SYNOPSIS

Issue Date: 09 May 2012

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

Protocol No.: 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): Dr. Jean-Francois Yale, McGill University Health Centre, Royal Victoria Hospital, [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: First subject in: 02 March 2010; last subject out (LPO): 15 December 2011; DBL lock for 26-week core study period: 19 January 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.

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

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

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 subjects (approximately 90) 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.

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) at entry into the 26-week, core placebo-controlled, double-blind period (26-week core period).

A 24-hour urine collection substudy was to be performed in a subset of approximately 90 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. 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 safety analysis set	90 (98.9)	90 (100)	89 (97.8)	179 (98.9)	269 (98.9)
mITT subjects who received rescue medication before the Week 26 visit	13 (14.3)	4 (4.4)	3 (3.3)	7 (3.9)	20 (7.4)
mITT subjects who discontinued before the Week 26 visit	13 (14.3)	15 (16.7)	7 (7.7)	22 (12.2)	35 (12.9)
mITT subjects who discontinued or received rescue medication before the Week 26 visit [a]	25 (27.5)	18 (20.0)	10 (11.0)	28 (15.5)	53 (19.5)
Subjects in the completers' analysis set [b]	65 (71.4)	72 (80.0)	79 (86.8)	151 (83.4)	216 (79.4)
mITT subjects in the PP analysis set	65 (71.4)	68 (75.6)	78 (85.7)	146 (80.7)	211 (77.6)
Subjects entered the extension period	75 (82.4)	73 (81.1)	82 (90.1)	155 (85.6)	230 (84.6)

[a] Includes mITT subjects who were excluded from the completers' analysis set.

[b] Includes mITT subjects who completed Week 26 visit and have not initiated rescue medication.

Key: CANA=canagliflozin, mITT=modified intent-to-treat, PP=per protocol, 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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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.

Single-blind placebo run-in period (2 weeks): At Week -2, all enrolled subjects were started on single-blind placebo capsules matching double-blind study drug. Subjects took placebo (1 capsule once-daily)

before the first meal of the day, as advised for double-blind study drug. Subjects took the last dose of single-blind placebo study drug on the day prior to the baseline (Day 1) visit.

Double-blind treatment period (total of 52-weeks):

- Core double-blind treatment period: 26 weeks, started at the Day 1 visit and completed at the Week 26 visit (or the end-of-treatment visit for subjects who discontinued study treatment early)
- Extension double-blind treatment period: 26 weeks, started at the Week 26 visit and completing at the Week 52 visit (or the end-of-treatment visit for subjects who discontinued study treatment early)
- Double-blind study drug: Subjects were randomly assigned in a 1:1:1 ratio to 1 of 3 treatment groups and received 1 capsule once-daily administration of either canagliflozin 100 mg, canagliflozin 300 mg, or matching placebo on Day 1 for 52 consecutive weeks (ie, 26-weeks core double-blind treatment period followed by 26-weeks extension double-blind treatment period).Subjects took their first dose of study drug on Day 1 at the study center after completion of all study procedures. Subjects were instructed to take their dose of double-blind study drug (ie, canagliflozin or placebo) before the first meal of the day, according to their randomized treatment assignment, for the duration of the study. On days of study visits when fasting blood samples and/or PK blood samples were collected (refer to the Time and Events Schedule in protocol), subjects were instructed to not take their study drug and background AHA on the morning of the scheduled clinic visit and to bring their study drug to the investigational site. The subject was instructed to take the dose of study drug after completion of all study procedures conducted on the day of the visit and immediately before the subject's next meal.

Post-treatment phase: 30-day follow-up contact

- Telephone follow-up contact (or optional study visit, at the discretion of the investigator) approximately 30 days after the last dose of study drug.

Evaluations:

Efficacy: The primary efficacy endpoint was the change in HbA_{1c} from baseline to Week 26. Key secondary efficacy endpoints included changes from baseline to Week 26 in FPG, systolic and diastolic blood pressure, and the proportion of subjects achieving HbA_{1c} <7.0% at Week 26. Additional efficacy endpoints included the percent change from baseline to Week 26 in body weight and in fasting plasma lipids (LDL-C, HDL-C, total cholesterol, and triglycerides). Time to initiation and proportion of subjects requiring glycemic rescue therapy at Week 26 were secondary efficacy endpoints, as was the proportion of subjects achieving HbA_{1c} <6.5% at Week 26.

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 approximately 90 subject 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: The primary hypothesis tested was that addition of canagliflozin was superior to addition of placebo as measured by the change in HbA_{1c} from baseline at Week 26. Assuming a group difference of 0.5% between the canagliflozin and placebo group, and a common standard deviation of 0.85% with respect to the change in HbA_{1c}, and using a 2-sample, 2-sided t-test with type I error rate of 0.05, it was estimated that 61 randomized subjects per treatment group were required to achieve at least 90% power to demonstrate the superiority of canagliflozin over placebo. To provide additional safety information, the study included a modestly greater study sample size of 80 subjects randomized per treatment group (total randomized population of 240 subjects).

Analysis Sets: The modified intent-to-treat (mITT) analysis set included all subjects who were randomly assigned to a treatment group and received at least 1 dose of study drug. The per protocol (PP) analysis set consisted of all mITT subjects who completed the 26-week double-blind treatment period, did not require rescue medication, and had no major protocol deviations that affected interpretation of the primary efficacy endpoint. The 26-week completers analysis set consisted of all mITT subjects who had completed 26 weeks of double-blind treatment (ie, documented in the eCRF by the investigator), and were not initiated on rescue medication (based upon protocol-specified criteria) prior to the Week 26 visit. The efficacy analysis for the primary efficacy endpoint in the 26-week completers set was considered supportive. The primary efficacy analyses to demonstrate superiority of canagliflozin relative to placebo, and all secondary efficacy analyses, were based on the mITT analysis set. The efficacy data measured after the initiation of rescue medication was censored and was not included in these analyses. A secondary analysis based on the PP analysis set was also conducted.

Efficacy data was analyzed according to the initial randomization assignment, regardless of the actual treatment received. The safety analysis set included the mITT subject population and safety data was analyzed according to the predominant treatment received ("as treated population") by the subject during the double-blind treatment phase (ie, for subjects that received a therapy different from the randomized treatment for the entire double-blind treatment phase). The approaches to handle study deviations are detailed in the statistical analysis plan (SAP).

Primary Efficacy Analyses: The primary efficacy endpoint was the change in HbA_{1c} from baseline to the Week 26 visit. The last-observation-carried-forward (LOCF) method was applied when Week 26 values were missing. In subjects that received rescue medication, measurements made prior to rescue were used as the last observation.

An analysis of covariance (ANCOVA) model with treatments and stratification factors as fixed effects and adjustment for HbA_{1c} and eGFR baseline covariates was used. The treatment difference (ie, each canagliflozin group minus placebo) in the least-squares (LS) means and their 2-sided 95% confidence interval (CI) were estimated based on this model.

As a supportive analysis, the change from baseline in HbA_{1c} was analyzed using a restricted maximum likelihood (REML)-based repeated measures approach. The analysis was based on observed data and included the fixed, categorical effects of treatment, stratification factors, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. An unstructured covariance was used to model the within-patient errors. The treatment comparisons were made between canagliflozin and placebo at Week 26 and significance tests were based on the difference of the LS means.

Secondary Efficacy Analyses: Secondary efficacy endpoints involved in hypothesis testing included the change in FPG from baseline to Week 26 and the proportion of subjects achieving HbA_{1c} <7.0% at Week 26. The change in FPG from baseline through Week 26 was analyzed in the mITT analysis set with an ANCOVA model similar to that used for the primary efficacy endpoint. The model included treatment and stratification factors as fixed effects, adjusting for the baseline measurement and baseline eGFR as covariates. The treatment differences (ie, each canagliflozin group minus placebo) in the LS means and their 2-sided 95% CIs were estimated based on this model. The categorical secondary efficacy endpoint (ie, proportion of subjects achieving HbA_{1c} <7.0% and <6.5%) and proportion of subjects requiring glycemic rescue medication) were analyzed with a logistic model with treatment and stratification factors, adjusting for baseline HbA_{1c} and eGFR. Continuous efficacy parameters such as the percent change from baseline to Week 26 in body weight, change from baseline in systolic and diastolic blood pressure, and percent change in fasting plasma lipids were analyzed in the mITT analysis set with an ANCOVA model similar to that used for the primary efficacy endpoint.

Multiplicity Adjustment: The hypotheses of the primary efficacy endpoint and major secondary efficacy endpoints were tested sequentially for the descending doses of canagliflozin using a closed testing procedure to control the overall type I error at 0.05.

Safety Analyses: The primary safety analyses excluded data collected after the initiation of glycemic rescue medication. A secondary safety analysis was conducted that included all data, regardless of the initiation of glycemic rescue medication (ie, including data collected after initiation of rescue medication). Subjects in the safety analysis set (mITT and 'as treated') were included in the denominators for the summary of adverse event, exposure, and concomitant medication data prior to receiving glycemic rescue medication. The rescue medication(s) used in the study were summarized by treatment group. The summaries of all adverse events, exposure, and concomitant medications including data after initiation of rescue medication were also provided. There was no imputation of missing values for clinical laboratory test results, vital sign measurements, and ECG evaluations in the analyses.

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 and results will be reported in the final CSR.

RESULTS:

STUDY POPULATION:

Subject and Treatment Information and Baseline Characteristics

A total of 911 subjects were screened and a total of 272 subjects were randomized to study treatment. Overall 87% of subjects completed the 26-week treatment period, with a similar proportion of the canagliflozin 100 mg and placebo groups, and a larger proportion of the canagliflozin 300 mg group completing the 26-week treatment period. Only a small proportion of subjects in each of the canagliflozin groups received rescue medication, compared with a moderate proportion (14.3%) of subjects in the placebo group. The mITT analysis set and the safety analysis set were identical. The allocation of treatment assignment in the safety analysis and the efficacy analysis were the same as no subject took incorrect double-blind study drug for a predominant part of the double-blind treatment period. In forming the PP analysis set, 5 subjects who completed the 26-week core double-blind period were determined (based upon assessment prior to unblinding) to meet the prespecified criteria of having a protocol deviation that could have potentially impacted efficacy (and were, therefore, not included in the PP analysis set). Because nearly 98% of subjects in the completers' analysis set were also in the PP analysis set, these analysis sets were very similar.

Reasons for Discontinuation (mITT)

(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]	13 (14.4)	15 (16.7)	7 (7.9)	22 (12.3)	35 (13.0)
Adverse event	4 (4.4)	4 (4.4)	2 (2.2)	6 (3.4)	10 (3.7)
Death	0	1 (1.1)	0	1 (0.6)	1 (0.4)
Noncompliance with study drug	0	1 (1.1)	0	1 (0.6)	1 (0.4)
Protocol violation	1 (1.1)	0	1 (1.1)	1 (0.6)	2 (0.7)
Withdrawal of consent	4 (4.4)	2 (2.2)	2 (2.2)	4 (2.2)	8 (3.0)
Other	4 (4.4)	7 (7.8)	2 (2.2)	9 (5.0)	13 (4.8)

[a] As indicated by the investigator on the eCRF for mITT subjects who discontinued before the Week 26 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 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" (4.8% of subjects), followed by adverse events (3.7%), and withdrawal of consent (3.0%). 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 related to the preclinical carcinogenicity findings (involving 6 subjects); no other discernable pattern was evident (other reasons, generally involving 1 to 2 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 withdrew consent 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 26-week double-blind treatment period was modestly greater in the canagliflozin groups compared with placebo, with nearly 80% of subjects in the canagliflozin 100 mg group and about 90% of subjects in the canagliflozin 300 mg group having at least 24 weeks of exposure, compared with approximately 73% 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, with approximately 10% of subjects Asians, and 1.9% of subjects black or African-American; approximately 8% of subjects were of Hispanic or Latino ethnicity.

Baseline mean weight 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 in the mITT population 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:

Primary Endpoint: Clinically useful and statistically significant reductions in HbA_{1c} at Week 26 compared with placebo were observed with both doses of canagliflozin: LS mean changes from baseline of -0.40% ($p<0.001$) and -0.30% ($p=0.012$) with the 300 mg and 100 mg canagliflozin doses, respectively, confirming the study's primary hypothesis and key secondary hypothesis, respectively.

Secondary Endpoints: Based on the pre-specified hierarchical testing sequence (testing HbA_{1c}, FPG, then proportion to HbA_{1c} goal, with each dose tested, in sequence, for each endpoint), canagliflozin 300 mg did not achieve statistical significance with respect to the secondary endpoint of the change from baseline in FPG, although it showed numerical improvement compared with placebo. Based on the hierarchical testing procedure, no further statistical testing was conducted (descriptive statistics are provided in the table below).

Change from Baseline to Week 26 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	Mean (95% CI)	p-value	Mean (95% CI)	p-value
HbA_{1c} Change (%)	-0.30 (-0.529;-0.066)	0.012	-0.40 (-0.635; -0.174)	<0.001
FPG Change (mmol/L)	-0.85 (-1.579;-0.128)	0.021	-0.67 (-1.405; 0.056)	0.070[a]
Achieving 7% HbA_{1c} target[b]	10.03 (-2.20; 22.30)	0.227	15.34 (2.79; 27.91)	0.017
Body Weight Percent Change(%)[c]	-1.6 (-2.3;-0.8)	<0.001	-1.8 (-2.6; -1.0)	<0.001
Systolic BP Change (mmHg)[c]	-5.73 (-9.545;-1.912)	0.003	-6.12 (-9.959; -2.280)	0.002
HDL-C Percent Change (%)[c]	2.5 (-1.9;7.0)	0.264	1.5 (-3.0; 5.9)	0.513
Triglycerides Percent Change (%)[c]	-1.7 (-13.8; 10.5)	0.785	3.9 (-8.1; 15.9)	0.521

[a] Canagliflozin 300 mg did not achieve statistical significance with respect to the change from baseline in FPG, no further statistical testing was conducted.

[b] For the proportion of patients achieving 7% HbA_{1c} target, p-value is based on logistic regression with terms for treatment and stratification factors and adjusting for the baseline Hb_{A1c} and baseline eGFR as covariates.

[c] Secondary endpoints (body weight, systolic BP, HDL-C, and triglycerides) were not pre-specified hypotheses

Key: AHA= antihyperglycemic agent, ANCOVA=analysis of covariance, BP=blood pressure, 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

Note: For continuous endpoints, the least squares mean is presented with associated p-values and CI based on ANCOVA models with terms for treatment and stratification factors (AHA washout, Atherosclerotic CV Disease History) and adjusting for the corresponding baseline value and baseline eGFR value (only for HbA_{1c}, FPG, and body weight) as covariates.

SAFETY RESULTS:

Adverse Events: The overall incidence of subjects with adverse events for the primary safety analysis (ie, excluding data after glycemic rescue medication was initiated) was slightly higher in the canagliflozin 100 mg group and similar in the canagliflozin 300 mg and placebo groups. A slightly higher incidence of drug-related adverse events was observed in the canagliflozin 100 mg group, and a moderately higher incidence was observed in the canagliflozin 300 mg group, relative to the placebo group. The overall incidence of adverse events leading to discontinuation was low across treatment groups, and modestly lower in the canagliflozin groups relative to the placebo group. A moderate incidence of serious adverse events was observed, as anticipated in subjects with a substantial incidence of co-morbid conditions and long-standing diabetes, but not notably different across treatment groups. 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 2 deaths reported during the core double-blind treatment period, with 1 death reported in the placebo group and 1 death in the canagliflozin 100 mg group (and 1 additional subject with an outcome of death that was non-treatment emergent, who died more than 30 days after discontinuation from the study).

Several specific adverse events occurred at a higher incidence in the canagliflozin groups relative to placebo, including balanitis, vulvovaginitis (and related terms), adverse events consistent with osmotic diuresis (eg, pollakiuria, thirst) and in adverse events related to a reduction in intravascular volume (eg, hypotension, postural dizziness), hypoglycemia, and urinary tract infections. The incidences of these specific adverse events were generally low and few subjects discontinued due to these adverse events. Higher incidences of drug-related adverse events compared to placebo were observed in both canagliflozin groups, and were mainly driven by numerically higher incidences of these specific adverse events.

Summary of Adverse Events - Prior to Initiation of Rescue Medication (Safety)

(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	66 (73.3)	70 (77.8)	66 (74.2)	136 (76.0)
Adverse events leading to discontinuation	5 (5.6)	3 (3.3)	2 (2.2)	5 (2.8)
Adverse events related to study drug [a]	20 (22.2)	23 (25.6)	29 (32.6)	52 (29.1)
Adverse events related to study drug [a] and leading to discontinuation	2 (2.2)	0	1 (1.1)	1 (0.6)
Serious adverse events	12 (13.3)	9 (10.0)	10 (11.2)	19 (10.6)
Serious adverse events leading to discontinuation	3 (3.3)	2 (2.2)	1 (1.1)	3 (1.7)
Serious adverse events related to study drug [a]	1 (1.1)	1 (1.1)	2 (2.2)	3 (1.7)
Serious adverse events related to study drug [a] and leading to discontinuation	1 (1.1)	0	1 (1.1)	1 (0.6)
Deaths	1 (1.1)	1 (1.1)	0	1 (0.6)

[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 to moderate increases serum phosphate were observed with canagliflozin. The mean percent changes from baseline for selected safety laboratory parameters are summarized below.

Mean Percent Changes from Baseline for Selected Safety Laboratory Parameters – Within 2 Days of the Last Dose of Study Drug[a]
(Study 28431754-DIA3004: Safety Analysis Set)

	Mean % Change from Baseline		
Parameter	Placebo	CANA 100 mg	CANA 300 mg
Hemoglobin	-0.5	5.3	3.1
ALT	8.2	10.1	-4.4
AST	4.3	5.5	-4.3
ALP	5.3	7.0	-2.1
GGT	10.6	8.3	-7.1
Serum bilirubin	4.1	4.5	7.4
BUN	2.6	11.9	11.2
Serum creatinine	3.8	9.7	10.7
eGFR	-2.8	-8.0	-8.6
Chloride	0.0	-0.2	0.0
Sodium	0.3	0.4	0.2
Magnesium	0.0	9.1	14.6
Phosphate	1.0	4.9	9.5
Potassium	0.6	-0.5	0.6
Serum urate	2.5	-0.3	-2.0

[a] This summary includes data collected up to a maximum of 2 days after a subject's last dose of study drug in the 26-week core-double blind period (data collected beyond 2 days after the subject's last dose of study drug are excluded from this summary).

Key: ALT=alanine aminotransferase, ALP=alkaline phosphatase, AST=aspartate aminotransferase, BUN=blood urea nitrogen, eGFR=estimated glomerular filtration rate, GGT=gamma-glutamyl transferase

Cross-reference: DLAB51CM_CORE

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. There was a low incidence of adverse events of postural dizziness observed in both canagliflozin treatment groups.

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 co-morbidities and diabetic complications:

- Both doses of canagliflozin provided clinically useful and statistically significant reductions in HbA_{1c}.
- Both doses of canagliflozin provided numerical percent reductions in body weight and numerical reductions in systolic blood pressure relative to placebo
- Canagliflozin was overall well tolerated
- There was a small increase in adverse events of genital mycotic infections (vulvovaginitis in females and balanitis in males) with canagliflozin that did not lead to discontinuation, and a slight increase in the incidence of urinary tract infection adverse events, without an increase in upper tract 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—sometimes requiring adjustments in concomitant medications (such as diuretics)—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 patients 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 the expected profile that had emerged from Phase 2b studies of canagliflozin.

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