group relative to placebo.

Based upon any postbaseline measurement, more canagliflozin-treated subjects compared with placebo-treated subjects had increases in hemoglobin (≥20 g/L from baseline) that met the PDLC criteria.

STUDY LIMITATIONS: This study was unblinded by the sponsor during the conduct of the trial so that data in this population could be used for the program-wide CV meta-analysis to examine CV safety for the initial marketing applications. The study remained blinded to investigators, study subjects, Endpoint Adjudication Committee, sponsor staff responsible for day-to-day interactions with the sites, and sponsor

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staff responsible for requesting and reviewing endpoint adjudication packages from sites throughout the conduct of the study.

CONCLUSION(S):

- In subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated risk for CV events, canagliflozin did not adversely affect CV safety and improved glucose control, body weight, and blood pressure.

- Canagliflozin reduced the progression and increased the regression of albuminuria, reduced the decline in eGFR and reduced the progression to a series of composite endpoints reflective of clinically meaningful declines in renal function.

- Safety findings were generally consistent with the safety profile of canagliflozin; however, an increased risk of fractures and lower extremity atraumatic amputation with canagliflozin were identified in this study.